ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2022 March 19; 12(3): 379-540

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

Contents

Monthly Volume 12 Number 3 March 19, 2022

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

Observational Study

Prospective Study

World Journal of Psychiatry

Monthly Volume 12 Number 3 March 19, 2022

Contents

LETTER TO THE EDITOR

World Journal of Psychiatry

Monthly Volume 12 Number 3 March 19, 2022

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Psychiatry*, Délio M Conde, MD, PhD, Professor, Department of Gynecology and Obstetrics, Federal University of Goiás, Goiânia 74605-050, Brazil. delioconde@ufg.br

AIMS AND SCOPE

The primary aim of *World Journal of Psychiatry* (*WJP*, *World J Psychiatry*) is to provide scholars and readers from various fields of psychiatry with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJP mainly publishes articles reporting research results and findings obtained in the field of psychiatry and covering a wide range of topics including adolescent psychiatry, biological psychiatry, child psychiatry, community psychiatry, ethnopsychology, psychoanalysis, psychosomatic medicine, *etc.*

INDEXING/ABSTRACTING

The *WJP* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2021 edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJP* as 4.571; IF without journal self cites: 4.429; 5-year IF: 7.697; Journal Citation Indicator: 0.73; Ranking: 46 among 156 journals in psychiatry; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

PUBLICATION DATE
March 19, 2022

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 379-392

DOI: 10.5498/wjp.v12.i3.379

ISSN 2220-3206 (online)

MINIREVIEWS

Neuroimmune crosstalk through brain-derived neurotrophic factor and its precursor pro-BDNF: New insights into mood disorders

Xiao-Pei Zhao, Hui Li, Ru-Ping Dai

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Siniscalco D

Received: March 29, 2021
Peer-review started: March 29, 2021
First decision: August 19, 2021
Revised: August 22, 2021
Accepted: January 22, 2022
Article in press: January 22, 2022
Published online: March 19, 2022

Xiao-Pei Zhao, Hui Li, Ru-Ping Dai, Department of Anesthesiology, The Second Xiangya Hospital, Central South University, Changsha 410011, Hunan Province, China

Corresponding author: Ru-Ping Dai, MD, PhD, Academic Research, Chief Doctor, Director, Doctor, Professor, Department of Anesthesiology, The Second Xiangya Hospital, Central South University, No. 139 Renmin Middle Road, Changsha 410011, Hunan Province, China.
xyeyyrupingdai@csu.edu.cn

Abstract

Mood disorders are the most common mental disorders, affecting approximately 350 million people globally. Recent studies have shown that neuroimmune interaction regulates mood disorders. Brain-derived neurotrophic factor (BDNF) and its precursor pro-BDNF, are involved in the neuroimmune crosstalk during the development of mood disorders. BDNF is implicated in the pathophysiology of psychiatric and neurological disorders especially in antidepressant pharmacotherapy. In this review, we describe the functions of BDNF/pro-BDNF signaling in the central nervous system in the context of mood disorders. In addition, we summarize the developments for BDNF and pro-BDNF functions in mood disorders. This review aims to provide new insights into the impact of neuroimmune interaction on mood disorders and reveal a new basis for further development of diagnostic targets and mood disorders.

Key Words: Brain-derived neurotrophic factor; pro-BDNF; Neural circuits; Neuroimmune; Mood disorders; Depression

Core Tip: The neuroimmune crosstalk plays a crucial role in the regulation of mood disorders. Recent studies have shown that the brain-derived neurotrophic factor (BDNF) and its precursor pro-BDNF are cardinal regulators in the neuroimmune axis. However, the roles and potential mechanisms of BDNF/pro-BDNF signaling in the neuroimmune crosstalk in the context of mood disorders remain unexplored. In this review, we summarize recent studies on the role of BDNF/TrkB signaling and pro-BDNF/p75^{NTR} signaling in the neuroimmune axis and how they influence the development of mood disorders.

Citation: Zhao XP, Li H, Dai RP. Neuroimmune crosstalk through brain-derived neurotrophic factor and its precursor pro-BDNF: New insights into mood disorders. *World J Psychiatry* 2022; 12(3): 379-392
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/379.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.379

INTRODUCTION

Mood disorders are complex diseases characterized by mood depression and anhedonia. Depressive episodes, manic episodes, bipolar disorder, as well as persistent mood disorders are the typical symptoms. In addition, mood disorders are among the most common mental disorders in the world and major contributors to the global burden of disease[1,2]. In Europe, for example, the current burden is greater than that from 10 years ago despite the availability of reasonably effective pharmacological and psychological interventions[3]. Moreover, the World Health Organization in 2008 ranked major depression as the third cause of the disease burden worldwide and predicted that the disease will rank first by 2030[4]. Furthermore, various studies have shown the impact of depression, anxiety and stress on different systems including the cardiovascular and immune systems[5]. However, the mechanisms and pathogenesis of the syndrome still remain unclear. Although antidepressants were previously used extensively in the treatment of mood disorders, current forms of treatment are largely suboptimal. It is therefore urgent and necessary to explore novel therapeutic targets for the treatment of mood disorders.

Several theories have been put forward to explain mood disorders, including the neural circuit hypothesis, neurotransmitter hypothesis, hypothalamus-pituitary-adrenal (HPA) axis dysfunction, neurotrophic hypothesis and cytokine hypothesis[1]. Among them, neurotrophins, particularly brain-derived neurotrophic factor (BDNF), are extensively studied for their role in mood disorders. Additionally, dysfunctions in BDNF and its precursor pro-BDNF in the central nervous system (CNS) are well known to play a critical role in the pathogenesis of mood disorders. However, it is still unclear whether peripheral BDNF can reflect changes in the levels of BDNF in the CNS. Moreover, recent studies have shown that there are changes in BDNF and pro-BDNF signaling in the immune cells of patients with depression[6]. Nonetheless, the exact mechanisms of BDNF/pro-BDNF in neuroimmune crosstalk are yet to be elucidated. The changes in BDNF/pro-BDNF signaling in the CNS and immune system suggest that this neurotrophin is a linker in neuroimmune crosstalk; an emerging topic that has gained popularity in the field of mood disorders.

INTRACELLULAR PROCESSING AND SIGNALING OF BDNF AND PRO-BDNF

BDNF is the second identified member of the neurotrophin family and the most widely distributed neurotrophin in the CNS as well as the peripheral nervous system[7]. Previous studies have reported that BDNF is expressed in neurons, astrocytes, Schwann cells, fibroblasts and possibly, smooth muscle cells[8]. In addition, regulation of BDNF processing is governed by complex regulatory mechanisms at the transcriptional, translational and posttranslational levels of gene expression[9]. The human BDNF gene is located on chromosome 11, region p13-14 and spans 70 kb. The gene has a complex structure as it consists of 11 exons (I-IX, plus Vh and VIIIh) in the 5' end and nine functional promoters. The coding sequence resides in exon 9 and has eight upstream exons that encode promoters regulating regional and cell-type-specific expression[10]. Moreover, the BDNF protein is initially synthesized into pro-BDNF in the endoplasmic reticulum. Pro-BDNF is then subsequently cleaved by proconvertases/furin to generate either a 28-kDa truncated form (truncated BDNF) or the 13.5-kDa mature BDNF. Following this, the mature BDNF is stored in the dense-core vesicle and is secreted upon neuronal activation. Additionally, BDNF signaling plays a critical role in promoting neuronal survival, phenotypic differentiation, axonal and dendritic growth and synapse formation[11,12].

BDNF function is mediated by two receptor systems, namely, TrkB and $p75^{NTR}$ (pan 75 neurotrophin receptor)[13]. Extensive research has shown that BDNF binds to its high-affinity receptor TrkB, causing the autophosphorylation of TrkB, subsequently activating the mitogen-activated protein kinase pathway, phospholipase C-γ pathway, phosphatidylinositol 3-kinase pathway and other signaling pathways. Additionally, BDNF-TrkB signaling affects the survival, development and function of neurons. They also promotes the formation of the dendritic spine, provides a structural basis for synapse formation and improves the transmission efficiency of synapses[14].

As the intermediate during the synthesis of BDNF, pro-BDNF can also be secreted outside the cells in different sites of the CNS, such as the cerebral cortex, cerebellum, substantia nigra, amygdala and hypothamalus[8]. In addition, pro-BDNF can be cleaved extracellularly into mature or truncated BDNF by matrix metalloproteinases/plasmin[12]. Pro-BDNF can also bind to its high affinity receptor, $p75^{NTR}$ with its co-receptor sortilin and exert an effect opposite to the biological function of mature BDNF, including neuronal apoptosis, pruning of axons and dendrites and long-term depression[13-15].

Therefore, it is important to discuss the roles of these two proteins involved in mood disorders. Moreover, activation of TrkB and $p75^{NTR}$ promotes and suppresses the growth of the dendritic spine, respectively. Therefore, cleavage of pro-BDNF may represent a new mechanism that controls the direction of BDNF regulation, *i.e.*, synaptic potentiation or synaptic depression.

Several signaling pathways are activated following the binding of pro-neurotrophin to $p75^{NTR}$. These signaling pathways which summarized in Figure 1 are mediated by the interaction of $p75^{NTR}$ to its adaptor proteins, including tumor necrosis factor receptor-associated factor 6, the neurotrophin receptor-interacting factor, melanoma-associated antigen (MAGE), neurotrophin receptor p75 interacting MAGE homolog, Schwann cell factor 1, rho GDP dissociation inhibitor (RhoGDI) and other proteins[16]. Additionally, there are three major downstream pathways for $p75^{NTR}$ including nuclear factor (NF)- κB signaling, RhoGDI and the RhoA signaling, and Jun kinase signaling cascade. Notably, NF-κB is a transcription factor that can be activated by $p75^{NTR}$ but not *via* Trk receptors. Moreover, RIP2 was previously shown to link $p75^{NTR}$ to the NF-κB pathway[17]. Activation of NF-κB also contributes to the NGF-dependent survival of developing sensory neurons, oligodendrocytes and Schwann cells[18-21]. It mediates the NGF-dependent increase in the expression of the survival factor Bcl-xL and a survival pathway in PC12 cells[22]. RhoA causes the actin cytoskeleton to become rigid, which limits the mobility of the growth cone and inhibits neuronal elongation in the developing nervous system[23]. Recent evidence suggests that RhoA activity is regulated by the cytoplasmic domain of $p75^{NTR}$[24]. Furthermore, the unbound state of $p75^{NTR}$ associates with RhoGDI, which subsequently interacts with RhoA and activates RhoA signaling[25]. It was also shown that neurotrophins inhibit the association between RhoGDI and $p75^{NTR}$, thus suppressing the release of RhoA and promoting the elongation of the growth cone[26,27]. Additionally, pro-neurotrophin binds to $p75^{NTR}$ and activates the c-Jun N-terminal kinases (JNK) signaling pathway, causing apoptosis of developing neurons[28]. In contrast, TrkA can prevent $p75^{NTR}$-mediated apoptosis induced by the JNK pathway[29].

ROLE OF BDNF/PRO-BDNF IN THE CNS IN DEPRESSION/BIPOLAR DISORDERS

The neurocircuits involved in regulating mood disorders include the hypothalamus, hippocampus, brain stem nuclei, temporal lobe, caudate, the anterior cingulate cortex (ACC), frontal cortex, basal forebrain, the extended amygdala, including the central nucleus of the amygdala (CeA) and medial nucleus of the amygdala (MeA), bed nucleus of the stria terminalis (BNST) and the shell of the nucleus accumbens (NAc)[11,30]. Clinical and experimental studies showed that depression may be driven by a dysregulated circuit function across multiple brain regions[31]. In addition, BDNF was also shown to be highly expressed in the cortex, hippocampus, limbic structures, cerebellum and the olfactory bulb[32]. Using specific antibodies against pro-BDNF, previous studies showed that pro-BDNF is widely and abundantly expressed throughout the adult brain. Moreover, experimental studies have shown that pro-BDNF, in different brain regions, regulates depressive behaviors. A previous study also reported that pro-BDNF is upregulated in the hippocampus, neocortex, the medial prefrontal cortex (PFC) and brainstem of individuals with a depression-like phenotype[33]. In contrast, there was a decrease in the expression of pro-BDNF in the NAc of rats with learned helplessness. These studies therefore suggest that the association of BDNF and pro-BDNF with the mood status is dependent on the specific location and the neural circuitry.

Hippocampus

Existing evidence shows that the BDNF in the hippocampus plays an important role in the pathogenesis of depression[34]. First, previous studies reported that the expression of hippocampal BDNF declined in different depression models. For instance, chronic-stress-induced models of depression showed decreasing levels of BDNF in the hippocampus and antidepressant treatment upregulated the expression of BDNF and TrkB in the hippocampus of rats[35]. It was also shown that chronic unpredictable mild stress (CUMS) decreased the levels of BDNF in the hippocampus and PFC, but increased the levels of BDNF in the basolateral nucleus of the amygdala (BLA). On the contrary, the blood oxygen level-dependent (BOLD) activity was elevated in the hippocampus and PFC but reduced in the BLA after exposure to CUMS, indicating that the levels of BDNF were negatively correlated with BOLD activity in the WT CUMS-exposed mice[30]. Second, it was reported that various antidepressants can restore the downregulation of BDNF in the hippocampus. Notably, antidepressant drugs increased the expression of BDNF mRNA in the hippocampi of rats[36]. In addition, treatment with monoamine oxidase inhibitors increased the expression of BDNF in specific hippocampal subfields. Consistent with these results, it is reported that administration of leptin exerted antidepressant effects and increased the expression of BDNF in the hippocampus[37]. Third, it has been shown that impairment of hippocampal BDNF signaling produces certain depression-related behaviors and reduces the effect of the antidepressants[38]. Previous studies have shown that upregulating the levels of hippocampal BDNF produces antidepressant effects. In addition, it is reported that direct incorporation of BDNF in the hippocampus of rodents mimics antidepressant treatment[12]. Moreover, it was previously shown that peripheral administration of BDNF produces anxiolytic and antidepressant effects. Therefore, the

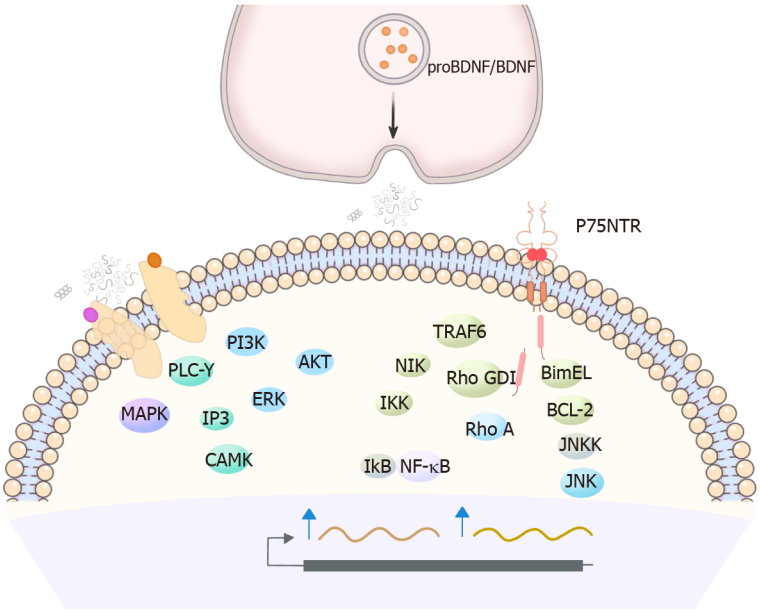


Figure 1 Role of brain-derived neurotrophic factor and pro-BDNF in neuroimmune crosstalk in mood disorders. Brain-derived neurotrophic factor (BDNF) or pro-BDNF can be stored in the dense-core vesicles and released upon neuronal activity. The released BDNF and pro-BDNF mainly bind to their high affinity receptors, TrkB and $p75^{NTR}$, respectively and mediate the downstream signaling pathways. BDNF-TrkB signaling leads to neuronal survival, development and long-term potentiation. In contrast, pro-BDNF-$p75^{NTR}$ signaling mediates neuronal apoptosis, axonal pruning and long-term depression. BDNF: Brain-derived neurotrophic factor; NF-κB: Nuclear factor-κB.

downregulation of BDNF in the hippocampus contributes to the pathogenesis of depression.

Several mechanisms have been proposed to underlie the role of hippocampal BDNF in depression. It is well known that BDNF/TrkB signaling activates the cAMP-response element binding protein (CREB) cascade and that antidepressant treatment upregulates the cAMP-CREB cascade in the hippocampus [39]. The activating cAMP-CREB signaling enhances the response to a tricyclic antidepressant. Therefore, downregulation of BDNF may inhibit downstream cAMP-CREB signaling and promote progression of mood disorders. In contrast, the inhibition of neurogenesis resulting from the reduced levels of BDNF may contribute to mood disorders, particularly depression. It is noteworthy that neurogenesis in adult animals is restricted to the subventricular zone of lateral ventricles and the dentate gyrus of the hippocampus. Furthermore, hippocampal neurogenesis is mediated by BDNF/TrkB signaling and is sensitive to a variety of environmental stimuli, including exercise, enrichment and antidepressant treatment[40]. It has also been shown that chronic antidepressant treatment increases neurogenesis in the hippocampus of adult rodents. Moreover, the effects of antidepressants on neurogenesis are dependent on intact BDNF signaling through TrkB[36]. According to a previous study, mice lacking TrkB in hippocampal neural progenitor cells failed to exhibit antidepressant-induced proliferation and neurogenesis[41].

It has also been shown that the levels of pro-BDNF and its receptors are increased in the hippocampus of rats with depression[42]. In addition, pro-BDNF negatively regulates dendritic complexity and depresses synaptic transmission in the hippocampus. There was an increase in the levels of hippocampal pro-BDNF in carioca high-conditioned freezing (a model of anxiety disorder) rats[43]. Additionally, injection of anti-pro-BDNF antibodies through the intracerebroventricular and intraperitoneal routes reverses the stress-induced depressive behavior[44]. In the major depressive disorder (MDD), reductions in the levels of pro-BDNF are seen in the right but not the left hippocampus, with no changes in the dentate gyrus[45]. Furthermore, exposure to the water maze increases the levels of the pro-BDNF protein in the dorsal hippocampus although the levels decrease in the ventral hippocampus. A recent study by our research group also demonstrated that pro-BDNF was upregulated in the hippocampus of rats with a depression-like or anxiety-like phenotype[44]. Moreover, intra-hippocampal injection of pro-BDNF antibodies attenuated the depression-like and anxiety-like behaviors, suggesting that pro-BDNF, in the hippocampus, is a common mediator of anxiety and depression[44].

Hypothalamus

The hypothalamus is a vital neuroendocrine region that not only influences the neuroendocrine and immune systems but also is closely related to the pathogenesis of depression. Additionally, many preclinical and clinical studies have proven that certain depressive characteristics are associated with abnormities in the hypothalamus. For instance, neuroimaging and postmortem brain microscopy studies showed widespread anatomical changes, volume deficits and neuron pathological changes in the hypothalamus of individuals with depression[46]. It has also been shown that intracerebroven-

tricular administration of BDNF in rats leads to an increase in the activity of the HPA axis[47]. According to previous studies, BDNF in the hypotha-lamus can regulate glucose and energy metabolism by acting directly on the hypotha-lamus. Moreover, a decrease in the levels of BDNF in hypothalamic nuclei may result in anorexia in rats[48,49]. It has been reported that trans-resveratrol increases the expression of BDNF in the frontal cortex, hippocampus and hypothalamus of rats with stroke, suggesting that BDNF protects neurons against cerebral ischemia[50].

PFC

The PFC is an important region of the brain that is involved in depression-like behavior. Previous studies reported that depressed suicide victims had low levels of BDNF in the hippocampus and PFC, especially in the ventromedial PFC[51]. Additionally, the antidepressant effects of ketamine were lost in mice lacking BDNF or TrkB or when the medial PFC was injected with anti-BDNF antibodies. Moreover, the chronic administration of different antidepressants such as escitalopram and fluoxetine is capable of increasing the levels of BDNF in the PFC of both rats and humans[52]. The mPFC-selective knockdown of BDNF showed diminished motivation but not impaired response-outcome learning[53].

ACC

The ACC is located in the medial subregion of the frontal lobe and is part of a neural system involved in motivating or energizing behavior and hierarchical reinforcement learning. It has been shown that there is a decrease in BDNF signaling in the subequal ACC of individuals with MDD[54]. Additionally, the Chaihu Shugan Powder significantly improves depressive behavior by increasing the mRNA expression levels of BDNF and TrkB in the hippocampus, amygdala and frontal lobe[55]. It is also reported that treatment with anti-pro-BDNF antibodies in the ACC restores the CUMS-induced decrease in the levels of BDNF mRNA in the cortex and hippocampus[56].

Midbrain

The midbrain, also known as the mesencephalon, is a region of the developing vertebrate brain that is composed of the tectum and tegmentum. The tectum makes up the rear portion of the midbrain and is composed of two paired rounded swellings, the superior and inferior colliculi. The tegmentum is located in front of the tectum. It consists of fiber tracts and three regions distinguished by their color, *i.e.*, the red nucleus, the periaqueductal gray (PAG) and the substantia nigra[57]. It has been shown that the BDNF and TrkB receptors are enriched in the dorsal PAG of the rat midbrain, which is considered to be a key structure in the pathophysiology of panic disorder. In addition, BDNF/TrkB signaling in the dorsal PAG is implicated in the beneficial effects of antidepressants in panic disorder[58,59]. Moreover, chronic infusion of BDNF into the midbrain is reported to increase the neurotransmission of 5-hydroxytryptamine (HT) and exert antidepressant effects in the learned helplessness and forced swim test depression models[60]. Moreover, direct administration of BDNF into the midbrain is sufficient to induce antidepressant-like behavior and neurogenesis[36]. A recent study also showed that BDNF-TrkB-mTORC1 signaling in the ventral PAG is required for sustained antidepressant effects[61].

INTERACTION OF PRO-BDNF/BDNF WITH NEUROTRANSMITTERS IN MOOD DISORDERS

The monoamine hypothesis postulates that depression is primarily caused by imbalances in the neurotransmission of monoamines, namely dopamine (DA), serotonin (5-HT) or norepinephrine (NE)[62]. In addition, numerous studies have suggested that BDNF signaling is closely associated with changes in the 5-HT and DA systems during the development and neuroplasticity of mood dysfunction.

5-HT system

Distinct effects of BDNF on the 5-HT system have been identified in depression. Notably, 5-HT is produced in the raphe nuclei of the brain stem region then spreads to terminal regions throughout the brain including the hypothalamus, cortex, hippocampus and amygdala. It also regulates a wide repertoire of functions such as behavior, cognition and mood[12,34]. Previous studies conducted on preschoolers have revealed a correlation between BDNF and 5-HT polymorphisms during brain development. The studies have also shown high levels of cortisol that could be a cause of depression. Additionally, the local administration of BDNF into the main cluster of the cell bodies of serotonergic neurons in the dorsal raphe nuclei (DRN) is reported to increase the length of dendrites and alter the electrophysiological activity of 5-HT neurons[63].

Infusion with BDNF results in hyperinnervation of 5-HT axons at the site of infusion in either the cerebral cortex or hippocampus. Moreover, BDNF has a profound effect on the sprouting of either intact 5-HT or neurotoxin-lesioned neurons[62]. Reduced levels of BDNF in $BDNF^{+/-}$ mice also leads to decreased functional activity in the $5\text{-}HT_1A$ receptor in the hippocampus and deficient $5\text{-}HT_2A$ receptors in the PFC and DRN of the midbrain. In addition, BDNF/TrkB is an upstream regulator of the $5\text{-}HT_2A$

pathway[64]. It is also reported that hippocampal BDNF improves some specific behavioral impairments including anxiety and anhedonia in 5-HT_4R KO mice[65].

Dopaminergic system

Depression is likely controlled by two interacting brain systems: the brain stress system HPA pathway and the brain reward system [ventral tegmental area-NAc (VTA-NAc) and VTA-PFC]. The VTA-NAc is the origin of dopaminergic neurons[12] and the dopaminergic VTA-NAc pathway is critical for reward and motivation. Notably, intrahippocampal infusion of BDNF produces antidepressant effects although it appears to play a prodepressive role in the VTA-NAc reward system. Additionally, many studies have shown that the levels of BDNF are increased in the VTA and NAc of depressed rats and mice although the levels are reduced in the hippocampus. Moreover, recent research has shown that intra-VTA injections of BDNF lead to an increase in depression-like behavior in rats as revealed by the forced swim test. It has also been shown that chronic neonatal stress not only leads to long-term changes in the expression of BDNF in the VTA, but also causes depression-like behavior in adults. In addition, the increased levels of BDNF seem to disinhibit the VTA DA neurons since knocking down BDNF in VTA prevents social-defeat-induced cross-sensitization to amphetamine. Furthermore, BDNF activity is closely associated with the excitability of VTA-DA neurons[66]. Chronic optogenetic phasic stimulation of VTA DA neurons increases the levels of NAc-BDNF and exacerbates social avoidance. Additionally, blocking BDNF-TrkB signaling in the NAc and VTA prevents aggravation of social avoidance. Therefore, BDNF signaling in the VTA-NAc pathway is required for the development of the susceptible phenotype induced by chronic social stress.

NAc is located in the basal forebrain, rostral to the preoptic areas. In addition, neurons in NAc integrate reward-related dopaminergic signals as well as glutamatergic input from the PFC, hippocampus, amygdala and hypothalamus[38,67]. In NAc, BDNF is expressed in dopaminergic and excitatory neurons projecting to NAc. TrkB is expressed in neurons expressing both the dopamine D1 and D2 receptors. Similar to VTA, it is reported that enhancing BDNF function in NAc can induce the behavioral changes associated with mood disorders, including anhedonia, anxiety and social interaction in rodents[38]. Moreover, inhibiting BDNF–TrkB signaling using dominant-negative TrkB-T1 in NAc, results in a dramatic antidepressant effect.

Moreover, previous research has enhanced basal dopaminergic and BDNF signaling to investigate their effects on behavioral changes. The results have shown significant comorbidity of substance dependence and depressive disorders[68]. However, the implication of pro-BDNF signaling in NAc on mood disorders is yet to be explored. Since the antidepressant effects on behavior despair are mediated by BDNF–TrkB signaling in the hippocampus, it is possible that pro-BDNF-$p75^{NTR}$ mechanisms are involved in the VTA-NAc-mediated anhedonic phenotype. Therefore, selective deletion of genes encoding receptor $p75^{NTR}$ in NAc may be helpful in explaining the specific role of pro-BDNF and mBDNF in depressive behaviors.

Glutamatergic and γ-aminobutyric acid systems

Pharmacological, genetic and postmortem evidence strongly suggests the involvement of synaptic dysfunction in affective disorders. Importantly, disorders are associated with a broad range of altered glutamatergic and glutamatergic and γ-aminobutyric acid (GABAergic) neurometabolism[69].

It is noteworthy that decreased levels of GABA in the plasma, cerebrospinal fluid, prefrontal and occipital cortices and dorsal anterolateral PFC neurons have been reported in patients with MDD[70]. Additionally, the effect of BDNF on the plasticity of GABAergic neurons in the hippocampus has been widely investigated in neuropsychiatric disorders. Previous studies using transgenic mouse models have shown that the genes with a high level of BDNF dependency were *Cort*, *Vgf*, *Sst*, *Tac1* and *Npy*. Those with intermediate BDNF dependency were *Snap25* and *Gad2* (*Gad65*) and those with little or no BDNF dependency were *Gad1* (*GAD67*), *Pvalb*, *Rgs4*, *Slc6a1*, *Calb2* and *Gabra1*[71]. BDNF regulates transmission at glutamatergic and GABAergic synapses through both pre- and postsynaptic mechanisms. In addition, BDNF promotes the release of GABA and increases the expression of cell membrane GABAA-R through the presynaptic tyrosine receptor kinase B[72]. It is also reported that postsynaptic BDNF promotes the expression and synaptic insertion of glutamate receptors. A previous study on promoter IV mutant BDNF (BDNF-KIV) mice uncovered the suppression of GABAergic transmission and an aberrant plasticity in the mPFC. This suggests that decreased activity-dependent transcription of BDNF results in altering synaptic function[73].

Additionally, previous studies have found a higher hippocampal mRNA expression of the GABAA-R subunit in the right hemisphere of rats. Intra-PFC infusion with allopregnanolone is also able to increase the gene expression of the γ2 GABAA-R subunit and BDNF in the right hemisphere of the same infused area, while bilateral injection increases the expression of BDNF in the hippocampus and PFC[53]. Moreover, deletion of the serotonin transporter induces neuroplastic impairments mediated by BDNF signaling in the spine and reduces the levels of GABAergic markers in both adulthood and during development[74]. Furthermore, the application of BDNF in the neocortical layer 2/3 rapidly suppresses GABAergic transmission through the release of endocannabinoids from the postsynaptic pyramidal cells, which act in a retrograde manner to suppress the release of presynaptic transmitters[75].

Several studies have shown that BDNF can also modulate the release and function of glutamatergic neurons. For example, a previous study showed that there was a decrease in the levels of the N-methyl-D-aspartate (NMDA) receptor and GABAergic transmission in $BDNF^{Met/Met}$ mice in which the processing of BDNF was impaired[41]. It is also reported that BDNF-dependent synaptic plasticity is involved in the antidepressant effect of low-dose ketamine, a noncompetitive antagonist of the NMDA receptor. According to a previous study, ketamine enhances BDNF signaling and augments plasticity at excitatory synapses[76]. In addition, activation of TrkB modulates presynaptic glutamate release in hippocampus[77]. Overall, these studies strongly suggest the critical role of BDNF-dependent synaptic activity in the regulation of affective behaviors.

BDNF/PRO-BDNF AS MEDIATORS OF NEUROIMMUNE CROSSTALK IN MOOD DISORDERS

More recent studies have been conducted to explore the neuroimmune crosstalk in mood disorders[78]. The crosstalk includes the communication between the nervous and immune systems, the effects of neuroendocrine hormones on the immune system, the innervation of lymphoid organs and the regulatory effects of cytokines on the HPA axis[79]. In addition, it is reported that microglia (resident immune cells in the CNS) as well as astrocytes can secrete some soluble agents such as chemokines, cytokines and neurotrophic factors to regulate immune responses in the CNS, and are implicated in the pathogenesis of mood disorders. Moreover, the levels of pro-BDNF/BDNF in the blood or mononuclear cells are associated with mood disorders, suggesting that peripheral pro-BDNF/BDNF can be diagnostic markers of mood disorders.

Neurotrophins, inflammatory mediators and oxidative stress are three well studied circulating diagnostic markers of mood disorders[80,81]. BDNF can also be used to indicate the efficacy of psychotropics. However, it is still debatable whether the levels of blood BDNF reflect the brain BDNF levels. In clinical studies, ELISA or western-blotting-based measurements of BDNF protein levels in body fluids or tissue samples are considered as potential proxies of brain function and associated diseases. Most clinical studies measure the levels of peripheral BDNF in saliva, serum, plasma, platelets and whole blood. The results show that peripheral blood BDNF appears to be a good indicator of brain BDNF levels. Additional studies have also corroborated that the levels of BDNF in whole blood and plasma are associated with the BDNF levels in the hippocampus[82].

A meta-analysis has shown that the levels of peripheral BDNF are equally reduced in patients with manic and depressive episodes[83]. In addition, previous studies have shown that there is a decrease in the levels of circulating BDNF in older and adolescent bipolar disorder patients in a euthymic state[84-86]. Moreover, a preliminary study showed that patients with bipolar mania had lower levels of the BDNF protein and mRNA, compared to healthy controls[87]. However, these findings were not consistent across all the studies. For instance, a previous study reported that the levels of mature BDNF and the ratio BDNF/proBDNF were significantly higher in patients with BD[88]. It was shown that pediatric bipolar patients had significantly higher levels of BDNF mRNA after eight weeks of treatment [89]. Moreover, a recent study reported that BD patients responsive to lithium had normal levels of serum BDNF[90]. Further research also revealed that lithium and valproic acid selectively activate the promoter IV of BDNF and trigger the respective downstream targets in neurons[91].

Pro-BDNF and its receptors, $p75^{NTR}$ and sortilin are upregulated in the serum of female patients with depression and positively correlated with depression scores[92]. Furthermore, the increased levels of pro-BDNF in the serum of patients with depression is reversed by long-term antidepressant treatment. It has been reported that the serum levels of BDNF in mood-stabilized bipolar disorder patients are significantly higher than those in healthy controls[93]. The serum levels of pro-BDNF in bipolar disorder patients are significantly lower than those in controls. These studies suggest that pro-BDNF/BDNF is closely related to the pathophysiology of bipolar disorder. However, further studies are required to explore how peripheral pro-BDNF/BDNF affects the pathogenesis of bipolar disorder.

Despite the close correlation between the levels of blood BDNF and various mood disorders, it is still unclear whether BDNF is able to cross the blood-brain barrier. While some studies argue that BDNF cannot directly traverse the blood-brain barrier, others indicate that BDNF is able to be transported[94,95]. Moreover, a number of studies have reported on additional problems related to the poor half-life and rapid degradation of BDNF[94,95]. More importantly, BDNF and pro-BDNF are enriched in human platelets but are undetectable in mice because the *BDNF* gene is not expressed in mouse megakaryocytes[96]. Therefore, it may be unrealistic to compare the peripheral BDNF levels in the mouse models of mood disorders with those of patients. Beyond the serum or plasma, peripheral BDNF/TrkB or pro-BDNF/$p75^{NTR}$ can be derived from immune cells.

BDNF/TRKB AND PRO-BDNF/P75^{NTR} SIGNALING DERIVED FROM IMMUNE CELLS IN MOOD DISORDERS

The hypotheses that inflammatory processes contribute to brain-related pathologies such as depressive disorders, has gained popularity particularly because of the activation of immune responses. Might it be possible that some immune cells such as nonspecific leukocytes and lymphocytes produce neurotransmitters and neuropeptides? Notably, immune mediators often interact with neurotransmitter receptors and also modulate neural pathways[97]. In turn, neuropeptides trigger the release of proinflammatory mediators that may amplify or facilitate inflammation by enhancing vasodilation, blood flow, vascular leakiness and leukocyte trafficking to sites of inflammation.

Similarly, BDNF and TrkB are expressed and released from microglia/monocytes, T and B cells. The released BDNF is in turn believed to exert neurotrophic effects[98]. In the CNS, BDNF and TrkB are expressed in the microglia which are the resident macrophages within the brain parenchyma[2]. When the microglia are activated, they can induce Ca^{2+}-response elements then bind to CREB and the calcium-responsive factor to mediate BDNF transcription[99,100]. Additionally, the released BDNF from the microglia can bind to TrkB and this has been implicated in neuropathic pain. However, it is still unclear what role the BDNF in the microglia plays in mood disorders and this requires to be studied further.

In addition, more recent studies have shown that pro-BDNF and p75^{NTR} are also expressed in monocytes, T and B cells and are upregulated in the different immune-mediated inflammatory cells (Figure 2)[101-103]. Previous research on septic mice also showed that pro-BDNF signaling contributes to the development of cognitive dysfunctions by interfering with the functions of immune cells[104]. Moreover, additional studies have shown that pro-BDNF and p75^{NTR} are upregulated in patients with multiple sclerosis as well as in mouse models and this contributes to the dysfunction of immune cells, mediated by pro-BDNF-p75^{NTR}-NF-κB signaling[105]. Our recent study showed that increased expression of proBDNF in M2-like monocytes may be highly associated with proinflammatory responses in the type-A aortic dissection disease[106]. Therefore, use of monoclonal antibodies against pro-BDNF may be a promising treatment to modulate the perturbed immune functions in the immune-mediated inflammatory diseases[105].

It is also reported that there is an increase in the levels of pro-BDNF, p75^{NTR} and sortilin in the peripheral blood mononuclear cells of patients with depression and this is associated with the severity of disease[92]. In addition, both pro-BDNF and p75^{NTR} are significantly upregulated in the lymphocytes of MDD subjects[92]. An early study reported that systemic administration of anti-pro-BDNF antibodies attenuated the depression-like behavior in rats. Given that it is hard for antibodies to reach the brain through the intact blood–brain barrier, it is likely that the therapeutic effect of systemic treatment with anti-pro-BDNF antibodies may be realized by neutralizing the peripheral pro-BDNF. Furthermore, a recent study by our research group showed that there was an increase in the levels of pro-BDNF and p75^{NTR} in the CD11b^{+} monocytes and macrophages in the intestinal laminar propria of mice under CUMS-induced depression[107].

Upregulation of pro-BDNF/p75^{NTR} in monocytes/macrophage is closely related to the activation of proinflammatory cytokines and gastrointestinal immobility. Our recent study showed that treatment with fluoxetine can inhibit upregulation of pro-BDNF/p75^{NTR}, cytokine activation and attenuate gastrointestinal immobility[107]. These results therefore indicate that pro-BDNF/p75 signaling may be involved in the gut-brain axis during depression. We also used a lipopolysaccharide-induced model of cognitive dysfunction in mice to show that there was an increase in the levels of pro-BDNF/p75^{NTR} in CD4^{+} T lymphocytes in the meninges. There was also an increase in the levels of the tumor necrosis factor-, interleukin (IL)-1, IL-6 and interferon-. Additionally, systemic administration but not the intracerebroventricular injection of anti-pro-BDNF antibodies attenuated cognitive dysfunction and inhibited the activation of proinflammatory cytokines[108]. A recent study also revealed that pro-BDNF and p75^{NTR} in monocytes played a role in neuroinflammation after chronic infection[109]. Therefore, pro-BDNF/p75^{NTR} signaling derived from immune cells may act as the inflammatory mediators to promote the interaction of neuroimmune during the development of depression or cognitive dysfunction.

CONCLUSION

BDNF/TrkB and pro-BDNF/p75^{NTR} signaling pathways are widely expressed in different regions of brain. BDNF signaling exert different effects on mood disorders. In contrast, pro-BDNF/p75^{NTR} signaling in CNS mainly promotes the development of mood disorders, such as depression and anxiety. Low levels of BDNF in circulation are negatively correlated with disease severity of depression. It should be noted, however, that BDNF is enriched in platelets and can be detected in human samples whereas BDNF is undetectable in the serum or platelets from mouse. This difference may limit the application of findings about BDNF/pro-BDNF signaling in mice to clinical practice. In contrast, pro-BDNF/p75^{NTR} signaling in immune cells is upregulated in patients with depression or depressive mice. Further studies should investigate the roles of pro-BDNF/p75^{NTR} in the neuroimmune crosstalk during the pathogenesis of mood disorders.

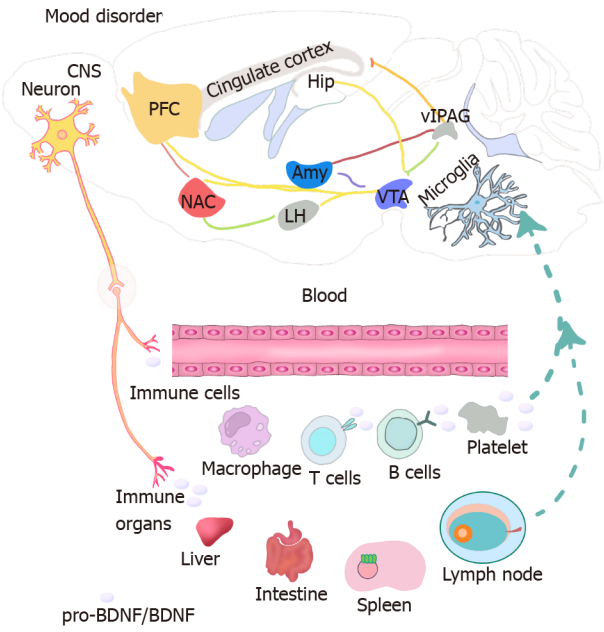


Figure 2 Intracellular signaling of pro-BDNF/brain-derived neurotrophic factor in the nervous system. Decreased levels of brain-derived neurotrophic factor (BDNF) are observed in most of the brain regions and contribute to the pathogenesis of mood disorders by interacting with different neurotransmitters. Pro-BDNF signaling is increased in the hippocampus and is implicated in anxiety-like behavior and depression. Moreover, there is an increase in pro-BDNF signaling in immune cells and this is correlated with disease activity in depression. Upregulated pro-BDNF signaling in immune cells may promote disease progression probably through interfering with the function of immune cells or directly acting on the neurons after being released from the microglia. Central nervous system dysfunction during mood disorders may also affect the immune functions and induce gastrointestinal immobility. CNS: Central nervous system; PFC: Prefrontal cortex; NAC: Nucleus accumbens; VTA: Ventral tegmental area; BDNF: Brain-derived neurotrophic factor; LH: Lateral hypothalamus.

FOOTNOTES

Author contributions: Zhao XP collected the data and wrote the paper; Li H and Dai RP collected the data and supervised the writing of the paper.

Supported by National Natural Science Foundation of China, No. 82071347 and No. 81771354 (to Dai RP).

Conflict-of-interest statement: The authors declare no conflict of interest.

Country/Territory of origin: China

ORCID number: Xiao-Pei Zhao 0000-0001-6195-5044; Hui Li 0000-0002-0959-455X; Ru-Ping Dai 0000-0002-1027-6698.

S-Editor: Gao CC
L-Editor: Kerr C
P-Editor: Gao CC

REFERENCES

1 **Racagni G**, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. *Dialogues Clin Neurosci* 2008; **10**: 385-400 [PMID: 19170396 DOI: 10.31887/DCNS.2008.10.4/gracagni]
2 **Jin Y**, Sun LH, Yang W, Cui RJ, Xu SB. The Role of BDNF in the Neuroimmune Axis Regulation of Mood Disorders. *Front Neurol* 2019; **10**: 515 [PMID: 31231295 DOI: 10.3389/fneur.2019.00515]
3 **Wittchen HU**. The burden of mood disorders. *Science* 2012; **338**: 15 [PMID: 23042853 DOI: 10.1126/science.1230817]
4 **Borgonetti V**, Les F, López V, Galeotti N. Attenuation of Anxiety-Like Behavior by *Helichrysum stoechas* (L.) Moench Methanolic Extract through Up-Regulation of ERK Signaling Pathways in Noradrenergic Neurons. *Pharmaceuticals (Basel)* 2020; **13** [PMID: 33348565 DOI: 10.3390/ph13120472]
5 **Bremner JD**, Campanella C, Khan Z, Shah M, Hammadah M, Wilmot K, Al Mheid I, Lima BB, Garcia EV, Nye J, Ward

L, Kutner MH, Raggi P, Pearce BD, Shah AJ, Quyyumi AA, Vaccarino V. Brain Correlates of Mental Stress-Induced Myocardial Ischemia. *Psychosom Med* 2018; **80**: 515-525 [PMID: 29794945 DOI: 10.1097/PSY.0000000000000597]

6 **Pandey GN**, Dwivedi Y, Rizavi HS, Ren X, Zhang H, Pavuluri MN. Brain-derived neurotrophic factor gene and protein expression in pediatric and adult depressed subjects. *Prog Neuropsychopharmacol Biol Psychiatry* 2010; **34**: 645-651 [PMID: 20227453 DOI: 10.1016/j.pnpbp.2010.03.003]

7 **Rybakowski JK**. BDNF gene: functional Val66Met polymorphism in mood disorders and schizophrenia. *Pharmacogenomics* 2008; **9**: 1589-1593 [PMID: 19018714 DOI: 10.2217/14622416.9.11.1589]

8 **Teixeira AL**, Barbosa IG, Diniz BS, Kummer A. Circulating levels of brain-derived neurotrophic factor: correlation with mood, cognition and motor function. *Biomark Med* 2010; **4**: 871-887 [PMID: 21133708 DOI: 10.2217/bmm.10.111]

9 **Altar CA**. Neurotrophins and depression. *Trends Pharmacol Sci* 1999; **20**: 59-61 [PMID: 10101965 DOI: 10.1016/s0165-6147(99)01309-7]

10 **Pruunsild P**, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human BDNF locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics* 2007; **90**: 397-406 [PMID: 17629449 DOI: 10.1016/j.ygeno.2007.05.004]

11 **Moonat S**, Pandey SC. Stress, epigenetics, and alcoholism. *Alcohol Res* 2012; **34**: 495-505 [PMID: 23584115]

12 **Roy M**, Tapadia MG, Joshi S, Koch B. Molecular and genetic basis of depression. *J Genet* 2014; **93**: 879-892 [PMID: 25572252 DOI: 10.1007/s12041-014-0449-x]

13 **Gupta VK**, You Y, Gupta VB, Klistorner A, Graham SL. TrkB receptor signalling: implications in neurodegenerative, psychiatric and proliferative disorders. *Int J Mol Sci* 2013; **14**: 10122-10142 [PMID: 23670594 DOI: 10.3390/ijms140510122]

14 **Bathina S**, Das UN. Brain-derived neurotrophic factor and its clinical implications. *Arch Med Sci* 2015; **11**: 1164-1178 [PMID: 26788077 DOI: 10.5114/aoms.2015.56342]

15 **Martinowich K**, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat Neurosci* 2007; **10**: 1089-1093 [PMID: 17726474 DOI: 10.1038/nn1971]

16 **Yamashita T**, Fujitani M, Hata K, Mimura F, Yamagishi S. Diverse functions of the p75 neurotrophin receptor. *Anat Sci Int* 2005; **80**: 37-41 [PMID: 15794129 DOI: 10.1111/j.1447-073x.2005.00095.x]

17 **Reichardt LF**. Neurotrophin-regulated signalling pathways. *Philos Trans R Soc Lond B Biol Sci* 2006; **361**: 1545-1564 [PMID: 16939974 DOI: 10.1098/rstb.2006.1894]

18 **Khursigara G**, Bertin J, Yano H, Moffett H, DiStefano PS, Chao MV. A prosurvival function for the p75 receptor death domain mediated *via* the caspase recruitment domain receptor-interacting protein 2. *J Neurosci* 2001; **21**: 5854-5863 [PMID: 11487608 DOI: 10.1523/JNEUROSCI.21-16-05854.2001]

19 **Hamanoue M**, Middleton G, Wyatt S, Jaffray E, Hay RT, Davies AM. p75-mediated NF-kappaB activation enhances the survival response of developing sensory neurons to nerve growth factor. *Mol Cell Neurosci* 1999; **14**: 28-40 [PMID: 10433815 DOI: 10.1006/mcne.1999.0770]

20 **Gentry JJ**, Casaccia-Bonnefil P, Carter BD. Nerve growth factor activation of nuclear factor kappaB through its p75 receptor is an anti-apoptotic signal in RN22 schwannoma cells. *J Biol Chem* 2000; **275**: 7558-7565 [PMID: 10713062 DOI: 10.1074/jbc.275.11.7558]

21 **Fogarty MP**, Downer EJ, Campbell V. A role for c-Jun N-terminal kinase 1 (JNK1), but not JNK2, in the beta-amyloid-mediated stabilization of protein p53 and induction of the apoptotic cascade in cultured cortical neurons. *Biochem J* 2003; **371**: 789-798 [PMID: 12534344 DOI: 10.1042/BJ20021660]

22 **Bui NT**, König HG, Culmsee C, Bauerbach E, Poppe M, Krieglstein J, Prehn JH. p75 neurotrophin receptor is required for constitutive and NGF-induced survival signalling in PC12 cells and rat hippocampal neurones. *J Neurochem* 2002; **81**: 594-605 [PMID: 12065668 DOI: 10.1046/j.1471-4159.2002.00841.x]

23 **Omelchenko A**, Firestein BL. Axonal Development: RhoA Restrains but Does Not Specify. *Curr Biol* 2019; **29**: R1179-R1181 [PMID: 31743672 DOI: 10.1016/j.cub.2019.10.003]

24 **Yamashita T**, Tohyama M. The p75 receptor acts as a displacement factor that releases Rho from Rho-GDI. *Nat Neurosci* 2003; **6**: 461-467 [PMID: 12692556 DOI: 10.1038/nn1045]

25 **Yamashita T**, Tucker KL, Barde YA. Neurotrophin binding to the p75 receptor modulates Rho activity and axonal outgrowth. *Neuron* 1999; **24**: 585-593 [PMID: 10595511 DOI: 10.1016/s0896-6273(00)81114-9]

26 **Hasegawa Y**, Fujitani M, Hata K, Tohyama M, Yamagishi S, Yamashita T. Promotion of axon regeneration by myelin-associated glycoprotein and Nogo through divergent signals downstream of Gi/G. *J Neurosci* 2004; **24**: 6826-6832 [PMID: 15282288 DOI: 10.1523/JNEUROSCI.1856-04.2004]

27 **Gehler S**, Gallo G, Veien E, Letourneau PC. p75 neurotrophin receptor signaling regulates growth cone filopodial dynamics through modulating RhoA activity. *J Neurosci* 2004; **24**: 4363-4372 [PMID: 15128850 DOI: 10.1523/JNEUROSCI.0404-04.2004]

28 **Akhter R**, Sanphui P, Das H, Saha P, Biswas SC. The regulation of p53 up-regulated modulator of apoptosis by JNK/c-Jun pathway in β-amyloid-induced neuron death. *J Neurochem* 2015; **134**: 1091-1103 [PMID: 25891762 DOI: 10.1111/jnc.13128]

29 **Kenchappa RS**, Tep C, Korade Z, Urra S, Bronfman FC, Yoon SO, Carter BD. p75 neurotrophin receptor-mediated apoptosis in sympathetic neurons involves a biphasic activation of JNK and up-regulation of tumor necrosis factor-alpha-converting enzyme/ADAM17. *J Biol Chem* 2010; **285**: 20358-20368 [PMID: 20421303 DOI: 10.1074/jbc.M109.082834]

30 **Huang P**, Gao T, Dong Z, Zhou C, Lai Y, Pan T, Liu Y, Zhao X, Sun X, Hua H, Wen G, Gao L, Lv Z. Neural circuitry among connecting the hippocampus, prefrontal cortex and basolateral amygdala in a mouse depression model: Associations correlations between BDNF levels and BOLD - fMRI signals. *Brain Res Bull* 2018; **142**: 107-115 [PMID: 29969645 DOI: 10.1016/j.brainresbull.2018.06.019]

31 **Ressler KJ**, Mayberg HS. Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nat Neurosci* 2007; **10**: 1116-1124 [PMID: 17726478 DOI: 10.1038/nn1944]

32 **Ide S**, Kakeda S, Watanabe K, Yoshimura R, Abe O, Hayashi K, Ueda I, Kishi T, Katsuki A, Umene-Nakano W, Iwata N, Nakamura J, Korogi Y. Relationship between a BDNF gene polymorphism and the brain volume in treatment-naive

patients with major depressive disorder: A VBM analysis of brain MRI. *Psychiatry Res* 2015; **233**: 120-124 [PMID: 26078197 DOI: 10.1016/j.pscychresns.2015.05.016]

33 **Lütcke H**, Murayama M, Hahn T, Margolis DJ, Astori S, Zum Alten Borgloh SM, Göbel W, Yang Y, Tang W, Kügler S, Sprengel R, Nagai T, Miyawaki A, Larkum ME, Helmchen F, Hasan MT. Optical recording of neuronal activity with a genetically-encoded calcium indicator in anesthetized and freely moving mice. *Front Neural Circuits* 2010; **4**: 9 [PMID: 20461230 DOI: 10.3389/fncir.2010.00009]

34 **Foster JA**, MacQueen G. Neurobiological factors linking personality traits and major depression. *Can J Psychiatry* 2008; **53**: 6-13 [PMID: 18286867 DOI: 10.1177/070674370805300103]

35 **Krystal AD**, Weiner RD. EEG correlates of the response to ECT: a possible antidepressant role of brain-derived neurotrophic factor. *J ECT* 1999; **15**: 27-38 [PMID: 10189617]

36 **Kafetzopoulos V**, Kokras N, Sotiropoulos I, Oliveira JF, Leite-Almeida H, Vasalou A, Sardinha VM, Papadopoulou-Daifoti Z, Almeida OFX, Antoniou K, Sousa N, Dalla C. The nucleus reuniens: a key node in the neurocircuitry of stress and depression. *Mol Psychiatry* 2018; **23**: 579-586 [PMID: 28397837 DOI: 10.1038/mp.2017.55]

37 **Rao U**. Biomarkers in pediatric depression. *Depress Anxiety* 2013; **30**: 787-791 [PMID: 24002798 DOI: 10.1002/da.22171]

38 **Krishnan V**, Nestler EJ. Linking molecules to mood: new insight into the biology of depression. *Am J Psychiatry* 2010; **167**: 1305-1320 [PMID: 20843874 DOI: 10.1176/appi.ajp.2009.10030434]

39 **Blendy JA**. The role of CREB in depression and antidepressant treatment. *Biol Psychiatry* 2006; **59**: 1144-1150 [PMID: 16457782 DOI: 10.1016/j.biopsych.2005.11.003]

40 **Li Y**, Luikart BW, Birnbaum S, Chen J, Kwon CH, Kernie SG, Bassel-Duby R, Parada LF. TrkB regulates hippocampal neurogenesis and governs sensitivity to antidepressive treatment. *Neuron* 2008; **59**: 399-412 [PMID: 18701066 DOI: 10.1016/j.neuron.2008.06.023]

41 **Ma Z**, Zang T, Birnbaum SG, Wang Z, Johnson JE, Zhang CL, Parada LF. TrkB dependent adult hippocampal progenitor differentiation mediates sustained ketamine antidepressant response. *Nat Commun* 2017; **8**: 1668 [PMID: 29162814 DOI: 10.1038/s41467-017-01709-8]

42 **Bai YY**, Ruan CS, Yang CR, Li JY, Kang ZL, Zhou L, Liu D, Zeng YQ, Wang TH, Tian CF, Liao H, Bobrovskaya L, Zhou XF. ProBDNF Signaling Regulates Depression-Like Behaviors in Rodents under Chronic Stress. *Neuropsychopharmacology* 2016; **41**: 2882-2892 [PMID: 27312407 DOI: 10.1038/npp.2016.100]

43 **Yang J**, Harte-Hargrove LC, Siao CJ, Marinic T, Clarke R, Ma Q, Jing D, Lafrancois JJ, Bath KG, Mark W, Ballon D, Lee FS, Scharfman HE, Hempstead BL. proBDNF negatively regulates neuronal remodeling, synaptic transmission, and synaptic plasticity in hippocampus. *Cell Rep* 2014; **7**: 796-806 [PMID: 24746813 DOI: 10.1016/j.celrep.2014.03.040]

44 **Zhong F**, Liu L, Wei JL, Hu ZL, Li L, Wang S, Xu JM, Zhou XF, Li CQ, Yang ZY, Dai RP. Brain-Derived Neurotrophic Factor Precursor in the Hippocampus Regulates Both Depressive and Anxiety-Like Behaviors in Rats. *Front Psychiatry* 2018; **9**: 776 [PMID: 30740068 DOI: 10.3389/fpsyt.2018.00776]

45 **Dunham JS**, Deakin JF, Miyajima F, Payton A, Toro CT. Expression of hippocampal brain-derived neurotrophic factor and its receptors in Stanley consortium brains. *J Psychiatr Res* 2009; **43**: 1175-1184 [PMID: 19376528 DOI: 10.1016/j.jpsychires.2009.03.008]

46 **Drevets WC**, Price JL, Furey ML. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Struct Funct* 2008; **213**: 93-118 [PMID: 18704495 DOI: 10.1007/s00429-008-0189-x]

47 **Wu Y**, Wei Z, Li Y, Wei C, Cheng P, Xu H, Li Z, Guo R, Qi X, Jia J, Jia Y, Wang W, Gao X. Perturbation of Ephrin Receptor Signaling and Glutamatergic Transmission in the Hypothalamus in Depression Using Proteomics Integrated With Metabolomics. *Front Neurosci* 2019; **13**: 1359 [PMID: 31920518 DOI: 10.3389/fnins.2019.01359]

48 **Gelfo F**, Tirassa P, De Bartolo P, Croce N, Bernardini S, Caltagirone C, Petrosini L, Angelucci F. NPY intraperitoneal injections produce antidepressant-like effects and downregulate BDNF in the rat hypothalamus. *CNS Neurosci Ther* 2012; **18**: 487-492 [PMID: 22672302 DOI: 10.1111/j.1755-5949.2012.00314.x]

49 **Angelucci F**, Ricci E, Padua L, Sabino A, Tonali PA. Music exposure differentially alters the levels of brain-derived neurotrophic factor and nerve growth factor in the mouse hypothalamus. *Neurosci Lett* 2007; **429**: 152-155 [PMID: 17980967 DOI: 10.1016/j.neulet.2007.10.005]

50 **Segi-Nishida E**, Sukeno M, Imoto Y, Kira T, Sakaida M, Tsuchiya S, Sugimoto Y, Okuno Y. Electroconvulsive seizures activate anorexigenic signals in the ventromedial nuclei of the hypothalamus. *Neuropharmacology* 2013; **71**: 164-173 [PMID: 23603200 DOI: 10.1016/j.neuropharm.2013.03.033]

51 **Pang C**, Cao L, Wu F, Wang L, Wang G, Yu Y, Zhang M, Chen L, Wang W, Lv W, Zhu J, Pan J, Zhang H, Xu Y, Ding L. The effect of trans-resveratrol on post-stroke depression *via* regulation of hypothalamus-pituitary-adrenal axis. *Neuropharmacology* 2015; **97**: 447-456 [PMID: 25937213 DOI: 10.1016/j.neuropharm.2015.04.017]

52 **Qi XR**, Zhao J, Liu J, Fang H, Swaab DF, Zhou JN. Abnormal retinoid and TrkB signaling in the prefrontal cortex in mood disorders. *Cereb Cortex* 2015; **25**: 75-83 [PMID: 23960204 DOI: 10.1093/cercor/bht203]

53 **Almeida FB**, Gomez R, Barros HMT, Nin MS. Hemisphere-dependent Changes in mRNA Expression of $GABA_A$ Receptor Subunits and BDNF after Intra-prefrontal Cortex Allopregnanolone Infusion in Rats. *Neuroscience* 2019; **397**: 56-66 [PMID: 30481569 DOI: 10.1016/j.neuroscience.2018.11.029]

54 **Gourley SL**, Swanson AM, Jacobs AM, Howell JL, Mo M, Dileone RJ, Koleske AJ, Taylor JR. Action control is mediated by prefrontal BDNF and glucocorticoid receptor binding. *Proc Natl Acad Sci U S A* 2012; **109**: 20714-20719 [PMID: 23185000 DOI: 10.1073/pnas.1208342109]

55 **Tripp A**, Oh H, Guilloux JP, Martinowich K, Lewis DA, Sibille E. Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. *Am J Psychiatry* 2012; **169**: 1194-1202 [PMID: 23128924 DOI: 10.1176/appi.ajp.2012.12020248]

56 **Deng Y**, Zhang CH, Zhang HN. [Effects of chaihu shugan powder on the behavior and expressions of BDNF and TrkB in the hippocampus, amygdala, and the frontal lobe in rat model of depression]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2011; **31**: 1373-1378 [PMID: 22097208]

57 **Yang CR**, Bai YY, Ruan CS, Zhou FH, Li F, Li CQ, Zhou XF. Injection of Anti-proBDNF in Anterior Cingulate Cortex (ACC) Reverses Chronic Stress-Induced Adverse Mood Behaviors in Mice. *Neurotox Res* 2017; **31**: 298-308 [PMID: 27957676 DOI: 10.1007/s12640-016-9687-4]

58 **Ruchalski K**, Hathout GM. A medley of midbrain maladies: a brief review of midbrain anatomy and syndromology for radiologists. *Radiol Res Pract* 2012; **2012**: 258524 [PMID: 22693668 DOI: 10.1155/2012/258524]

59 **Casarotto PC**, de Bortoli VC, Corrêa FM, Resstel LB, Zangrossi H Jr. Panicolytic-like effect of BDNF in the rat dorsal periaqueductal grey matter: the role of 5-HT and GABA. *Int J Neuropsychopharmacol* 2010; **13**: 573-582 [PMID: 20047714 DOI: 10.1017/S146114570999112X]

60 **Kozicz T**, Tilburg-Ouwens D, Faludi G, Palkovits M, Roubos E. Gender-related urocortin 1 and brain-derived neurotrophic factor expression in the adult human midbrain of suicide victims with major depression. *Neuroscience* 2008; **152**: 1015-1023 [PMID: 18329817 DOI: 10.1016/j.neuroscience.2007.12.050]

61 **Siuciak JA**, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). *Pharmacol Biochem Behav* 1997; **56**: 131-137 [PMID: 8981620 DOI: 10.1016/S0091-3057(96)00169-4]

62 **Yang PS**, Peng HY, Lin TB, Hsieh MC, Lai CY, Lee AS, Wang HH, Ho YC. NMDA receptor partial agonist GLYX-13 alleviates chronic stress-induced depression-like behavior through enhancement of AMPA receptor function in the periaqueductal gray. *Neuropharmacology* 2020; **178**: 108269 [PMID: 32791085 DOI: 10.1016/j.neuropharm.2020.108269]

63 **Duman RS**. Role of neurotrophic factors in the etiology and treatment of mood disorders. *Neuromolecular Med* 2004; **5**: 11-25 [PMID: 15001809 DOI: 10.1385/NMM:5:1:011]

64 **Kraus C**, Castrén E, Kasper S, Lanzenberger R. Serotonin and neuroplasticity - Links between molecular, functional and structural pathophysiology in depression. *Neurosci Biobehav Rev* 2017; **77**: 317-326 [PMID: 28342763 DOI: 10.1016/j.neubiorev.2017.03.007]

65 **Chhibber A**, Woody SK, Karim Rumi MA, Soares MJ, Zhao L. Estrogen receptor β deficiency impairs BDNF-5-HT_{2A} signaling in the hippocampus of female brain: A possible mechanism for menopausal depression. *Psychoneuroendocrinology* 2017; **82**: 107-116 [PMID: 28544903 DOI: 10.1016/j.psyneuen.2017.05.016]

66 **Amigó J**, Díaz A, Pilar-Cuéllar F, Vidal R, Martín A, Compan V, Pazos A, Castro E. The absence of 5-HT_4 receptors modulates depression- and anxiety-like responses and influences the response of fluoxetine in olfactory bulbectomised mice: Adaptive changes in hippocampal neuroplasticity markers and 5-HT_{1A} autoreceptor. *Neuropharmacology* 2016; **111**: 47-58 [PMID: 27586007 DOI: 10.1016/j.neuropharm.2016.08.037]

67 **Douma EH**, de Kloet ER. Stress-induced plasticity and functioning of ventral tegmental dopamine neurons. *Neurosci Biobehav Rev* 2020; **108**: 48-77 [PMID: 31666179 DOI: 10.1016/j.neubiorev.2019.10.015]

68 **Quintero GC**. Role of nucleus accumbens glutamatergic plasticity in drug addiction. *Neuropsychiatr Dis Treat* 2013; **9**: 1499-1512 [PMID: 24109187 DOI: 10.2147/NDT.S45963]

69 **Autry AE**, Monteggia LM. Brain-derived neurotrophic factor and neuropsychiatric disorders. *Pharmacol Rev* 2012; **64**: 238-258 [PMID: 22407616 DOI: 10.1124/pr.111.005108]

70 **Reddy-Thootkur M**, Kraguljac NV, Lahti AC. The role of glutamate and GABA in cognitive dysfunction in schizophrenia and mood disorders - A systematic review of magnetic resonance spectroscopy studies. *Schizophr Res* 2020 [PMID: 32107102 DOI: 10.1016/j.schres.2020.02.001]

71 **Fogaça MV**, Duman RS. Cortical GABAergic Dysfunction in Stress and Depression: New Insights for Therapeutic Interventions. *Front Cell Neurosci* 2019; **13**: 87 [PMID: 30914923 DOI: 10.3389/fncel.2019.00087]

72 **Kerman IA**. New insights into BDNF signaling: relevance to major depression and antidepressant action. *Am J Psychiatry* 2012; **169**: 1137-1140 [PMID: 23128919 DOI: 10.1176/appi.ajp.2012.12081053]

73 **Zhu G**, Sun X, Yang Y, Du Y, Lin Y, Xiang J, Zhou N. Reduction of BDNF results in GABAergic neuroplasticity dysfunction and contributes to late-life anxiety disorder. *Behav Neurosci* 2019; **133**: 212-224 [PMID: 30714802 DOI: 10.1037/bne0000301]

74 **Sakata K**, Woo NH, Martinowich K, Greene JS, Schloesser RJ, Shen L, Lu B. Critical role of promoter IV-driven BDNF transcription in GABAergic transmission and synaptic plasticity in the prefrontal cortex. *Proc Natl Acad Sci U S A* 2009; **106**: 5942-5947 [PMID: 19293383 DOI: 10.1073/pnas.0811431106]

75 **Calabrese F**, Guidotti G, Middelman A, Racagni G, Homberg J, Riva MA. Lack of serotonin transporter alters BDNF expression in the rat brain during early postnatal development. *Mol Neurobiol* 2013; **48**: 244-256 [PMID: 23564488 DOI: 10.1007/s12035-013-8449-z]

76 **Zhao L**, Levine ES. BDNF-endocannabinoid interactions at neocortical inhibitory synapses require phospholipase C signaling. *J Neurophysiol* 2014; **111**: 1008-1015 [PMID: 24335212 DOI: 10.1152/jn.00554.2013]

77 **Ninan I**. Synaptic regulation of affective behaviors; role of BDNF. *Neuropharmacology* 2014; **76** Pt C: 684-695 [PMID: 23747574 DOI: 10.1016/j.neuropharm.2013.04.011]

78 **Björkholm C**, Monteggia LM. BDNF - a key transducer of antidepressant effects. *Neuropharmacology* 2016; **102**: 72-79 [PMID: 26519901 DOI: 10.1016/j.neuropharm.2015.10.034]

79 **Pereira DB**, Rebola N, Rodrigues RJ, Cunha RA, Carvalho AP, Duarte CB. Trkb receptors modulation of glutamate release is limited to a subset of nerve terminals in the adult rat hippocampus. *J Neurosci Res* 2006; **83**: 832-844 [PMID: 16477614 DOI: 10.1002/jnr.20784]

80 **Niu Z**, Yang L, Wu X, Zhu Y, Chen J, Fang Y. The Relationship Between Neuroimmunity and Bipolar Disorder: Mechanism and Translational Application. *Neurosci Bull* 2019; **35**: 595-607 [PMID: 31214924 DOI: 10.1007/s12264-019-00403-7]

81 **Dantzer R**. Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. *Physiol Rev* 2018; **98**: 477-504 [PMID: 29351513 DOI: 10.1152/physrev.00039.2016]

82 **Rowland T**, Perry BI, Upthegrove R, Barnes N, Chatterjee J, Gallacher D, Marwaha S. Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar disorder: systematic review and meta-analyses. *Br J Psychiatry* 2018; **213**: 514-525 [PMID: 30113291 DOI: 10.1192/bjp.2018.144]

83 **Sagar R**, Pattanayak RD. Potential biomarkers for bipolar disorder: Where do we stand? *Indian J Med Res* 2017; **145**: 7-

16 [PMID: 28574009 DOI: 10.4103/ijmr.IJMR_1386_16]
84 **Lopes TDS**, Silva WDS, Ribeiro SB, Figueiredo CA, Campbell FQ, Daltro GC, Valenzuela A, Montoya P, Lucena RCS, Baptista AF. Does Transcranial Direct Current Stimulation Combined with Peripheral Electrical Stimulation Have an Additive Effect in the Control of Hip Joint Osteonecrosis Pain Associated with Sickle Cell Disease? *Front Hum Neurosci* 2017; **11**: 633 [PMID: 29326577 DOI: 10.3389/fnhum.2017.00633]
85 **Fernandes BS**, Molendijk ML, Köhler CA, Soares JC, Leite CM, Machado-Vieira R, Ribeiro TL, Silva JC, Sales PM, Quevedo J, Oertel-Knöchel V, Vieta E, González-Pinto A, Berk M, Carvalho AF. Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. *BMC Med* 2015; **13**: 289 [PMID: 26621529 DOI: 10.1186/s12916-015-0529-7]
86 **Cevher Binici N**, Inal Emiroğlu FN, Resmi H, Ellidokuz H. Serum Brain-derived Neurotrophic Factor Levels among Euthymic Adolescents with Bipolar Disorder Type I. *Noro Psikiyatr Ars* 2016; **53**: 267-271 [PMID: 28373806 DOI: 10.5152/npa.2015.8832]
87 **Lin CC**, Huang TL. Brain-derived neurotrophic factor and mental disorders. *Biomed J* 2020; **43**: 134-142 [PMID: 32386841 DOI: 10.1016/j.bj.2020.01.001]
88 **Diniz BS**. Decreased Brain-Derived Neurotrophic Factor (BDNF) in Older Adults with Bipolar Disorder: Meaning and Utility? *Am J Geriatr Psychiatry* 2016; **24**: 602-603 [PMID: 27426208 DOI: 10.1016/j.jagp.2016.03.003]
89 **Lin CC**, Lee CT, Lo YT, Huang TL. Brain-derived neurotrophic factor protein and mRNA levels in patients with bipolar mania - A preliminary study. *Biomed J* 2016; **39**: 272-276 [PMID: 27793269 DOI: 10.1016/j.bj.2016.08.001]
90 **Södersten K**, Pålsson E, Ishima T, Funa K, Landén M, Hashimoto K, Ågren H. Abnormality in serum levels of mature brain-derived neurotrophic factor (BDNF) and its precursor proBDNF in mood-stabilized patients with bipolar disorder: a study of two independent cohorts. *J Affect Disord* 2014; **160**: 1-9 [PMID: 24709015 DOI: 10.1016/j.jad.2014.01.009]
91 **Pandey GN**, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. *J Am Acad Child Adolesc Psychiatry* 2008; **47**: 1077-1085 [PMID: 18664999 DOI: 10.1097/CHI.0b013e31817eecd9]
92 **Rybakowski JK**. Response to lithium in bipolar disorder: clinical and genetic findings. *ACS Chem Neurosci* 2014; **5**: 413-421 [PMID: 24625017 DOI: 10.1021/cn5000277]
93 **Yasuda S**, Liang MH, Marinova Z, Yahyavi A, Chuang DM. The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. *Mol Psychiatry* 2009; **14**: 51-59 [PMID: 17925795 DOI: 10.1038/sj.mp.4002099]
94 **Zhou L**, Xiong J, Lim Y, Ruan Y, Huang C, Zhu Y, Zhong JH, Xiao Z, Zhou XF. Upregulation of blood proBDNF and its receptors in major depression. *J Affect Disord* 2013; **150**: 776-784 [PMID: 23537780 DOI: 10.1016/j.jad.2013.03.002]
95 **Hashimoto K**. Ethnic differences in the serum levels of proBDNF, a precursor of brain-derived neurotrophic factor (BDNF), in mood disorders. *Eur Arch Psychiatry Clin Neurosci* 2016; **266**: 285-287 [PMID: 26338800 DOI: 10.1007/s00406-015-0641-x]
96 **Tosi G**, Duskey JT, Kreuter J. Nanoparticles as carriers for drug delivery of macromolecules across the blood-brain barrier. *Expert Opin Drug Deliv* 2020; **17**: 23-32 [PMID: 31774000 DOI: 10.1080/17425247.2020.1698544]
97 **Molinari C**, Morsanuto V, Ruga S, Notte F, Farghali M, Galla R, Uberti F. The Role of BDNF on Aging-Modulation Markers. *Brain Sci* 2020; **10** [PMID: 32397504 DOI: 10.3390/brainsci10050285]
98 **Chacón-Fernández P**, Säuberli K, Colzani M, Moreau T, Ghevaert C, Barde YA. Brain-derived Neurotrophic Factor in Megakaryocytes. *J Biol Chem* 2016; **291**: 9872-9881 [PMID: 27006395 DOI: 10.1074/jbc.M116.720029]
99 **Cox MA**, Duncan GS, Lin GHY, Steinberg BE, Yu LX, Brenner D, Buckler LN, Elia AJ, Wakeham AC, Nieman B, Dominguez-Brauer C, Elford AR, Gill KT, Kubli SP, Haight J, Berger T, Ohashi PS, Tracey KJ, Olofsson PS, Mak TW. Choline acetyltransferase-expressing T cells are required to control chronic viral infection. *Science* 2019; **363**: 639-644 [PMID: 30733420 DOI: 10.1126/science.aau9072]
100 **Kerschensteiner M**, Gallmeier E, Behrens L, Leal VV, Misgeld T, Klinkert WE, Kolbeck R, Hoppe E, Oropeza-Wekerle RL, Bartke I, Stadelmann C, Lassmann H, Wekerle H, Hohlfeld R. Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor *in vitro* and in inflammatory brain lesions: a neuroprotective role of inflammation? *J Exp Med* 1999; **189**: 865-870 [PMID: 10049950 DOI: 10.1084/jem.189.5.865]
101 **Lu Q**, Qu Y, Ding Y, Kang X. p75NTR/proBDNF Modulates Basal Cell Carcinoma (BCC) Immune Microenvironment *via* Necroptosis Signaling Pathway. *J Immunol Res* 2021; **2021**: 6652846 [PMID: 33604392 DOI: 10.1155/2021/6652846]
102 **Tao X**, West AE, Chen WG, Corfas G, Greenberg ME. A calcium-responsive transcription factor, CaRF, that regulates neuronal activity-dependent expression of BDNF. *Neuron* 2002; **33**: 383-395 [PMID: 11832226 DOI: 10.1016/s0896-6273(01)00561-x]
103 **Zheng F**, Zhou X, Moon C, Wang H. Regulation of brain-derived neurotrophic factor expression in neurons. *Int J Physiol Pathophysiol Pharmacol* 2012; **4**: 188-200 [PMID: 23320132]
104 **Fauchais AL**, Lalloué F, Lise MC, Boumediene A, Preud'homme JL, Vidal E, Jauberteau MO. Role of endogenous brain-derived neurotrophic factor and sortilin in B cell survival. *J Immunol* 2008; **181**: 3027-3038 [PMID: 18713973 DOI: 10.4049/jimmunol.181.5.3027]
105 **Zhou XF**, Song XY, Zhong JH, Barati S, Zhou FH, Johnson SM. Distribution and localization of pro-brain-derived neurotrophic factor-like immunoreactivity in the peripheral and central nervous system of the adult rat. *J Neurochem* 2004; **91**: 704-715 [PMID: 15485500 DOI: 10.1111/j.1471-4159.2004.02775.x]
106 **Schuhmann B**, Dietrich A, Sel S, Hahn C, Klingenspor M, Lommatzsch M, Gudermann T, Braun A, Renz H, Nockher WA. A role for brain-derived neurotrophic factor in B cell development. *J Neuroimmunol* 2005; **163**: 15-23 [PMID: 15885304 DOI: 10.1016/j.jneuroim.2005.01.023]
107 **Kozlov EM**, Grechko AV, Chegodaev YS, Wu WK, Orekhov AN. Contribution of Neurotrophins to the Immune System Regulation and Possible Connection to Alcohol Addiction. *Biology (Basel)* 2020; **9** [PMID: 32231011 DOI: 10.3390/biology9040063]
108 **Hu ZL**, Luo C, Hurtado PR, Li H, Wang S, Hu B, Xu JM, Liu Y, Feng SQ, Hurtado-Perez E, Chen K, Zhou XF, Li CQ, Dai RP. Brain-derived neurotrophic factor precursor in the immune system is a novel target for treating multiple sclerosis.

Theranostics 2021; **11**: 715-730 [PMID: 33391501 DOI: 10.7150/thno.51390]

109 **Shen WY**, Luo C, Reinaldo Hurtado P, Hurtado-Perez E, Luo RY, Hu ZL, Li H, Xu JM, Zhou XF, Dai RP. The regulatory role of ProBDNF in monocyte function: Implications in Stanford type-A aortic dissection disease. *FASEB J* 2020; **34**: 2541-2553 [PMID: 31908023 DOI: 10.1096/fj.201901905RR]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 393-409

DOI: 10.5498/wjp.v12.i3.393

ISSN 2220-3206 (online)

MINIREVIEWS

Digital phenotyping in depression diagnostics: Integrating psychiatric and engineering perspectives

Jayesh Kamath, Roberto Leon Barriera, Neha Jain, Efraim Keisari, Bing Wang

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Alkhatib AJ, Liu X

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: September 5, 2021
Revised: September 23, 2021
Accepted: February 12, 2022
Article in press: February 12, 2022
Published online: March 19, 2022

Jayesh Kamath, Department of Psychiatry and Immunology, University of Connecticut School of Medicine, University of Connecticut Health Center, Farmington, CT 06030, United States

Jayesh Kamath, Roberto Leon Barriera, Neha Jain, Efraim Keisari, Department of Psychiatry, University of Connecticut School of Medicine, University of Connecticut Health Center, Farmington, CT 06032, United States

Bing Wang, Department of Computer Science and Engineering, University of Connecticut, Storrs, CT 06269, United States

Corresponding author: Jayesh Kamath, MD, PhD, Professor, Department of Psychiatry and Immunology, University of Connecticut School of Medicine, University of Connecticut Health Center, 263 Farmington Avenue, Farmington, CT 06030, United States. jkamath@uchc.edu

Abstract

Depression is a serious medical condition and is a leading cause of disability worldwide. Current depression diagnostics and assessment has significant limitations due to heterogeneity of clinical presentations, lack of objective assessments, and assessments that rely on patients' perceptions, memory, and recall. Digital phenotyping (DP), especially assessments conducted using mobile health technologies, has the potential to greatly improve accuracy of depression diagnostics by generating objectively measurable endophenotypes. DP includes two primary sources of digital data generated using ecological momentary assessments (EMA), assessments conducted in real-time, in subjects' natural environment. This includes active EMA, data that require active input by the subject, and passive EMA or passive sensing, data passively and automatically collected from subjects' personal digital devices. The raw data is then analyzed using machine learning algorithms to identify behavioral patterns that correlate with patients' clinical status. Preliminary investigations have also shown that linguistic and behavioral clues from social media data and data extracted from the electronic medical records can be used to predict depression status. These other sources of data and recent advances in telepsychiatry can further enhance DP of the depressed patients. Success of DP endeavors depends on critical contributions from both psychiatric and engineering disciplines. The current review integrates important perspectives from both disciplines and discusses parameters for successful interdisciplinary collaborations. A clinically-relevant model for incorporating DP in clinical setting is presented. This model, based on investigations conducted by our group, delineates development of a depression predic-

tion system and its integration in clinical setting to enhance depression diagnostics and inform the clinical decision making process. Benefits, challenges, and opportunities pertaining to clinical integration of DP of depression diagnostics are discussed from interdisciplinary perspectives.

Key Words: Digital phenotyping; Depression; Ecological momentary assessment; Telepsychiatry; Passive sensing; Smart phone

Core Tip: There are systematic/quantitative reviews and meta-analyses of digital phenotyping (DP) in depression available in literature. These reviews are primarily published by engineering groups and provide limited psychiatric perspective, especially clinical relevance and clinical integration. The current review presents an overview of digital phenotyping of depression diagnostics and assessment from both psychiatric and engineering perspective. The overview includes major advances in the field of DP of depression diagnostics, including active and passive ecological momentary assessment, DP using data from social media, and DP using data from electronic medical records. We briefly discuss investigations conducted by our group and present a model for clinical integration of DP informed by those investigations conducted by our group. Finally, we discuss benefits, challenges, and opportunities pertaining to clinical integration of DP of depression diagnostics from an interdisciplinary perspective.

Citation: Kamath J, Leon Barriera R, Jain N, Keisari E, Wang B. Digital phenotyping in depression diagnostics: Integrating psychiatric and engineering perspectives. *World J Psychiatry* 2022; 12(3): 393-409
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/393.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.393

INTRODUCTION

Major depressive disorder (MDD) is a common, serious, and debilitating illness affecting all ages; children and adolescents, adults, and elderly[1]. It affects more than 264 million people worldwide and is associated with significant morbidity, increased mortality due to high suicide risk, diminished functioning, and poor quality of life[1,2].

In 2017, the worldwide prevalence of MDD was estimated to be at 4.4% globally[2]. The lifetime risk of depression was much higher (15%-18%)[2]. Consistent with this high risk, in terms of disease burden, MDD represented the third highest cause of Years Lived with Disability (YLD) globally[3]. In the United Sates (US), MDD accounted for 3.7% of all US adjusted disability years with significant economic burden and societal costs[4,5]. The National Survey on Drug and Health (NSDUH) conducted in 2017 found that an estimated 17.3 million or 7.1% of US adults have experienced at least one major depressive episode[4].

Similar to other fields of medicine, there has been a strong impetus in psychiatry to personalize depression assessment and treatment[6,7]. However, despite decades of research, few clinically relevant biomarkers, genetic variations or clinical characteristics have been identified that can aid in depression diagnosis and treatment[6,7]. Advances in digital technologies provide an exciting opportunity to personalize depression care[8]. Smart phones with their digital sensors and increasingly advanced computing capabilities have the potential to serve as "human sensors" by capturing granular changes in behavioral patterns[8,9]. Electronic medical records can gather large amounts of data across multiple disciplines of medicine, generate personalized patient reports, and seamlessly transfer data between large health care systems. Telepsychiatry can help us reach patients in real-time and conduct assessments in their natural settings. Integration and application of these technologies has the potential to significantly advance and personalize depression care.

Several recent systematic reviews of digital technologies and their application in depression care are available in literature[9-12]. These reviews are focused on either clinical or engineering/technical aspects of digital phenotyping technologies in depression care[9-12]. The objective of the current review is to integrate, evaluate, and synthesize evidence-informed literature from both clinical and engineering perspectives. The goal is to present a clinically-relevant, evidence informed review beneficial to clinicians, engineers, and researchers from diverse disciplines. Another goal is to help advance multidisciplinary collaborations with clear clinical objectives. We will summarize gaps, challenges, and opportunities from clinical, engineering, and legal perspectives. Finally, informed by investigations conducted by our research group[13-16], we will present a model for integration of digital phenotyping technologies in clinical setting to improve depression care.

DEPRESSION DIAGNOSIS AND ASSESSMENT: CURRENT STANDARD OF CARE

MDD is a heterogeneous disorder with potentially diverse and multifactorial presentations[17,18]. Decades of research has shown that depression is the result of a complex interplay between genetic and environmental vulnerabilities initiating a cascade of neurobiological changes in diverse bodily systems [19,20]. Diagnosis of MDD includes confirmation of symptomatic threshold, patient distress, and functional impairment as a result of depression symptoms[21]. Diagnosis also involves ruling out medical, psychiatric, and substance use disorders that may present with depression symptomatology [21]. Two major taxonomies available for diagnosing depressive disorders include American Psychiatric Association's The Diagnostic and Statistical Manual of Mental Disorders (5th edition; [DSM-5]) and World Health Organization's The International Statistical Classification of Diseases and Related Health Problems (11th edition; [ICD-11])[21,22]. Diagnostic criteria for MDD are same in both classifications. Depression is characterized by two primary symptoms; depressed mood and loss of pleasure or interest lasting at least 2 weeks[21,22]. To meet the threshold for a Major Depressive Episode (MDE), these core symptoms should be accompanied by at least four more symptoms (for a total of at least five) as noted in Table 1[21,22]. Additionally, significant distress and measurable negative impact on functioning are required for a depression diagnosis (Table 1)[21,22]). Symptoms of depression can be grouped into three major categories; psychological or emotional, neurovegetative, and neurocognitive (Figure 1)[23]. Psychological symptoms are primarily subjective in nature *i.e.,* they depend on a patient's experience and their perception of these symptoms. It can be argued that psychological symptoms (*e.g.,* anhedonia/Lack of interest or pleasure) have behavioral consequences and lead to a change in functioning. Neurovegetative and neurocognitive symptoms are objective in nature and have measurable behavioral manifestations with subsequent impact on functioning. Patient reporting of subjective symptoms is inherently based on their experience and perception of these symptoms. This subjective vs. objective nature of depression symptoms with discussion of their direct or indirect behavioral manifestation and impact on functioning is critical to digital phenotyping in depression diagnostics. This distinction has a direct clinical relevance for application of digital phenotyping diagnostics in real-world clinical settings.

Patient self-rated and clinician-rated depression questionnaires are frequently used in screening and diagnosis of MDD[24,25]. Commonly used patient self-rated instruments include the 9-item Patient Health Questionnaire (PHQ-9), the Beck Depression Inventory (BDI), the 16-item Quick Inventory of Depression Symptomatology-Self Rated (QIDS16-SR), and the Center for Epidemiologic Studies Depression Scale (CES-D)[24,26]. In real world clinical settings, self-rated instruments are used more frequently than clinician-administered instruments as they are easier to administer and demand fewer resources[27]. These instruments also play a critical role in the continuum of depression care and help personalize patient care.

Limitations of current depression diagnosis and assessment

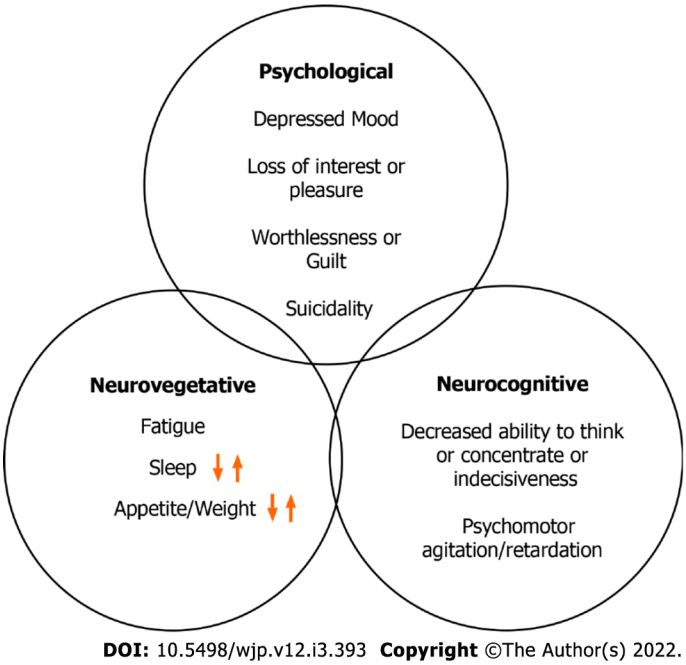
The DSM of Mental Disorders (DSM-5) endeavors to categorize psychiatric symptomatology into specific disorders[21]. Despite evidence supporting such categorization, DSM-based diagnosis of depression remains subjective, as it relies upon patient report, clinician observation, and clinical judgment. In real world settings, clinicians struggle with the limitations of DSM-based diagnosis due to heterogeneity of patient presentations not fully captured by DSM criteria[28]. Limitations of DSM-based depression diagnosis and assessment are further exacerbated by challenges in clinical setting such as brief (15 to 20 minutes) patient visits with limited time for clinical assessments, and complexity of patient presentations with multiple comorbidities[29]. Administration of depression rating scales can add some objectivity to clinical assessments. However, evidence indicates that few clinicians use rating scales in their clinical practice[30]. This is due to several reasons, including lack of adequate resources to administer such scales[30]. Furthermore, the rating scales rely on a patient's memory and capture a narrow spectrum of a patient's overall mental state[31]. A major DSM criterion for depression diagnosis is two weeks of persistent symptomatology[21]. Evidence suggests that patient reports during clinical encounters may be largely influenced by their symptoms during the days leading up to the clinical encounter[31]. Due to their reliance on patient recall, clinical assessments may fail to fully capture the severity of the neurovegetative and neurocognitive symptoms of depression (*e.g.,* fatigue, sleep disturbances, concentration)[31,32]. Current clinical assessments also fail to capture functional impact of depression, a core criterion (criterion B) for depression diagnosis[31,33]. These assessments provide a cross-sectional evaluation of a patient's mental state as they are administered infrequently, usually every 4 to 6 weeks during the patient's clinic visit.

DIGITAL PHENOTYPING IN DEPRESSION

Digital Phenotyping is defined as "moment-to-moment quantification of the individual-level human phenotype in situ using data collected from personal digital devices"[34,35]. DP has the potential to greatly improve the accuracy of depression diagnosis and assessment by adding much needed

Table 1 Summary of major depressive disorder criteria

Five (or more) of the following symptoms present for at least 2 wk period
Depressed mood
Anhedonia *i.e.,* diminished interest or pleasure
Weight loss or weight gain
Sleep disturbances (insomnia or hypersomnia)
Psychomotor agitation or retardation
Fatigue
Feelings of worthlessness or excessive inappropriate guilt
Cognitive difficulties
Suicidal thoughts and/or behaviors
Other Criteria:
Symptoms cause clinically significant distress or functional impairment
Symptoms are not better explained by other psychiatric or medical diagnosis



DOI: 10.5498/wjp.v12.i3.393

Figure 1 Depression symptomatology.

objectivity to the process. By generating objectively measurable endophenotypes, it can serve as a behavioral biomarker to personalize depression care[34,35]. The generated phenotype provides an ecological and continuous representation of a patient's physical, emotional, behavioral, social, and cognitive activities in real-time[35,36]. At present, DP relies on two primary sources of data, active and passive data, generated by Ecological Momentary Assessments (EMA) conducted using personal digital devices. Active EMA consist of data reported directly by the user, and passive EMA consists of data automatically collected from digital devices and platforms[9,11,37]. The digital devices that currently serve as DP sources include smart phones, wearable sensors, and data collected from human-computer interactions[9,37]. DP in depression diagnostics involves a multistep process[38,39]. The first step involves obtaining signals from the digital devices to generate raw data. Once the data is collected, the goal is to find patterns that correlate with patient's clinical status. This step involves use of machine learning algorithms to find predictive behavioral features from the raw data sets. The final step is to integrate the features and electronic self-reports (active EMA) to generate an ecological, continuous, and personalized digital phenotype of the patients that can enhance depression diagnostics and assessment in clinical setting[38,39].

ECOLOGICAL MOMENTARY ASSESSMENT IN DEPRESSION DIAGNOSTICS

EMA involve repeated sampling of an individual's behaviors and experiences in real-time, in the person's natural environment[40]. EMA conducted digitally as part of DP in depression diagnostics strives to minimize recall bias seen with assessments conducted in clinical settings[9,11]. In addition, it seeks to maximize ecological validity and allows the investigation of processes that influence behavior in real world settings[9,11]. As mentioned earlier, EMA can be categorized into active and passive EMA [9,11]. Any data or assessments that need active input by participants falls under Active EMA (*e.g.*, electronic assessments using depression questionnaires). Passive EMA includes any data or assessments collected passively (*i.e.*, without participant's active input)[9,11].

Table 2 delineates depression symptomatology and major categories of active and passive EMA used to measure these symptoms. 'Subjective symptoms' such as depressed mood, guilt/negative beliefs, and suicidality can be primarily measured using active EMA such as depression questionnaires. 'Subjective symptoms with direct behavioral manifestations' such as anhedonia and concentration difficulties can be measured using both active and passive EMA. Similarly, both active and passive EMA measurements play an important role in evaluation of 'objective symptoms with subjective patient experiences' such as psychomotor agitation or retardation and appetite. Finally, 'objective symptoms with direct behavioral manifestations' such as fatigue and sleep are primarily measured using passive EMA. As shown in Figure 2, active EMA such as self-report questionnaires can be used to measure depression symptoms, distress due to these symptoms, and their impact on functioning, while passive EMA can significantly contribute to the assessments of objective behavioral manifestations such as neurovegetative symptoms and impact on functioning.

Active EMA

In active EMA, patients are prompted to enter information into their electronic devices at specific time intervals based on the type of assessment conducted[9,11]. A variety of standardized and non-standardized questionnaires can be used, allowing researchers to collect a varied amount of information from patients in real-time, in their natural environments[9,11].

Standardized assessments used in active EMA are generally self-report and self-administered questionnaires[9,11]. These assessments are validated to assess symptoms of depression[9,11]. Some examples of standardized assessments that have been used in EMA studies include: Patient Health Questionnaire (PHQ-9), Hamilton Depression Rating Scale (HDRS), Quick Inventory of Depressive Symptomatology (QIDS), and Beck Depression Inventory (BDI)[9,11]. While these depression assessment questionnaires are the same as those conducted in-person during a clinic visit, the major difference is that the active EMA are conducted in real-time, in participants' natural environment, and can be conducted more frequently to minimize recall bias[9,11]. Active EMA can be used for screening or to guide treatments based on depression status[41]. When used with passive EMA (passive sensing), they are frequently used as 'ground truth' to develop machine learning models[11,14]. In mobile health (mHealth) studies, these are administered at baseline and then at specific intervals (*e.g.*, PHQ-9 administered bi-weekly, QIDS administered weekly)[13,14].

Non-standardized assessments used in active EMA usually lack validation studies supporting their use in depression diagnosis or monitoring. However, they may provide important clinical information and leverage mHealth technology to conduct brief assessments in real-time and in the patients' natural environment[11,13]. Examples include general questions about mood, anxiety, sleep time and quality, medication adherence, medication tolerability, and physical activity[11,13]. Information gathered using these assessments can be combined with passive EMA data to improve detection of depressive symptomatology[11,14]. For example, studies have shown negative correlation between self-reported mood and the amount of time the phone screen was on and the percentage of social and entertainment apps used by the participant[11]. These assessments can be used for daily monitoring of symptoms[11,13]. The frequency of their administration varies between studies depending on the assessment and the study objective[11,13].

Several studies have highlighted the issue of recall bias with self-report depression questionnaires conducted every 4 to 6 week during patients' clinic visits[9,11]. Evidence indicates that patients with depression tend to judge their symptoms to be more severe or remember negative experiences more prominently when asked to recall them retrospectively[9,42]. Active EMA *via* mobile devices allows the collection of information in real-time, minimizing recall bias[9,11,42]. Obtaining this information in real-time also allows clinicians to put variations of mood in patients' situational and social context. This may reveal subtle patterns of emotional expression that would otherwise be missed by traditional depression assessments[43]. Daily monitoring of mood may improve patients' insight in their illness and allows them to become active participants in their treatment[11,43]. This may help them recognize patterns in their mood changes or negative feelings, triggers that lead to these changes, and help them examine if their coping strategies were effective[43]. Active EMA can also be used to monitor suicidal ideation, a critical aspect in depression management. One study found that 58% of their participants logged suicidal ideation during EMA assessment but denied it on retrospective review[44].

Table 2 Depression symptoms, ecological momentary assessment active, and ecological momentary assessment passive

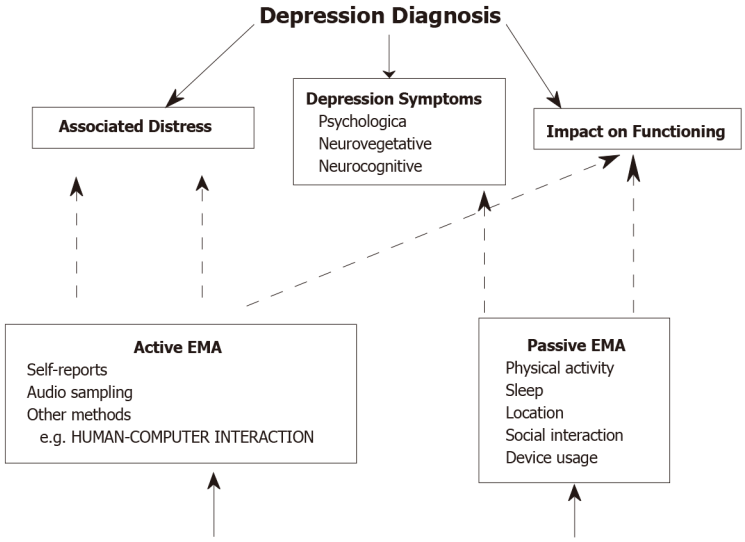
Depression symptoms
Depressed mood. anhedonia
Fatigue, sleep disturbances (insomnia or hypersomnia)
Psychomotor agitation or retardation, cognitive difficulties
Appetite problems
Guilt/negative beliefs
Suicidal thoughts/behaviors
EMA active
Standardized assessments
Self-report depression questionnaires (*e.g.*, PHQ-9)
Non-standardized assessments
Daily mood, anxiety, sleep ratings
Acoustic and paralinguistic information with audio sampling *e.g.*, voice intonation
EMA passive (behavioral feature categories, features, and sensors used)
Physical activity and sleep
Activity time-accelerometer
Inactivity-accelerometer, GPS
Distance-accelerometer, GPS
Movement duration and speed-GPS
Sleep duration, latency, efficiency-fitbit, accelerometer
Location
Home stay-GPS
Location clusters and variance-GPS
Entropy-GPS
Circadian rhythm-GPS
Social communication
Call duration/frequency, missed calls, number of conversations-call log
Sms text (incoming and outgoing)-sms text message log
Device
Social media engagement, social media app usage
Screen active duration and frequency
Social media engagement duration/frequency-app usage
Response time notification
Computer-keyboard interactions

EMA: Ecological momentary assessment; GPS: Global positioning system; PHQ-9: Patient Health Questionnaire-9.

Active EMA includes alternate ways to assess affect and cognition using samples collected from patients[45]. Analyses of acoustic samples have identified acoustic cues that can predict individuals' emotions and affective state[46]. This includes features such as prosodic features, spectral-based features, and glottal features[46].

Passive EMA

Passive sensing using smart phones and wearables can capture multiple dimensions of human behavior. Studies conducted in patients with depression have provided preliminary evidence of feasibility and efficacy of using passive sensing data for clinical inferences[9-11]. Passive sensing can capture and



DOI: 10.5498/wjp.v12.i3.393

Figure 2 Depression diagnosis and ecological momentary assessment.

monitor behavioral correlates of all three clusters of depression symptomatology: psychological, neurovegetative, and neurocognitive. However, it is especially useful to capture the neurovegetative and neurocognitive symptoms (*e.g.*, fatigue, sleep, concentration), as these symptoms have direct impact on behavior and functioning[13,14]. Several studies have shown consistent and statistically significant correlations between objective behavioral features collected *via* mobile phones and wearable devices and depressive symptomatology[9,10,14].

The process of passive sensing involves collecting raw and continuous data from multiple sensors present in mobile phones and wearable devices such as a Fitbit[13,14]. These include sensors such as the accelerometer, Global Positioning System sensor (GPS), light sensor, and microphone[9,10]. Data is also gathered on device analytics such as call logs, Short Message Service (SMS) texting patterns, and device activity[9,10]. Behavioral features are extracted from the raw data. The features are expected to capture behaviors, such as location clusters captured by GPS reflecting the number of locations visited by the individual. In patients with depression, behavioral features capture changes in behavior as a reflection of depression status and severity. The features are grouped into specific categories as correlates of depression symptomatology (*e.g.*, reduced activity and decreased number of locations visited by the individual may be reflective of anhedonia and fatigue)[9,10].

Table 2 describes categories of behavioral features, their correlates in depression symptomatology, and features that have shown consistent and statistically significant correlations with depression symptoms[9,10]. In studies conducted in non-clinical samples, features *home stay (more time at home)* and *screen active duration (longer phone usage*) showed consistent positive correlations with depression symptomatology[9,10]. In the same sample, features that showed consistent negative correlations with depression symptoms include *amount of vigorous activity, location variance, and distance covered*[9,10]. In clinical samples, features that showed consistent positive correlations with mood symptoms include *screen active duration* and *incoming call frequency and duration* (amount of time spent by the individual on incoming calls)[9,10]. Features that showed consistent negative correlations with depression symptoms in clinical samples include the *amount of visible cell towers* (reflecting mobility), *SMS text messages received*, and *outgoing call frequency and duration*[9,10]. Recently, our group developed techniques to identify Internet usage sessions (*i.e.*, time periods when a user is online)[15]. A novel set of features were extracted based on usage sessions from the Internet traffic meta-data[15]. Machine learning models developed using these features were successfully able to predict depression status of the participants [15].

In addition to the analyses of acoustic samples provided by patients, passively gathered acoustics samples (from patients' digital devices) have also been used to predict patients' affective state[45]. Studies have shown that participants' affective state and cognitive traits can be predicted using alternate methods, such as language analyses and human-computer interactions[45,47].

Challenges and limitations of active and passive EMA

For both active and passive EMA, the degree of patients' technical knowledge can be a critical factor affecting compliance. Technical problems and inappropriate operating systems have been cited as among the most common reasons for participant drop out in EMA studies[41,42]. For active EMA, this may include technical issues with data entry and uploading of data. For passive EMA, it usually

involves uploading of passive sensory data to the servers[41,42].

Assessments conducted in active EMA can become inconvenient and burdensome for participants [11]. This can lead to non-compliance. Studies have found that patient compliance with assessments decreases with time depending on their content and frequency of administration[9,11]. The need for active data entry may deter patients from adopting active EMA[37]. The standardized assessments administered electronically on a weekly or bi-weekly basis (*e.g.*, PHQ-9) can be conducted more frequently than in-office settings but still suffer from a similar recall-bias due to the duration they cover [9,11,42]. Although, one might argue that this recall bias is much less compared to their administration in office settings (usually every 4-6 week) due the higher frequency of their electronic administration. From a research perspective, daily mood monitoring can serve as a type of intervention, confounding the study design. Studies have shown that daily symptom recording, without any other direct treatment/intervention, improved symptoms of depression[11].

For passive EMA, other major technological challenges include battery drainage concerns reported by participants due to passive sensing on their mobile devices[48,49]. Studies have reported lack of sensor precision affecting data analyses (*e.g.*, inaccurate location data)[48,49]. Another major issue is missing sensory data[15,50,51]. As an example, the energy management system on a phone may turn off GPS when the battery level is low. In addition, it is well known that GPS does not perform well in certain common environments (*e.g.*, indoors), where it either fails to collect data or collects data with large errors[15]. Other challenges include heterogeneous data collection from different sensing devices[52, 53]. As an example, because of the different operating systems and the specific sensors used by Android and iOS, the two predominant smart phone platforms, the methods of data collection on these two platforms differ substantially. Consequently, the behavioral parameters derived from the different sources of sensing data exhibit significant differences[52,53]. The large volume of collected data may present a challenge for secure storage, statistical analysis, and clinical application[48]. Other technological challenges include data security and privacy, in particular, when the data needs to be shared with clinician's office[13,48].

Depression questionnaires and clinical interviews are used as 'ground truth' to find correlations with passive sensory data and to develop machine learning models[9,10]. A major limitation of this approach is the fact that the 'ground truth' (*i.e.*, the questionnaires and interviews) is still subjective. This may change over time as we gather larger amounts of data leading to better machine learning models based on passive sensory data. However, what if there is a significant discrepancy between active EMA (*i.e.*, patients' perception of their symptoms) and passive EMA (*i.e.*, objective behavioral data gathered by sensors on their mobile devices and analyzed using machine learning models)? In clinical settings, such a discrepancy may pose a challenge for clinicians with their decision-making process.

Privacy, legal, and ethical challenges

Digital phenotyping technologies have the potential to revolutionize mental health research and clinical care. However, they also present ethical, legal, privacy, and regulatory challenges[54]. A key initial consideration when developing and subsequently implementing digital depression assessment technologies is that of consent and, specifically, of informed consent, a key bioethics principal[55]. Participants agreeing to digital phenotyping in research or clinical settings should understand the risks and benefits of any monitoring hardware or software, or of any subsequent intervention. Ethical constituents of informed consent include sharing information with the patient, assessing decisional capacity of the patient, and examining a patient's voluntarism[56]. For many of these technologies, a clinician must assess a participant's understanding of the scope and granularity of data being collected. Since there is a broad range of technology literacy in the general public and few participants will have a full understanding of the data they are sharing or of its potential uses, the informed aspect of informed consent is ever more crucial[55,57]. One must also ensure that participants understand that consent is an ongoing process and can be withdrawn at any time.

Data privacy and protection are also key issues. When acquiring data, there must be adequate encryption to ensure data is securely transmitted from the source (*e.g.*, a smartphone) to a storage device (*e.g.*, servers). Once data is collected, there must be clear guidelines as to who can access this data and for what purpose. Storing data then becomes one of the biggest issues due to the scope and nature of data that is collected. Even with safeguards in place, data breaches are common in healthcare settings [55,57]. Another salient feature of data is that of ownership. Key questions to consider that largely remain unanswered are: Who owns the data created? What can be done with the data in the future? Who can profit from the data? As data collection moves from requiring user input (active EMA) to collecting passive data (passive EMA), the security and privacy challenge of bystanders, who do not provide consent, comes into play[57].

Once the ethical, security, and privacy concerns are managed, those who implement the various mHealth modalities must consider their liability. Liability can stem from failure to act on information (*e.g.*, suicidal ideation), errors that stem from malfunction of apps, misunderstanding or misinterpretation of information by patients[58]. In the studies by our group[13,14], a study clinician is on call at all times to act on suicidal ideation that is entered into the study app when participants completed their weekly depression questionnaires. When these apps evolve to use more passive data and are ultimately predictive, what happens when the software predicts there is a risk of suicide? When must a clinician

act? At what level would the risk of suicide have to be for the information to be actionable? Moving forward, these issues must be carefully addressed, both from patient safety and provider liability perspectives.

INTEGRATING ACTIVE AND PASSIVE EMA

Depression symptomatology includes both subjective and objective symptoms. Psychological symptoms such as depressed mood, guilt and negative beliefs, and suicidality are subjective in nature (*i.e.*, these symptoms depend on patients' subjective experience and perception of their status). Assessment of these symptoms requires clinical interview and/or use of depression questionnaires. Similarly, patient's *distress* due to depression (criterion B), a required criterion, is also subjective and requires clinical assessment. Active EMA may be necessary to fully evaluate these subjective symptoms and criteria. One may argue that behavioral and functional consequences of these symptoms can be captured using passive EMA, providing a more comprehensive assessment of these symptoms.

Neurovegetative and neurocognitive symptoms such as fatigue, sleep disturbances, psychomotor agitation/retardation, and concentration difficulties are objective symptoms with direct behavioral manifestations. Active EMA using interview and depression questionnaires may provide assessment of these symptoms based on patient perception of these symptoms but may fail to capture the actual behavioral manifestations. Similarly, *functional impairment*, another essential criterion (criterion B) for depression diagnosis, can be more fully captured using passive EMA. Similar to the subjective symptoms, patients' own assessment and perception of their status assessed using clinical interview and depression questionnaires (active EMA) can provide a more comprehensive assessment of objective symptoms. In summary, at present time, utilization of both active and passive EMA may be necessary to generate a more comprehensive digital phenotype of the patient[13].

LifeRhythm: Integration of active and passive EMA to predict depression symptomatology

Our group, in a 4-year project funded by the National Science Foundation, demonstrated successful prediction of depression symptomatology integrating active and passive EMA (Figure 3). The *LifeRhythm* project involved a two-phase study conducted in college age participants with depression, in comparison with a control group without depression diagnosis[14-16,52]. In Phase I of the project, a smart phone application, *LifeRhythm*, was developed to passively collect sensory data (location, activity, social interaction) for both Android and iOS, the two predominant smartphone platforms. Feature extraction techniques were developed to extract behavioral features from the sensory data as correlates of depression symptomatology and machine-learning models were developed to predict self-report depression questionnaire scores and depression status. These techniques and prediction models were then validated and refined in Phase II of the study. In Phase II, wristbands (Fitbit devices) were added to the sensory diagnostics for characterizing specific behavioral features (*e.g.*, sleep disturbances and activity level). A total of 182 participants were recruited in this two-phase study and were followed over an 8 month study period. Three sets of data were collected during participant's study participation: sensory data collected by the *LifeRhythm* app (EMA passive), self-report depression questionnaire completed electronically by the participant every two weeks (EMA active), and clinical assessments conducted by a study clinician. Study findings demonstrated that passive sensory data (EMA passive) predicted self-report depression scores and depression status per clinical interview conducted by the study clinician[14-16,52]. Notably, integration of passive sensing (EMA passive) and self-report depression scores (EMA active) showed better prediction power compared to passive or active EMA alone.

DepWatch: Integrating active and passive EMA in clinical setting to predict treatment response

At present, we are investigating development of a depression prediction system, *DepWatch*, and its integration in clinical setting to inform the clinical decision making process (Figure 4). This 4-year project, funded by the National Institute of Mental Health, builds on the findings and insights gained from the *LifeRhythm* project[13]. It includes two study phases. The objective of Phase I is to develop machine learning models to predict response or lack of response to antidepressant treatment, when patients meeting a specific threshold for depression symptoms undergo adjustments to their antidepressant medication regimen. Similar to the *LifeRhythm* project, passive sensory data (EMA passive) is collected using the app developed by our team for both Android and iOS platforms. Active EMA conducted electronically include daily self-report mood and anxiety ratings, weekly self-report depression questionnaire, weekly self-report medication safety and tolerability assessments, and other clinical information collected at baseline. Participants also undergo monthly clinical assessments conducted by a study clinician to assess their depression status and their response/non-response to antidepressant treatment compared to their baseline status. A total of 250 participants meeting a specific threshold for depression severity and starting or adjusting antidepressant treatment are currently being enrolled in the Phase I. Machine learning models will be developed using passive and active EMA data. *DepWatch*, an automatic data collection, analytic, and prediction system will be developed based on the

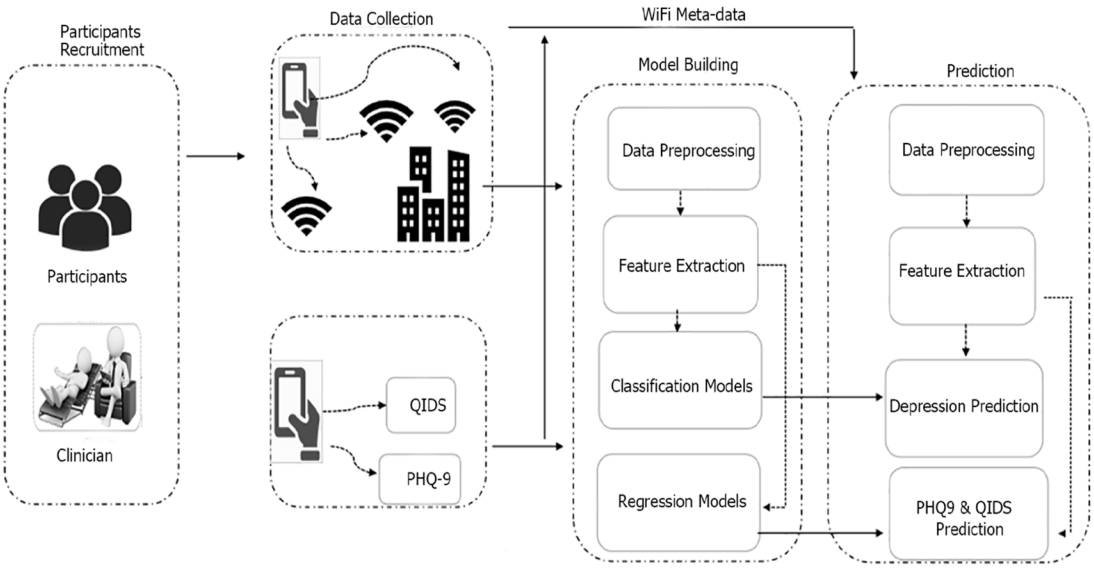


Figure 3 *LifeRhythm*: Integration of active and passive ecological momentary assessment to predict depression. Adapted from Ware *et al*[86] with permission from the Association for Computing Machinery (ACM) Citation: Ware S, Yue C, Morillo R, Lu J, Shang C, Kamath J, Bamis A, Bi J, Russell A, Wang B. Large-scale Automatic Depression Screening Using Meta-data from WiFi Infrastructure. *Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies* 2018; 2: 1-27. Copyright © The Association for Computing Machinery (ACM).

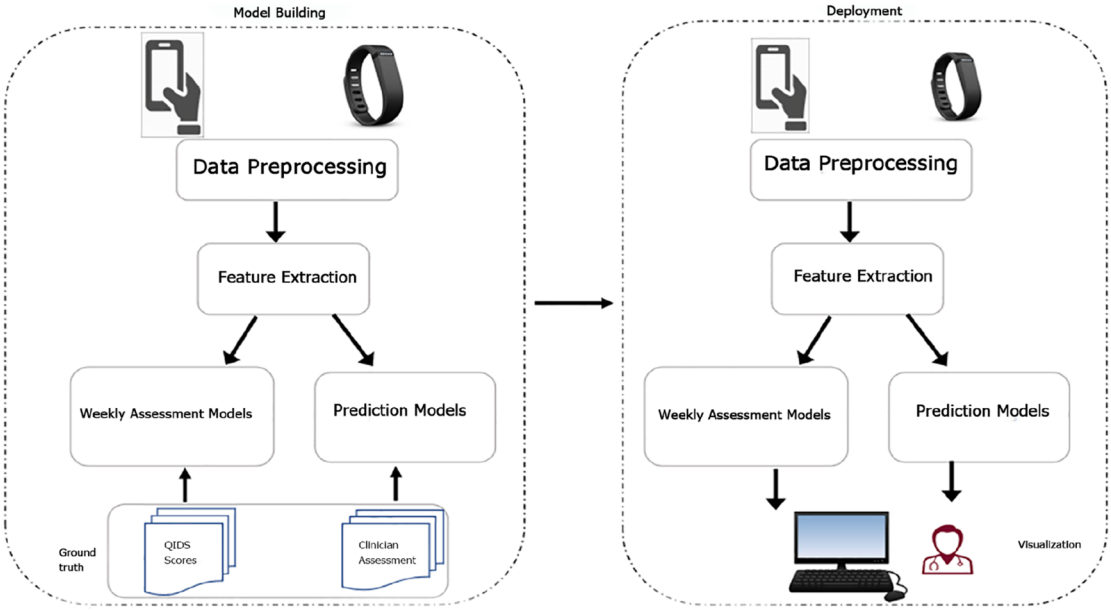


Figure 4 *DepWatch*: Integrating active and passive ecological momentary assessment in clinical setting. Adapted from Kamath *et al*[13] an open access article distributed under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) with permission from the J Psychiatr Brain Sci (JPBS). Citation: Kamath J, Bi J, Russell A, Wang B. Grant Report on SCH: Personalized Depression Treatment Supported by Mobile Sensor Analytics. *J Psychiatr Brain Sci* 2020; 5: e200010. Copyright © The J Psychiatr Brain Sci (JPBS).

machine learning algorithms developed in Phase I and other relevant clinical information. In Phase II, the *DepWatch* prediction system will be investigated for its usefulness and applications as a clinical support system in the real-world clinical setting, compared to standard of care. Three clinicians will use *DepWatch* to support their clinical decision making process for their patients. A total of 128 participants under care of the three participating clinicians will be enrolled in Phase II[13].

PREDICTING DEPRESSION STATUS USING OTHER DIGITAL TOOLS

Predicting depression status using social media

Preliminary investigations are exploring behavioral and linguistic cues from social media data to predict depression status. Data can be extracted from a variety of social platforms including popular sites such as Twitter, Facebook, Instagram, and Reddit[59,60]. These investigations have used several variables/features of interest in social media data that may predict depression status. These include Language analyses (*e.g.*, length, characteristics of the posts), Emotion and Cognition analyses (*e.g.*, affect and intensity of posts reflecting anxiety or anger), Behavior analyses (*e.g.*, posting frequency, interaction with others on the platform), Demographics analyses (*e.g.*, age, gender inferred using computational techniques), and Image analysis (*e.g.*, visual information from the images posted)[59]. Machine learning and statistical modeling are applied to the extracted data to develop and validate algorithms to predict depression status[59,60]. At present, the major limitation of this promising area of research includes the "ground truth" definition of depression and the methods used to identify and operationalize depression status[59]. Some studies have demonstrated strong construct validity by using evidence-based and clinically-relevant practices to define depression (*e.g.*, use of depression questionnaire or use of ICD-10 diagnostic codes)[59,61]. Despite these current limitations, data mining from social media has a promising future in digital phenotyping. This innovative tool, in conjunction with EMA, can be used to augment digital phenotyping in depression diagnostics.

Predicting depression status using EMR

Digital phenotyping of depression status can be enhanced by using extracted data from EMRs[60,62]. Studies conducted to date have primarily utilized features (extracted from EMR) interdependent with depression diagnosis to predict clinical depression. Such features include depression billing codes, medication information, and structured and unstructured notes containing explicit diagnostic information. Computational methods, such as natural language processing (NLP), have been developed to extract data from narrative clinical notes in EMR. NPL is an automated method of extracting and processing text into meaningful concepts based on a set of rules[63]. Recent studies have used non-psychiatric features in EMR and have applied machine learning approaches to the extracted data to predict depression status[62]. These EMR data extraction techniques can be used in conjunction with EMA to improve depression diagnostics as part of digital phenotyping strategy.

TELEPSYCHIATRY

The use of teleconferencing technology in psychiatry dates back to the 1950s, when the Nebraska Psychiatric Institute started using teleconferencing to provide group therapy, consultation-liaison services, and medical student training[64]. Initial research focused mainly on increasing access to care in remote geographical areas and comparing the efficacy of video visits with in-person visits[65]. Growth of telepsychiatry was slow and patchy until recently. This was primarily due to technological challenges and usability issues, lack of willingness among healthcare professionals to modify well-established routines (*e.g.*, face to face interactions), lack of financial resources, and lack of organizational innovation [66,67]. For decades, telepsychiatry was considered effective and feasible, but not desirable.

With the COVID-19 pandemic of 2020, there was a paradigm shift. The personnel and financial barriers to the use of telepsychiatry were removed overnight, and practices across the United States transitioned to telehealth. The number of telehealth visits increased by 50% over the first quarter of 2020, compared with the same period in 2019[68].

The efficacy of telepsychiatry has been well established over the past few decades[69,70]. Multiple reviews have analyzed studies of various telepsychiatry outcomes, including feasibility, adherence, clinical outcomes, and cost. One review of 22 controlled studies concluded that telepsychiatry could adequately perform all functions of management of mental illness, including monitoring, surveillance, mental health promotion, mental illness prevention, and biopsychosocial treatment programs, more efficiently and as well as or more effectively than in-person care[71]. Other reviews have reported similar results[72,73].

Telepsychiatry: Challenges and opportunities

Challenges of widespread, successful adoption of telepsychiatry practice can be divided into systemic challenges and personnel challenges. Systemic challenges include federal and state licensure and reimbursement policies that restrict the use of telepsychiatry, platform and internet bandwidth issues, availability of leadership support, and the "digital divide", which describes a lack of reliable device/internet access in underserved populations. Personnel challenges include a lack of clinician training and support, fear of technology amongst both patients and providers, physical and cognitive disabilities that limit the use of technology, patient safety issues, and provider concern that telepsychiatry does not provide the same range and depth of data that is provided in an in-person encounter [74,75].

One way to address this concern about the lack of personal interaction with the patient is to integrate EMA and DP based approaches with telepsychiatry visits. Incorporating both passive and active EMA data with the information available to the clinician might not only address the concern about the availability of "real time" patient data to the clinician, it may also augment and improve the clinician's ability to accurately assess the neurovegetative symptoms of depression such as sleep and activity. In a study by Moore *et al*, sixty-seven older adults completed paper-and-pencil measures of mindfulness, depression, and anxiety along with two weeks of identical items reported during ambulatory monitoring *via* EMA before and after participation in a randomized trial of Mindfulness-Based Stress Reduction (MBSR). EMA measures of depression substantially outperformed paper-and-pencil measures with the same items[76].

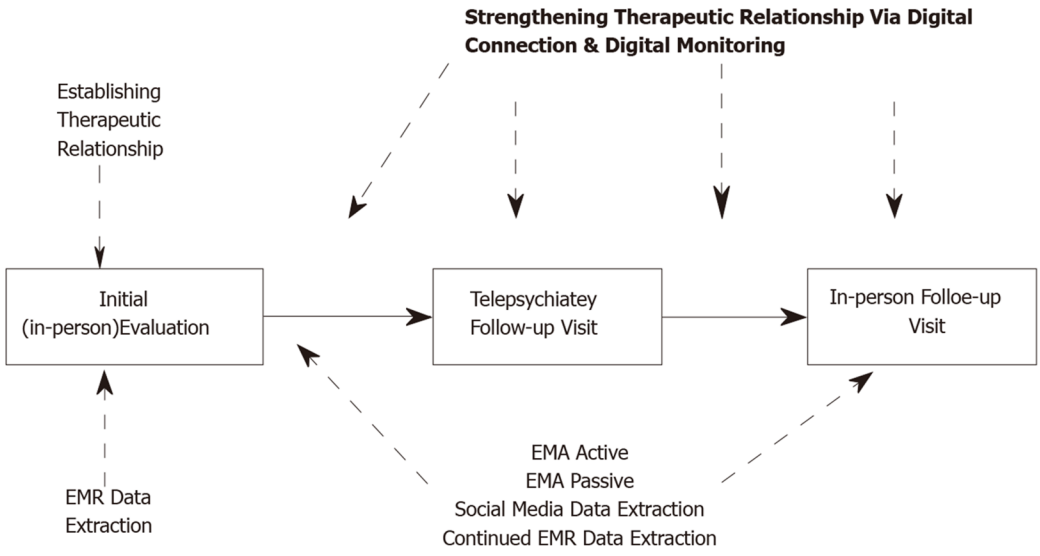
Passive and active EMA may improve the clinician's ability to predict and diagnose depression in underdiagnosed subgroups such as older adults[77]. Incorporating active EMA approaches more frequently may allow clinicians to increase engagement with an isolated, depressed patient. Combining EMA with telepsychiatry may improve access to care for patients with anergia/amotivation, and offers the opportunity to provide rapid interventions based on activity data[78].

CLINICAL INTEGRATION OF DIGITAL PHENOTYPING

The therapeutic alliance between patients and their provider is the cornerstone of depression care. It is well established that a strong therapeutic relationship is a robust predictor for treatment response across all therapeutic interventions, including pharmacological interventions[79]. The current model of clinical care has a significant negative impact on this therapeutic relationship due to brief medication management visits, fragmentation of care, limited contact between patients and their clinicians, and lack of meaningful monitoring in between patients' clinic visits. One of the objectives of integrating DP into clinical care is to enhance the therapeutic relationship between patients and their providers[80]. A digital connection between patients and their providers and monitoring *via* active and passive EMA in between patients' clinic visits can reinforce the therapeutic relationship[80]. The other major objective of using DP is to improve accuracy and clinical relevance of diagnostic assessment. As noted earlier, depression assessment should evaluate three major areas: depression symptoms, patient distress, and impact on functioning. Current clinical assessment focuses primarily on patient symptoms and distress. Digital data can enhance assessment of symptoms and distress (*e.g.*, use of active EMA in-between visits). More importantly, digital data, specifically passive EMA, can greatly enhance clinical assessments by providing objective data on behavioral consequences of symptoms/distress with its impact on functioning. As shown in Figure 5, DP and other digital tools can be incorporated into clinical practice at multiple stages of depression diagnostics and management. Initial patient evaluation (in-person) can be improved using patient specific data gathered from EMR using machine learning algorithms. Active and passive EMA can provide continuous monitoring in between patient visits and inform patient-provider discussion and assessment during in-person or virtual visits. These digital and in-person interactions between patients and their providers can increase patients' engagement in their care and support shared decision-making. Use of virtual telepsychiatry visits interspersed by in-person visits can help increase frequency of patient-provider contact, further strengthening the therapeutic relationship.

MACHINE LEARNING AND FUTURE OF DIGITAL PHENOTYPING

Current diagnostic systems, DSM-5 and ICD-11, were originally conceived using careful observations of symptoms by expert clinicians[21]. These taxonomies are useful for grouping individuals into broad diagnostic categories but it is becoming increasingly evident that the diagnostic categories lack neurobiological validity as well as clinical predictability[81]. It is also becoming evident that these diagnostic categories are spectrum disorders with heterogeneous clinical presentations and diverse underlying etiological and pathophysiological factors[81]. The current 'best-possible' evidence-informed treatment choices are successful only in limited number of patients partially due to this heterogeneity of clinical presentations with diverse underlying pathophysiology[82]. To address this critical gap, the National Institute of Mental Health (NIMH) launched a research initiative called the Research Domain Criteria (RDoC) project[83]. The RDoC initiative, a translational program, intends to synergistically integrate self-reports, neuropsychological tests, brain measurements, and genetic profiles to create precision medicine in psychiatry[83]. Machine learning approaches offer a rich set of tools towards achieving the goal of endophenotype modelling proposed by the RDoC initiative[84]. Machine learning models developed for the field of psychiatry are typically supervised machine learning models that employ a two-step process: training and testing. The collected data is divided into training and testing datasets. A learning algorithm is first fitted on the training dataset to train the model. The 'trained' model is then empirically evaluated by testing it on the testing dataset[84]. This two-step approach is consistent with the 'precision psychiatry' objectives of the RDoC initiative[83,84]. Data gathered from diverse



DOI: 10.5498/wjp.v12.i3.393

Figure 5 Hybrid clinical care model: Integration of in-person and digital care. EMA: Ecological momentray assessment; EMR: Electronic medical record.

retrospective and prospective datasets (*e.g.*, genetic profiles, neuroimaging, EMR, active and passive EMA data) can be integrated and analyzed using machine learning approaches to generate objectively measurable and clinically predictable endophenotypes. The models generated can then be validated in a new set of patients to predict clinical outcomes including treatment outcomes. The machine learning approaches can translate complex discoveries into clinically relevant predictions bringing us closer to the goal of precision psychiatry.

CONCLUSION

If we are to fulfill the promise of DP in depression diagnostics, it is critical that teams of psychiatric and engineering researchers work together to address the numerous challenges we have described. All investigations and digital tools under development should be scrutinized for their clinical relevance and real-world applicability. Investigations in the field of DP, to date, are spearheaded primarily by engineers with limited involvement of psychiatric researchers. This is problematic because, at present, clinical acumen of psychiatric clinicians play a central role in depression diagnosis, assessment, and management. The purportedly objective measures (*e.g.*, depression questionnaires) are important tools, yet remain subjective in nature and play a limited secondary role in clinical settings. The field of DP needs to draw upon the experience and expertise of psychiatric clinicians as 'ground truth' combined with depression questionnaires. It is essential to include psychiatric investigators who have background and expertise in clinical care and clinical research into the research team. A major role of clinical investigators as part of the research team would be to assess clinical relevance of digital tools under development compared to the standard of clinical care.

Once the digital tools show promise in predicting depression status as assessed by the 'ground truth' (clinical judgment and depression questionnaires), the next step would be to challenge the subjectivity of the 'ground truth' by focusing on a different, objectively measurable outcome. As noted earlier, depression questionnaires and clinician interview are fundamentally subjective as they rely on patients' memory/perception and on clinicians' clinical judgment. In comparison, change in functioning with its behavioral manifestations may be a better and a more objective 'ground truth'. In clinical setting, change in functioning is considered an important marker of depression status as it reflects depression symptoms, distress, and is associated with objective behavioral consequences. Furthermore, change in functioning with its behavioral consequences can be quantified objectively using DP tools. In the past decade, depression research has been striving towards 'remission' as an outcome[85,86]. This goal of achieving remission is directly related to patients' functional improvement. DP may provide us with objective tools to measure both remission and functional improvement.

In conclusion, we live in a time when most of the global population carry smart phones in their pockets and broadband access is rapidly increasing even in remote areas. DP based on smart phones and other digital tools can significantly enhance depression diagnostics. Objective continuous measurement of behavioral manifestations of depression using patients' own devices can provide clinically useful markers. Such 'behavioral biomarkers' can be used to refine diagnostic processes and

management. These objective markers (passive EMA) combined with assessments conducted in patients' milieu (active EMA) and strengthened therapeutic relationship and monitoring due to continuous digital connection between patients and their providers can help us move closer to the goal of personalized and patient-centered care.

FOOTNOTES

Author contributions: Kamath J and Wang B are the primary authors of this manuscript and are Co-Principal Investigators of the studies described in the manuscript; Barriera RL wrote the active ecological momentary assessments sections; Jain N wrote the telepsychiatry sections; Keisari E wrote the privacy, legal, and ethical challenges section; all three contributed to other sections of the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Country/Territory of origin: United States

ORCID number: Jayesh Kamath 0000-0002-6982-4302; Roberto Leon Barriera 0000-0002-6518-4758; Neha Jain 0000-0003-1804-7758; Efraim Keisari 0000-0001-8089-3221; Bing Wang 0000-0002-7632-6512.

S-Editor: Wang LL
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **World Health Organization 2020**. [cited 26 June 2021]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
2 **World Health Organization 2017**. Depression and other Common Mental Health Disorders: Global Health Estimates. [cited 26 June 2021]. Available from: https://www.who.int/publications/i/item/depression-global-health-estimates
3 **GBD 2017 Disease and Injury Incidence and Prevalence Collaborators**. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1789-1858 [PMID: 30496104 DOI: 10.1016/S0140-6736(18)32279-7]
4 **National Institute of Mental Health**. Major Depression. [cited 26 June 2021]. Available from: https://www.nimh.nih.gov/health/statistics/major-depression#part_155029
5 **Greenberg PE**, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry* 2015; **76**: 155-162 [PMID: 25742202 DOI: 10.4088/JCP.14m09298]
6 **Maj M**, Stein DJ, Parker G, Zimmerman M, Fava GA, De Hert M, Demyttenaere K, McIntyre RS, Widiger T, Wittchen HU. The clinical characterization of the adult patient with depression aimed at personalization of management. *World Psychiatry* 2020; **19**: 269-293 [PMID: 32931110 DOI: 10.1002/wps.20771]
7 **Cohen ZD**, DeRubeis RJ. Treatment Selection in Depression. *Annu Rev Clin Psychol* 2018; **14**: 209-236 [PMID: 29494258 DOI: 10.1146/annurev-clinpsy-050817-084746]
8 **Insel TR**. Digital Phenotyping: Technology for a New Science of Behavior. *JAMA* 2017; **318**: 1215-1216 [PMID: 28973224 DOI: 10.1001/jama.2017.11295]
9 **Colombo D**, Fernández-Álvarez J, Patané A, Semonella M, Kwiatkowska M, García-Palacios A, Cipresso P, Riva G, Botella C. Current State and Future Directions of Technology-Based Ecological Momentary Assessment and Intervention for Major Depressive Disorder: A Systematic Review. *J Clin Med* 2019; **8** [PMID: 30959828 DOI: 10.3390/jcm8040465]
10 **Rohani DA**, Faurholt-Jepsen M, Kessing LV, Bardram JE. Correlations Between Objective Behavioral Features Collected From Mobile and Wearable Devices and Depressive Mood Symptoms in Patients With Affective Disorders: Systematic Review. *JMIR Mhealth Uhealth* 2018; **6**: e165 [PMID: 30104184 DOI: 10.2196/mhealth.9691]
11 **Dogan E**, Sander C, Wagner X, Hegerl U, Kohls E. Smartphone-Based Monitoring of Objective and Subjective Data in Affective Disorders: Where Are We and Where Are We Going? *J Med Internet Res* 2017; **19**: e262 [PMID: 28739561 DOI: 10.2196/jmir.7006]
12 **Firth J**, Torous J, Nicholas J, Carney R, Pratap A, Rosenbaum S, Sarris J. The efficacy of smartphone-based mental health interventions for depressive symptoms: a meta-analysis of randomized controlled trials. *World Psychiatry* 2017; **16**: 287-298 [PMID: 28941113 DOI: 10.1002/wps.20472]
13 **Kamath J**, Bi J, Russell A, Wang B. Grant Report on SCH: Personalized Depression Treatment Supported by Mobile Sensor Analytics. *J Psychiatr Brain Sci* 2020; **5** [PMID: 32529036 DOI: 10.20900/jpbs.20200010]

14 **Ware S**, Yue C, Lu J, Chao S, Jinbo B, Kamath J, Russel A, Bamis A, Wang B. Predicting Depressive Symptoms Using Smartphone Data. Smart Health 2020, 100093 [DOI: 10.1016/j.smhl.2019.100093]

15 **Yue C**, Ware S, Morillo R, Lu J, Shang C, Bi J, Kamath J, Russell A, Bamis A, Wang B. Automatic Depression Prediction Using Internet Traffic Characteristics on Smartphones. *Smart Health (Amst)* 2020; **18** [PMID: 33043105 DOI: 10.1016/j.smhl.2020.100137]

16 **Yue C**, Ware S, Morillo R, Lu J, Shang C, Bi J, Kamath J, Russel A, Bamis A, Wang B. Fusing Location Data for Depression Prediction In: 2017 IEEE SmartWorld, Ubiquitous Intelligence and Computing, Advanced and Trusted Computed, Scalable Computing and Communications, Cloud and Big Data Computing, Internet of People and Smart City Innovation (SmartWorld/SCALCOM/UIC/ATC/CBDCom/IOP/SCI); 2017 Aug 4-8; San Francisco, USA. New York (US): IEEE, 2018 [DOI: 10.1109/uic-atc.2017.8397515]

17 **Zimmerman M**, Ellison W, Young D, Chelminski I, Dalrymple K. How many different ways do patients meet the diagnostic criteria for major depressive disorder? *Compr Psychiatry* 2015; **56**: 29-34 [PMID: 25266848 DOI: 10.1016/j.comppsych.2014.09.007]

18 **Thase ME**. The multifactorial presentation of depression in acute care. *J Clin Psychiatry* 2013; **74** Suppl 2: 3-8 [PMID: 24191971 DOI: 10.4088/JCP.12084su1c.01]

19 **Pitsillou E**, Bresnehan SM, Kagarakis EA, Wijoyo SJ, Liang J, Hung A, Karagiannis TC. The cellular and molecular basis of major depressive disorder: towards a unified model for understanding clinical depression. *Mol Biol Rep* 2020; **47**: 753-770 [DOI: 10.1007/s11033-019-05129-3]

20 **Malhi GS**, Mann JJ. Depression. *Lancet* 2018; **392**: 2299-2312 [PMID: 30396512 DOI: 10.1016/S0140-6736(18)31948-2]

21 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders (5th edition), 2013. [cited 26 June 2021]. Available from: https://doi.org/10.1176/appi.books.9780890425596

22 **World Health Organization**. International statistical classification of diseases and related health problems (11th edition), 2019. [cited 26 June 2021]. Available from: https://icd.who.int/

23 **Kendler KS**. The Phenomenology of Major Depression and the Representativeness and Nature of DSM Criteria. *Am J Psychiatry* 2016; **173**: 771-780 [PMID: 27138588 DOI: 10.1176/appi.ajp.2016.15121509]

24 **Lakkis NA**, Mahmassani DM. Screening instruments for depression in primary care: a concise review for clinicians. *Postgrad Med* 2015; **127**: 99-106 [PMID: 25526224 DOI: 10.1080/00325481.2015.992721]

25 **Uher R**, Perlis RH, Placentino A, Dernovšek MZ, Henigsberg N, Mors O, Maier W, McGuffin P, Farmer A. Self-report and clinician-rated measures of depression severity: can one replace the other? *Depress Anxiety* 2012; **29**: 1043-1049 [PMID: 22933451 DOI: 10.1002/da.21993]

26 **Rush AJ**, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R, Thase ME, Kocsis JH, Keller MB. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 2003; **54**: 573-583 [PMID: 12946886 DOI: 10.1016/s0006-3223(02)01866-8]

27 **Maurer DM**, Raymond TJ, Davis BN. Depression: Screening and Diagnosis. *Am Fam Physician* 2018; **98**: 508-515 [PMID: 30277728]

28 **Park SC**, Kim JM, Jun TY, Lee MS, Kim JB, Yim HW, Park YC. How many different symptom combinations fulfil the diagnostic criteria for major depressive disorder? *Nord J Psychiatry* 2017; **71**: 217-222 [PMID: 27981876 DOI: 10.1080/08039488.2016.1265584]

29 **O'Dowd T**. Depression and multimorbidity in psychiatry and primary care. *J Clin Psychiatry* 2014; **75**: e1319-e1320 [PMID: 25470098 DOI: 10.4088/JCP.14com09504]

30 **Hong RH**, Murphy JK, Michalak EE, Chakrabarty T, Wang Z, Parikh SV, Culpepper L, Yatham LN, Lam RW, Chen J. Implementing Measurement-Based Care for Depression: Practical Solutions for Psychiatrists and Primary Care Physicians. *Neuropsychiatr Dis Treat* 2021; **17**: 79-90 [PMID: 33469295 DOI: 10.2147/NDT.S283731]

31 **Robinson J**, Khan N, Fusco L, Malpass A, Lewis G, Dowrick C. Why are there discrepancies between depressed patients' Global Rating of Change and scores on the Patient Health Questionnaire depression module? *BMJ Open* 2017; **7**: e014519 [PMID: 28473513 DOI: 10.1136/bmjopen-2016-014519]

32 **Hobbs C**, Lewis G, Dowrick C, Kounali D, Peters TJ. Comparison between self-administered depression questionnaires and patients' own views of changes in their mood: a prospective cohort study in primary care. *Psychol Med* 2021; **51**: 853-860 [PMID: 31957623 DOI: 10.1017/S0033291719003878]

33 **Urban EJ**, Charles ST, Levine LJ, Almeida DM. Depression history and memory bias for specific daily emotions. *PLoS One* 2018; **13**: e0203574 [DOI: 10.1371/journal.pone.0203574]

34 **Torous J**, Staples P, Onnela JP. Realizing the potential of mobile mental health: new methods for new data in psychiatry. *Curr Psychiatry Rep* 2015; **17**: 602 [PMID: 26073363 DOI: 10.1007/s11920-015-0602-0]

35 **Onnela JP**, Rauch SL. Harnessing Smartphone-Based Digital Phenotyping to Enhance Behavioral and Mental Health. *Neuropsychopharmacology* 2016; **41**: 1691-1696 [PMID: 26818126 DOI: 10.1038/npp.2016.7]

36 **Huckvale K**, Venkatesh S, Christensen H. Toward clinical digital phenotyping: a timely opportunity to consider purpose, quality, and safety. *NPJ Digit Med* 2019; **2**: 88 [PMID: 31508498 DOI: 10.1038/s41746-019-0166-1]

37 **Yim SJ**, Lui LMW, Lee Y, Rosenblat JD, Ragguett RM, Park C, Subramaniapillai M, Cao B, Zhou A, Rong C, Lin K, Ho RC, Coles AS, Majeed A, Wong ER, Phan L, Nasri F, McIntyre RS. The utility of smartphone-based, ecological momentary assessment for depressive symptoms. *J Affect Disord* 2020; **274**: 602-609 [PMID: 32663993 DOI: 10.1016/j.jad.2020.05.116]

38 **Hirschtritt ME**, Insel TR. Digital Technologies in Psychiatry: Present and Future. *Focus (Am Psychiatr Publ)* 2018; **16**: 251-258 [PMID: 31975919 DOI: 10.1176/appi.focus.20180001]

39 **Dwyer DB**, Falkai P, Koutsouleris N. Machine Learning Approaches for Clinical Psychology and Psychiatry. *Annu Rev Clin Psychol* 2018; **14**: 91-118 [PMID: 29401044 DOI: 10.1146/annurev-clinpsy-032816-045037]

40 **Shiffman S**, Stone AA, Hufford MR. Ecological momentary assessment. *Annu Rev Clin Psychol* 2008; **4**: 1-32 [PMID: 18509902 DOI: 10.1146/annurev.clinpsy.3.022806.091415]

41 **Schueller SM**, Aguilera A, Mohr DC. Ecological momentary interventions for depression and anxiety. *Depress Anxiety* 2017; **34**: 540-545 [PMID: 28494123 DOI: 10.1002/da.22649]

42 **Kim H**, Kim S, Kong SS, Jeong Y-R, Kim H, Kim N. Possible Application of Ecological Momentary Assessment to Older Adults' Daily Depressive Mood: Integrative Literature Review. *JMIR Ment Heal* 2020; **7**: e13247 [DOI: 10.2196/13247]

43 **Wichers M**, Simons CJP, Kramer IMA, et al Momentary assessment technology as a tool to help patients with depression help themselves.
Acta Psychiatr Scand 2011; 124: 262-272 [DOI: 10.1111/j.1600-0447.2011.01749.x]

44 **Gratch I**, Choo TH, Galfalvy H, Keilp JG, Itzhaky L, Mann JJ, Oquendo MA, Stanley B. Detecting suicidal thoughts: The power of ecological momentary assessment. *Depress Anxiety* 2021; **38**: 8-16 [PMID: 32442349 DOI: 10.1002/da.23043]

45 **Liang Y**, Zheng X, Zeng D. A survey on big data-driven digital phenotyping of mental health. *Information Fusion* 2019; **52**: 290-307 [DOI: 10.1016/j.inffus.2019.04.001]

46 **Ayadi M**, Kamel M, Kartay F. Survey on speech emotion recognition: Features, classification schemes, and databases. *Pattern Recognition* 2011; **44**: 572-587 [DOI: 10.1016/j.patcog.2010.09.020]

47 **Dagum P**. Digital biomarkers of cognitive function. *NPJ Digit Med* 2018; **1**: 10 [PMID: 31304295 DOI: 10.1038/s41746-018-0018-4]

48 **Cornet VP**, Holden RJ. Systematic review of smartphone-based passive sensing for health and wellbeing. *J Biomed Inform* 2018; **77**: 120-132 [PMID: 29248628 DOI: 10.1016/j.jbi.2017.12.008]

49 **Burns MN**, Begale M, Duffecy J, Gergle D, Karr CJ, Giangrande E, Mohr DC. Harnessing context sensing to develop a mobile intervention for depression. *J Med Internet Res* 2011; **13**: e55 [PMID: 21840837 DOI: 10.2196/jmir.1838]

50 **Palmius N**, Tsanas A, Saunders KEA, Bilderbeck AC, Geddes JR, Goodwin GM, De Vos M. Detecting Bipolar Depression From Geographic Location Data. *IEEE Trans Biomed Eng* 2017; **64**: 1761-1771 [PMID: 28113247 DOI: 10.1109/TBME.2016.2611862]

51 **Saeb S**, Zhang M, Karr CJ, Schueller SM, Corden ME, Kording KP, Mohr DC. Mobile Phone Sensor Correlates of Depressive Symptom Severity in Daily-Life Behavior: An Exploratory Study. *J Med Internet Res* 2015; **17**: e175 [PMID: 26180009 DOI: 10.2196/jmir.4273]

52 **Farhan A**, Yue C, Morillo R, Ware S, Lu J, Bi J, Kamath J, Russell A, Bamis A, Wang B. Behavior vs. introspection: Refining prediction of clinical depression *via* smartphone sensing data. Proc. of Wireless Health, 2016 [DOI: 10.1109/wh.2016.7764553]

53 **Lu J**, Shang C, Yue C, Morillo R, Ware S, Kamath J, Russell A, Bamis A, Wang B, Bi J. Joint Modeling of Heterogeneous Sensing Data for Depression Assessment via Multi-task Learning, Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies (IMWUT), 2018 [DOI: 10.1145/3191753]

54 **Keisari EJ**, Patel P, Wang B, Kamath J. Investigation of mobile health (mHealth) technologies in the management of depression: Ethical, legal, and regulatory challenges. American Society of Clinical Psychopharmacology Annual Meeting, 2020 [DOI: 10.4324/9781003074984-31]

55 **Torous J**, Roberts LW. The Ethical Use of Mobile Health Technology in Clinical Psychiatry. *J Nerv Ment Dis* 2017; **205**: 4-8 [PMID: 28005647 DOI: 10.1097/NMD.0000000000000596]

56 **Roberts LW**. A clinical guide to psychiatric ethics. Arlington, VA: American Psychiatric Publishing, Inc. 2016 [DOI: 10.1097/nmd.0000000000000439]

57 **Cvrkel T**. The ethics of mHealth: Moving forward. *J Dent* 2018; **74** Suppl 1: S15-S20 [PMID: 29929583 DOI: 10.1016/j.jdent.2018.04.024]

58 **Armontrout J**, Torous J, Fisher M, Drogin E, Gutheil T. Mobile Mental Health: Navigating New Rules and Regulations for Digital Tools. *Curr Psychiatry Rep* 2016; **18**: 91 [PMID: 27553979 DOI: 10.1007/s11920-016-0726-x]

59 **Chancellor S**, De Choudhury M. Methods in predictive techniques for mental health status on social media: a critical review. *NPJ Digit Med* 2020; **3**: 43 [PMID: 32219184 DOI: 10.1038/s41746-020-0233-7]

60 **Su C**, Xu Z, Pathak J, Wang F. Deep learning in mental health outcome research: a scoping review. *Transl Psychiatry* 2020; **10**: 116 [PMID: 32532967 DOI: 10.1038/s41398-020-0780-3]

61 **Eichstaedt JC**, Smith RJ, Merchant RM, Ungar LH, Crutchley P, Preoţiuc-Pietro D, Asch DA, Schwartz HA. Facebook language predicts depression in medical records. *Proc Natl Acad Sci U S A* 2018; **115**: 11203-11208 [PMID: 30322910 DOI: 10.1073/pnas.1802331115]

62 **Nemesure MD**, Heinz MV, Huang R, Jacobson N. Predictive modeling of depression and anxiety using electronic health records and a novel machine learning approach with artificial intelligence. *Sci Rep* 2021; **11**: 1980 [DOI: 10.1038/s41598-021-81368-4]

63 **Perlis RH**, Iosifescu DV, Castro VM, Murphy SN, Gainer VS, Minnier J, Cai T, Goryachev S, Zeng Q, Gallagher PJ, Fava M, Weilburg JB, Churchill SE, Kohane IS, Smoller JW. Using electronic medical records to enable large-scale studies in psychiatry: treatment resistant depression as a model. *Psychol Med* 2012; **42**: 41-50 [PMID: 21682950 DOI: 10.1017/S0033291711000997]

64 **Bashshur R**, Shannon GW. History of telemedicine: evolution, context, and transformation. *Healthc Inform Res* 2010; **16**: 65-66 [DOI: 10.4258/hir.2010.16.1.65]

65 **Hilty DM**, Marks SL, Urness D, Yellowlees PM, Nesbitt TS. Clinical and educational telepsychiatry applications: a review. *Can J Psychiatry* 2004; **49**: 12-23 [PMID: 14763673 DOI: 10.1177/070674370404900103]

66 **Sanders C**, Rogers A, Bowen R, Bower P, Hirani S, Cartwright M, Fitzpatrick R, Knapp M, Barlow J, Hendy J, Chrysanthaki T, Bardsley M, Newman SP. Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study. *BMC Health Serv Res* 2012; **12**: 220 [PMID: 22834978 DOI: 10.1186/1472-6963-12-220]

67 **Reginatto B**. Addressing barriers to wider adoption of telehealth in the homes of older people: An exploratory study in the Irish context. In The fourth International Conference on eHealth, Telemedicine and Social Medicine 2012: 175-183 [DOI: 10.1109/etelemed.2009.8]

68 **Koonin LM**, Hoots B, Tsang CA, Leroy Z, Farris K, Jolly T, Antall P, McCabe B, Zelis CBR, Tong I, Harris AM. Trends in the Use of Telehealth During the Emergence of the COVID-19 Pandemic -United States, January-March 2020. *MMWR*

Morb Mortal Wkly Rep 2020; **69**: 1595-1599 [PMID: 33119561 DOI: 10.15585/mmwr.mm6943a3]

69 **De Las Cuevas C**, Arredondo MT, Cabrera MF, Sulzenbacher H, Meise U. Randomized clinical trial of telepsychiatry through videoconference *vs* face-to-face conventional psychiatric treatment. *Telemed J E Health* 2006; **12**: 341-350 [PMID: 16796502 DOI: 10.1089/tmj.2006.12.341]

70 **Hilty DM**, Ferrer DC, Parish MB, Johnston B, Callahan EJ, Yellowlees PM. The effectiveness of telemental health: a 2013 review. *Telemed J E Health* 2013; **19**: 444-454 [PMID: 23697504 DOI: 10.1089/tmj.2013.0075]

71 **Bashshur RL**, Shannon GW, Bashshur N, Yellowlees PM. The Empirical Evidence for Telemedicine Interventions in Mental Disorders. *Telemed J E Health* 2016; **22**: 87-113 [PMID: 26624248 DOI: 10.1089/tmj.2015.0206]

72 **Hubley S**, Lynch SB, Schneck C, Thomas M, Shore J. Review of key telepsychiatry outcomes. *World J Psychiatry* 2016; **6**: 269-282 [PMID: 27354970 DOI: 10.5498/wjp.v6.i2.269]

73 **Berryhill MB**, Culmer N, Williams N, Halli-Tierney A, Betancourt A, Roberts H, King M. Videoconferencing Psychotherapy and Depression: A Systematic Review. *Telemed J E Health* 2019; **25**: 435-446 [PMID: 30048211 DOI: 10.1089/tmj.2018.0058]

74 **Wagnild G**, Leenknecht C, Zauher J. Psychiatrists' satisfaction with telepsychiatry. *Telemed J E Health* 2006; **12**: 546-551 [PMID: 17042708 DOI: 10.1089/tmj.2006.12.546]

75 **Brooks E**, Turvey C, Augusterfer EF. Provider barriers to telemental health: obstacles overcome, obstacles remaining. *Telemed J E Health* 2013; **19**: 433-437 [PMID: 23590176 DOI: 10.1089/tmj.2013.0068]

76 **Moore RC**, Depp CA, Wetherell JL, Lenze EJ. Ecological momentary assessment *vs* standard assessment instruments for measuring mindfulness, depressed mood, and anxiety among older adults. *J Psychiatr Res* 2016; **75**: 116-123 [PMID: 26851494 DOI: 10.1016/j.jpsychires.2016.01.011]

77 **Kim H**, Lee S, Hong S, Kang H, Kim N. Depression Prediction by Using Ecological Momentary Assessment, Actiwatch Data, and Machine Learning: Observational Study on Older Adults Living Alone. *JMIR Mhealth Uhealth* 2019; **7**: e14149 [PMID: 31621642 DOI: 10.2196/14149]

78 **Hevel DJ**, Dunton GF, Maher JP. Acute Bidirectional Relations Between Affect, Physical Feeling States, and Activity-Related Behaviors Among Older Adults: An Ecological Momentary Assessment Study. *Ann Behav Med* 2021; **55**: 41-54 [PMID: 32441738 DOI: 10.1093/abm/kaaa027]

79 **Lambert M**, Barley D. Research summary on the therapeutic relationship and psychotherapy outcome. *Psychother: Theory, Res Pract Train* 2001; **38**: 357-361 [DOI: 10.1037/0033-3204.38.4.357]

80 **Torous J**, Hsin H. Empowering the digital therapeutic relationship: virtual clinics for digital health interventions. *NPJ Digit Med* 2018; **1**: 16 [PMID: 31304301 DOI: 10.1038/s41746-018-0028-2]

81 **Insel TR**, Cuthbert BN. Medicine. Brain disorders? *Science* 2015; **348**: 499-500 [PMID: 25931539 DOI: 10.1126/science.aab2358]

82 **Wong EH**, Yocca F, Smith MA, Lee CM. Challenges and opportunities for drug discovery in psychiatric disorders: the drug hunters' perspective. *Int J Neuropsychopharmacol* 2010; **13**: 1269-1284 [PMID: 20716397 DOI: 10.1017/S1461145710000866]

83 **Insel T**, Cuthbert B, Garvey M, Heinssen R, Pine DS, Quinn K, Sanislow C, Wang P. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry* 2010; **167**: 748-751 [DOI: 10.1176/appi.ajp.2010.09091379]

84 **Bzdok D**, Meyer-Lindenberg A. Machine Learning for Precision Psychiatry: Opportunities and Challenges. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2018; **3**: 223-230 [PMID: 29486863 DOI: 10.1016/j.bpsc.2017.11.007]

85 **Lam RW**, McIntosh D, Wang J, Enns MW, Kolivakis T, Michalak EE, Sareen J, Song WY, Kennedy SH, MacQueen GM, Milev RV, Parikh SV, Ravindran AV; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 1. Disease Burden and Principles of Care. *Can J Psychiatry* 2016; **61**: 510-523 [PMID: 27486151 DOI: 10.1177/0706743716659416]

86 **Ware S**, Yue C, Morillo R, Lu J, Shang C, Kamath J, Bamis A, Bi J, Russell A, Wang B. Large-scale Automatic Depression Screening Using Meta-data from WiFi Infrastructure. Proceedings of the ACM on Interactive, Mobile, Wearable and Ubiquitous Technologies 2018; 195: 1-27 [DOI: 10.1145/3287073]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 410-424

DOI: 10.5498/wjp.v12.i3.410

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Basic Study

Magnesium-L-threonate exhibited a neuroprotective effect against oxidative stress damage in HT22 cells and Alzheimer's disease mouse model

Ying Xiong, Yu-Ting Ruan, Jing Zhao, Yu-Wen Yang, Li-Ping Chen, Ying-Ren Mai, Qun Yu, Zhi-Yu Cao, Fei-Fei Liu, Wang Liao, Jun Liu

Specialty type: Neurosciences

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Aguzzi A, Switzerland; Al-Shahi Salman R, United Kingdom

Received: October 11, 2021
Peer-review started: October 11, 2021
First decision: November 17, 2021
Revised: December 15, 2021
Accepted: March 6, 2022
Article in press: March 6, 2022
Published online: March 19, 2022

Ying Xiong, Ying-Ren Mai, Qun Yu, Zhi-Yu Cao, Jun Liu, Department of Neurology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, Guangdong Province, China

Yu-Ting Ruan, Department of Rehabilitation Medicine, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510000, Guangdong Province, China

Jing Zhao, Department of Radiology, The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, Guangdong Province, China

Yu-Wen Yang, Li-Ping Chen, Department of Medical Ultrasound, Guangzhou First People's Hospital, School of Medicine, South China University of Technology, Guangzhou 510180, Guangdong Province, China

Fei-Fei Liu, Department of Medical Ultrasound, Xiang'an Hospital of Xiamen University, Xiamen 361000, Fujian Province, China

Wang Liao, Department of Neurology, The Second Affiliated Hospital, Guangzhou Medical University, Guangzhou 510000, Guangdong Province, China

Corresponding author: Jun Liu, MD, Professor, Department of Neurology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, No. 107 Yanjiang West Road, Guangzhou 510120, Guangdong Province, China. liujun6@mail.sysu.edu.cn

Abstract

BACKGROUND

Oxidative stress results in the production of excess reactive oxygen species (ROS) and triggers hippocampal neuronal damage as well as occupies a key role in the pathological mechanisms of neurodegenerative disorders such as Alzheimer's disease (AD). A recent study confirmed that magnesium had an inhibitory effect against oxidative stress-related malondialdehyde *in vitro*. However, whether Magnesium-L-threonate (MgT) is capable of suppressing oxidative stress damage in amyloid β $(Aβ)_{25-35}$-treated HT22 cells and the AD mouse model still remains to be investigated.

AIM

To explore the neuroprotective effect of MgT against oxidative stress injury *in vitro* and *in vivo*, and investigate the mechanism.

METHODS

$A\beta_{25-35}$-induced HT22 cells were preconditioned with MgT for 12 h. APPswe/PS1dE9 (APP/PS1) mice were orally administered with MgT daily for 3 mo. After MgT treatment, the viability of $A\beta_{25-35}$-treated HT22 cells was determined *via* conducting cell counting kit-8 test and the cognition of APP/PS1 mice was measured through the Morris Water Maze. Flow cytometry experiments were applied to assess the ROS levels of HT22 cells and measure the apoptosis rate of HT22 cells or hippocampal neurons. Expression of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax), hypoxia-inducible factor (HIF)-1α, NADPH oxidase (NOX) 4, $A\beta_{1-42}$ and phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway proteins was quantified by Western blot.

RESULTS

In vitro data confirmed that $A\beta_{25-35}$-induced HT22 cells had a significantly lower cell viability, higher ROS level and higher apoptosis rates compared with those of control cells (all $P < 0.001$). MgT prevented the $A\beta_{25-35}$-triggered oxidative stress damage by elevating viability and decreasing ROS formation and apoptosis of HT22 cells (all $P < 0.001$). APP/PS1 mice exhibited worse cognitive performance and higher apoptosis rate of hippocampal neurons than wild-type (WT) mice (all $P < 0.01$). Meanwhile, significant higher expression of $A\beta_{1-42}$ and NOX4 proteins was detected in APP/PS1 mice than those of WT mice (both $P < 0.01$). MgT also ameliorated the cognitive deficit, suppressed the apoptosis of hippocampal neuron and downregulated the expression of $A\beta_{1-42}$ and NOX4 proteins in APP/PS1 mouse (all $P < 0.05$). Moreover, MgT intervention significantly downregulated HIF-1α and Bax, upregulated Bcl-2 and activated the PI3K/Akt pathway both *in vitro* and *in vivo* (all $P < 0.05$).

CONCLUSION

MgT exhibits neuroprotective effects against oxidative stress and hippocampal neuronal apoptosis in $A\beta_{25-35}$-treated HT22 cells and APP/PS1 mice.

Key Words: Alzheimer's disease; Magnesium; Neuroprotective effect; Oxidative stress; Hippocampal; Neuronal apoptosis

Core Tip: The dysfunction of oxidative stress is considered to stimulate the production of reactive oxygen species and induce hippocampal neuron damage which are the significant hallmarks of neurodegenerative diseases such as Alzheimer's disease. Recent studies have explored the *in vitro* anti-malondialdehyde effect of magnesium. However, the potential neuroprotective effect of Magnesium-L-threonate (MgT) against oxidative stress remains to be explored. Our study demonstrated that MgT exhibited neuroprotective effects on suppressing oxidative stress and hippocampal neuronal apoptosis *in vitro* and *in vivo*, suggesting the promising therapeutic potential of MgT in oxidative stress-associated neurodegenerative disorders.

Citation: Xiong Y, Ruan YT, Zhao J, Yang YW, Chen LP, Mai YR, Yu Q, Cao ZY, Liu FF, Liao W, Liu J. Magnesium-L-threonate exhibited a neuroprotective effect against oxidative stress damage in HT22 cells and Alzheimer's disease mouse model. *World J Psychiatry* 2022; 12(3): 410-424
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/410.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.410

INTRODUCTION

As a progressive neurodegenerative disease, Alzheimer's disease (AD) occupies most cases of dementia, and it is clinically characterized by the deterioration of cognitive ability and brings a massive burden on AD patients' survival quality and social medical cost[1]. Although the pathological mechanism of AD is still incompletely elucidated, it was reported that oxidative stress occupied a key role in the pathogenic mechanism of this disease[2]. Numerous researches indicated that oxidative stress was a vital issue during the development of the neurodegenerative diseases, including AD, amyotrophic lateral sclerosis and so on. Oxidative stress could also accelerate amyloid β (Aβ) aggregation and induce neuronal

apoptosis in the brain tissues, especially in the hippocampus[3-7]. Hence, the exploration of antioxidative stress agents suggests a promising therapeutic option for achieving a neuroprotective effect against neurodegenerative diseases associated with hippocampal neuronal damage.

Magnesium is one of the essential cations in the intracellular environment and is only second to potassium in concentration. Magnesium is involved in the synthesis of many enzymes that are important in various biological processes[8]. The concentration of brain magnesium is decreased in AD patients when compared with control subjects[9]. Based on this finding, recent research has assessed the application of the novel magnesium compound Magnesium-L-threonate (MgT), which increases brain magnesium concentration after oral administration, for ameliorating AD-associated pathological changes[10-12]. Although MgT exhibits a protective effect against synaptic damage in an AD mouse model[11], its effects on oxidative stress and hippocampal neuronal damage remain unexplored. It has been recently confirmed that magnesium has an inhibitory effect against oxidative-stress-related malondialdehyde (MDA) *in vitro*[13,14]; therefore, it has become of interest to investigate whether MgT is capable of suppressing oxidative stress damage *in vivo*. Therefore, this research explored the potential protective effects of MgT against oxidative stress and neuronal injury in $A\beta_{25-35}$-treated HT22 cells and in APPswe/PS1dE9 (APP/PS1) mouse hippocampus.

For the in vitro experiment, in order to evaluate the capacity of MgT against $A\beta_{25-35}$-triggered oxidative stress and neuronal damage and explore the related mechanism, HT22 cell was chosen as the cell model, and it is well known as the immortalized murine hippocampal neuron[15]. We also explored the *in vivo* potential neuroprotective effects of MgT against oxidative stress, Aβ production and hippocampal neuronal damage in APP/PS1 mouse, a typical animal model of AD[16].

MATERIALS AND METHODS

Experimental materials

MgT was acquired from Macklin (Shanghai, China); $A\beta_{25-35}$ was purchased from MedChemExpress LLC (New Jersey, USA); The cell counting kit-8 (CCK-8) detection kit was provided from APExBIO Technology LLC (Houston, USA); A fluorescein isothiocyanate-annexin V/propidium iodide apoptosis agent was obtained from BD (New Jersey, USA); A reactive oxygen species (ROS) testing kit was supplied from Beyotime Biotechnology (Shanghai, China); The antibodies were purchased from Cell Signaling Technology (Danvers, USA), BioLegend (San Diego, USA) and Abcam (Cambridge, USA); The rest of experimental materials were bought from Thermo Fisher Scientific (Waltham, USA), CWBIO (Beijing, China) and Gibco (New York, USA).

HT22 cell culture and drug administration

Based on the previously described method, HT22 cell culture and differentiation procedures were carried out[17,18]. Briefly, HT22 cell was cultured in the normal cell culture medium and then differentiated in N2 supplement-containing neurobasal medium for 1 d prior to drug administrations. According to the previous research[19], when it was exposed to 40 μmol/L $A\beta_{25-35}$ for 1 d, the viability of HT22 cell would significantly decrease. Therefore, this study chose 40 μmol/L as the appropriate concentration of $A\beta_{25-35}$ administration. Before $A\beta_{25-35}$ treatment, the dilution of $A\beta_{25-35}$ was carried out by using sterile saline and then it was kept at 37°C for 7 d for peptide pre-aging, as reported previously [19]. In order to investigate whether MgT could be applied to inhibit the oxidative stress damage triggered by $A\beta_{25-35}$ administration, HT22 cell was preconditioned with or without 50 μmol/L MgT for 12 h prior to be processed with 40 μmol/L $A\beta_{25-35}$ for 1 d.

Cell viability detection

The viability was assessed *via* the CCK-8 experiment for HT22 cell exposed to $A\beta_{25-35}$ and MgT. Briefly, after different drug treatments for the three groups, each well of HT22 cells was incubated with 10 μL CCK-8 and the absorbance value was acquired at 450 nm by using an absorbance reader (California, USA).

Quantitative assessment of ROS production

Total intracellular ROS generation was detected using an oxidation-sensitive fluorogenic dichlorodihydro-fluorescein diacetate (DCFH-DA) probe and further quantified with flow cytometry, as described previously[20]. Briefly, after drug administration, HT22 cells were washed and reacted with 10 μmol/L DCFH-DA probe during this experiment procedure. The cell samples were collected and finally detected using the flow cytometer (BD, USA). The percentages of DCFH-DA labeled cells represented the intracellular ROS level.

Mice and drug administrations

APP/PS1 male mice and wild-type (WT) litter-mate male mice were acquired from the Nanjing Biomedical Research Institute of Nanjing University (Nanjing, China). The animal experiment received

the approbation from the local animal ethical and welfare committee. All protocols were designed to minimize discomfort or pain to the mice. The mice were housed in a specific-pathogen-free environment (23 ± 1 °C, 12 h/12 h light/dark, 50% humidity) with free access to water and food.

In the animal experiment procedure, 6-mo-old mice weighing 33-35 g were set as three groups (three mice per group): MgT-treated APP/PS1 mice (registered as 'TG + MgT group'), control APP/PS1 mice (TG group) and control WT mice (WT group). MgT-treated mice received daily administration of MgT (910 mg/kg/d) *via* drinking water for 3 mo on the basis of the previously described method[11]. The remaining mice (TG and WT groups) were treated with drinking water. After drug treatment, mice were used for the Morris Water Maze test and then killed under deep anesthesia (intraperitoneal injection, 150 mg/kg pentobarbital sodium) to collect the hippocampal tissues for further biochemical investigations.

Morris water maze test

All mice were behaviorally tested for cognitive ability using the Morris water maze after 3 mo of treatments with or without MgT, as previously described[1]. At the beginning, each mouse was pretrained in this water maze with the visible platform for 1 d. Subsequently, all mice received the hidden platform training for 5 d (4 trails per day, 90 s per trial). For each trail, the mice were released from four starting quadrant positions in a different order and swam for 90 s. If the exploration time of mouse was less than 90 s, the trails would stop and the time to find the hidden platform was recognized as escape latency. If the mouse missed the setting time, it would be guided to arrive in the platform and the escape latency of 90 s was recorded. For each mouse, before the statistical analysis was carried out, the escape latencies of four trails were averaged. Finally, the platform was taken out and the mice were tested on a 90 s probe test at 24 h after the hidden platform training. After each trail, mice should be dried with a clean towel and put on an electric blanket to keep their body warm. For each mouse, the latency to arrive in the removed platform, the percentage of the time spent in the target quadrant (the quadrant where the platform was previously settled) and the number of times crossed the target position (the previous location of the platform) were measured during the probe test.

Apoptosis detection

A fluorescein isothiocyanate-annexin V/propidium iodide testing agent was utilized to measure the apoptosis rate of HT22 cells. After drug administration, HT22 cells were washed, trypsin digested and incubated with this testing agent before flow cytometry. The allophycocyanin-annexin V/propidium iodide kit was also applied to assess the apoptosis rate of hippocampal neurons. After isolation of the hippocampal tissue, a single cell suspension was prepared, stained with anti-NeuN antibody, followed by appropriate Alexa-Fluor-488-conjugated secondary antibody, and finally detected with this kit for flow cytometric examination.

Western blotting

The proteins in HT22 cells or hippocampal tissue were quantified, probed with a series of specific primary antibodies and visualized with a Digital Imaging machine (Gel Logic, Rochester, New York, USA). The relative protein density was quantified as previously described[21]. The involved primary antibodies were diluted to 1:1000, except for glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (1:2000).

Statistical analysis

Significance was measured using one-way analysis of variance with Fisher's least significant difference tests for multiple comparison using Prism 6 software (Graphpad, San Diego, CA, USA). For each group, data were shown as mean ± SE and $P < 0.05$ indicated significant differences.

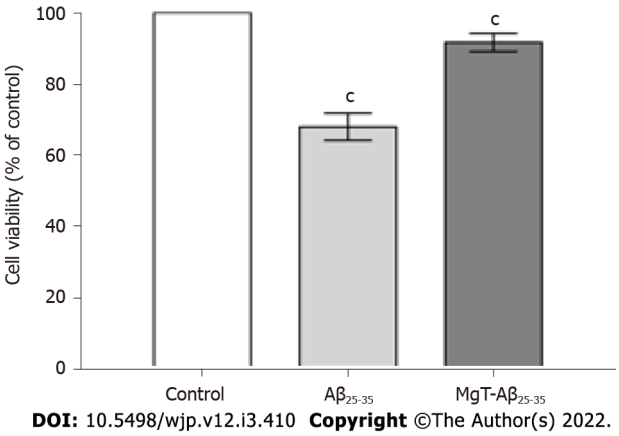
RESULTS

MgT attenuated cytotoxicity in the $A\beta_{25-35}$-treated HT22 cell

As demonstrated in Figure 1, $A\beta_{25-35}$-exposed cells showed obvious lower cell viability than control cells ($P < 0.001$). Compared with $A\beta_{25-35}$-exposed cells, the viability of MgT-$A\beta_{25-35}$-exposed cells was obviously elevated ($P < 0.001$). Thus, all data of the CCK8 test illustrated that the pretreatment with MgT inhibited the cytotoxicity in the $A\beta_{25-35}$-exposed HT22 cell model.

MgT suppressed ROS generation and hypoxia-inducible factor-1α overexpression in $A\beta_{25-35}$-treated HT22 cell

Intracellular ROS level measured by the DCFH-DA test exhibited an obvious increase in $A\beta_{25-35}$-administrated cells *vs* control cells ($P < 0.001$). Compared with $A\beta_{25-35}$-treated cells, the ROS level was remarkably decreased in MgT-$A\beta_{25-35}$-treated cells ($P < 0.001$) (Figure 2A and B). As indicated in Figure 2C and D, hypoxia-inducible factor (HIF)-1α protein expression was increased in the $A\beta_{25-35}$-



DOI: 10.5498/wjp.v12.i3.410

Figure 1 Magnesium-L-threonate administration inhibited the cytotoxicity in the amyloid β_{25-35}-administrated HT22 cells. $n = 3$. $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate.

exposed HT22 cells ($P < 0.001$), which was effectively downregulated by MgT treatment ($P < 0.01$).

MgT inhibited the apoptosis and regulated the expression of apoptotic-related proteins in the $A\beta_{25-35}$-treated HT22 cell

The effects of MgT treatment in regulating apoptosis and apoptotic-associated proteins expression were also measured, aiming to further assess the neuroprotective effect of MgT against neuronal damage in the $A\beta_{25-35}$-treated HT22 cell. As displayed in Figure 3A and B, $A\beta_{25-35}$-administrated group owned a higher apoptosis rate of HT22 cells than control group ($P < 0.001$), and the apoptosis rate was obviously reduced after MgT intervention ($P < 0.001$). What's more, the $A\beta_{25-35}$-administrated group had a lower B-cell lymphoma 2 (Bcl-2) protein (an anti-apoptotic molecule[22]) expression level and a higher Bcl-2-associated X (Bax) protein (a pro-apoptotic molecule[23]) expression level than control group (both $P < 0.001$), while MgT treatment effectively promoted Bcl-2 expression ($P < 0.001$) and blocked Bax expression ($P < 0.01$) (Figure 3C-E).

MgT restored downregulated phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway in $A\beta_{25-35}$-exposed HT22 cell

The effects of MgT administration on regulating PI3K/Akt pathway, which was a classical pathway related to cell apoptosis[24], were also detected. As shown in Figure 4, $A\beta_{25-35}$-exposed cells showed lower ratios of phosphorylated (p)-PI3K/PI3K and p-Akt/Akt than control cells (both $P < 0.001$). After MgT administration, these two ratios were significantly upregulated (both $P < 0.001$).

MgT ameliorated impaired cognition of AD mouse

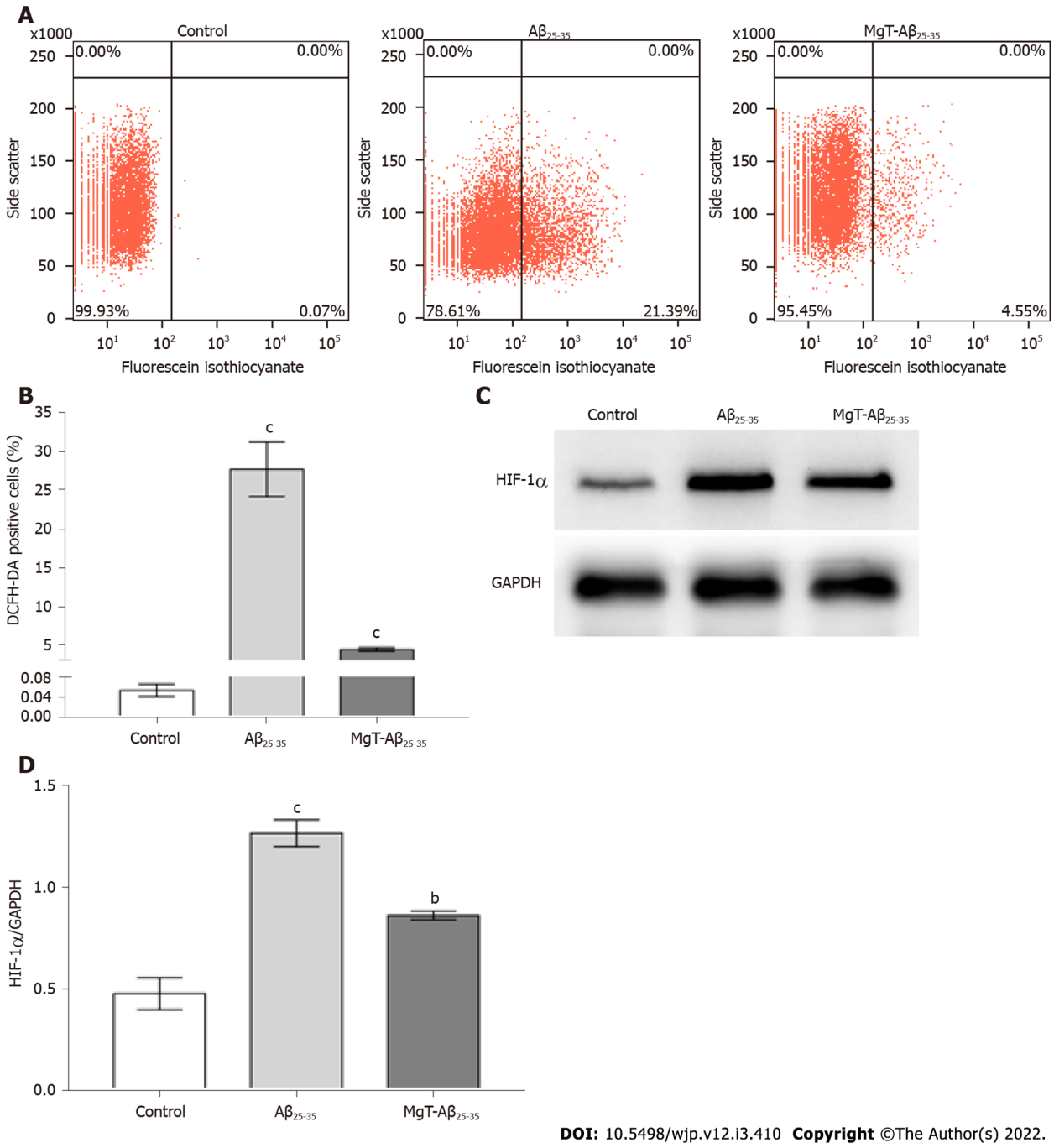
The behavioral performance was recorded with the Morris water maze method to assess the effect of MgT intervention against memory deficit in AD mouse. Compared with WT group, TG group exhibited prolonged escape latency, while the escape latency was shortened in the TG + MgT group *vs* TG group (Figure 5A). The number of platform crossings and the percentage of target quadrant exploration time were significantly decreased in the TG group *vs* WT group (both $P < 0.01$), while these two cognitive scores were increased after MgT administration (crossings, $P < 0.01$; target quadrant exploration time; $P < 0.05$) (Figure 5B–D). The TG group had a longer latency to locate the removed platform than WT group ($P < 0.001$), and the latency was shorter in the TG + MgT group *vs* TG group ($P < 0.01$) (Figure 5E). Nevertheless, no obvious differences regarding the swimming speed and body weight were discovered among all groups (Figure 5F and G).

MgT suppressed hippocampal $A\beta_{1-42}$, HIF-1α and NADPH oxidase (NOX)4 protein expression in AD mouse

Compared with WT group, elevated expression of HIF-1α, NOX4 (a reliable marker of oxidative stress [25,26]) and $A\beta_{1-42}$ proteins was seen in the TG group (HIF-1α and $A\beta_{1-42}$, $P < 0.001$; NOX4, $P < 0.01$), while these indexes were all decreased in the TG + MgT group *vs* TG group (all $P < 0.01$) (Figure 6).

MgT prevented hippocampal neuronal apoptosis and regulated apoptosis-associated protein expression in AD mouse

The effects of MgT administration in ameliorating neuronal apoptosis and regulating the expression of apoptotic-associated proteins were also examined to further demonstrate the neuroprotective effect of MgT on APP/PS1 mouse hippocampus. As listed in Figure 7A and B, the apoptosis rate of hippocampal



DOI: 10.5498/wjp.v12.i3.410

Figure 2 Magnesium-L-threonate treatment suppressed the elevated reactive oxygen species level and hypoxia-inducible factor-1α protein expression in the amyloid β_{25-35}-exposed HT22 cells. A, B: The percentages of dichloro-dihydro-fluorescein diacetate positive cells of each group; C: Protein band images of hypoxia-inducible factor (HIF)-1α and glyceraldehyde-3-phosphate dehydrogenase of each group; D: The HIF-1α protein expression level of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate; HIF: hypoxia-inducible factor; DCFH-DA: dichloro-dihydro-fluorescein diacetate; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

neuron was elevated in the TG group *vs* WT group ($P < 0.01$), while TG + MgT group had a significant lower apoptosis rate than TG group ($P < 0.01$). Moreover, the downregulation of Bcl-2 expression and the upregulation of Bax expression were noticed in TG group *vs* WT group (both $P < 0.001$), while MgT treatment promoted Bcl-2 expression ($P < 0.01$) and suppressed Bax expression ($P < 0.001$) (Figure 7C-E).

MgT activated the PI3K/Akt pathway in AD mouse

The effect of MgT administration on the PI3K/Akt pathway was also detected in the *in vivo* experiment of this study. As shown in Figure 8, p-PI3K/PI3K and p-Akt/Akt ratios were reduced in TG group *vs* WT group (both $P < 0.001$), while these two ratios were obviously elevated after MgT administration (p-PI3K/PI3K ratio, $P < 0.05$; p-Akt/Akt ratio, $P < 0.001$).

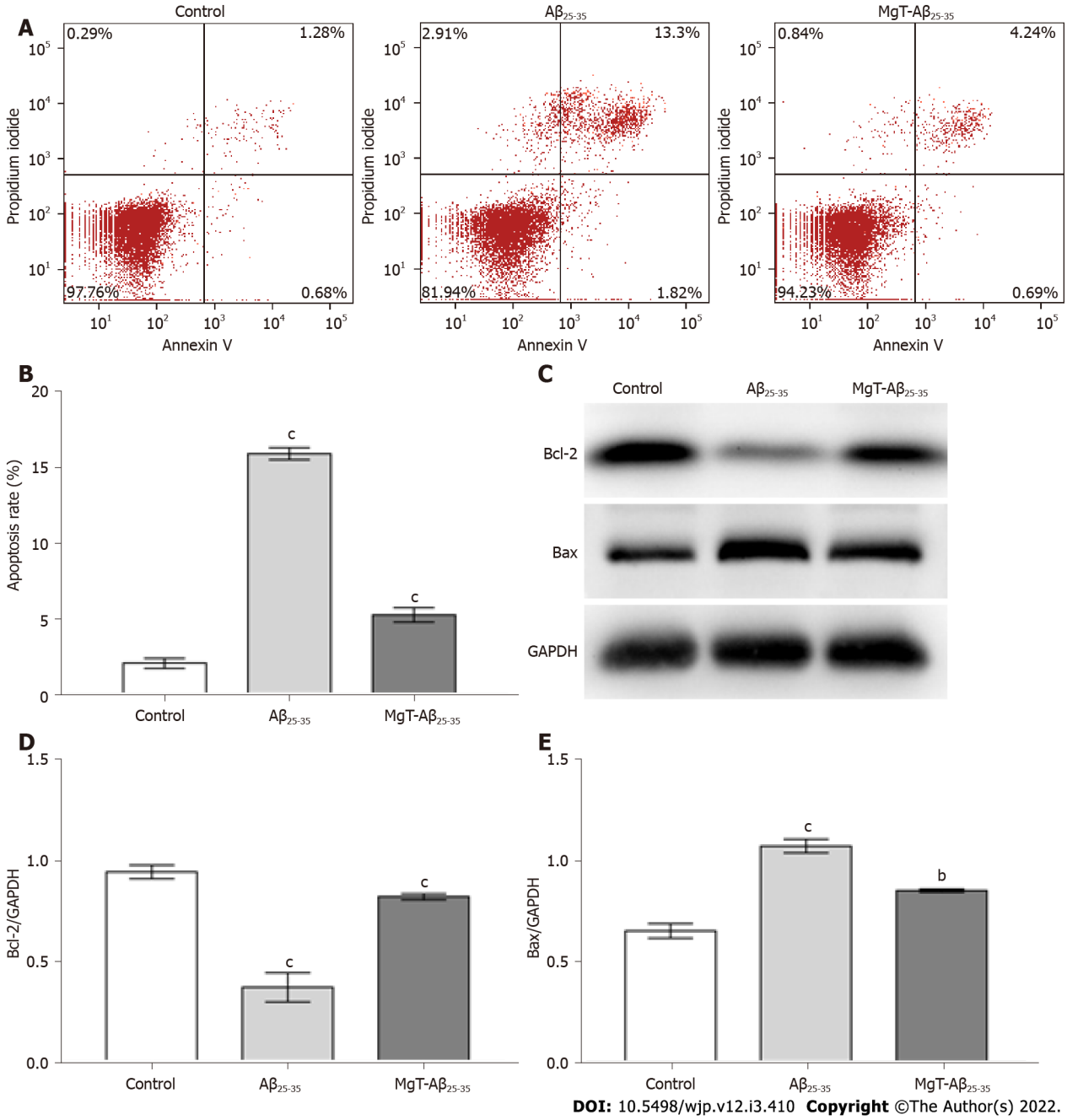
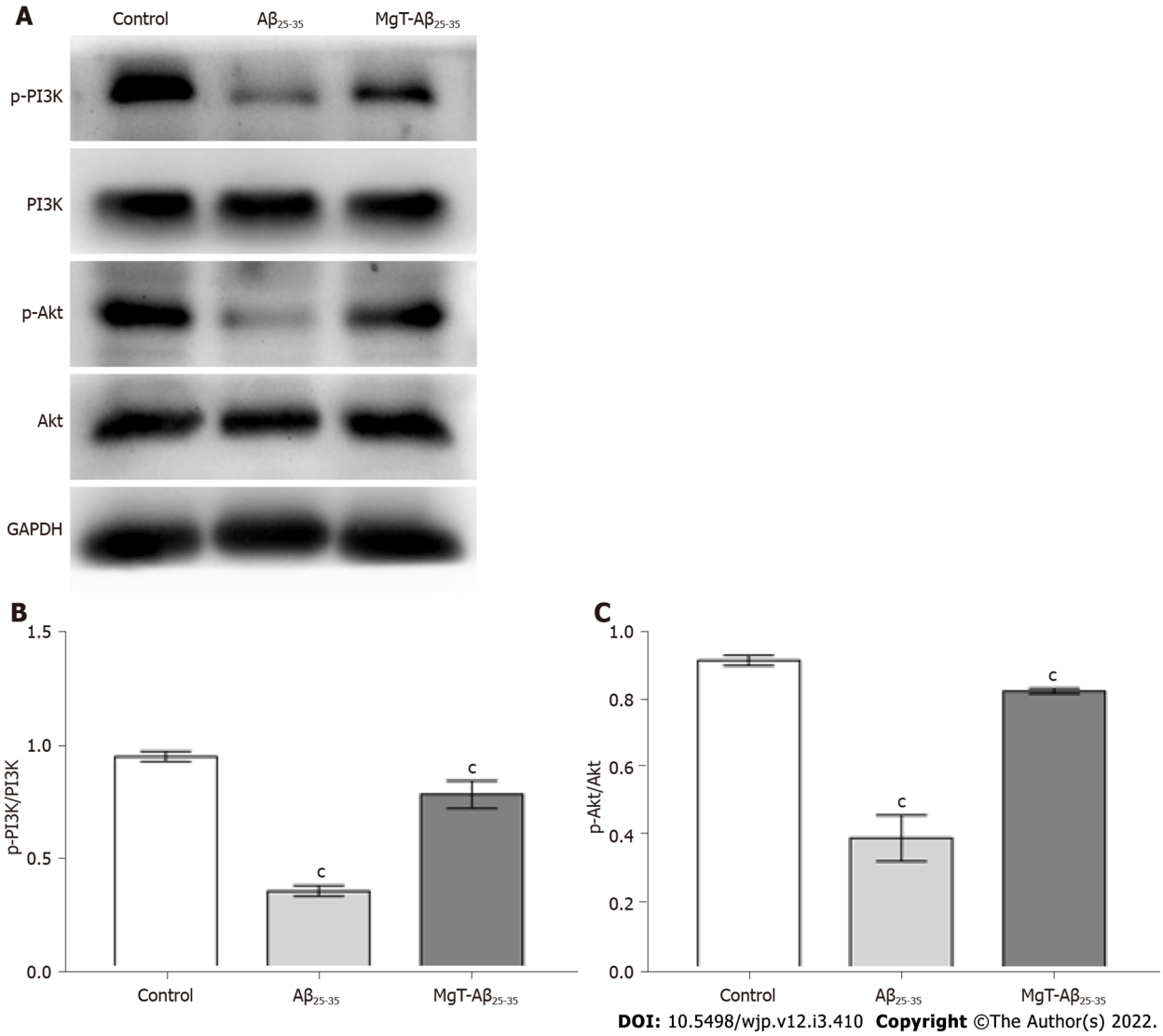


Figure 3 Magnesium-L-threonate administration prevented the apoptosis and regulated the apoptotic-associated proteins expression in the amyloid β_{25-35}-administrated HT22 cells. A, B: The apoptosis rate of each group; C: Protein band images of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax) and glyceraldehyde-3-phosphate dehydrogenase in each group; D: The Bcl-2 protein expression level of each group; E: The Bax protein expression level of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

DISCUSSION

It was demonstrated that oxidative stress could trigger neuronal damage in the hippocampus tissues of the brain, which is the vital pathological mechanism of neurodegenerative diseases, including AD[27]. Recently, the findings of the *in vitro* study certified that extracellular magnesium concentration could act as a regulator that effectively influenced the level of MDA, a pathological marker closely associated with oxidative stress damage[13,14]. Several researches indicated that MgT could elevate the level of brain magnesium *via* oral administration[10,12]. Therefore, this research attempted to validate the effects of MgT against oxidative stress and neuronal damage in the $A\beta_{25-35}$-treated HT22 cell and the hippocampus of APP/PS1 mouse, and investigated the involved mechanism.

Growing evidences have proved that during the pathological progression of neurogenerative disease, such as AD, abnormal oxidative stress resulted in the generation of ROS and hippocampal neuronal apoptosis thus leading to the deterioration of brain function[27,28]. The *in vitro* experiment part of this

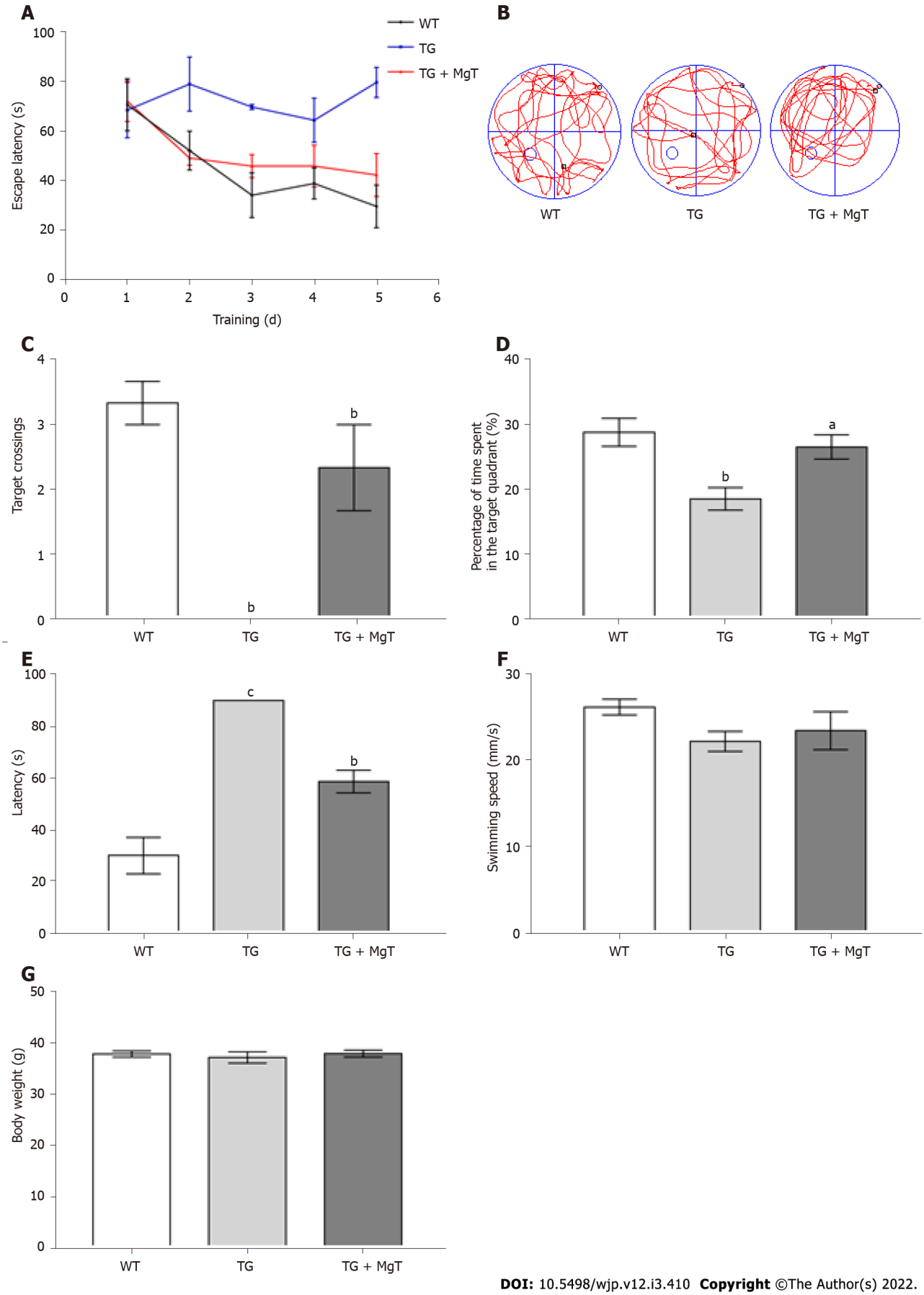


DOI: 10.5498/wjp.v12.i3.410

Figure 4 Magnesium-L-threonate treatment suppressed the downregulation of phosphatidylinositol-3-kinase/protein kinase B pathway in the amyloid β_{25-35}-exposed HT22 cells. A: Protein band images of phosphorylated (p)-phosphatidylinositol-3-kinase (PI3K), PI3K, p-protein kinase B (Akt), Akt and glyceraldehyde-3-phosphate dehydrogenase of each group; B: The p-PI3K/PI3K ratio of each group; C: The p-Akt/Akt ratio of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. Aβ: Amyloid β; MgT: Magnesium-L-threonate; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

study, oxidative stress, was detected by assessing the ROS level and cell apoptosis was detected by measuring the apoptosis rate and quantifying the expression of apoptosis-associated proteins. The *in vitro* data revealed that MgT remarkably blocked the oxidative stressors $A\beta_{25-35}$-induced[28] oxidative damage and apoptosis in the HT22 cells as proved by the elevation of cell viability, the reduction of ROS generation, the decrease of apoptosis rate and Bax expression, and the upregulation of Bcl-2 expression after MgT administration. In line with these *in vitro* results, the *in vivo* data confirmed the suppressive effect of MgT treatment against oxidative stress-triggered hippocampal neuronal damage *via* downregulating the expression level of the oxidative stress marker NOX4 protein and inhibiting the apoptosis of the hippocampal neuron in the AD mouse model. Additionally, it has been confirmed that the increased ROS induced by oxidative stress can lead to abnormal production of Aβ which can worsen the pathological process of AD[29]. In our *in vivo* study, the measurement of $A\beta_{1-42}$ expression by western blotting confirmed the inhibitory effect of MgT against Aβ production in the AD mouse model.

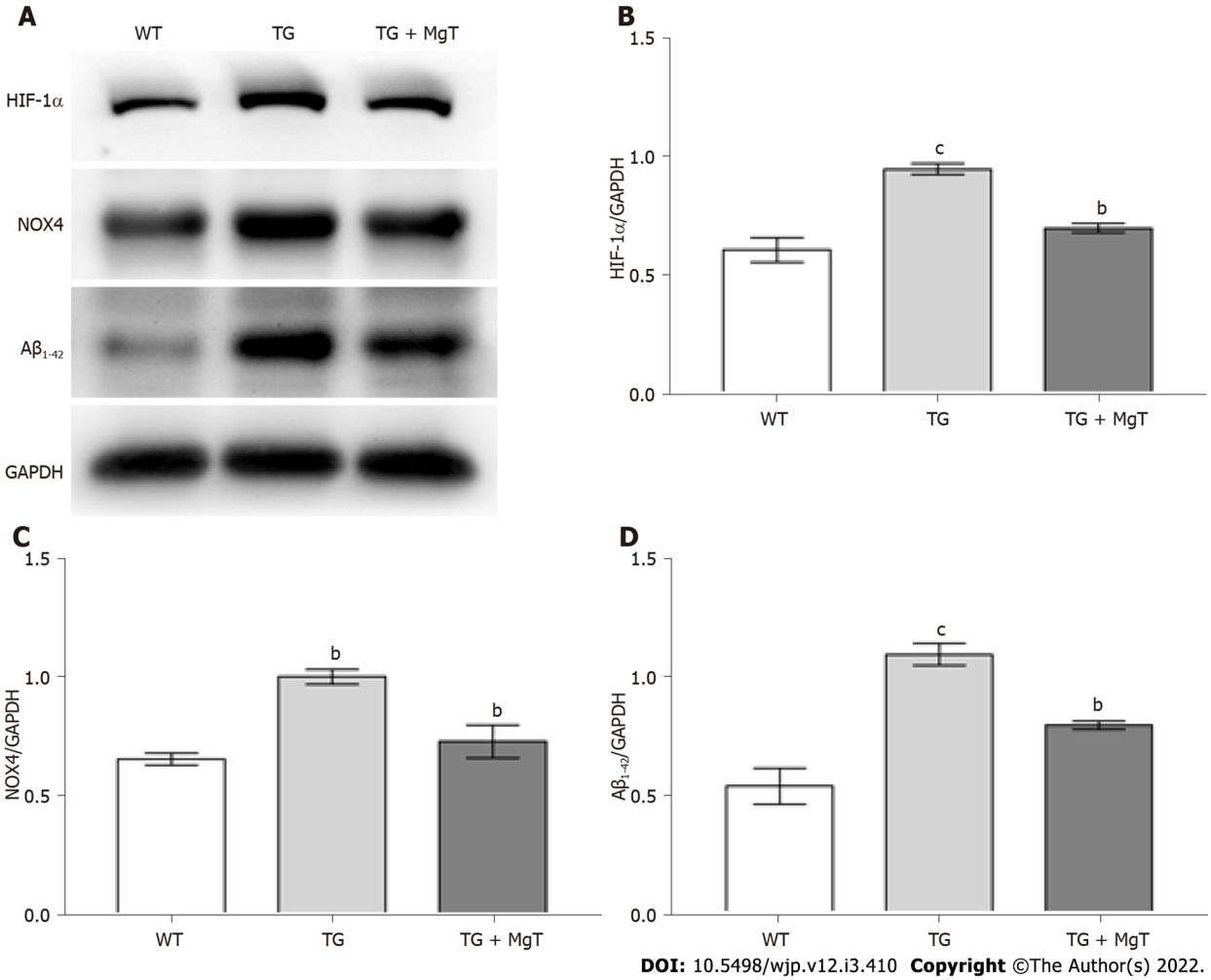
Numerous researches verified the key role of HIF-1α in the mediation of oxygen homeostasis within the cellular environment. A close relationship was discovered between HIF-1α level and oxygen balance: HIF-1α level remained low under the physiological situation while it was significantly elevated under the hypoxia condition[30,31]. Moreover, recent study revealed that the high glucose-triggered oxidative stress accelerated Aβ aggregation *via* the regulation of the ROS/HIF-1α mechanism *in vitro*, which supported a strong relationship between ROS and HIF-1α, and that the crosstalk between the two could deteriorate the Aβ production under abnormal oxidative stress condition[32]. Another research also indicated the crosstalk between HIF-1α and ROS in RAW 264.7 cell model[33]. Therefore, the effect



DOI: 10.5498/wjp.v12.i3.410

Figure 5 Magnesium-L-threonate administration prevented the memory deficit of APPswe/PS1dE9 mouse. A: The escape latency of each group; B: The swimming track explored the removed platform of each group; C: The number of platform crossings of each group; D: The percentage of the time spent in the

target quadrant of each group; E: The latency located the removed platform of each group; F: The swimming speed of each group; G: The body weight of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; TG: APPswe/PS1dE9 mice group; WT: Wild-type mice group.



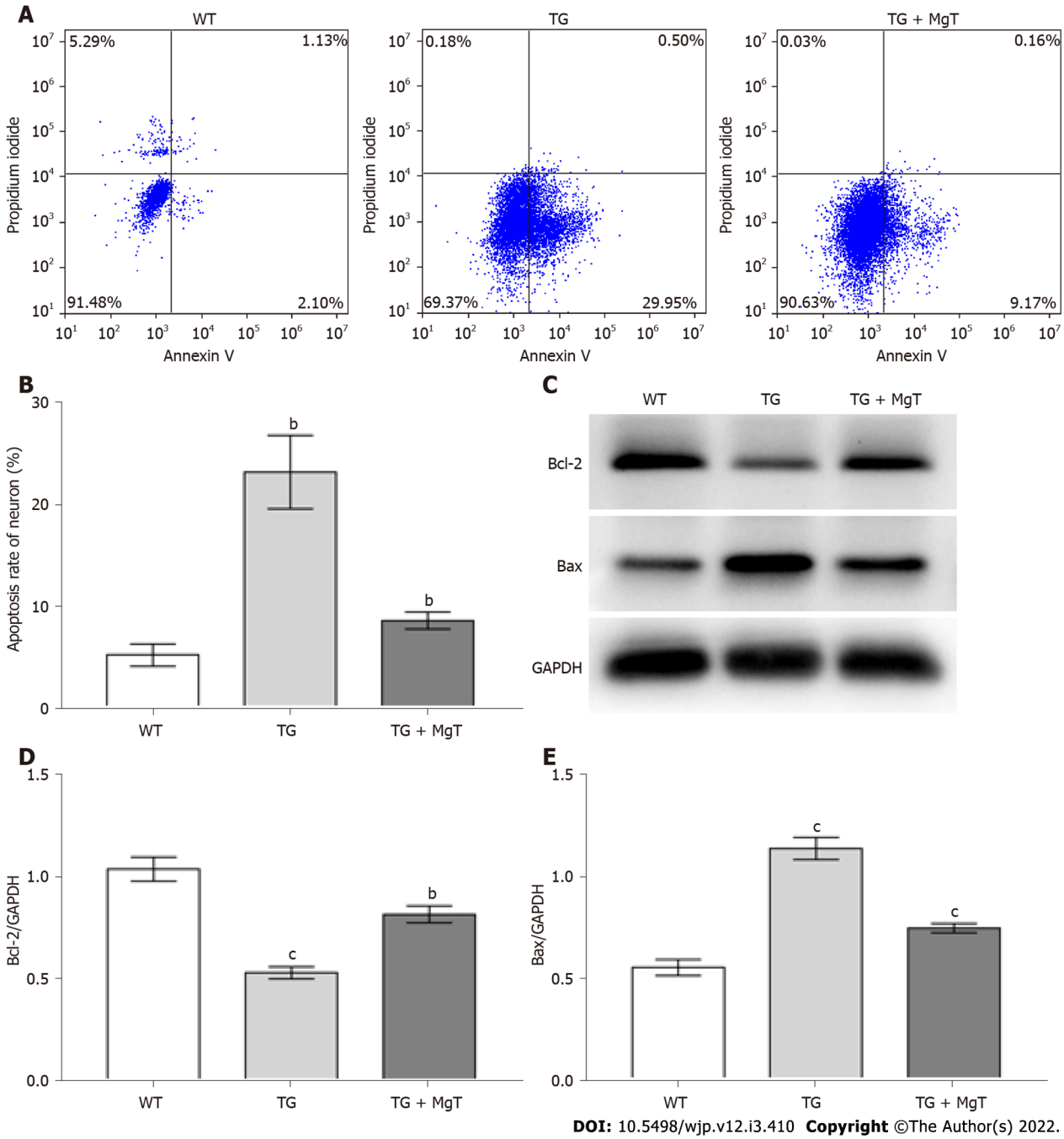
DOI: 10.5498/wjp.v12.i3.410

Figure 6 Magnesium-L-threonate treatment prevented the upregulation of amyloid $\beta_{1\text{-}42}$, hypoxia-inducible factor-1α and NADPH oxidase 4 proteins in APPswe/PS1dE9 mouse hippocampus. A: Protein band images of hypoxia-inducible factor (HIF)-1α, NADPH oxidase (NOX) 4, amyloid β $(Aβ)_{1\text{-}42}$ and glyceraldehyde-3-phosphate dehydrogenase of each group; B: The HIF-1α protein expression of each group; C: The NOX4 protein expression of each group; D: The $Aβ_{1\text{-}42}$ protein expression of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; TG: APPswe/PS1dE9 mice group; WT: Wild-type mice group; Aβ: Amyloid β; HIF: hypoxia-inducible factor; NOX: NADPH oxidase; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

of MgT administration on HIF-1α expression was also investigated. The observations from *in vivo* and *in vitro* investigations indicated that MgT significantly suppressed the HIF-1α overexpression in $Aβ_{25\text{-}35}$-treated HT22 cells and APP/PS1 mice.

PI3K/Akt pathway is an important cellular pathway occupying a pivotal role in the mediation of cell apoptosis[34]. A recent study demonstrated that Rotundifuran-induced ROS production could lead to cell apoptosis *via* suppressing the PI3K/Akt pathway in the cervical cancer cell model[35]. Another study also showed that inhibition of apoptosis was correlated with the ROS-mediated PI3K/Akt pathway in a streptozotocin-treated INS-1 cell model[24]. Based on the above findings, dysregulation of the PI3K/Akt signaling pathway supports the relationship between oxidative stress and apoptosis. The present experimental procedure also detected the effect of MgT administration on the PI3K/Akt pathway. According to the results from Western blotting, the PI3K/Akt pathways were downregulated in $Aβ_{25\text{-}35}$-administrated HT22 cells and APP/PS1 mice, which were restored by MgT administration.

In light of the findings that MgT administration exhibited neuroprotective effects against oxidative stress and hippocampal neuronal apoptosis in this AD mouse model, which were the vital pathological mechanisms underlying the cognitive deficit of AD[3,36], the cognitive ability of MgT-treated APP/PS1 mouse was measured. In this experiment, the results acquired from the Morris water maze test confirmed that MgT treatment ameliorated the cognitive deficit in this AD animal model, but the further mechanism underlying the memory protective effect of MgT needs to be further investigated.



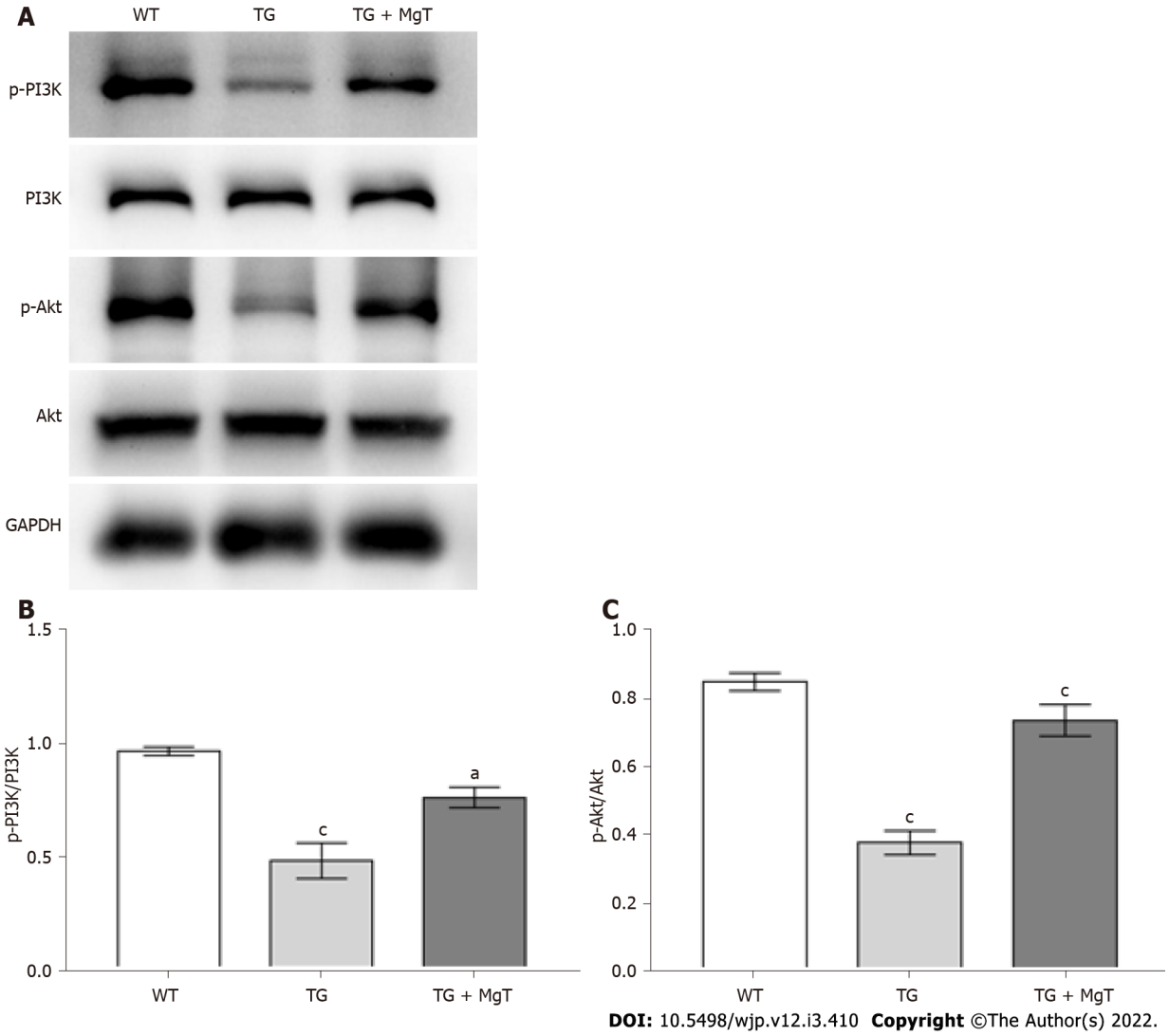
DOI: 10.5498/wjp.v12.i3.410

Figure 7 Magnesium-L-threonate administration regulated the neuronal apoptosis and mediated the expression of apoptotic-related proteins in APPswe/PS1dE9 mouse hippocampus. A, B: The apoptosis rate of hippocampal neuron of each group; C: Protein band images of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax) and glyceraldehyde-3-phosphate dehydrogenase of each group; D: The Bcl-2 protein expression level of each group; E: The Bax protein expression level of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; TG: APPswe/PS1dE9 mice group; WT: Wild-type mice group; Bcl-2: B-cell lymphoma 2; Bax: Bcl-2-associated X; GAPDH: glyceraldehyde-3-phosphate dehydrogenase.

There are several limitations in this experiment. In this study, APP/PS1 mice were applied as the animal model of AD. Although this animal model was a typical and common model of AD and it could be employed to mimic the cognitive impairment and pathological changes of AD[16], it might not reflect all types of this disease. Therefore, it is necessary to conduct further explorations to validate the above-mentioned effects of MgT on other types of Alzheimer's disease, animal models of other neurodegenerative diseases and clinical trials.

CONCLUSION

It can be demonstrated in this study that MgT intervention has neuroprotective effects against oxidative



DOI: 10.5498/wjp.v12.i3.410

Figure 8 Magnesium-L-threonate treatment activated the phosphatidylinositol-3-kinase/protein kinase B pathway in APPswe/PS1dE9 mouse hippocampus. A: Protein band images of phosphorylated (p)-phosphatidylinositol-3-kinase (PI3K), PI3K, p-protein kinase B (Akt), Akt and glyceraldehyde-3-phosphate dehydrogenase of each group; B: The p-PI3K/PI3K ratio of each group; C: The p-Akt/Akt ratio of each group. $n = 3$. $^{a}P < 0.05$, $^{b}P < 0.01$, $^{c}P < 0.001$ *vs* former group. MgT: Magnesium-L-threonate; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; WT: Wild-type mice group; TG: APPswe/PS1dE9 mice group.

stress and hippocampal neuronal damage in $A\beta_{25-35}$-treated HT22 cells and AD mouse model. Our study suggests a promising therapeutic agent for the amelioration of oxidative stress and hippocampal neuronal damage-associated neurodegenerative disorders.

ARTICLE HIGHLIGHTS

Research background

The increasing prevalence of Alzheimer's disease (AD) in the elderly population has posed a huge financial and medical burden on the society. Effective methods to block the progression of the cognitive deterioration in AD patients are urgently required. As oxidative stress accounts for a pivotal role in the pathological mechanism of neurodegenerative diseases, including AD, anti-oxidative stress treatments may provide a promising therapeutic direction. Recent study had explored the anti-malondialdehyde effect of magnesium *in vitro*, however the potential anti-oxidative stress damage effect of Magnesium-L-threonate (MgT) still remains to be verified.

Research motivation

This research investigated the suppressive effect of MgT against oxidative stress injury, thus developing a therapeutic reference basis for the future explorations.

Research objectives

This research aimed to determine the neuroprotective effect of MgT against oxidative stress damage and explore the related mechanism which may bring a research foundation for the feasibility of MgT.

Research methods

As the cell and animal models, amyloid β $(Aβ)_{25-35}$-treated HT22 cells and APPswe/PS1dE9 (APP/PS1) mice were treated with MgT administration. After the MgT administration, cell counting kit-8 detection was applied to analysis the viability of HT22 cells and the Morris Water Maze test was used to record the cognition of APP/PS1 mice. Reactive oxygen species (ROS) production of HT22 cells and cell apoptosis of both models were all quantified by using the flow cytometry assay. The expression of hypoxia-inducible factor (HIF)-1α, NADPH oxidase (NOX) 4, $Aβ_{1-42}$, B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X (Bax) and phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway proteins was quantified by Western blotting.

Research results

MgT effectively suppressed the HT22 cellular injury triggered by $Aβ_{25-35}$-induced oxidative stress by elevating the viability, blocking the ROS formation and downregulating HIF-1α. MgT significantly ameliorated the impaired cognitive performance of APP/PS1 mouse and inhibited the upregulation of $Aβ_{1-42}$, NOX4 and HIF-1α protein expression. In addition, MgT obviously suppressed the cell apoptosis, regulated apoptotic-related proteins and upregulated the PI3K/Akt pathway in both models. In future research, further explorations are required to confirm the above-mentioned effects of MgT in more disease models.

Research conclusions

This study demonstrates the protective effect of MgT against oxidative stress injury in $Aβ_{25-35}$-treated HT22 cells and APP/PS1 mice.

Research perspectives

This study provides a promising therapeutic agent to ameliorate the oxidative stress damage-associated neurodegenerative diseases. More investigations to demonstrate this effect of MgT on other types of Alzheimer's disease, *in vivo* models of other neurodegenerative diseases and clinical experiments are required in further research.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Xi-Yan Wang for editing assistance.

FOOTNOTES

Author contributions: Xiong Y and Ruan YT contributed to designing this study, collecting samples, carrying out experiments and writing the manuscript; Zhao J, Yang YW, Chen LP and Mai YR contributed to collecting samples and revising the manuscript; Yu Q, Cao ZY, Liu FF and Liao W contributed to analyzing the data and revising the manuscript; Liu J had full access to all of the data in the study, and took responsibility for the integrity of the data and the accuracy of the data analysis; all authors have approved the final article.

Supported by National Natural Science Foundation of China, No. 81870836; Natural Science Foundation of Guangdong Province, China, No. 2020A1515010210; Science and Technology Program of Guangzhou, China, No. 202007030010; and Guangdong Basic and Applied Basic Research Foundation, China, No. 2020A1515110317 and No. 2021A1515010705.

Institutional animal care and use committee statement: All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC), Sun Yat-sen University (Approval No. SYSU-IACUC-2019-000005).

Conflict-of-interest statement: All authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

Country/Territory of origin: China

ORCID number: Ying Xiong 0000-0001-7435-933X; Yu-Ting Ruan 0000-0002-8530-6097; Jing Zhao 0000-0002-9270-3250; Yu-Wen Yang 0000-0002-5245-6988; Li-Ping Chen 0000-0002-4736-2952; Ying-Ren Mai 0000-0002-4814-5749; Qun Yu 0000-0003-2554-6504; Zhi-Yu Cao 0000-0001-9397-2754; Fei-Fei Liu 0000-0001-6066-1933; Wang Liao 0000-0001-7615-3626; Jun Liu 0000-0002-6214-972X.

S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Wang JL

REFERENCES

1 **Fan S**, Zheng Y, Liu X, Fang W, Chen X, Liao W, Jing X, Lei M, Tao E, Ma Q, Zhang X, Guo R, Liu J. Curcumin-loaded PLGA-PEG nanoparticles conjugated with B6 peptide for potential use in Alzheimer's disease. *Drug Deliv* 2018; **25**: 1091-1102 [PMID: 30107760 DOI: 10.1080/10717544.2018.1461955]
2 **Kola A**, Dudek D, Valensin D. Metal Complexation Mechanisms of Polyphenols Associated to Alzheimer's Disease. *Curr Med Chem* 2021; **28**: 7278-7294 [PMID: 34325628 DOI: 10.2174/0929867328666210729120242]
3 **Sieteiglesias V**, González-Burgos E, Bermejo-Bescós P, Divakar PK, Gómez-Serranillos MP. Lichens of Parmelioid Clade as Promising Multitarget Neuroprotective Agents. *Chem Res Toxicol* 2019; **32**: 1165-1177 [PMID: 31125207 DOI: 10.1021/acs.chemrestox.9b00010]
4 **Tang KS**. The potential role of nanoyttria in alleviating oxidative stress biomarkers: Implications for Alzheimer's disease therapy. *Life Sci* 2020; **259**: 118287 [PMID: 32814066 DOI: 10.1016/j.lfs.2020.118287]
5 **Montine TJ**, Montine KS, McMahan W, Markesbery WR, Quinn JF, Morrow JD. F2-isoprostanes in Alzheimer and other neurodegenerative diseases. *Antioxid Redox Signal* 2005; **7**: 269-275 [PMID: 15650414 DOI: 10.1089/ars.2005.7.269]
6 **Reddy PH**. Amyloid precursor protein-mediated free radicals and oxidative damage: implications for the development and progression of Alzheimer's disease. *J Neurochem* 2006; **96**: 1-13 [PMID: 16305625 DOI: 10.1111/j.1471-4159.2005.03530.x]
7 **Mecocci P**, Boccardi V, Cecchetti R, Bastiani P, Scamosci M, Ruggiero C, Baroni M. A Long Journey into Aging, Brain Aging, and Alzheimer's Disease Following the Oxidative Stress Tracks. *J Alzheimers Dis* 2018; **62**: 1319-1335 [PMID: 29562533 DOI: 10.3233/JAD-170732]
8 **de Baaij JH**, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. *Physiol Rev* 2015; **95**: 1-46 [PMID: 25540137 DOI: 10.1152/physrev.00012.2014]
9 **Cilliler AE**, Ozturk S, Ozbakir S. Serum magnesium level and clinical deterioration in Alzheimer's disease. *Gerontology* 2007; **53**: 419-422 [PMID: 17992016 DOI: 10.1159/000110873]
10 **Slutsky I**, Abumaria N, Wu LJ, Huang C, Zhang L, Li B, Zhao X, Govindarajan A, Zhao MG, Zhuo M, Tonegawa S, Liu G. Enhancement of learning and memory by elevating brain magnesium. *Neuron* 2010; **65**: 165-177 [PMID: 20152124 DOI: 10.1016/j.neuron.2009.12.026]
11 **Li W**, Yu J, Liu Y, Huang X, Abumaria N, Zhu Y, Huang X, Xiong W, Ren C, Liu XG, Chui D, Liu G. Elevation of brain magnesium prevents synaptic loss and reverses cognitive deficits in Alzheimer's disease mouse model. *Mol Brain* 2014; **7**: 65 [PMID: 25213836 DOI: 10.1186/s13041-014-0065-y]
12 **Abumaria N**, Yin B, Zhang L, Li XY, Chen T, Descalzi G, Zhao L, Ahn M, Luo L, Ran C, Zhuo M, Liu G. Effects of elevation of brain magnesium on fear conditioning, fear extinction, and synaptic plasticity in the infralimbic prefrontal cortex and lateral amygdala. *J Neurosci* 2011; **31**: 14871-14881 [PMID: 22016520 DOI: 10.1523/JNEUROSCI.3782-11.2011]
13 **Altura BM**, Gebrewold A, Zhang A, Altura BT. Low extracellular magnesium ions induce lipid peroxidation and activation of nuclear factor-kappa B in canine cerebral vascular smooth muscle: possible relation to traumatic brain injury and strokes. *Neurosci Lett* 2003; **341**: 189-192 [PMID: 12697280 DOI: 10.1016/s0304-3940(03)00134-4]
14 **Zhao H**, Zhang X, Zhang B, Qu X. Gastroprotective effects of diosgenin against HCl/ethanol-induced gastric mucosal injury through suppression of NF-κβ and myeloperoxidase activities. *Open Life Sci* 2021; **16**: 719-727 [PMID: 34316512 DOI: 10.1515/biol-2021-0075]
15 **Fang WL**, Zhao DQ, Wang F, Li M, Fan SN, Liao W, Zheng YQ, Liao SW, Xiao SH, Luan P, Liu J. Neurotropin® alleviates hippocampal neuron damage through a HIF-1α/MAPK pathway. *CNS Neurosci Ther* 2017; **23**: 428-437 [PMID: 28271615 DOI: 10.1111/cns.12689]
16 **Trinchese F**, Liu S, Battaglia F, Walter S, Mathews PM, Arancio O. Progressive age-related development of Alzheimer-like pathology in APP/PS1 mice. *Ann Neurol* 2004; **55**: 801-814 [PMID: 15174014 DOI: 10.1002/ana.20101]
17 **Liu J**, Li L, Suo WZ. HT22 hippocampal neuronal cell line possesses functional cholinergic properties. *Life Sci* 2009; **84**: 267-271 [PMID: 19135458 DOI: 10.1016/j.lfs.2008.12.008]
18 **Zhao ZY**, Luan P, Huang SX, Xiao SH, Zhao J, Zhang B, Gu BB, Pi RB, Liu J. Edaravone protects HT22 neurons from H2O2-induced apoptosis by inhibiting the MAPK signaling pathway. *CNS Neurosci Ther* 2013; **19**: 163-169 [PMID: 23253171 DOI: 10.1111/cns.12044]
19 **Fan S**, Zhang B, Luan P, Gu B, Wan Q, Huang X, Liao W, Liu J. PI3K/AKT/mTOR/p70S6K Pathway Is Involved in Aβ

25-35-Induced Autophagy. *Biomed Res Int* 2015; **2015**: 161020 [PMID: 26583091 DOI: 10.1155/2015/161020]

20 **Huang C**, Gan D, Luo F, Wan S, Chen J, Wang A, Li B, Zhu X. Interaction Mechanisms Between the NOX4/ROS and RhoA/ROCK1 Signaling Pathways as New Anti- fibrosis Targets of Ursolic Acid in Hepatic Stellate Cells. *Front Pharmacol* 2019; **10**: 431 [PMID: 31130857 DOI: 10.3389/fphar.2019.00431]

21 **Zheng Y**, Fang W, Fan S, Liao W, Xiong Y, Liao S, Li Y, Xiao S, Liu J. Neurotropin inhibits neuroinflammation *via* suppressing NF-κB and MAPKs signaling pathways in lipopolysaccharide-stimulated BV2 cells. *J Pharmacol Sci* 2018; **136**: 242-248 [PMID: 29551285 DOI: 10.1016/j.jphs.2018.02.004]

22 **Ji KY**, Kim KM, Kim YH, Shim KS, Lee JY, Kim T, Chae S. Serum Starvation Sensitizes Anticancer Effect of *Anemarrhena asphodeloides via* p38/JNK-Induced Cell Cycle Arrest and Apoptosis in Colorectal Cancer Cells. *Am J Chin Med* 2021; **49**: 1001-1016 [PMID: 33827386 DOI: 10.1142/S0192415X21500488]

23 **Alzain AA**, Brisson L, Delaye PO, Pénichon M, Chadet S, Besson P, Chevalier S, Allouchi H, Mohamed MA, Roger S, Enguehard-Gueiffier C. Bioinspired imidazo[1,2-a:4,5-c']dipyridines with dual antiproliferative and anti-migrative properties in human cancer cells: The SAR investigation. *Eur J Med Chem* 2021; **218**: 113258 [PMID: 33813152 DOI: 10.1016/j.ejmech.2021.113258]

24 **Wang J**, Dong Z, Lou L, Yang L, Qiu J. MiR-122 Participates in Oxidative Stress and Apoptosis in STZ-Induced Pancreatic *β* Cells by Regulating PI3K/AKT Signaling Pathway. *Int J Endocrinol* 2021; **2021**: 5525112 [PMID: 34054947 DOI: 10.1155/2021/5525112]

25 **Fakih D**, Zhao Z, Nicolle P, Reboussin E, Joubert F, Luzu J, Labbé A, Rostène W, Baudouin C, Mélik Parsadaniantz S, Réaux-Le Goazigo A. Chronic dry eye induced corneal hypersensitivity, neuroinflammatory responses, and synaptic plasticity in the mouse trigeminal brainstem. *J Neuroinflammation* 2019; **16**: 268 [PMID: 31847868 DOI: 10.1186/s12974-019-1656-4]

26 **Balkrishna A**, Rustagi Y, Bhattacharya K, Varshney A. Application of Zebrafish Model in the Suppression of Drug-Induced Cardiac Hypertrophy by Traditional Indian Medicine Yogendra Ras. *Biomolecules* 2020; **10** [PMID: 32295034 DOI: 10.3390/biom10040600]

27 **Nunomura A**, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, Jones PK, Ghanbari H, Wataya T, Shimohama S, Chiba S, Atwood CS, Petersen RB, Smith MA. Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* 2001; **60**: 759-767 [PMID: 11487050 DOI: 10.1093/jnen/60.8.759]

28 **Tan MA**, Zakharova E, An SSA. Diaportheone A Analogues Instigate a Neuroprotective Effect by Protecting Neuroblastoma SH-SY5Y Cells from Oxidative Stress. *Biology (Basel)* 2021; **10** [PMID: 33807686 DOI: 10.3390/biology10030199]

29 **Mariani E**, Polidori MC, Cherubini A, Mecocci P. Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview. *J Chromatogr B Analyt Technol Biomed Life Sci* 2005; **827**: 65-75 [PMID: 16183338 DOI: 10.1016/j.jchromb.2005.04.023]

30 **Zhang X**, Zhou K, Wang R, Cui J, Lipton SA, Liao FF, Xu H, Zhang YW. Hypoxia-inducible factor 1alpha (HIF-1alpha)-mediated hypoxia increases BACE1 expression and beta-amyloid generation. *J Biol Chem* 2007; **282**: 10873-10880 [PMID: 17303576 DOI: 10.1074/jbc.M608856200]

31 **Li RL**, He LY, Zhang Q, Liu J, Lu F, Duan HX, Fan LH, Peng W, Huang YL, Wu CJ. HIF-1α is a Potential Molecular Target for Herbal Medicine to Treat Diseases. *Drug Des Devel Ther* 2020; **14**: 4915-4949 [PMID: 33235435 DOI: 10.2147/DDDT.S274980]

32 **Lee HJ**, Ryu JM, Jung YH, Lee SJ, Kim JY, Lee SH, Hwang IK, Seong JK, Han HJ. High glucose upregulates BACE1-mediated Aβ production through ROS-dependent HIF-1α and LXRα/ABCA1-regulated lipid raft reorganization in SK-N-MC cells. *Sci Rep* 2016; **6**: 36746 [PMID: 27829662 DOI: 10.1038/srep36746]

33 **Lu Y**, Rong J, Lai Y, Tao L, Yuan X, Shu X. The Degree of *Helicobacter pylori* Infection Affects the State of Macrophage Polarization through Crosstalk between ROS and HIF-1*α*. *Oxid Med Cell Longev* 2020; **2020**: 5281795 [PMID: 33376580 DOI: 10.1155/2020/5281795]

34 **Yan W**, Ma X, Zhao X, Zhang S. Baicalein induces apoptosis and autophagy of breast cancer cells *via* inhibiting PI3K/AKT pathway *in vivo* and *vitro*. *Drug Des Devel Ther* 2018; **12**: 3961-3972 [PMID: 30510404 DOI: 10.2147/DDDT.S181939]

35 **Gong G**, Shen YL, Lan HY, Jin JM, An P, Zhang LJ, Chen LL, Peng W, Luan X, Zhang H. The Cyr61 Is a Potential Target for Rotundifuran, a Natural Labdane-Type Diterpene from *Vitex trifolia* L., to Trigger Apoptosis of Cervical Cancer Cells. *Oxid Med Cell Longev* 2021; **2021**: 6677687 [PMID: 34234887 DOI: 10.1155/2021/6677687]

36 **Shao L**, Dong C, Geng D, He Q, Shi Y. Ginkgolide B protects against cognitive impairment in senescence-accelerated P8 mice by mitigating oxidative stress, inflammation and ferroptosis. *Biochem Biophys Res Commun* 2021; **572**: 7-14 [PMID: 34332327 DOI: 10.1016/j.bbrc.2021.07.081]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 425-449

DOI: 10.5498/wjp.v12.i3.425

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Clinical high-risk criteria of psychosis in 8–17-year-old community subjects and inpatients not suspected of developing psychosis

Frauke Schultze-Lutter, Petra Walger, Maurizia Franscini, Nina Traber-Walker, Naweed Osman, Helene Walger, Benno G Schimmelmann, Rahel Flückiger, Chantal Michel

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Seeman MV

Received: April 14, 2021
Peer-review started: April 14, 2021
First decision: July 14, 2021
Revised: July 26, 2021
Accepted: September 19, 2021
Article in press: September 19, 2021
Published online: March 19, 2022

Frauke Schultze-Lutter, Petra Walger, Naweed Osman, Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Düsseldorf 40629, North-Rhine Westphalia, Germany

Frauke Schultze-Lutter, Department of Psychology, Faculty of Psychology, Airlangga University, Surabaya 60286, Indonesia

Frauke Schultze-Lutter, Benno G Schimmelmann, Rahel Flückiger, Chantal Michel, University Hospital of Child and Adolescent Psychiatry and Psychotherapy, University of Bern, Bern 3000, Switzerland

Maurizia Franscini, Nina Traber-Walker, Department of Child and Adolescent Psychiatry and Psychotherapy, University of Zürich, Zürich 8032, Germany

Helene Walger, Department of Psychiatry and Psychotherapy, Ludwig-Maximilian-University, Munich 80336, Bavaria, Germany

Benno G Schimmelmann, University Hospital of Child and Adolescent Psychiatry, University Hospital Hamburg-Eppendorf, Hamburg 20246, Germany

Corresponding author: Frauke Schultze-Lutter, MSc, PhD, Assistant Professor, Department of Psychiatry and Psychotherapy, Medical Faculty, Heinrich-Heine University, Bergische Landstraße 2, Düsseldorf 40629, North-Rhine Westphalia, Germany. frauke.schultze-lutter@lvr.de

Abstract

BACKGROUND

In children and adolescents compared to adults, clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and less clinically relevant. Based on high rates of non-converters to psychosis, especially in children and adolescents, it was suggested that CHR criteria were: (1) Pluripotential; (2) A transdiagnostic risk factor; and (3) Simply a severity marker of mental disorders rather than specifically psychosis-predictive. If any of these three alternative explanatory models were true, their prevalence should differ between persons with and without mental disorders, and their severity should be associated with functional impairment as a measure of severity.

AIM

To compare the prevalence and severity of CHR criteria/symptoms in children and adolescents of the community and inpatients.

METHODS

In the mainly cross-sectional examinations, 8–17-year-old community subjects (n = 233) randomly chosen from the population register of the Swiss Canton Bern, and inpatients (n = 306) with primary diagnosis of attention-deficit/hyperactivity disorder (n = 86), eating disorder (n = 97), anxiety including obsessive–compulsive disorder (n = 94), or autism spectrum disorder (n = 29), not clinically suspected to develop psychosis, were examined for CHR symptoms/criteria. Positive items of the Structured Interview for Psychosis-Risk Syndromes (SIPS) were used to assess the symptomatic ultra-high-risk criteria, and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY) was used to assess the 14 basic symptoms relevant to basic symptom criteria. We examined group differences in frequency and severity of CHR symptoms/criteria using χ^2 tests and nonparametric tests with Cramer's V and Rosenthal's r as effect sizes, and their association with functioning using correlation analyses.

RESULTS

The 7.3% prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5% rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups, while the frequency and severity of CHR symptoms differed only minimally. Group differences were found in only four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS [χ^2 (4) = 9.425; P = 0.051, Cramer's V = 0.132; and Z = -4.281, P < 0.001; Rosenthal's r = 0.184], and *thought pressure* [χ^2 (4) = 11.019; P = 0.026, Cramer's V = 0.143; and Z = -2.639, P = 0.008; Rosenthal's r = 0.114], *derealization* [χ^2 (4) = 32.380; P < 0.001, Cramer's V = 0.245; and Z = -3.924, P < 0.001; Rosenthal's r = 0.169] and *visual perception disturbances* [χ^2 (4) = 10.652; P = 0.031, Cramer's V = 0.141; and Z = -2.822, P = 0.005; Rosenthal's r = 0.122] of the SPI-CY. These were consistent with a transdiagnostic risk factor or dimension, *i.e.*, displayed higher frequency and severity in inpatients, in particular in those with eating, anxiety/obsessive–compulsive and autism spectrum disorders. Low functioning, however, was at most weakly related to the severity of CHR criteria/symptoms, with the highest correlation yielded for *suspiciousness/persecutory ideas* (Kendall's tau = -0.172, P < 0.001).

CONCLUSION

The lack of systematic differences between inpatients and community subjects does not support suggestions that CHR criteria/symptoms are pluripotential or transdiagnostic syndromes, or merely markers of symptom severity.

Key Words: Psychotic disorders; Risk assessment; Minors; Community; Inpatients; Psychosocial functioning

Core tip: Clinical high-risk of psychosis (CHR) criteria and symptoms are more prevalent but less psychosis-predictive and clinically relevant in minors compared to adults, and, therefore, alternatively proposed as pluripotential, transdiagnostic risk factors, or severity markers of mental disorders. If any of these explanatory models were true, their prevalence should differ between 8–17-year-old community subjects (n = 233) and inpatients (n = 306), included in our study, and their severity should be associated with psychosocial functioning. Yet, CHR criteria and symptoms hardly differed between groups and were at most weakly associated with functioning. Consequently, our study did not support any alternative explanatory model of CHR criteria.

Citation: Schultze-Lutter F, Walger P, Franscini M, Traber-Walker N, Osman N, Walger H, Schimmelmann BG, Flückiger R, Michel C. Clinical high-risk criteria of psychosis in 8–17-year-old community subjects and inpatients not suspected of developing psychosis. *World J Psychiatry* 2022; 12(3): 425-449

URL: https://www.wjgnet.com/2220-3206/full/v12/i3/425.htm

DOI: https://dx.doi.org/10.5498/wjp.v12.i3.425

INTRODUCTION

Delays in treatment of beginning or first psychosis in children and adolescents

Psychotic disorders are severe mental disorders with often chronic course that incur high costs and burden to both society and affected patients[1-4]. Since the 1980s, multiple retrospective studies reported an association of a negative outcome of first-episode psychosis with a longer duration of untreated – or rather, inadequately treated – first-episode psychosis, as well as with untreated illness, *i.e.*, the untreated duration of both the initial prodrome and first-episode psychosis[5-8]. These negative effects of the duration of untreated psychosis or of untreated illness also occurred when patients had sought professional help for mental problems early but were not recognized as suffering from psychotic symptoms or a developing psychotic disorder[9]. Consequently, patients were treated for other, apparently more predominant complaints, frequently depressive or anxiety disorders[9]. Such delays in providing adequate treatment were further prolonged when the psychosis and/or the prodrome had an early onset in childhood and adolescence, that is, before age of 18 years[5,10,11]. This possibly explains the assumed inherent more negative course of early-onset compared to adult-onset psychoses[11]. Potential explanations of the longer duration of untreated psychosis and of untreated illness in children and adolescents with a psychotic disorder include the masking of the emergence of a psychotic disorder by other comorbid conditions such as substance abuse, depressive and anxiety syndromes, and a higher risk to overlook positive symptoms – especially if parents and primary care providers assume that the adolescents' symptoms are the expression of a sort of adolescent crisis[11-13]. Additionally, insufficient awareness and training of the general and mental health network (pediatricians, general physicians, school psychologists, and child and adolescent psychiatrists) might result in failures to adequately and routinely assess psychotic symptomatology in adolescents[12]. Finally, the greater frequency of insidious-onset illness trajectories[10-12] may further impede a timely detection. Thus, it was concluded that children and adolescents with developing, or already manifest, psychotic disorders would require specific early detection strategies to reduce duration of untreated psychosis and of untreated illness, in order to improve long-term outcomes[12,13].

Early detection of psychosis – the clinical high-risk approach

Based on findings regarding the negative effects of extended duration of untreated psychosis and of untreated illness, and the need to specifically intervene earlier in the course of illness, clinical high-risk for psychosis (CHR) criteria were gradually developed and initially validated in adult patient samples within the 1990s[14-17].

The two dominant current CHR approaches are the ultra-high-risk (UHR) approach developed to detect psychosis in the year before the onset of the first episode[16,17] and the basic symptom approach developed to detect signs of emerging psychosis as early as possible[14,15,18]. The UHR approach (Table 1) consists of three criteria, of which only the attenuated psychotic symptoms (APS) syndrome and the brief intermittent psychotic symptoms (BIPS) syndrome demonstrated sufficient psychosis-predictive validity in meta-analyses[19,20]. The third criterion, combining genetic risk and functional deterioration, was not uniquely related to an elevated psychosis risk[19,20].

The basic symptom approach (Table 1) consists of two partly symptomatically overlapping criteria: Cognitive Disturbances (COGDIS) and Cognitive–Perceptive Basic Symptoms (COPER), of which COPER thus far did not demonstrate sufficient evidence in terms of sufficient number of studies[19].

Consequently, within the framework of the Guidance Project of the European Psychiatric Association (EPA), the APS and BIPS syndromes of the UHR approach and COGDIS of the basic symptom approach (henceforth: EPA criteria) were recommended for alternative use in the early detection of psychosis in the clinic[19]. While both the UHR and the basic symptom approach – irrespective of each other – performed equally well in predicting conversion to psychosis within 6 months to 2 years, at which time they were associated with a conversion rate of 20%–30%, the basic symptom criteria were associated with significantly higher conversion rates at longer observation times compared to the UHR criteria[19].

In clinical samples, however, CHR criteria were associated with a significantly lower risk of conversion to psychosis in children and adolescents compared to adults[19,21]. Furthermore, in the community, children and adolescents reported CHR symptoms and criteria more frequently compared to adults[22,23]. These findings suggested that APS and BIPS may be less clinically relevant below the age threshold of 16 years, while perceptual and cognitive basic symptoms may be less clinically relevant below the age threshold of 18 and 23 years, respectively [22,23].

Taken together, these findings emphasize a need to account for developmental aspects in the early detection of psychosis[12,13] and to improve the specificity of the CHR approach by adding other predictors, for example, in a stepwise manner[24].

Alternative explanatory models of clinical high-risk states

In light of the moderate conversion rates and an undisputed need for further improvement of CHR criteria as well as the reported various nonpsychotic outcomes of CHR patients[25,26], it was also argued that CHR criteria, in particular the APS and BIPS syndromes, would not be specific to the development of psychosis[27-30]. Rather, it was argued that these would represent a pluripotent

Table 1 Clinical high-risk criteria: (1) Ultra-high risk criteria in the definition of the criteria of psychosis-risk syndromes of the structured interview for Psychosis-Risk Syndromes, Structured Interview for Psychosis-Risk Syndromes[43] and (2) the basic symptom criteria in the definition of the Schizophrenia Proneness Instrument, Child and Youth version[44]

(1) Ultra-high risk criteria
Brief intermittent psychotic symptom (BIPS) syndrome
At least 1 of the following SIPS positive items scored 6 "severe and psychotic"
P1 Unusual thought content/delusional ideas
P2 Suspiciousness/persecutory ideas
P3 Grandiose ideas
P4 Perceptual abnormalities/hallucinations
P5 Disorganized communication
Symptoms reached a psychotic level of intensity in the past 3 mo
Present for at least several minutes per day at a frequency of at least once per month but less than required for rating of a conversion to psychosis, *i.e.*, less than at least 1 h per day at an average frequency of 4 d/wk over 1 mo
Attenuated positive symptom (APS) syndrome
At least 1 of the 5 SIPS positive items (see above) scored 3 "moderate" to 5 "severe but not psychotic"
Symptoms have begun within the past year or currently rate one or more scale points higher compared to 12 mo ago
Symptoms have occurred at an average frequency of at least once per week in the past month
Genetic risk and functional deterioration syndrome
Patient meets criteria for schizotypal personality disorder according to SIPS
Patient has first-degree relative with a psychotic disorder
Patient has experienced at least 30% drop in the Global Assessment of Functioning score over the last month compared to 12 mo ago
[1 and 3] or [2 and 3] or all are met
(2) Basic symptom criteria
A general requirement for basic symptoms is that they deviate from what is considered the 'normal' self and, thus, have not always been present in the same severity
Cognitive–perceptive basic symptoms (COPER)
At least 1 of the following basic symptoms scored 3 "weekly occurrences" to 6 "daily occurrences" within the past 3 mo: thought interference; thought perseveration; thought pressure; thought blockages[1]; disturbance of receptive speech; decreased ability to discriminate between ideas and perception, fantasy and true memories; unstable ideas of reference; derealization; visual perception disturbances (excl. hypersensitivity to light or blurred vision); acoustic perception disturbances (excl. hypersensitivity to sounds); first occurrence ≥ 12 mo ago
Cognitive disturbances (COGDIS)
At least 2 of the following basic symptoms scored 3 "weekly occurrences" to 6 "daily occurrences" within the past 3 mo: inability to divide attention; thought interference; thought pressure; thought blockages[1]; disturbance of receptive speech; disturbance of expressive speech; unstable ideas of reference; disturbances of abstract thinking[1]; captivation of attention by details of the visual field

[1]Assessable only from age of 13 yr onwards.

syndrome[27,28], a transdiagnostic risk factor[29], a transdiagnostic dimension of psychopathology[30], or merely a marker for the severity of nonpsychotic states[30]. Despite them frequently being used in synonym[29], pluripotential and transdiagnostic relate to different concepts.

Being derived from biology and initially applied to (embryonic) cells, pluripotent is defined as "not fixed as to potential development", and used to describe precursor cells that are only found in early embryonic states[31]. Thus, translated to psychiatric disorders, a pluripotential syndrome would be the first diagnostically neutral stage of potentially more severe psychopathology, which only later would acquire a degree of diagnostic specificity[27,28]. In this case, similar to embryonic pluripotent cells, a CHR state would completely transform into another disorder in that it would not be recognizable anymore. Examples are APS that will not be detectable once they have been transformed into frank psychotic symptoms, *i.e.*, after the conversion to psychosis.

In contrast, transdiagnostic risk factors would be distributed across the community and would be present in various disorders, in which they would still be assessable, and mediate the association between environmental exposures and disorders[32]. Similarly, a transdiagnostic dimension of psychopathology may be present in various disorders but not at all or only in very mild subclinical forms in the

community outside states of mental ill health. In these cases, CHR symptoms would develop in the wake of other mental problems.

Lastly, a severity marker of psychopathology would be generally present in mental disorders, in which it would be most pronounced or frequent in those with severe mental disorders and/or most functional impairment due to their mental problems. Furthermore, it would be more frequent in acute states of illness compared to (partly) remitted states. In this case, CHR symptoms and criteria should be increasingly present with declining functioning.

Mental problems in childhood and adolescence often lack continuity into adulthood[33] and specificity for mental disorders[34], and frequently present as insidious onset of disorders, initially with mild forms of mental problems[12,35]. Consequently, children and adolescents represent an excellent age group to study the nature of symptoms and syndromes, such as CHR symptoms and criteria[36], and in particular, to study which of the three alternative models best fits the data.

Study aims

The aim of this study was to examine which of these alternative explanatory models of CHR criteria and symptoms – pluripotential syndrome, transdiagnostic risk factor/dimension, and severity marker – best fits the data of an age group in which CHR criteria and symptoms are likely the least psychosis-specific [19,21]. To that end, we cross-sectionally studied the frequency of CHR criteria and symptoms in an 8–17-year-old randomly recruited sample of the Swiss community and in 8–17-year-old inpatients whose main diagnosis was a disorder that, earlier, had been longitudinally associated with an elevated risk to develop psychosis in adulthood[36,37] (Supplementary Table 1). The three alternative explanatory models were associated with in the following differential premises: (1) In the case of the CHR criteria and symptoms acting as a pluripotential syndrome, these should not be detectable after the onset of severe mental disorder, *i.e.*, after their transformation in a diagnostically specific disorder in the inpatient group. Rather, CHR criteria and symptoms should still be detectable as a potential precursor state in the community subjects of that roughly a third must be expected to develop a mental disorder in their lifetime[39]. Consequently, if CHR criteria and symptoms would be more frequent in community subjects compared to inpatients, then they are likely pluripotential; (2) In the case of CHR criteria and symptoms representing a transdiagnostic risk factor or dimension, they would be expected to accumulate in the extreme range of persons with mental disorders. Thus, if CHR criteria and symptoms would be more frequent in the inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension; and (3) Lastly, in the case of CHR criteria and symptoms being a severity marker of psychopathology, they should be associated with illness severity and, relatedly, the degree of functional impairment. Consequently, if CHR criteria and symptoms would show a significant negative correlation with functioning, then they likely represent a severity marker of psychopathology.

MATERIALS AND METHODS

Sample description

We recruited the samples as part of the multicenter naturalistic 'Bi-national Evaluation of At-Risk Symptoms in children and adolescents' (BEARS-Kid) study between September 2013 and December 2017. Recruitment of inpatients took place at the Child and Adolescent Psychiatric Departments of the Universities of Bern, Switzerland, Zurich, Switzerland, and Cologne, Germany; recruitment of community subjects was exclusively carried out in Bern. General inclusion criteria were: age between 8.0 and 17.9 years, and sufficient language skills in German or English. General exclusion criteria were: past or present diagnosis of a psychotic disorder; current antipsychotic medication; a clinical indication of an IQ ≤ 70; presence of disturbance due to the direct physiological effects of a general medical condition or of substance use; and clinical suspicion of an emerging psychosis and, consequently, consultation of the local early detection service. Because co-occurrence of mental disorders is rather the rule than the exception in patients with mental disorders, in clinical as well as in community samples [40,41], we did not use (co-) morbidities with mental disorders as an exclusion criterion in either the inpatient and community sample in order not to limit representativeness.

For the recruitment of a representative community sample, the Agency for Informatics and Organization of the Canton Bern randomly drew a sample (including addresses) stratified for age and sex from the population register of the city of Bern and its urban hinterland (approximately 200 000 residents). Subsequently, we searched directories and the Internet for telephone numbers. The availability of a working telephone number served as an eligibility criterion in this group. We established first contact by an information letter, personally addressing each potential participant and his/her parents. Next, we contacted parents and/or their children by telephone, informed them in detail, and asked them to give written informed consent and assent. In children below age 16.0 years, we contacted parents first. Nine hundred and eighty persons were drawn from the register, for 176 of them, we could not ascertain a working telephone number, and 41 persons were drawn twice. Of the remaining 763 persons, 234 agreed to participate, yet one person later on withdrew consent. A total of 353 did not agree to participate, mainly for lack of interest (35.6%) or time (35.9%). We excluded 52

persons because they had reached 18 years old by the time contact was made (53.9%), had moved away from the greater Bern area (32.7%), or lacked the ability to participate in the study for language or physical health reasons (13.5%). With 124 persons, all attempts (at least 40) to reach them on the telephone remained fruitless. Thus, according to the standard definitions of the American Association for Public Opinion Research[42], the contact rate was 82.7%, the cooperation rate was 39.9%, the refusal rate was 49.2%, and the response rate was 32.6%.

The inpatient sample was recruited in all three participating centers during their inpatient stay or during their subsequent day clinic stay; seven inpatients (2.3%) had been strongly advised to undergo inpatient treatment but had refused. For inclusion, the main diagnosis according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders, DMS-IV[38] had to be one for which Rubino *et al* [37] had reported at least a 2.5 times increased prevalence of subsequent schizophrenia (Supplementary Table S1): attention deficit hyperactivity disorder (ADHD) (inattentive, hyperactive and impulsive subtype); anxiety disorders (social and severe specific phobia, mainly school phobia); obsessive–compulsive disorder; and eating disorder (anorexia and bulimia nervosa). Additionally, we included patients with Asperger's syndrome, which had not been considered by Rubino *et al*[37] but has been recognized explicitly as a developmental disorder with an increased risk of psychotic episodes in young adulthood in DSM-IV[38]. We recruited 539 inpatients, 97 with eating disorders, 86 with ADHD, 94 with anxiety and obsessive–compulsive disorders, and 29 with Asperger's syndrome.

We followed up 423 subjects (78.5%) after 1 year; 243 inpatients, 23 (9.5%) with a CHR criterion at baseline; and 180 community subjects, 15 (8.3%) with a CHR criterion at baseline. A total of 331 subjects (61.4%) participated in the 2-year follow-up; 189 inpatients, 16 (8.5%) with a CHR criterion at baseline, and 142 community subjects, 10 (7.0%) with a CHR criterion at baseline.

Clinical high-risk assessments

We used well-established semistructured interview assessments to assess CHR criteria and symptoms, which had demonstrated good inter-rater reliability in trained raters[43-45]. The Structured Interview for Psychosis-Risk Syndromes (SIPS)[43], including a revised version of the Global Assessment of Functioning scale, was carried out for the evaluation of the five APS and BIPS (Table 1) as well as the genetic risk and functional decline criterion of the UHR criteria in the SIPS definition of the Criteria of Psychosis-Risk Syndromes (COPS) (Table 1). The five criteria-relevant positive items of the SIPS are syndromally rated for psychopathological severity on a seven-point Likert scale, ranging from 0 (not present) to 6 (severe and psychotic). In doing so, APS are defined by any SIPS positive item with a score between 3 and 5, and BIPS by any SIPS positive item with a score of 6. We rated a SIPS-positive item as present when its score was 3–6. We calculated the sum score of the five positive items across all scores (0–6) as a severity estimate of symptomatic UHR criteria.

We used the Schizophrenia Proneness Instrument, Child and Youth version, SPI-CY[44,45] for the evaluation of the 14 basic symptoms included in COPER and COGDIS (Table 2). Basic symptoms were rated for their severity according to their frequency of occurrence on a seven-point Likert scale, ranging from 0 (not present) to 6 (present daily). We rated basic symptoms as present when their score was 1–6. We calculated the sum scores of the nine basic symptoms included in COGDIS and of the 10 basic symptoms included in COPER as a severity estimate of COGDIS and COPER, respectively.

Basic symptoms included in COPER and COGDIS differ from APS/BIPS as defined by a score of 3 on the SIPS-positive items by the more immediate insight into basic symptoms that results from the lack of externalization or of their consideration of possibly being meaningful, and from the immediate control of these[14,15,44,45]. Thus, other than in attenuated hallucinations or illusions (SIPS positive item P4), which are at least briefly perceived as true perceptions of existence, real stimuli [43], in perceptual basic symptoms, the misperceived real object or sound is not considered as a true change of the stimulus for even a split-second[44]. Rather, the insight into the pathological nature of the misperceptions of features of a real object or sound is immediate and complete, and thus, contrary to APS, perceptual basic symptoms are not puzzling to the degree that they are considered to indicate a meaningful change in the surroundings[43], apart from a change in one's own mental processes[44]. With this, perceptual basic symptoms rate 1–2 in the SIPS positive item P4, *i.e.*, as sensitivity or perceptual changes that are noticed but not considered to be significant in terms of what is going on in the world[43]. Furthermore, cognitive basic symptoms are not related to thought content and, consequently, are not rated as any unusual thought content or attenuated delusional idea on SIPS positive items P1–P3. Additionally, for their immediate recognition as unusual, commonly brief disruptions in normal thought processing[44], cognitive basic symptoms rarely impair the individual's own way of structuring and verbally presenting thoughts in terms of *conceptual disorganization* (SIPS positive item P5), *i.e.*, by talking about irrelevant topics or going off track to a degree that is unusual to the individual[43]. Moreover, the basic symptoms *derealization* and *unstable idea of reference* are only "as if" feelings with full reality testing and no (temporary) consideration as realistic ideas or of meaningfulness[44]; thus, they differ from attenuated nihilistic ideas or attenuated ideas of reference that are scored at APS-level in the SIPS positive item P1 – or in P2, if the idea of reference has a paranoid touch[43]. Finally, *impaired discrimination between ideas and perception* in terms of basic symptoms always occurs with real stimuli or memories of real events that are briefly considered as possible phantasies[44]; thus, it does not even briefly introduce unusual ideas as required for an attenuated delusion[43] and, for this reason, also rates

Table 2 Sociodemographic and clinical characteristics of the sample (*n* = 539)

	Inpatients (*n* = 306)	Community subjects (*n* = 233)	Statistics; effect size
Age: mean ± SD (Median)	14.4 ± 2.5 (14.9)	13.0 ± 2.9 (12.9)	U = 26032.5, $^{c}P < 0.001$: $r = 0.231$
Sex: *n* (%) male	133 (43.5)	102 (43.8)	$\chi^2_{(1)} = 0.013$, $P = 0.908$; V = 0.005
Migration background[1]: *n* (%)	52 (17.0)	64 (27.5)	$\chi^2_{(1)} = 8.593$, $^{b}P = 0.003$; V = 0.126
Graduated from school: *n* (%)	28 (9.2)	15 (6.4)	$\chi^2_{(1)} = 1.326$, $P = 0.250$; V = 0.050
Current school class (*n* = 491): mean ± SD	7.5 ± 2.5 (8)	6.2 ± 2.6 (6)	U = 20894.5, $^{c}P < 0.001$; $r = 0.253$
Family history of psychotic disorder: *n* (%)	4 (1.3)	1 (0.4)	$\chi^2_{(1)} = 1.105$, $P_{exact} = 0.396$, V = 0.045
Any lifetime nonpsychotic axis-I disorder[2]: *n* (%)	306 (100)	22 (9.4)	$\chi^2_{(1)} = 455.368$, $^{c}P < 0.001$; V = 0.919
Any present nonpsychotic axis-I disorder[2]: *n* (%)	306 (100)	13 (5.6)	$\chi^2_{(1)} = 488.187$, $^{c}P < 0.001$; V = 0.952
Number present axis-I disorders[2]: mean ± SD (Median)	1.5 ± 0.7 (1)	0.1 ± 0.3 (0)	U = 1499.5, $^{c}P < 0.001$; $r = 0.883$
Any present depressive disorder: *n* (%)	55 (18.0)	0	$\chi^2_{(1)} = 46.638$, $^{c}P < 0.001$; V = 0.294
Any present manic episode[3]: *n* (%)	0	1 (0.4)	$\chi^2_{(1)} = 1.316$, $P = 0.251$; V = 0.049
Any present anxiety disorder[2]: *n* (%)	68 (22.2)	2 (0.9)	$\chi^2_{(1)} = 53.426$, $^{c}P < 0.001$; V = 0.315
Any present obsessive–compulsive disorder: *n* (%)	35 (11.4)	1 (0.4)	$\chi^2_{(1)} = 25.720$, $^{c}P < 0.001$; V = 0.218
Any present adjustment disorder: *n* (%)	3 (1.0)	0	$\chi^2_{(1)} = 2.297$, $P = 0.262$; V = 0.065
Any present eating disorder: *n* (%)	98 (32.0)	0	$\chi^2_{(1)} = 91.203$, $^{c}P < 0.001$; V = 0.411
Any present somatoform disorder: *n* (%)	4 (1.3)	0	$\chi^2_{(1)} = 3.069$, $P = 0.137$; V = 0.075
Any present substance use disorder: *n* (%)	4 (1.3)	2 (0.9)	$\chi^2_{(1)} = 0.242$, $P = 0.623$; V = 0.021
Any present tic disorder: *n* (%)	9 (2.9)	0	$\chi^2_{(1)} = 6.969$, $^{b}P = 0.008$; V = 0.114
Any present attention deficit hyperactivity disorder: *n* (%)	103 (33.7)	7 (3.0)	$\chi^2_{(1)} = 76.532$, $^{c}P < 0.001$; V = 0.377
Any present conduct disorder: *n* (%)	18 (5.9)	2 (0.9)	$\chi^2_{(1)} = 9.345$, $^{b}P = 0.002$; V = 0.132
Any present developmental disorder: *n* (%)	31 (10.1)	0	$\chi^2_{(1)} = 25.045$, $^{c}P < 0.001$; V = 0.216
Global Assessment of Functioning score (0-100): mean ± SD (Median)	52.3 ± 8.8 (53)	81.0 ± 10.0 (85)	U = 1516.0, $^{c}P < 0.001$; $r = 0.819$
SOFAS (0-100): mean ± SD (Median)	60.0 ± 11.0 (60)	84.3 ± 7.9 (88)	U = 3001.5, $^{c}P < 0.001$; $r = 0.786$

[1]defined by first or second nationality other than the country of residence;
[2]does not include simple specific phobias of objects with little functional relevance but includes severe specific phobias such as school phobia;
[3]no participant met criteria of a bipolar disorder at baseline. SOFAS: Social and Occupational Functioning Assessment Scale[42]. V: Cramer's V; *r*: Rosenthal's *r*: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

at most 2 on the SIPS positive item P1.

Assessments of mental disorders and functioning

We used the Mini-International Neuropsychiatric Interview for Children and Adolescents, M.I.N.I. KID [46] for the assessment of past and present mental disorders according to the DSM-IV, including past and present affective or nonaffective psychotic disorders that served as exclusion criterion. The M.I.N.I. KID had demonstrated good construct validity with other interview assessments of DSM-IV disorders and expert diagnoses as well as good inter-rater and test–retest reliability[46].

We estimated symptom-independent current and highest-within-last-12-mo global levels of psychosocial functioning using the Social and Occupational Functioning Assessment Scale (SOFAS) of DSM-IV[38]. We used SOFAS scores to define functioning in the analyses of the correlation between severity of mental disorders and CHR symptoms and criteria.

Assessment procedure and quality assurance

We conducted the baseline assessments of inpatients in the clinic, and community participants could choose between being assessed in the clinic or at their homes, mostly choosing the latter. Thus, we could not blind raters to the group assignment. Therefore, in order to avoid systematic assessment bias due to this nonblinding of groups, interviewers were restricted to the assessment of either the inpatient or the community sample. Interviewers were clinical psychologists who had received an intensive training for about 3 months, especially in the semistructured context-dependent personalized assessment of CHR symptoms and mental disorders, in order to achieve a ≥ 95% concordance rate with the trainers (in all instances the first or the last author). Only when an interviewer had achieved this level of agreement with the experts, they were allowed to conduct interviews independently. We had chosen the concordance rate over Cohen's kappa, because kappa is dependent on the prevalence of an event[47] and tends to decrease when a response/event is rare or very frequent. Thus, because low prevalence rates were expected for the community sample in particular, we chose the concordance rate to define the minimum inter-rater reliability[48,49]. In the training, we paid close attention not only to the validity and reliability of positive ratings but also to those of negative ratings, *i.e.*, to not jump to a negative rating at the first negation of a symptom. Weekly supervision of symptom ratings performed by the first or last author further ensured excellent, valid and reliable data quality across centers.

At 1- and 2-year follow-ups, we interviewed participants for CHR symptoms and criteria as well as conversion to psychosis using the SPI-CY, SIPS and psychoses section of the M.I.N.I. KID. Potential conversions were also discussed in the weekly supervisions.

Data analysis

We used SPSS version 24 for all analyses that the first and last author, both trained in biostatistics, conducted. We compared frequency rates of CHR symptoms and criteria between groups by χ^2 test or Fisher's exact tests in case of expected cell frequencies below $n = 5$ in 2 × 2 tables. Standardized residuals were used to detect significantly deviating cell frequencies of standardized residuals ≥ |1.96|; the effect size was calculated using Cramer's V.

We compared the severity of the ordinal CHR symptoms and criteria as well as the ordinal level of functioning as assessed with the SOFAS, which were all non-normally distributed (Kolmogorov–Smirnov test: all $P < 0.001$), between groups using Kruskal–Wallis with post-hoc Mann–Whitney *U* tests; the effect size of the Mann–Whitney *U* tests was calculated using Rosenthal's r.

We analyzed the correlations between severity of CHR symptoms and criteria, and functioning using Kendall's tau, which controls for tied pairs, and, additionally, using partial correlation analyses with group as the control variable.

To not decrease the sensitivity to detect group differences and, thus, to support one of the alternative explanatory models of the CHR state, we did not adjust for multiple testing. Although such an adjustment of the alpha level would have greatly reduced the type I error, *i.e.*, the false rejection of a true null hypothesis, the detection of meaningful small to moderate group differences would have become unlikely[50]. Thus, in light of this, the nonadjustment of alpha was regarded as a more conservative testing of the alternative models. Additionally, testing for group differences in CHR criteria and symptoms independently (weak testing criterion[50]), the power of the study, the ability to correctly reject a false null hypothesis assuming group equality, can be assumed to be independent of the multiple testing[50]. At a given alpha of 0.05, a sample size of $n = 539$ in two or five groups, and an assumed small to medium effect of 0.2, G*Power version 3.1. estimated the power of the different group comparisons of frequency or severity of CHR criteria and symptoms between 0.911 and 0.997.

RESULTS

Group characteristics

Inpatients and community subjects did not differ in distribution of sex, family history of psychotic disorder, or number of those already graduated from school (Table 2). However, inpatients were slightly older and, when still at school, attended a higher school class. Furthermore, we detected a small effect of migration background with higher frequency in the community sample. Unsurprisingly, we detected strong group effects for clinical variables, demonstrating that, compared to community subjects, inpatients suffered more frequently from mental disorders and had a lower level of functioning (Table 2).

Group differences in frequency of CHR symptoms and criteria

Neither inpatients nor community subjects reported any BIPS. Furthermore, the genetic risk and functional decline syndrome was rare and only occurred in two inpatients, without reaching a level of significance (Table 3). Also, we detected only at most weak and nonsignificant group effects with respect to all other single or combined CHR criteria, which, overall, were reported by < 10% of both samples (Table 3). In doing so, the most frequent CHR criterion was COPER (Table 3). We found similar

Table 3 Frequency of clinical high-risk criteria in the two groups (*n* = 539)

	Inpatients (*n* = 306)	Community subjects (*n* = 233)	χ^2 test; Cramer's V
BIPS syndrome: *n* (%)	0	0	--
APS syndrome: *n* (%)	7 (2.3)	5 (2.1)	$\chi^2_{(1)} = 0.012$; $P = 0.912$, V = 0.005
Genetic risk and functional decline syndrome: *n* (%)	2 (0.6)	0	$\chi^2_{(1)} = 1.529$; $P_{exact} = 0.508$, V = 0.053
COGDIS: *n* (%)	10 (3.3)	4 (1.7)	$\chi^2_{(1)} = 1.258$; $P = 0.262$, V = 0.048
COPER: *n* (%)	21 (6.9)	10 (4.3)	$\chi^2_{(1)} = 1.613$; $P = 0.204$, V = 0.055
Any 1 of 5 CHR criteria: *n* (%)	29 (9.5)	17 (7.3)	$\chi^2_{(1)} = 0.806$; $P = 0.369$, V = 0.039
Any 1 of 3 EPA criteria: *n* (%)	15 (4.9)	9 (3.9)	$\chi^2_{(1)} = 0.336$; $P = 0.562$, V = 0.025
No CHR criterion: *n* (%)	277 (90.5)	216 (92.7)	$\chi^2_{(7)} = 5.676$; $P = 0.578$, V = 0.103
Only genetic risk and functional decline: *n* (%)	2 (0.7)	0	
Only COPER: *n* (%)	12 (3.9)	8 (3.4)	
Only COGDIS: *n* (%)	2 (0.7)	2 (0.9)	
COPER and COGDIS: *n* (%)	6 (2.0)	2 (0.9)	
Only APS: *n* (%)	4 (1.3)	5 (2.1)	
APS and COPER: *n* (%)	1 (0.3)	0	
APS, COPER and COGDIS: *n* (%)	2 (0.7)	0	

BIPS: Brief intermittent psychotic symptoms; APS: Attenuated psychotic symptoms; COGDIS: Cognitive Disturbances; COPER: Cognitive–Perceptive Basic Symptoms; EPA: European Psychiatric Association. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

results when we compared frequencies of CHR criteria across the different inpatient groups and community subjects (Table 4); thus, these results did not indicate that CHR criteria were especially associated with any of the four diagnostic categories.

Between inpatients and community subjects, we detected differences of weak effect size with respect to CHR symptoms for only three basic symptoms, two of them only included in COPER (Supplementary Table 2): (1) *Pressure of thought* (8.5% in inpatients vs 3.0% in community subjects; Cramer's V = 0.113, yet, all standardized residuals < |1.96|); (2) *Derealization* (11.4% in inpatients *vs* 2.6% in community subjects; Cramer's V = 0.165, both standardized residuals of symptom present > |1.96|), and (3) *Visual perception disturbances* (11.4% in inpatients *vs* 4.7% in community subjects; Cramer's V = 0.119, standardized residuals of symptom present in community subjects > |1.96|).

When we considered the different diagnostic categories, we found some additional, yet unsystematic group differences - often only at single cell level in terms of a significant standardized residual (Tables 5 and 6). The strongest, near moderate group effect yielded for *derealization*, which showed an increased prevalence in eating disorders, and anxiety and obsessive-compulsive disorders, and a decreased prevalence in community subjects (Table 5). All other effect sizes of group comparisons with at least one significant standardized residual of any cell were only small (Tables 5 and 6). *Visual perception disturbances* were again significantly less frequent in community subjects (Table 5). *Thought pressure* and *impaired discrimination between ideas and true memories, and phantasy* were only more prevalent in anxiety and obsessive-compulsive disorders, *thought interference* and *captivation of attention* in Asperger's syndrome, and *unstable ideas of reference* in eating disorders (Table 5). With regard to APS, *unusual thought content / delusional ideas* (SIPS positive item P1) were most frequent in anxiety and obsessive-compulsive disorders (Table 6), which was mainly due to frequent report of *thought insertion* and *broadcasting* as well as *unusual, somatic* and *nihilistic ideas* at attenuated level. Furthermore, patients with Asperger's syndrome most frequently reported *suspiciousness/persecutory ideas* (SIPS positive item P2), mainly attenuated *ideas of being redlined* or *observed* (Table 6). Of all CHR symptoms, both inpatients and community subjects most frequently reported *perceptual abnormalities/hallucinations* (SIPS positive item P4) (Table 6).

Group differences in severity of CHR symptoms and criteria

The severity of CHR criteria and symptoms hardly differed between inpatients and community subjects (Table 7). Only the sum score of the ten basic symptoms of COPER, the single basic symptoms *thought pressure*, *derealization* and *visual perception disturbances* as well as the SIPS positive item *suspiciousness/persecutory ideas* (P2) were significantly more severe in inpatients (Table 7). Again, more indications of

Table 4 Frequency of clinical high-risk criteria in the four diagnostic subsamples and the community sample (*n* = 539)

	ED (*n* = 97)	ADHD (*n* = 86)	AnxD and OCD (*n* = 94)	ASS (*n* = 29)	Community subjects (*n* = 233)	χ^2 test; Cramer's V
APS syndrome: *n* (%)	4 (4.1)	0	3 (3.2)	0	5 (2.1)	$\chi^2_{(4)} = 4.632$; $P = 0.327$, V = 0.093
Genetic risk and functional decline syndrome: *n* (%)	0	1 (1.2)	1 (1.1)	0	0	$\chi^2_{(4)} = 4.016$; $P = 0.404$, V = 0.086
COGDIS: *n* (%)	4 (4.1)	2 (2.3)	4 (4.3)	0	4 (1.7)	$\chi^2_{(4)} = 3.427$; $P = 0.489$, V = 0.080
COPER: *n* (%)	9 (9.3)	3 (3.5)	8 (8.5)	1 (3.4)	10 (4.3)	$\chi^2_{(4)} = 5.558$; $P = 0.235$, V = 0.102
Any 1 of 5 CHR criteria: *n* (%)	11 (11.3)	5 (5.8)	12 (12.8)	1 (3.4)	17 (7.3)	$\chi^2_{(4)} = 5.369$; $P = 0.252$, V = 0.100
Any 1 of 3 EPA criteria: *n* (%)	7 (7.2)	2 (2.3)	6 (6.4)	0	9 (3.9)	$\chi^2_{(4)} = 5.022$; $P = 0.285$, V = 0.097
No CHR criterion: *n* (%)	86 (88.7)	81 (94.2)[1]	82 (87.2)	28 (96.6)	216 (92.7)	$\chi^2_{(28)} = 20.675$; $P = 0.839$, V = 0.098
Only genetic risk and functional decline: *n* (%)	0	1 (1.2)	1 (1.1)	0	0	
Only COPER: *n* (%)	4 (4.1)	2 (2.3)	5 (5.3)	1 (3.4)	8 (3.4) [1]	
Only COGDIS: *n* (%)	0	1 (1.2) [1]	1 (1.1)	0	2 (0.9)	
COPER and COGDIS: *n* (%)	3 (3.1)	1 (1.2)	2 (2.1)	0	2 (0.9)	
Only APS: *n* (%)	2 (2.1)	0	2 (2.1)	0	5 (2.1)	
APS and COPER: *n* (%)	1 (1.0)	0	0	0	0	
APS, COPER and COGDIS: *n* (%)	1 (1.0)	0	1 (1.1)[1]	0	0	

[1]Indicates that 1 subject of this category converted to psychosis within 2 years. No brief intermittent psychotic symptoms (BIPS) criteria met. ED: Eating disorder; ADHD: attention-deficit hyperactivity disorder; AnxD and OCD: anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome; APS: attenuated psychotic symptoms; COGDIS: Cognitive Disturbances; COPER: Cognitive-Perceptive Basic Symptoms: EPA: European Psychiatric Association; CHR: Clinical high-risk. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

group differences were globally indicated when diagnostic groups were analyzed separately in Kruskal–Wallis tests (Table 8). The sum scores of SIPS positive items and of the basic symptoms of COPER, the basic symptoms *captivation of attention by details of the visual field*, *thought pressure*, *derealization* and *visual perception disturbances* as well as the SIPS positive items *unusual thought content/delusional ideas* (P1) and *suspiciousness/persecutory ideas* (P2) significantly differed between groups (Table 8). Mann–Whitney tests of these variables (Supplementary Table 3) revealed that the severity of the basic symptoms of COPER was higher in eating disorders than in both ADHD and community subjects, higher in anxiety and obsessive–compulsive disorders than in ADHD and community subjects, and more pronounced in Asperger's syndrome compared to community subjects. The severity scores of the five SIPS positive items and of *unusual thought content/delusional ideas* (P1) were significantly higher in anxiety and obsessive-compulsive disorders compared to eating disorders, ADHD and community subjects. *Captivation of attention by details of the visual field* was significantly more pronounced in Asperger's syndrome compared to eating disorders, but less pronounced in Asperger's syndrome compared to ADHD; furthermore, it was more severe in anxiety and obsessive–compulsive disorders compared to community subjects. *Thought pressure* only differed between eating disorders and community subjects, with higher score in the former. Severity ratings of *derealization* were higher in eating disorders than in community subjects, and higher in anxiety and obsessive-compulsive disorders compared to both ADHD and community subjects. *Visual perception disturbances* scored higher in eating disorders, anxiety and obsessive–compulsive disorders, and Asperger's syndrome than in community subjects. Finally, ratings of *suspiciousness/persecutory ideas* (SIPS positive item P2) were higher in eating disorders than in community subjects, higher in anxiety and obsessive–compulsive disorders compared to community subjects as well as to ADHD, in which it was higher than in Asperger's syndrome; further, they were more severe in Asperger's syndrome compared to community subjects.

Table 5 Frequency of criteria-relevant basic symptoms in the four diagnostic subsamples and the community sample (*n* = 539)

	ED (*n* = 97)	ADHD (*n* = 86)	AnxD and OCD (*n* = 94)	ASS (*n* = 29)	Community subjects (*n* = 233)	χ^2 test; Cramer's V
Inability to divide attention: *n* (%)	1 (1.0)	0	2 (2.1)	0	0	$\chi^2_{(4)} = 6.534$; $P = 0.163$, V = 0.101
Captivation of attention: *n* (%)	0	0	1 (1.1)	**2 (6.9)**	4 (1.7)	$\chi^2_{(4)} = 9.855$; [a]$P = 0.043$, V = 0.135
Disturbance of abstract thinking[1]: *n* (%)	0	0	0	0	2 (1.3)	$\chi^2_{(4)} = 3.129$; $P = 0.536$, V = 0.088
Disturbance of expressive speech: *n* (%)	5 (5.2)	3 (3.5)	5 (5.3)	2 (6.9)	15 (5.6)	$\chi^2_{(4)} = 0.752$; $P = 0.945$, V = 0.037
Disturbance of receptive speech: *n* (%)	1 (1.0)	1 (1.2)	3 (3.2)	0	1 (0.4)	$\chi^2_{(4)} = 5.013$; $P = 0.286$, V = 0.096
Thought interference: *n* (%)	2 (2.0)	1 (1.2)	3 (3.2)	**3 (10.3)**	5 (2.1)	$\chi^2_{(4)} = 8.009$; $P = 0.091$, V = 0.122
Thought blockages[1]: *n* (%)	9 (10.0)	5 (11.1)	8 (9.2)	2 (9.1)	13 (8.3)	$\chi^2_{(4)} = 0.403$; $P = 0.982$, V = 0.032
Thought pressure: *n* (%)	8 (8.2)	4 (4.7)	**11 (11.7)**	3 (10.3)	7 (3.0)	$\chi^2_{(4)} = 11.019$; [a]$P = 0.026$, V = 0.143
Unstable ideas of reference: *n* (%)	**3 (3.1)**	0	1 (1.1)	0	1 (0.4)	$\chi^2_{(4)} = 6.673$; $P = 0.154$, V = 0.111
Thought perseveration: *n* (%)	0	2 (2.3)	3 (3.2)	1 (3.4)	3 (1.3)	$\chi^2_{(4)} = 3.964$; $P = 0.411$, V = 0.086
Impaired discrimination between true memories and phantasy: *n* (%)	1 (1.0)	1 (1.2)	**6 (6.4)**	0	7 (3.0)	$\chi^2_{(4)} = 7.310$; $P = 0.120$, V = 0.116
Derealization: *n* (%)	**17 (17.5)**	2 (2.3)	**14 (14.9)**	2 (6.9)	**6 (2.6)**	$\chi^2_{(4)} = 32.380$; [c]$P < 0.001$, V = 0.245
Visual perception disturbances: *n* (%)	13 (13.4)	7 (8.1)	10 (10.6)	5 (17.2)	**11 (4.7)**	$\chi^2_{(4)} = 10.652$; [a]$P = 0.031$, V = 0.141
Acoustic perception disturbances: *n* (%)	12 (12.4)	6 (7.1)	10 (10.6)	2 (6.9)	17 (7.3)	$\chi^2_{(4)} = 3.063$; $P = 0.547$, V = 0.075

[1]Assessable only from age of 13 years onwards, thus only calculated on *n* = 404. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome. In **bold**, cells with standardized residuals ≥ |1.96|. This equals significant deviation from the expected cell frequency. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

Association of functioning with CHR symptoms and criteria

In both bivariate and partial correlation analyses, correlations between functioning and severity of CHR criteria and symptoms were at most of small effect size.

In simple bivariate correlation analyses between functioning, *i.e.*, SOFAS scores, and severity of CHR criteria and symptoms, we detected few significant correlations of small effect size with the sum score of COPER (tau = -0.140, $P < 0.001$), the sum score of SIPS positive items (tau = -0.113, $P < 0.001$), the SIPS positive items *suspiciousness/persecutory ideas* (P2: tau = -0.172, $P < 0.001$), *perceptual abnormalities/hallucinations* (P4; tau = -0.112, $P = 0.001$), and *disorganized communication* (P5; tau = -0.076, $P = 0.034$) as well as the basic symptoms *thought pressure* (tau = -0.078, $P = 0.028$), *derealization* (tau = -0.116, $P = 0.001$), and visual (tau = -0.096, $P = 0.007$) and *acoustic perception disturbances* (tau = -0.073, $P = 0.040$). All of these four basic symptoms are part of COPER; only *thought pressure* is also part of COGDIS. For the severity of COGDIS and other CHR symptoms, the correlations with functioning were between tau = -0.065 ($P = 0.056$) for *thought interference* and tau = 0.018 ($P = 0.614$) for *disturbances of abstract thinking*.

When group was controlled for in partial correlation analyses, the correlations between functioning and the sum score of COPER ($r = -0.087$, $P = 0.044$), the sum score of SIPS positive items ($r = -0.164$, $P < 0.001$), the SIPS positive items *suspiciousness/persecutory ideas* (P2; $r = -0.120$, $P = 0.005$), *perceptual abnormalities/hallucinations* (P4; $r = -0.165$, $P < 0.001$), and *disorganized communication* (P5; $r = -0.126$, $P = 0.003$) remained, and in the case of SIPS items, became even slightly more pronounced. Contrary to this, none of the single basic symptoms with a significant correlation with functioning in bivariate analyses was again significant when group was controlled for. Rather, *thought inference* ($r = -0.102$, $P = 0.019$) and *disturbances of expressive speech* ($r = -0.094$, $P = 0.030$) became significant. The remaining correlations with functioning were between $r = -0.078$ ($P = 0.071$) for *acoustic perception disturbances* and $r = 0.019$ ($P =$

Table 6 Frequency of brief intermittent and attenuated psychotic symptoms in the four diagnostic subsamples and the community sample (*n* = 539)

	ED (*n* = 97)	ADHD (*n* = 86)	AnxD and OCD (*n* = 94)	ASS (*n* = 29)	Community subjects (*n* = 233)	χ^2 test; Cramer's V
P1: Unusual thought content/delusional ideas: *n*(%)	6 (6.2)	4 (4.7)	**14 (14.9)**[1]	4 (13.8)	13 (5.6)	$\chi^2_{(4)} = 11.391$; [a]$P = 0.023$, V = 0.145
P2: Suspiciousness/persecutory ideas: *n*(%)	2 (2.1)	1 (1.2)	4 (4.3)	**3 (10.3)**[2]	4 (1.7)	$\chi^2_{(4)} = 9.425$; $P = 0.051$, V = 0.132
P3: Grandiose ideas: *n*(%)	0	0	0	0	1 (0.4)	$\chi^2_{(4)} = 1.316$; $P = 0.859$, V = 0.049
P4: Perceptual abnormalities/hallucinations: *n*(%)	14 (14.2)	20 (23.3)	22 (23.4)	8 (27.6)	54 (23.2)	$\chi^2_{(4)} = 4.150$; $P = 0.368$, V = 0.088
P5: Disorganized communication: *n*(%)	0	0	0	0	1 (0.4)	$\chi^2_{(4)} = 1.316$; $P = 0.859$, V = 0.049

[1]most frequent in AnxD and OCD: thought insertion and broadcasting; unusual, somatic and nihilistic idea;
[2]most frequent in ASS: ideas of being redlined or observed (common rating). In **bold**, cells with standard residuals ≥ |1.96|. This equals a significant deviation (less or more) from the expected cell frequency. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: Anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome. V: Cramer's V: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

0.666) for *thought perseveration*.

Conversion to psychosis

Altogether, four had developed a psychosis within 2 years (*i.e.*, 0.7% of the whole sample and 1.2% of the 2-year follow-up sample). Only one of the converters had not met a CHR criterion at baseline (Table 4). Three conversions had occurred in the inpatient sample, including the one without CHR criteria at baseline, and one in the community subjects (Table 4), in a female without any mental disorder at baseline. Thus, with regard to the total baseline sample (n = 539), the 2-year conversion rate in subjects without CHR criteria was 0.2% and the 2-year conversion rate in subjects with CHR criteria was 6.5% ($\chi^2_{(1)} = 22.807$, Fisher's exact $P = 0.002$; Cramer's V = 0.206). With regard to the 2-year follow-up sample (n = 331), these numbers were 0.3% and 11.5% ($\chi^2_{(1)} = 25.220$, Fisher's exact $P = 0.002$; Cramer's V = 0.276).

DISCUSSION

In light of the relevant nonconversion rates in CHR samples, in particular in UHR samples[19,20], and their various outcomes[25,26], it has been suggested that CHR criteria might better be regarded as a pluripotent syndrome, or a transdiagnostic risk or severity marker[27-30]. If either of these were true, relevant and systematic differences in the frequency and severity of CHR criteria and symptoms between patients with severe mental illness requiring inpatient treatment and community subjects should be present. We examined this in two child and adolescent samples of the BEARS-Kid study with respect to both the UHR and the basic symptom approach.

We had chosen this age group because higher nonconversion rates compared to adult samples were reported for this group[19,21], and because CHR symptoms and criteria were shown to be more prevalent and less clinically relevant in children and adolescents[22,23,51-53]. Consequently, we expected that CHR symptoms and criteria would most likely show characteristics indicative of a pluripotent syndrome, of a transdiagnostic risk factor or of a severity marker in this age group.

Age and the CHR state

Both community and clinical studies on the effect of age on CHR symptoms and criteria indicated an age threshold around age of 16 years for APS and BIPS, with perceptual APS/BIPS being more prevalent below this age and all APS/BIPS being less clinically relevant[22,23,51,53]. For perceptual and cognitive basic symptoms, the age thresholds for prevalence and clinical significance were around age of 18 and 23 years, respectively[23,52]. Thus, all participants were at an age below the threshold suggested for basic symptoms, while the suggested age threshold for APS/BIPS was within the age range of our sample. Consequently, the observed group difference in age could have biased the overall older inpatient group towards reporting a lower number of APS/BIPS compared to the younger community sample; consequently, hiding relevant group effects. Therefore, were repeated the analyses of APS/BIPS in the age group below the suggested age threshold; *i.e.*, with 8- to 15-year-old (Supplementary Tables 4–6), which led to comparable results.

Table 7 Severity of clinical high-risk criteria and symptoms (mean SD, median) in inpatients and the community sample (*n* = 539)

	Inpatients (*n* = 306)	Community subjects (*n* = 233)	Mann–Whitney U; Rosenthal's r
Sum score of SIPS positive items	2.5 ± 2.5, 2	2.1 ± 2.3, 1	Z = -1.852, P = 0.064; r = 0.080
Sum score of 9 basic symptoms of COGDIS	0.8 ± 2.5, 0	0.4 ± 1.2, 0	Z = -1.125, P = 0.260, r = 0.048
Sum score of 10 basic symptoms of COPER	1.6 ± 3.6, 0	0.6 ± 1.7, 0	Z = -3.852, [c]P < 0.001; r = 0.166
P1: Unusual thought content / delusional ideas	0.9 ± 1.0, 1	0.8 ± 0.9, 1	Z = -1.341, P = 0.180; r = 0.058
P2: Suspiciousness / persecutory ideas	0.4 ± 0.8, 0	0.2 ± 0.6, 0	Z = -4.281, [c]P < 0.001; r = 0.184
P3: Grandiose ideas	0.1 ± 0.3, 0	0.1 ± 0.4, 0	Z = -0.426, P = 0.670; r = 0.018
P4: Perceptual abnormalities / hallucinations	1.0 ± 1.4, 0	1.0 ± 1.2, 0	Z = -1.119, P = 0.263; r = 0.048
P5: Disorganized communication	0.1 ± 0.3, 0	0.1 ± 0.3, 0	Z = -0.397, P = 0.691; r = 0.017
Inability to divide attention	0.1 ± 0.5, 0	0	Z = -1.514, P = 0.130; r = 0.065
Captivation of attention	0.0 ± 0.2, 0	0.0 ± 0.3, 0	Z = -0.757, P = 0.449; r = 0.033
Disturbance of expressive speech	0.2 ± 0.8, 0	0.1 ± 0.4, 0	Z = -0.268, P = 0.789; r = 0.012
Disturbance of abstract thinking[1]	0	0.0 ± 0.1, 0	Z = -1.622, P = 0.105; r = 0.070
Thought interference	0.1 ± 0.6, 0	0.1 ± 0.4, 0	Z = -0.591, P = 0.555; r = 0.025
Thought blockages[1]	0.2 ± 0.8, 0	0.1 ± 0.6, 0	Z = -1.044, P = 0.297; r = 0.045
Thought pressure	0.2 ± 0.9, 0	0.1 ± 0.5, 0	Z = -2.639, [b]P = 0.008; r = 0.114
Disturbance of receptive speech	0.0 ± 0.3, 0	0.0 ± 0.1, 0	Z = -1.324, P = 0.185; r = 0.057
Unstable ideas of reference	0.0 ± 0.2, 0	0.0 ± 0.2, 0	Z = -1.046, P = 0.296; r = 0.045
Impaired discrimination between ideas/true memories and phantasy	0.1 ± 0.6, 0	0.0 ± 0.3, 0	Z = -0.230, P = 0.818; r = 0.010
Thought perseveration	0.0 ± 0.3, 0	0.0 ± 0.2, 0	Z = -0.607, P = 0.544; r = 0.026
Derealization	0.4 ± 1,1, 0	0.0 ± 0.2, 0	Z = -3.924, [c]P < 0.001.; r = 0.169
Visual perception disturbances	0.3 ± 1.1, 0	0.1 ± 0.4, 0	Z = -2.822, [b]P = 0.005; r = 0.122
Acoustic perception disturbances	0.2 ± 0.9, 0	0.2 ± 0.8, 0	Z = -1.014, P = 0.311; r = 0.044

[1]Assessable only from age of 13 years onwards, thus only calculated on n = 404.
r: Rosenthal's *r*: 0.1 = weak effect; 0.3 = moderate effect; 0.5 = strong effect.

Compared to adult samples, group differences indicative of a potential pluripotent or transdiagnostic nature of CHR symptoms and criteria should be even more obvious in children and adolescents below these age thresholds. Yet, overall, our results revealed only few group differences of small effect size in frequency and severity of CHR symptoms and no group differences in frequency of CHR criteria. Additionally, at most weak associations were found between CHR symptoms or sum scores of symptoms with level of psychosocial functioning as a proxy measure of severity of mental ill health.

The CHR state as a pluripotent syndrome

Being derived from biology and commonly applied to describe a property of cells, pluripotent (from "pluri": several, and "potent": being able) describes the property of immature or stem cells that are capable of giving rise to several different cell types, into which they transform[31,54]. When extended to psychiatry, a pluripotential syndrome would be the first, diagnostically indistinct expression of any developing more severe psychopathology, which only later may acquire a degree of diagnostic specificity[27,28]. In doing so, similar to pluripotent cells, a pluripotent mental state would be completely absorbed in the final, manifest mental state or disorder. Thus, if they were pluripotent, CHR criteria and symptoms would no longer be detectable in patients with manifest mental disorders; *i.e.*, after their transformation into a diagnostically specific disorder. Yet, they might already be detectable in healthy persons who might be at risk of developing a mental disorder in future, such as children and adolescents of the community, of whom a third can be expected to develop a mental disorder in their lifetime[39]. Thus, from a pluripotent point of view, we expected a higher rate of CHR criteria and symptoms in community subjects compared to inpatients.

Table 8 Severity of clinical high-risk criteria and symptoms (mean ± SD, median) in the four diagnostic subsamples and the community sample (N = 539)

	ED (n = 97)	ADHD (n = 86)	AnxD and OCD (n = 94)	ASS (n = 29)	Community subjects (*n* = 233)	Kruskal–Wallis (results of *post hoc* Mann–Whitney tests)
Sum score of SIPS positive items	2.1 ± 2.4, 1	2.0 ± 2.1, 1	3.1 ± 2.6, 2	3.3 ± 3.3, 2	2.1 ± 2.3, 1	$\chi^2_{(4)} = 18.866$, $^cP = 0.001$ (AnxD and OCD>ED = ADHD = GPS)
Sum score of COGDIS	0.8 ± 2.1, 0	0.5 ± 1.7, 0	1.2 ± 3.5, 0	0.7 ± 1.7, 0	0.4 ± 1.2, 0	$\chi^2_{(4)} = 7.692$, $P = 0.104$
Sum score of COPER	1.8 ± 3.6, 0	1.1 ± 3.3, 0	2.2 ± 4.2, 0	1.1 ± 1.7, 0	0.6 ± 1.7, 0	$\chi^2_{(4)} = 26.988$, $^cP < 0.001$ (ED = AnxD and OCD = ASS > GPS; AnxD and OCD = ED > ADHD)
P1: Unusual thought content	0.8 ± 0.9, 1	0.7 ± 0.9, 1	1.2 ± 1.1, 1	1.2 ± 1.3, 1	0.8 ± 0.9, 1	$\chi^2_{(4)} = 12.397$, $^aP = 0.015$ (AnxD and OCD > ED = ADHD = GPS)
P2: Suspiciousness/persecutory ideas	0.4 ± 0.8, 0	0.2 ± 0.6, 0	0.5 ± 0.9, 0	0.7 ± 1.1, 0	0.2 ± 0.6, 0	$\chi^2_{(4)} = 30.502$, $^cP < 0.001$ (ASS = AnxD and OCD = ED > GPS; AnxD and OCD = ASS > ADHD)
P3: Grandiose ideas	0.1 ± 0.3, 0	0.1 ± 0.2, 0	0.2 ± 0.5, 0	0.1 ± 0.3, 0	0.1 ± 0.4, 0	$\chi^2_{(4)} = 4.029$, $P = 0.402$
P4: Perceptual abnormalities	0.8 ± 1.3, 0	1.0 ± 1.5, 0	1.2 ± 1.4, 1	1.3 ± 1.6, 1	1.0 ± 1.2, 0	$\chi^2_{(4)} = 6.391$, $P = 0.172$
P5: Disorganized communication	0.0 ± 0.2, 0	0.0 ± 0.2, 0	0.1 ± 0.4, 0	0.1 ± 0.3, 0	0.1 ± 0.3, 0	$\chi^2_{(4)} = 3.129$, $P = 0.539$
Inability to divide attention	0.0 ± 0.4, 0	0	0.1 ± 0.9, 0	0	0	$\chi^2_{(4)} = 6.537$, $P = 0.163$
Captivation of attention	0	0	0.0 ± 0.2, 0	0.1 ± 0.4, 0	0.0 ± 0.3, 0	$\chi^2_{(4)} = 9.749$, $^aP = 0.045$ (ASS > ED = ADHD)
Disturbance of expressive speech	0.2 ± 0.9, 0	0.1 ± 0.6, 0	0.2 ± 1.0, 0	0.1 ± 0.4, 0	0.1 ± 0.4, 0	$\chi^2_{(4)} = 0.675$, $P = 0.954$
Disturbance of abstract thinking[1]	0	0	0	0	0.0 ± 0.1, 0	$\chi^2_{(4)} = 2.632$, $P = 0.621$
Thought interference	0.1 ± 0.5, 0	0.1 ± 0.5, 0	0.1 ± 0.6, 0	0.3 ± 1.0, 0	0.1 ± 0.4, 0	$\chi^2_{(4)} = 7.912$, $P = 0.095$
Thought blockages[1]	0.2 ± 0.8, 0	0.2 ± 0.9, 0	0.3 ± 1.0, 0	0.1 ± 0.4, 0	0.1 ± 0.6, 0	$\chi^2_{(4)} = 2.048$, $P = 0.727$
Thought pressure	0.3 ± 0.9, 0	0.1 ± 0.6, 0	0.4 ± 1.2, 0	0.1 ± 0.4, 0	0.1 ± 0.5, 0	$\chi^2_{(4)} = 10.944$, $^aP = 0.027$ (ED = AnxD and OCD > GPS)
Disturbance of receptive speech	0.0 ± 0.1, 0	0.0 ± 0.2, 0	0.1 ± 0.5, 0	0	0.0 ± 0.07, 0	$\chi^2_{(4)} = 5.047$, $P = 0.283$
Unstable ideas of reference	0.1 ± 0.3, 0	0	0.0 ± 0.1, 0	0	0.0 ± 0.2, 0	$\chi^2_{(4)} = 6.643$, $P = 0.156$
Impaired discrimination between	0.0 ± 0.3, 0	0.1 ± 0.7, 0	0.2 ± 0.7, 0	0	0.0 ± 0.3, 0	$\chi^2_{(4)} = 7.344$, $P = 0.119$
Thought perseveration	0	0.1 ± 0.4, 0	0.1 ± 0.4, 0	0.0 ± 0.1, 0	0.0 ± 0.2, 0	$\chi^2_{(4)} = 3.954$, $P = 0.412$
Derealization	0.4 ± 1.1, 0	0.1 ± 0.7, 0	0.6 ± 1.5, 0	0.2 ± 0.7, 0	0.0 ± 0.2, 0	$\chi^2_{(4)} = 32.930$, $^cP < 0.001$ (ED = AnxD and OCD > ADHD = GPS)
Visual perception disturbances	0.4 ± 1.2, 0	0.3 ± 1.2, 0	0.3 ± 1.0, 0	0.3 ± 0.7, 0	0.1 ± 0.4, 0	$\chi^2_{(4)} = 10.764$, $^aP = 0.029$ (ED = AnxD and OCD = ASS > GPS)
Acoustic perception disturbances	0.3 ± 1.0, 0	0.2 ± 0.7, 0	0.3 ± 1.0, 0	0.1 ± 0.3, 0	0.2 ± 0.8, 0	$\chi^2_{(4)} = 3.227$, $P = 0.521$

[1]assessable only from age of 13 years onwards, thus only calculated on *n* = 404. ED: Eating disorder; ADHD: Attention-deficit hyperactivity disorder; AnxD and OCD: Anxiety disorder, including obsessive-compulsive disorder; ASS: Asperger's syndrome; GPS: community subjects.

Contrary to this expectation, we found no global pattern of differences in CHR criteria between inpatients and community subjects, and the four group differences in the prevalence of CHR symptoms; *i.e.*, in *suspiciousness/persecutory ideas*, *thought pressure*, *derealization* and *visual perception disturbances*, pointed towards a slightly higher rather than lower prevalence in inpatients. This lack of support for

assuming pluripotency of the UHR criteria specifically, is in line with results of the longitudinal data of two North American CHR studies[55]. Comparing outcome of help-seeking patients with and without UHR criteria, these studies detected no group differences in rates of new emergence of nonpsychotic disorders, thus not supporting diagnostic pluripotency of the UHR states[55]. Furthermore, the authors noted that the persistence of the generally frequent baseline comorbidities to UHR states would not qualify as support for assuming pluripotency of UHR states, even when only the UHR state is remitted at baseline[55]. Indeed, the above definition of a pluripotent state would rule out the concurrent presence of both the pluripotent state and its assumed outcome.

The missing empirical support for regarding the CHR state as a pluripotent syndrome is somewhat unsurprising in light of the frequent indistinct use of the term pluripotential for states that were equaled to earliest, unspecific mental states of mental disorders[31]. Yet, in models of developing psychosis, these earliest and unspecific states are commonly distinguished from the more specific CHR states[10,18,56]. Then again, pluripotent states or trajectories have been equated to transdiagnostic ones[30] despite their considerably differing assumptions with regard to the course of their constituting symptoms – transformation and, thus, forever vanishing of pluripotential states and symptoms *versus* maintenance or even increase of transdiagnostic symptoms.

The CHR state as a general transdiagnostic risk factor

In contrast to a pluripotent state, a transdiagnostic risk factor as well as a transdiagnostic dimension of psychopathology would still be present in various mental disorders[32], while they would be present in the community to a clearly lesser degree or not at all outside states of mental ill health. Thus, if CHR criteria and symptoms would represent a transdiagnostic risk factor or a transdiagnostic psychopathological dimension, they should accumulate in the extreme range of persons with mental disorders and, hence, should be more frequent or severe in inpatients compared to community subjects. Indeed, a large body of research indicates that so-called psychotic-like experiences, commonly assessed by self-report questionnaires or fully-standardized lay-person interviews, can be measured in the community, in which they are linked to the presence of non-psychotic disorder, particularly common mental disorder [28,57]. Thus, it was argued that psychotic-like experiences are transdiagnostic phenomena that, among others, also predict greater illness severity[57].

In our analyses, these assumptions were not supported for CHR criteria. The prevalence rates of CHR criteria did not differ between the community subjects (7.3%) and the inpatient sample (8.2%). Yet, both rates were higher than the 2.4% rate of clinician-assessed CHR criteria in young adults of the community aged 16–40 years[58]. In line with earlier findings[22,23], this indicates an effect of age across broader age ranges but not within children and adolescents. This lack of support for a transdiagnostic model of CHR criteria is likely related to the differences in assessments and definition. Studies on psychotic-like experiences commonly do not use CHR instruments for the assessment of APS/BIPS by trained clinicians in semi-structured interviews, which makes such psychotic-like experiences a poor and invalid proxy of APS that overestimates the presence of APS by far[59-62]. Furthermore, studies on psychotic-like experiences commonly disregard the onset/worsening and frequency requirements of CHR criteria[62] (Table 1).

With regard to CHR symptoms and irrespective of these additional requirements, we found some group differences in frequency and severity, in particular with respect to the severity of some single CHR symptoms. Yet, these findings were mostly unsystematically and randomly distributed, except for the UHR-relevant APS *suspiciousness/persecutory ideas*, the two COPER-relevant basic symptoms *derealization* and *visual perception disturbances*, and the COPER- and COGDIS-relevant basic symptom *thought pressure*. These four CHR symptoms were more frequent and severe in inpatients, in particular in eating disorders, and anxiety and obsessive–compulsive disorders; additionally, the paranoid APS was more frequent and severe in autism-spectrum disorder. Thus, they may be the most likely candidates of all CHR symptoms for transdiagnostic risk factors or a transdiagnostic psychopathological dimension.

Suspiciousness/persecutory ideas (P2) of the SIPS in terms of APS/BIPS include symptoms ranging from a general lack of trust in and suspiciousness of others, as well as vague ideas of threat or that others do not mean well to more concrete ideas of being followed, observed or in danger and paranoid ideas of reference[43]. Their severity can range from ideas still being doubted to various degrees and not significantly impeding behavior, to holding these ideas with absolute conviction, resulting in significant impact on behavior[43]. Social fears related to one's own possibly inadequate or embarrassing behavior (but not to the negative intentions of others) were not scored here. In adolescents, ideas of reference that exclusively involved peers and the idea that they might think or talk badly about the patient/subject were also not rated, as the critical comparison with peers is a common phenomenon in adolescents' identity formation and, consequently, as these ideas are possibly related to lower levels of self-esteem [63,64].

In our study, the paranoid APS was most frequent and severe in anxiety, obsessive–compulsive, and in autism-spectrum disorders. This is in line with reports that paranoia is not specific to psychosis but occurs in a wide range of disorders[65] and also frequently in community samples of adolescents[65,66]. In particular, paranoia was significantly positively associated with anxiety but not autistic symptoms, and negatively associated with symptoms of ADHD[63]. The latter is also in line with our finding that none of the ADHD patients reported paranoid APS. Other studies have linked autistic traits

and psychotic-like experiences, including paranoia, in the adult community[67] and reported similarly high levels of paranoia in psychotic and autism-spectrum disorders[68]. In contrast to psychotic disorders in which paranoia was based upon victimization, suspicion, and threat of harm, in autism-spectrum disorders, paranoia was based less upon these but more so upon social cynicism[68]. Yet, certain (developing) personality accentuations or disorders that involve paranoia and suspiciousness, in particular paranoid, schizotypal and borderline personality[69,70], might have contributed our findings. However, for the ongoing personality development in this age group, we had not assessed these in our study on children and adolescents.

Of the basic symptoms, *thought pressure* that is part of both COPER and COGDIS was more frequent and severe in inpatients, particularly in anxiety and obsessive–compulsive disorders. *Thought pressure* involves the subjective occurrence of a great number of thematically unrelated and often unrecognized, fragmented thoughts whose (dis)appearance is hard to control[44]. Thereby, *thought pressure* is distinct from intrusive thoughts of obsessive–compulsive disorder that involve a certain topic. Furthermore, in their assessment, the occurrence within states of extreme emotional arousal, such as in panic attacks, has to be excluded[44]. Thus, this finding is not explained by phenomenological similarities between *thought pressure* and cognitive symptoms in anxiety and obsessive–compulsive disorders. Yet, these similar cognitive symptoms might signal a general liability to difficulties in suppressing irrelevant or inadequate thoughts that, as suggested for intrusive thoughts, might be related to altered functional connectivity in the temporal gyri[71]. More qualitative and basic research into the link between *thought pressure* and anxiety and obsessive–compulsive disorders is clearly needed.

Visual perception disturbances include various, often fleeting misperceptions of real visible objects including oneself and other persons that are immediately recognized as false perceptions, and are not even for a split-second considered as changes in the outside world[44]. As with all basic symptoms, they have to have started at a certain point in life[44] and thus, contrary to schizotypy-related perceptual aberrations, have no trait characteristic[15,72,73]. Furthermore, they must be unrelated to a somatic condition or substance use[44]. As outlined above in the section "Assessments", they rate on the SIPS below the APS-relevant range with a score of 2[43,44,73]. Examples of *visual perception disturbances* include changes in the perception of the color or color intensity of objects, in the perception and estimation of the size of, or distance to objects, and in the shape of objects, as well as perceptions that resemble floaters or flashes of light in the vision as known, for example, from auras of migraine, retinal detachment or optic neuritis[44]. Therefore, they are different from unformed attenuated or frank visual hallucinations that are not perceived as "in the eye" but are located – at least initially – in the outside world[43,73]. Despite being a part of COPER, *visual perception disturbances* were found to be on the periphery of a network of symptoms of psychosis in an adult patient sample[74]. Such a peripheral position was also found for the depression items of the SIPS and of the Positive And Negative Syndrome Scale[75], though at the opposite side of the network, likely indicating that these symptoms are less specific to psychosis. Thus, *visual perception disturbances* that longitudinally had been significantly linked to the development of psychosis in adults[14] might be a more general expression of severe mental problems in childhood and early adolescence. This view is supported by reports that visual hallucinations were more frequent in children and adolescents with psychosis compared to adult psychosis patients[76], and that attenuated and transient hallucinations as well as perceptual disturbances were more frequent and less clinically relevant in children and adolescents[22,23], who likely grow out of them over time due to progressing neurocognitive and brain maturation[52].

Derealization is defined by an alienation from the surrounding and/or the experience of the external environment as unfamiliar, with other people appearing as if only acting a role and the world appearing as if being two-dimensional or a stage set in the presence of knowledge of its reality[44]. It often co-occurs with more frequent depersonalization experiences; and together, they might form a syndrome in itself[77-79]. Both are part of the definition of panic disorders[77,78] and are therefore not rated as basic symptoms when exclusively occurring within a panic attack. Thus, as in *thought pressure*, our finding of increased *derealization* in anxiety and obsessive–compulsive disorders is not explained by this phenomenological overlap. Yet, as personality disorders had not been assessed in this study, we did not exclude their possible occurrence as part of a developing Borderline or schizotypal personality accentuation or disorder[78]. *Depersonalization* and, to a lesser degree, *derealization* are frequent phenomena in the general population with higher rates in psychiatric patients, in particular those with affective and anxiety disorders[77,78]. *Derealization* and *depersonalization* might have partly different neurobiological underpinnings[80]; and only *derealization* was found to be predictive of future psychosis and, thus included into COPER[14]. However, in line with our current findings, studies reported that both *derealization* and *depersonalization* might be responses to strong emotions, such as embarrassment, or might be attempts at coping, in particular in affective and anxiety disorders[81]. Additionally, one study on bulimia reported a link between threatening stimuli and dissociative states, in particular derealization, in which it was assumed to fulfill a similar function as binge eating itself; *i.e.*, lowering awareness of generalized threat and negative self-esteem[82]. Thus, the increased prevalence and severity of *derealization* in patients with eating disorders, and anxiety and obsessive–compulsive disorders might be related to their propensity to perceive high emotional arousal, especially threat.

Derealization and *visual perception disturbances* are only part of the basic symptom criterion COPER (Table 1) that is likely less specific but more sensitive compared to COGDIS[15]. Although not more frequent, our analyses revealed that COPER was more severe in inpatients, in particular those with eating disorders, and anxiety and obsessive–compulsive disorders. Therefore, the inclusion of *derealization* and *visual perception disturbances* in COPER in addition to that of *thought pressure* might have conveyed the higher severity, though not frequency of COPER in inpatients, in particular in eating, autism-spectrum, and anxiety and obsessive–compulsive disorders.

The CHR state as a general transdiagnostic severity marker

A transdiagnostic severity marker of psychopathology would be expected to be generally present in mental disorders and to be most pronounced in those with severe mental disorders and, relatedly, in those with most severe functional impairment due to their mental problems. Thus, the severity and likelihood of presence of CHR criteria and symptoms would be expected to significantly increase with decreasing psychosocial functioning as a proxy measure of illness severity. As already discussed, CHR symptoms and criteria differed only to a minimal degree in their prevalence between inpatients and community subjects, in whom they were also rare. They hardly exceeded 10% in inpatients, except for *derealization* and *visual perception disturbances* (both 11.4%) and *perceptual abnormalities/hallucinations* (P4) that were present in 20.9% of inpatients but also in 23.4% of community subjects. Furthermore, CHR symptoms and criteria demonstrated an association with psychosocial functioning, the proxy severity measure. However, this association was, at most, of small effect size even when becoming significant. This finding indicates that CHR criteria and symptoms would be poor transdiagnostic severity markers of mental problems; at least when psychosocial functioning is used as a proxy measure.

With regard to basic symptoms, only COPER became significant in both bivariate and partial group-controlled correlation analyses, showing a small maximum effect of Tau = -0.140. Significant single basic symptoms differed between the two types of analyses. In doing so, *thought pressure*, *derealization*, and *visual* and *acoustic perception disturbances* became significant in bivariate, and *thought inference* and *disturbances of expressive speech* became significant in partial analyses, in no case exceeding tau = -0.116. Of these six symptoms, all but *disturbances of expressive speech* are part of COPER, while only *thought pressure* and *interference* as well as *disturbances of expressive speech* are part of COGDIS. Since *thought pressure*, *derealization*, and *visual perception disturbances* showed significant group differences, this strong group effect may mostly explain their association with functioning in bivariate correlation that, consequently, was strongly reduced in partial correlations.

Results on the APS syndrome and single APS were more consistent. In both bivariate and partial correlation analyses, the sum score of SIPS positive items as well as the single SIPS positive items *suspiciousness/persecutory ideas* (P2), *perceptual abnormalities/hallucinations* (P4), and *disorganized communication* (P5) were significantly negatively correlated with psychosocial functioning. Yet, as in basic symptoms, these correlations were only of weak effect size and did not exceed r = -0.165 (respectively r = -0.201 in 8–15-year-olds) in *perceptual abnormalities/hallucinations* (P4). This is in line with a recent community study, whose n = 211 participants had been 11-13 years old at baseline[84]. Authors reported an association between psychotic experiences assessed with the Schedule for Affective Disorders and Schizophrenia for School-aged Children (K-SADS[83]) and poorer functioning[84]. Furthermore, n = 86 (40.8%) and n = 56 (26.5%) participated in the first and second follow-up at age 14–16 years and 17–21 years, respectively[84]. Participants with psychotic experiences at baseline had persistently poorer global functioning throughout adolescence and into early adulthood. As in our cross-sectional results, this effect was above and beyond what was explained by presence of a mental disorder, suggesting an underlying vulnerability which extends beyond diagnosable mental disorder [84]. Unfortunately, the authors did not report effect sizes and did not distinguish between the different psychotic experiences. Therefore, it remains unclear if these associations were also of only small effect size and if they were mainly driven by similar (attenuated) psychotic symptoms.

In our study, only the comparably frequent and, (regarding content) heterogeneous SIPS positive item *unusual thought content/delusional ideas* and the extremely rare SIPS positive item *grandiose ideas* were not significantly related to functioning. *Unusual thought content/delusional ideas* (P1) includes all but paranoid and grandiose ideas[43]. Thus, it is probable that the included unusual ideas differ in their association with functioning; e.g., that attenuated *Ich-Störungen* may more strongly impair functioning than magical thinking. For this reason, future studies should examine single attenuated delusional ideas differentially to further determine which APS might or might not have the potential of a transdiagnostic severity marker. Similarly, a more differential examination is needed for *perceptual abnormalities/hallucinations* (P4) that involves different sensory modalities, as these were differentially, though inconsistently related to conversion to psychosis in UHR samples[85-87].

The lack of strong correlations between CHR symptoms and criteria, and functioning might be perceived as challenging the notion that these possess clinical relevance. However, symptoms are generally defined by a departure from normal function – not necessarily psychosocial function – or feeling, which is apparent to the patient, reflecting the presence of an unusual state or of a disease[38]. Thus, functional impairment is not always a prerequisite even for some psychotic disorders, such delusional disorders that, according to the DSM[38], do not have to lead to functional impairment *per se*. Moreover, in ICD-10 (and the future ICD-11), functional impairment is not a requirement for any

psychotic disorder[88]. Furthermore, in the SIPS and their anchor points for severity ratings of the positive items[43], a rating of 3 (or lower) does not require an impact on functioning, while a rating of 4 requires only potential and partial impact on functioning; a significant impact on functioning is only required for severe APS of score 5 or BIPS score of 6. Yet, ratings of 5 were rare, occurring in only 13 instances, and ratings of 6 never occurred. Rather, ratings of 3 dominated in those with APS: 68.3% scored 3 on P1, 85.7% on P2 and 66.1% on P4; and the single case of APS on P3 and P5, respectively, had a rating of 3 each. Additionally, other than in the current version of Comprehensive Assessment of At-Risk Mental States, the APS syndrome of the SIPS does not require a significant functional decline or impairment[19]. Thus, the lack of an association with functional impairment does not limit the qualification of CHR symptoms and criteria as symptoms or syndromes.

As for the basic symptoms, affected persons can commonly cope with these mostly fleeting experiences (e.g., by increased willpower or concentration) for as long as their number or frequency does not exceed their coping capacities, and for as long as the employed coping strategies are not maladaptive (such as social withdrawal or other avoidance strategies)[44,52,89]. Thus, for their subjective perception as not normal, basic symptoms may induce distress and worries about one's own mental health[52,89] but not necessarily impairment in psychosocial functioning. Consequently, functional impairment is not a general prerequisite for symptoms or syndromes, in particular in the prevention of disorders that, within psychiatry, also aims for the prevention of functional impairment [90]. In light of this, making functional impairment an obligatory requirement of CHR criteria was explicitly discouraged in recent recommendations for diagnosing a CHR state within the framework of the EPA Guidance project[19].

The CHR state as a precursor state of psychoses

Four subjects developed psychosis within 2 years; *i.e.*, 0.7% of the whole sample (n = 539) and 1.2% of the 2-year follow-up sample (n = 331). These numbers are higher than the reported annual incidence rate in the community of this age of 0.1%[91]. Conversions to psychosis mainly occurred in inpatients, of whom 1.0% converted to psychosis compared to just 0.4% in the community sample. Three quarters of the few conversion-to-psychoses cases occurred in the inpatient sample, in which also the non-CHR-related conversion occurred, and three quarters of converters had met CHR criteria at baseline. Thus, with conversion rates between 6.5% across all CHR subjects at baseline, and 11.5% for CHR subjects with a 2-year follow-up, the 2-year conversion rates within CHR subjects were within the range of pooled conversions rates reported for child and adolescent CHR samples of early detection services of 9.5%[19]. At this, our conversion rates were slightly higher than the 3-year conversion rates reported for 16–40-year-olds of the community that were 4.7% for all five CHR criteria and 11.1% for the three EPA criteria[92].

Of note, the effect sizes of the association of CHR criteria at baseline with subsequent conversion to psychosis were the highest of all reported effect sizes, approaching a moderate effect size in case of the two-year follow-up sample (Cramer's V = 0.276).

Strengths and limitations

Our study has several strengths and limitations. Clear strengths include the large sample size, the CHR assessment with well-established instruments, and the thorough training in and supervision of the assessment of CHR symptoms and criteria in order to minimize rater and center effects, and to maximize interrater reliability. Furthermore, in order to reduce a potential systematic assessment bias due to the impossible blinding of raters to groups, the inpatient and community sample was assessed by different interviewers. Another strength is the inclusion of a severely ill inpatient sample with main disorders that had been reported to be related to an increased prevalence of schizophrenia in adulthood [37] (Supplementary Table 1). Thus, our inpatient sample – in theory – was biased towards reporting increased rates of CHR symptoms and, consequently, towards revealing any transdiagnostic nature of CHR criteria and symptoms.

Limitations to our study are the mainly cross-sectional nature and the nonassessment of nonpsychotic mental disorders at follow-up. This would have allowed us to compare conversion rates to psychosis with conversion to, or persistence of other mental disorders, and would have allowed us to study the relationship of different mental disorders to the course of CHR criteria and symptoms.

The conduction of multiple analyses and the related nonadjustment for multiple testing might have been another possible limitation. Yet, as discussed already in the section "Data analysis", because all of our hypotheses assumed group differences, the type I error (alpha), *i.e.*, the rejection of a true null hypothesis, would have be become less likely, if we had corrected the alpha-level for multiple comparisons. However, even without correction for multiple testing, the null hypothesis was rarely rejected; this resulted in the main conclusion of a lack of a general group difference. This main conclusion would not have changed, had we corrected the alpha-level for multiple comparison and, consequently, had detected even fewer (and likely no) group differences. In light of this, the nonadjustment of the type I error can be regarded as the more conservative testing of the overall hypotheses assuming group differences. Additionally, the high power of the study, the ability to correctly reject a false null hypothesis assuming group equality, must be assumed to be uncompromised by the current nonadjusted analyses[50]. Thus, any adjustment for multiple testing would not have led

to a different conclusion. Furthermore, the conduction of multiple analyses had offered the advantage to detect any possibly robust pattern indicative of any one of the three examined alternative explanatory models of CHR states and symptoms.

CONCLUSION

Overall, our results did not support the general predications that CHR criteria and symptoms would represent a pluripotent syndrome[27,28], a transdiagnostic risk factor[33], a transdiagnostic dimension of psychopathology[30], or even merely a marker for the severity of nonpsychotic states[30]. To that end, our data gave no support for a general diagnostic pluripotency of CHR symptoms and criteria that exceeds their undoubted and frequently demonstrated pluripotency for psychosis outcomes[55]. Furthermore, for lack of any clinically relevant, *i.e.*, at least moderate correlation with functioning, there was also no sufficient support for CHR symptoms and criteria as general severity markers of psychopathology. Indications of some transdiagnostic risk factors or dimension status with respect to eating, autism-spectrum, and anxiety and obsessive–compulsive disorders, however, were found for four CHR symptoms, two of them exclusive to COPER: *suspiciousness/persecutory ideas* (P2), *thought pressure*, *derealization* and *visual perception disturbances*. The fact that these indications did not extend to any CHR criterion highlights the importance of the additional requirements of CHR criteria on onset/worsening and occurrence for their potential specificity for the psychosis-spectrum. Indeed, with regard to the CHR criteria, we found the strongest, nearly moderate effect for their association with subsequent psychosis. This association, however, seems not strong enough to conclusively explain their role in children and adolescents by their psychosis-predictive potential.

Overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than *what* they are. Our results may support the view that CHR criteria should be regarded as a self-contained disorder or syndrome, similar to the proposition of the attenuated psychosis syndrome in DSM-5[93]. To evaluate this assumption, future community studies evaluating the effect of CHR criteria on help seeking and mental wellbeing are needed. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, then CHR criteria would fulfil general criteria for mental disorders (defined as a clinically significant behavioral or psychological syndrome associated with disability and/or severe distress); and consequently, the assumption of a CHR Syndrome would be supported. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to detect factors that convey their higher clinical relevance in adulthood.

ARTICLE HIGHLIGHTS

Research background

Many patients with clinical high-risk of psychosis (CHR) criteria do not develop psychosis, in particular if they are still in their childhood and adolescence. Therefore, CHR criteria were suggested to be not a risk indicator of psychosis development but (1) A pluripotential syndrome that will transform itself into all kinds of mental disorder; (2) A transdiagnostic risk factor from that all kind of different disorders develop; or (3) Simply a severity marker of mental disorders.

Research motivation

The simple nonconversion to psychosis and the persistence or new-occurrence rate of nonpsychotic mental disorders in CHR samples, however, do not allow for the conclusion of any of the three alternative explanatory models, which might explain why they are often proposed interchangeably. Thus, to gain more insight into the nature of CHR symptoms and criteria, we examined the differential implications that each of these models has on the occurrence of CHR criteria and symptoms and their association with a proxy measure of illness severity in patients with severe mental disorders; *i.e.*, inpatients and community subjects. We expected that any pattern of group differences indicative of one of the alternative explanatory models should become particularly apparent in a child and adolescent sample, as CHR symptoms and criteria were reported to be more frequent but less clinically relevant and less associated with psychosis in children and adolescents compared to adults.

Research objectives

Following a propositional logic approach, we examined which of the three alternative explanatory models of CHR criteria and symptoms would best fit our data. The three alternative explanatory models were associated with the following differential premises with respect to the data: (1) If CHR criteria and symptoms are more frequent in community subjects compared to inpatients, then they are likely

pluripotential. This has been assumed because a pluripotent syndrome would have transformed into a mental disorder and, thus, not be present in inpatients, but in a community sample wherein a proportion can be expected to develop a mental disorder in future; (2) If CHR criteria and symptoms are more frequent in inpatients compared to community subjects, then they likely represent a transdiagnostic risk factor or dimension. This has been assumed because they would aggregate in persons with mental illness; and (3) If CHR criteria and symptoms show a clinically relevant, significant negative correlation with functioning as a proxy measure of illness severity, then they likely represent a severity marker of psychopathology.

Research methods

As part of the Bi-national Evaluation of At-Risk Symptoms in children and adolescents (BEARS-Kid) study, we cross-sectionally examined the frequency and severity of CHR criteria and symptoms in an 8–17-year-old randomly recruited sample of the Swiss community (n = 233) and in 8–17-year-old inpatients (n = 306) whose main diagnosis was a disorder that, earlier, had been associated with an elevated risk for psychosis in adulthood (obsessive compulsive and anxiety, attention deficit, eating, and autism-spectrum disorder) using χ^2 and nonparametric analyses. Furthermore, the associations between psychosocial functioning, and CHR criteria and symptoms were analyzed with bivariate and partial correlation analyses, the latter controlling for group membership. CHR criteria and symptoms according to the ultra-high risk and the basic symptom approach were assessed in clinical interviews by trained psychologists using the Structured Interview for Psychosis-Risk Syndromes (SIPS) and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY). Furthermore, we followed up 78.5% of the participants after 1 year, and 61.4% after 2 years past baseline for a conversion to psychosis.

Research results

The 7.3% prevalence rate of CHR criteria in community subjects did not differ significantly from the 9.5% rate in inpatients. Frequency and severity of CHR criteria never differed between the community and the four inpatient groups. The frequency and severity of CHR symptoms differed between the community and the four inpatient groups only in four CHR symptoms: *suspiciousness/persecutory ideas* of the SIPS as well as tho*ught pressure*, *derealization* and *visual perception disturbances* of the SPI-CY. The persistent pattern of these differences was consistent with a transdiagnostic risk factor or dimension; *i.e.*, these symptoms were more frequent and severe in inpatients, in particular in those with eating, anxiety/obsessive–compulsive and autism-spectrum disorders. Furthermore, low functioning was – if at all – at most weakly related to the severity of CHR criteria and symptoms; the highest, yet weak correlation was for *suspiciousness/persecutory ideas*. Four participants had developed a psychotic disorder within two years past baseline. In doing so, the 2-year conversion rate in participants with CHR criteria was 11.5% and, the comparison of the conversion rate in participants with and without CHR criteria at baseline exhibited the highest, near moderate effect size of all comparisons.

Research conclusions

This study was the first to systematically study alternative explanatory models for current CHR states, which propose that CHR criteria and symptoms would represent a pluripotent syndrome, a transdiagnostic risk factor or dimension, or even merely a marker for the severity of any mental disorder. The general lack of systematic differences in the frequency and severity of CHR criteria and symptoms between inpatients and community subjects, and the lack of a sufficiently strong association between functioning, and CHR criteria and symptoms did not support any of these alternative explanatory models. Rather, the strongest, though still only moderate effect was found for the association of CHR criteria and the subsequent development of a psychotic disorder within two years. This association, however, appears not strong enough to conclusively explain the role of CHR criteria and symptoms in children and adolescents by their psychosis-predictive potential. Thus, overall, our results more clearly indicate what CHR symptoms and criteria are *not* rather than indicating *what* they are.

Only four CHR symptoms – *suspiciousness/persecutory ideas* of the SIPS, and *thought pressure*, *derealization* and *visual perception disturbances* of the SPI-CY – exhibited a pattern of group differences indicative of a transdiagnostic risk factor, in particular with respect to eating, autism-spectrum, and anxiety and obsessive–compulsive disorders. Thus, their inclusion and definition in current CHR criteria should be critically examined in future studies.

Research perspectives

Our results add to the growing support of the view that CHR criteria should be regarded as a self-contained disorder or syndrome. To more fully test this assumption, future community studies should evaluate the effect of CHR criteria on help seeking and mental wellbeing. If persons meeting CHR criteria generally suffer from their CHR symptoms, seek help for them, and/or experience disturbances in psychosocial functioning irrespective of, or in addition to, the effects of any other potential comorbid mental disorder, CHR criteria would fulfil general criteria for mental disorders in terms of a CHR Syndrome. Thus, further research on CHR symptoms and criteria, and their cause and meaning in children and adolescents is needed to better understand their significance in this age group, and to

detect factors that convey their higher clinical relevance in adulthood.

ACKNOWLEDGEMENTS

The authors thank their Australian colleague, Mrs. Madelyn Thomson, for her careful language assistance.

FOOTNOTES

Author contributions: Schultze-Lutter F and Schimmelmann BG designed the study; Walger P, Franscini M, Traber-Walker N, Flückiger R and Michel C were involved in the acquisition of data; Schultze-Lutter F and Michel C analyzed and interpreted the data for the work and drafted the first version of this work; all authors revised the article critically for important intellectual content, and agreed to the submitted version.

Supported by the conjoint research grant of the Swiss National Science Foundation, SNSF, No. 144100; and the German Research Foundation, DFG, No. 231563730, within the Lead Agency Process (SNSF as exclusive evaluating and approving lead agency).

Institutional review board statement: The study was reviewed and approved by the Kantonale Ethikkommission Bern, the Institutional Review Board of the University of Bern (No. 174/10), the Kantonale Ethik-Kommission Zürich, the Institutional Review Board of the University of Zurich (No. 2010-0415/3), and the Ethikkommision Köln, the Institutional Review Board of the Medical Faculty of the University of Cologne (No. 11-071).

Informed consent statement: All study participants, and their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Schimmelmann BG received honoraria for presentations by Takeda and InfectoPharm outside the reported work. All other authors reported no conflict of interest.

Data sharing statement: Data is available upon reasonable request for clearly defined scientific purposes from the corresponding author at frauke.schultze-lutter@lvr.de. Participants of the BEARS-Kid study gave informed consent for sharing of anonymized data.

STROBE statement: The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement checklist of items.

Country/Territory of origin: Germany

ORCID number: Frauke Schultze-Lutter 0000-0003-1956-9574; Petra Walger 0000-0003-1150-1145; Maurizia Franscini 0000-0002-0231-8368; Nina Traber-Walker 0000-0001-7164-9550; Naweed Osman 0000-0001-9761-0099; Helene Walger 0000-0002-4060-4146; Benno G Schimmelmann 0000-0002-8980-1466; Rahel Flückiger 0000-0003-1228-7267; Chantal Michel 0000-0003-1165-6681.

Corresponding Author's Membership in Professional Societies: International Early Psychosis Association (IEPA), Schizophrenia International Research Society (SIRS), European Scientific Association for Schizophrenia and other Psychosis (ESAS), European Psychiatric Association (EPA, Section Prevention), World Psychiatric Association (WPA), Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde (DGPPN), European Society of Child and Adolescent Psychiatry (ESCAP), International Consortium for Schizotypy Research (ICSR).

S-Editor: Wang LL
L-Editor: Kerr C
P-Editor: Yu HG

REFERENCES

1 **Gustavsson A**, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, Dodel R, Ekman M, Faravelli C, Fratiglioni L,

Gannon B, Jones DH, Jennum P, Jordanova A, Jönsson L, Karampampa K, Knapp M, Kobelt G, Kurth T, Lieb R, Linde M, Ljungcrantz C, Maercker A, Melin B, Moscarelli M, Musayev A, Norwood F, Preisig M, Pugliatti M, Rehm J, Salvador-Carulla L, Schlehofer B, Simon R, Steinhausen HC, Stovner LJ, Vallat JM, Van den Bergh P, van Os J, Vos P, Xu W, Wittchen HU, Jönsson B, Olesen J; CDBE2010Study Group. Cost of disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**: 718-779 [PMID: 21924589 DOI: 10.1016/j.euroneuro.2011.08.008]

2 **Wittchen HU**, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC. The size and burden of mental disorders and other disorders of the brain in Europe 2010. *Eur Neuropsychopharmacol* 2011; **21**: 655-679 [PMID: 21896369 DOI: 10.1016/j.euroneuro.2011.07.018]

3 **Whiteford HA**, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, Charlson FJ, Norman RE, Flaxman AD, Johns N, Burstein R, Murray CJ, Vos T. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**: 1575-1586 [PMID: 23993280]

4 **Gore FM**, Bloem PJ, Patton GC, Ferguson J, Joseph V, Coffey C, Sawyer SM, Mathers CD. Global burden of disease in young people aged 10-24 years: a systematic analysis. *Lancet* 2011; **377**: 2093-2102 [PMID: 21652063]

5 **Stentebjerg-Olesen M**, Pagsberg AK, Fink-Jensen A, Correll CU, Jeppesen P. Clinical Characteristics and Predictors of Outcome of Schizophrenia-Spectrum Psychosis in Children and Adolescents: A Systematic Review. *J Child Adolesc Psychopharmacol* 2016; **26**: 410-427 [PMID: 27136403 DOI: 10.1089/cap.2015.0097]

6 **Penttilä M**, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *Br J Psychiatry* 2014; **205**: 88-94 [PMID: 25252316 DOI: 10.1192/bjp.bp.113.127753]

7 **Farooq S**, Large M, Nielssen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. *Schizophr Res* 2009; **109**: 15-23 [PMID: 19233621 DOI: 10.1016/j.schres.2009.01.008]

8 **Dell'osso B**, Altamura AC. Duration of untreated psychosis and duration of untreated illness: new vistas. *CNS Spectr* 2010; **15**: 238-246 [PMID: 20414173 DOI: 10.1017/s1092852900000079]

9 **Köhn D**, Pukrop R, Niedersteberg A, Schultze-Lutter F, Ruhrmann S, Bechdolf A, Berning J, Maier W, Klosterkötter J. [Pathways to care: help-seeking behavior in first-episode psychosis]. *Fortschr Neurol Psychiatr* 2004; **72**: 635-642 [PMID: 15529235 DOI: 10.1055/s-2004-818418]

10 **Schultze-Lutter F**, Rahman J, Ruhrmann S, Michel C, Schimmelmann BG, Maier W, Klosterkötter J. Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. *Soc Psychiatry Psychiatr Epidemiol* 2015; **50**: 1831-1841 [PMID: 26155901 DOI: 10.1007/s00127-015-1093-3]

11 **Schimmelmann BG**, Conus P, Cotton S, McGorry PD, Lambert M. Pre-treatment, baseline, and outcome differences between early-onset and adult-onset psychosis in an epidemiological cohort of 636 first-episode patients. *Schizophr Res* 2007; **95**: 1-8 [PMID: 17628441 DOI: 10.1016/j.schres.2007.06.004]

12 **Schimmelmann BG**, Walger P, Schultze-Lutter F. The significance of at-risk symptoms for psychosis in children and adolescents. *Can J Psychiatry* 2013; **58**: 32-40 [PMID: 23327754 DOI: 10.1177/070674371305800107]

13 **Schimmelmann BG**, Schultze-Lutter F. Early detection and intervention of psychosis in children and adolescents: urgent need for studies. *Eur Child Adolesc Psychiatry* 2012; **21**: 239-241 [PMID: 22526975 DOI: 10.1007/s00787-012-0271-z]

14 **Klosterkötter J**, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; **58**: 158-164 [PMID: 11177117 DOI: 10.1001/archpsyc.58.2.158]

15 **Schultze-Lutter F**, Debbané M, Theodoridou A, Wood SJ, Raballo A, Michel C, Schmidt SJ, Kindler J, Ruhrmann S, Uhlhaas PJ. Revisiting the Basic Symptom Concept: Toward Translating Risk Symptoms for Psychosis into Neurobiological Targets. *Front Psychiatry* 2016; **7**: 9 [PMID: 26858660 DOI: 10.3389/fpsyt.2016.00009]

16 **Yung AR**, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, Patton GC, Jackson HJ. Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry Suppl* 1998; **172**: 14-20 [PMID: 9764121 DOI: 10.1192/S0007125000297602]

17 **Phillips LJ**, Yung AR, McGorry PD. Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. *Aust N Z J Psychiatry* 2000; **34** Suppl: S164-S169 [PMID: 11129303 DOI: 10.1080/000486700239]

18 **Klosterkötter J**, Schultze-Lutter F, Ruhrmann S. Kraepelin and psychotic prodromal conditions. *Eur Arch Psychiatry Clin Neurosci* 2008; **258** Suppl 2: 74-84 [PMID: 18516519 DOI: 10.1007/s00406-008-2010-5]

19 **Schultze-Lutter F**, Michel C, Schmidt SJ, Schimmelmann BG, Maric NP, Salokangas RK, Riecher-Rössler A, van der Gaag M, Nordentoft M, Raballo A, Meneghelli A, Marshall M, Morrison A, Ruhrmann S, Klosterkötter J. EPA guidance on the early detection of clinical high risk states of psychoses. *Eur Psychiatry* 2015; **30**: 405-416 [PMID: 25735810 DOI: 10.1016/j.eurpsy.2015.01.010]

20 **Fusar-Poli P**, Cappucciati M, Borgwardt S, Woods SW, Addington J, Nelson B, Nieman DH, Stahl DR, Rutigliano G, Riecher-Rössler A, Simon AE, Mizuno M, Lee TY, Kwon JS, Lam MM, Perez J, Keri S, Amminger P, Metzler S, Kawohl W, Rössler W, Lee J, Labad J, Ziermans T, An SK, Liu CC, Woodberry KA, Braham A, Corcoran C, McGorry P, Yung AR, McGuire PK. Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk: A Meta-analytical Stratification. *JAMA Psychiatry* 2016; **73**: 113-120 [PMID: 26719911 DOI: 10.1001/jamapsychiatry.2015.2324]

21 **Cornblatt BA**, Carrión RE, Auther A, McLaughlin D, Olsen RH, John M, Correll CU. Psychosis Prevention: A Modified Clinical High Risk Perspective From the Recognition and Prevention (RAP) Program. *Am J Psychiatry* 2015; **172**: 986-994 [PMID: 26046336 DOI: 10.1176/appi.ajp.2015.13121686]

22 **Schimmelmann BG**, Michel C, Martz-Irngartinger A, Linder C, Schultze-Lutter F. Age matters in the prevalence and clinical significance of ultra-high-risk for psychosis symptoms and criteria in the general population: Findings from the BEAR and BEARS-kid studies. *World Psychiatry* 2015; **14**: 189-197 [PMID: 26043337 DOI: 10.1002/wps.20216]

23 **Schultze-Lutter F**, Schimmelmann BG, Flückiger R, Michel C. Effects of age and sex on clinical high-risk for psychosis in the community. *World J Psychiatry* 2020; **10**: 101-124 [PMID: 32477906 DOI: 10.5498/wjp.v10.i5.101]

24 **Schmidt A**, Cappucciati M, Radua J, Rutigliano G, Rocchetti M, Dell'Osso L, Politi P, Borgwardt S, Reilly T, Valmaggia L, McGuire P, Fusar-Poli P. Improving Prognostic Accuracy in Subjects at Clinical High Risk for Psychosis: Systematic Review of Predictive Models and Meta-analytical Sequential Testing Simulation. *Schizophr Bull* 2017; **43**: 375-388 [PMID: 27535081 DOI: 10.1093/schbul/sbw098]

25 **Michel C**, Ruhrmann S, Schimmelmann BG, Klosterkötter J, Schultze-Lutter F. Course of clinical high-risk states for psychosis beyond conversion. *Eur Arch Psychiatry Clin Neurosci* 2018; **268**: 39-48 [PMID: 28054132 DOI: 10.1007/s00406-016-0764-8]

26 **Beck K**, Andreou C, Studerus E, Heitz U, Ittig S, Leanza L, Riecher-Rössler A. Clinical and functional long-term outcome of patients at clinical high risk (CHR) for psychosis without transition to psychosis: A systematic review. *Schizophr Res* 2019; **210**: 39-47 [PMID: 30651204 DOI: 10.1016/j.schres.2018.12.047]

27 **McGorry P**, van Os J. Redeeming diagnosis in psychiatry: timing *vs* specificity. *Lancet* 2013; **381**: 343-345 [PMID: 23351805]

28 **Fusar-Poli P**, Yung AR, McGorry P, van Os J. Lessons learned from the psychosis high-risk state: towards a general staging model of prodromal intervention. *Psychol Med* 2014; **44**: 17-24 [PMID: 23414600 DOI: 10.1017/S0033291713000184]

29 **McGorry PD**, Hartmann JA, Spooner R, Nelson B. Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* 2018; **17**: 133-142 [PMID: 29856558 DOI: 10.1002/wps.20514]

30 **van Os J**, Guloksuz S. A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry* 2017; **16**: 200-206 [PMID: 28498576 DOI: 10.1002/wps.20423]

31 **Evans MJ**, Kaufman MH. Establishment in culture of pluripotential cells from mouse embryos. *Nature* 1981; **292**: 154-156 [PMID: 7242681 DOI: 10.1038/292154a0]

32 **Krueger RF**, Eaton NR. Transdiagnostic factors of mental disorders. *World Psychiatry* 2015; **14**: 27-29 [PMID: 25655146 DOI: 10.1002/wps.20175]

33 **Zarrella I**, Russolillo LA, Caviglia G, Perrella R. Continuity and discontinuity between psychopathology of childhood and adulthood: a review on retrospective and prospective studies. *Res Psychother* 2017; **20**: 248 [PMID: 32913738 DOI: 10.4081/ripppo.2017.248]

34 **Sterba S**, Egger HL, Angold A. Diagnostic specificity and nonspecificity in the dimensions of preschool psychopathology. *J Child Psychol Psychiatry* 2007; **48**: 1005-1013 [PMID: 17915001 DOI: 10.1111/j.1469-7610.2007.01770.x]

35 **Kircanski K**, Zhang S, Stringaris A, Wiggins JL, Towbin KE, Pine DS, Leibenluft E, Brotman MA. Empirically derived patterns of psychiatric symptoms in youth: A latent profile analysis. *J Affect Disord* 2017; **216**: 109-116 [PMID: 27692699 DOI: 10.1016/j.jad.2016.09.016]

36 **Mennigen E**, Bearden CE. Psychosis Risk and Development: What Do We Know From Population-Based Studies? *Biol Psychiatry* 2020; **88**: 315-325 [PMID: 32061373 DOI: 10.1016/j.biopsych.2019.12.014]

37 **Rubino IA**, Frank E, Croce Nanni R, Pozzi D, Lanza di Scalea T, Siracusano A. A comparative study of axis I antecedents before age 18 of unipolar depression, bipolar disorder and schizophrenia. *Psychopathology* 2009; **42**: 325-332 [PMID: 19672135 DOI: 10.1159/000232975]

38 **American Psychiatric Association**. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington: American Psychiatric Association, 1994

39 **Steel Z**, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, Silove D. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol* 2014; **43**: 476-493 [PMID: 24648481 DOI: 10.1093/ije/dyu038]

40 **Noterdaeme M**, Schlamp D, Linder M, Kischel KH. [Analysis of comorbid psychiatric disorders in child and adolescent psychiatry using the standardised basic documentation]. *Psychiatr Prax* 2004; **31** Suppl 1: S126-S128 [PMID: 15570527 DOI: 10.1055/s-2004-828452]

41 **Alonso J**, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lépine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martínez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacín C, Romera B, Taub N, Vollebergh WA; ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project. 12-Month comorbidity patterns and associated factors in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004; 28-37 [PMID: 15128385 DOI: 10.1111/j.1600-0047.2004.00328.x]

42 **American Association for Public Opinion Research**. Standard Definitions Final Dispositions of Case Codes and Outcome Rates for Surveys. 2016. [cited 20 February 2021]. Available from: http://www.aapor.org/AAPOR_Main/media/publications/Standard-Definitions20169theditionfinal.pdf. Cited 6 February 2019

43 **McGlashan TH**, Walsh BC, Woods SW. The psychosis-risk syndrome. Handbook for diagnosis and follow-up. New York: Oxford University, 2010

44 **Schultze-Lutter F**, Marshall M, Koch E. Schizophrenia Proneness Instrument, Child and Youth version; Extended English Translation (SPI-CY EET). Rome, Italy: Giovanni Fioriti Editore s.r.l., 2012

45 **Fux L**, Walger P, Schimmelmann BG, Schultze-Lutter F. The Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY): practicability and discriminative validity. *Schizophr Res* 2013; **146**: 69-78 [PMID: 23473813 DOI: 10.1016/j.schres.2013.02.014]

46 **Sheehan DV**, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, Milo KM, Stock SL, Wilkinson B. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). *J Clin Psychiatry* 2010; **71**: 313-326 [PMID: 20331933 DOI: 10.4088/JCP.09m05305whi]

47 **Byrt T**, Bishop J, Carlin JB. Bias, prevalence and kappa. *J Clin Epidemiol* 1993; **46**: 423-429 [PMID: 8501467 DOI: 10.1016/0895-4356]

48 **Burn CC**, Pritchard J, Whay H. Observer reliability for working equine welfare assessment: Problems with high

prevalences of certain results. *Anim Welf* 2009; **18**: 177-187
49 **Burn CC**, Weir AA. Using prevalence indices to aid interpretation and comparison of agreement ratings between two or more observers. *Vet J* 2011; **188**: 166-170 [PMID: 20570535 DOI: 10.1016/j.tvjl.2010.04.021]
50 **Hager W**. Basics of planning experiments for testing empirical hypotheses in Psychology. In: Lüer G. [General Experimental Psychology]. Stuttgart: Fischer, 1987, 43-264
51 **Schultze-Lutter F**, Hubl D, Schimmelmann BG, Michel C. Age effect on prevalence of ultra-high risk for psychosis symptoms: replication in a clinical sample of an early detection of psychosis service. *Eur Child Adolesc Psychiatry* 2017; **26**: 1401-1405 [PMID: 28456857 DOI: 10.1007/s00787-017-0994-y]
52 **Walger H**, Antonucci LA, Pigoni A, Upthegrove R, Salokangas RKR, Lencer R, Chisholm K, Riecher-Rössler A, Haidl T, Meisenzahl E, Rosen M, Ruhrmann S, Kambeitz J, Kambeitz-Ilankovic L, Falkai P, Ruef A, Hietala J, Pantelis C, Wood SJ, Brambilla P, Bertolino A, Borgwardt S, Koutsouleris N, Schultze-Lutter F. Basic Symptoms Are Associated With Age in Patients With a Clinical High-Risk State for Psychosis: Results From the PRONIA Study. *Front Psychiatry* 2020; **11**: 552175 [PMID: 33312133 DOI: 10.3389/fpsyt.2020.552175]
53 **Theodoridou A**, Hengartner MP, Heekeren K, Dvorsky D, Schultze-Lutter F, Gerstenberg M, Walitza S, Rössler W. Influence of demographic characteristics on attenuated positive psychotic symptoms in a young, help-seeking, at-risk population. *Early Interv Psychiatry* 2019; **13**: 53-56 [PMID: 28417595 DOI: 10.1111/eip.12444]
54 **Orlic D**, Bodine DM. What defines a pluripotent hematopoietic stem cell (PHSC): will the real PHSC please stand up! *Blood* 1994; **84**: 3991-3994 [PMID: 7994018 DOI: 10.1182/blood.V84.12.3991.bloodjournal84123991]
55 **Woods SW**, Powers AR 3rd, Taylor JH, Davidson CA, Johannesen JK, Addington J, Perkins DO, Bearden CE, Cadenhead KS, Cannon TD, Cornblatt BA, Seidman LJ, Tsuang MT, Walker EF, McGlashan TH. Lack of Diagnostic Pluripotentiality in Patients at Clinical High Risk for Psychosis: Specificity of Comorbidity Persistence and Search for Pluripotential Subgroups. *Schizophr Bull* 2018; **44**: 254-263 [PMID: 29036402 DOI: 10.1093/schbul/sbx138]
56 **McGorry PD**, Purcell R, Hickie IB, Yung AR, Pantelis C, Jackson HJ. Clinical staging: a heuristic model for psychiatry and youth mental health. *Med J Aust* 2007; **187**: S40-S42 [PMID: 17908024 DOI: 10.5694/j.1326-5377.2007.tb01335.x]
57 **van Os J**, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* 2016; **15**: 118-124 [PMID: 27265696 DOI: 10.1002/wps.20310]
58 **Schultze-Lutter F**, Michel C, Ruhrmann S, Schimmelmann BG. Prevalence and clinical relevance of interview-assessed psychosis-risk symptoms in the young adult community. *Psychol Med* 2018; **48**: 1167-1178 [PMID: 28889802 DOI: 10.1017/S0033291717002586]
59 **Michel C**, Kutschal C, Schimmelmann B, Schultze-Lutter F. Convergent and concurrent validity of the Frankfurt Complaint Questionnaire as a screener for psychosis risk. *J Risk Res* 2016; **20**: 1-17 [DOI: 10.1080/13669877.2016.1179209]
60 **Schultze-Lutter F**, Renner F, Paruch J, Julkowski D, Klosterkötter J, Ruhrmann S. Self-reported psychotic-like experiences are a poor estimate of clinician-rated attenuated and frank delusions and hallucinations. *Psychopathology* 2014; **47**: 194-201 [PMID: 24192655 DOI: 10.1159/000355554]
61 **Moriyama TS**, van Os J, Gadelha A, Pan PM, Salum GA, Manfro GG, Mari JJ, Miguel EC, Rohde LA, Polanczyk GV, McGuire P, Bressan RA, Drukker M. Differences Between Self-Reported Psychotic Experiences, Clinically Relevant Psychotic Experiences, and Attenuated Psychotic Symptoms in the General Population. *Front Psychiatry* 2019; **10**: 782 [PMID: 31736802 DOI: 10.3389/fpsyt.2019.00782]
62 **Schultze-Lutter F**, Klosterkötter J, Gaebel W, Schmidt SJ. Psychosis-risk criteria in the general population: frequent misinterpretations and current evidence. *World Psychiatry* 2018; **17**: 107-108 [PMID: 29352561 DOI: 10.1002/wps.20498]
63 **Wong KK**, Raine A. Developmental Aspects of Schizotypy and Suspiciousness: a Review. *Curr Behav Neurosci Rep* 2018; **5**: 94-101 [PMID: 29577010 DOI: 10.1007/s40473-018-0144-y]
64 **Wong KK**, Raine A. Peer Problems and Low Self-esteem Mediate the Suspicious and Non-suspicious Schizotypy-Reactive Aggression Relationship in Children and Adolescents. *J Youth Adolesc* 2019; **48**: 2241-2254 [PMID: 31520236 DOI: 10.1007/s10964-019-01125-9]
65 **Bird JC**, Evans R, Waite F, Loe BS, Freeman D. Adolescent Paranoia: Prevalence, Structure, and Causal Mechanisms. *Schizophr Bull* 2019; **45**: 1134-1142 [PMID: 30534970 DOI: 10.1093/schbul/sby180]
66 **Bird JC**, Fergusson EC, Kirkham M, Shearn C, Teale AL, Carr L, Stratford HJ, James AC, Waite F, Freeman D. Paranoia in patients attending child and adolescent mental health services. *Aust N Z J Psychiatry* 2021; 4867420981416 [PMID: 33423520 DOI: 10.1177/0004867420981416]
67 **Martinez AP**, Wickham S, Rowse G, Milne E, Bentall RP. Robust association between autistic traits and psychotic-like experiences in the adult general population: epidemiological study from the 2007 Adult Psychiatric Morbidity Survey and replication with the 2014 APMS. *Psychol Med* 2020; 1-7 [PMID: 32441234 DOI: 10.1017/S0033291720001373]
68 **Pinkham AE**, Sasson NJ, Beaton D, Abdi H, Kohler CG, Penn DL. Qualitatively distinct factors contribute to elevated rates of paranoia in autism and schizophrenia. *J Abnorm Psychol* 2012; **121**: 767-777 [PMID: 22686868 DOI: 10.1037/a0028510]
69 **Muñoz-Negro JE**, Prudent C, Gutiérrez B, Cervilla JA. Paranoia and risk of personality disorder in the general population. *Personal Ment Health* 2019; **13**: 107-116 [PMID: 30989831 DOI: 10.1002/pmh.1443]
70 **Lee R**. Mistrustful and Misunderstood: A Review of Paranoid Personality Disorder. *Curr Behav Neurosci Rep* 2017; **4**: 151-165 [PMID: 29399432 DOI: 10.1007/s40473-017-0116-7]
71 **Shi TC**, Pagliaccio D, Cyr M, Simpson HB, Marsh R. Network-based functional connectivity predicts response to exposure therapy in unmedicated adults with obsessive-compulsive disorder. *Neuropsychopharmacology* 2021; **46**: 1035-1044 [PMID: 33446895 DOI: 10.1038/s41386-020-00929-9]
72 **Michel C**, Flückiger R, Kindler J, Hubl D, Kaess M, Schultze-Lutter F. The trait-state distinction between schizotypy and clinical high risk: results from a one-year follow-up. *World Psychiatry* 2019; **18**: 108-109 [PMID: 30600631 DOI: 10.1002/wps.20595]
73 **Flückiger R**, Michel C, Grant P, Ruhrmann S, Vogeley K, Hubl D, Schimmelmann BG, Klosterkötter J, Schmidt SJ, Schultze-Lutter F. The interrelationship between schizotypy, clinical high risk for psychosis and related symptoms:

Cognitive disturbances matter. *Schizophr Res* 2019; **210**: 188-196 [PMID: 30683524 DOI: 10.1016/j.schres.2018.12.039]
74 **Jimeno N**, Gomez-Pilar J, Poza J, Hornero R, Vogeley K, Meisenzahl E, Haidl T, Rosen M, Klosterkötter J, Schultze-Lutter F. Main Symptomatic Treatment Targets in Suspected and Early Psychosis: New Insights From Network Analysis. *Schizophr Bull* 2020; **46**: 884-895 [PMID: 32010940 DOI: 10.1093/schbul/sbz140]
75 **Kay SR**, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261-276 [PMID: 3616518 DOI: 10.1093/schbul/13.2.261]
76 **Driver DI**, Thomas S, Gogtay N, Rapoport JL. Childhood-Onset Schizophrenia and Early-onset Schizophrenia Spectrum Disorders: An Update. *Child Adolesc Psychiatr Clin N Am* 2020; **29**: 71-90 [PMID: 31708054 DOI: 10.1016/j.chc.2019.08.017]
77 **Hunter EC**, Sierra M, David AS. The epidemiology of depersonalisation and derealisation. A systematic review. *Soc Psychiatry Psychiatr Epidemiol* 2004; **39**: 9-18 [PMID: 15022041 DOI: 10.1007/s00127-004-0701-4]
78 **Michal M**, Beutel ME. [Depersonalisation/derealization - clinical picture, diagnostics and therapy]. *Z Psychosom Med Psychother* 2009; **55**: 113-140 [PMID: 19402018 DOI: 10.13109/zptm.2009.55.2.113]
79 **Büetiger JR**, Hubl D, Kupferschmid S, Schultze-Lutter F, Schimmelmann BG, Federspiel A, Hauf M, Walther S, Kaess M, Michel C, Kindler J. Trapped in a Glass Bell Jar: Neural Correlates of Depersonalization and Derealization in Subjects at Clinical High-Risk of Psychosis and Depersonalization-Derealization Disorder. *Front Psychiatry* 2020; **11**: 535652 [PMID: 33024435 DOI: 10.3389/fpsyt.2020.535652]
80 **Dewe H**, Watson DG, Kessler K, Braithwaite JJ. The depersonalized brain: New evidence supporting a distinction between depersonalization and derealization from discrete patterns of autonomic suppression observed in a non-clinical sample. *Conscious Cogn* 2018; **63**: 29-46 [PMID: 29929064 DOI: 10.1016/j.concog.2018.06.008]
81 **Čolić J**, Bassett TR, Latysheva A, Imboden C, Bader K, Hatzinger M, Mikoteit T, Lieb R, Gloster AT, Hoyer J. Depersonalization and derealization in embarrassing social interactions: an experience sampling study in social phobia, major depression and controls. *J Anxiety Disord* 2020; **70**: 102189 [PMID: 32070861 DOI: 10.1016/j.janxdis.2020.102189]
82 **Hallings-Pott C**, Waller G, Watson D, Scragg P. State dissociation in bulimic eating disorders: an experimental study. *Int J Eat Disord* 2005; **38**: 37-41 [PMID: 15971242 DOI: 10.1002/eat.20146]
83 **Kaufman J**, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997; **36**: 980-988 [PMID: 9204677 DOI: 10.1097/00004583-199707000-00021]
84 **Healy C**, Campbell D, Coughlan H, Clarke M, Kelleher I, Cannon M. Childhood psychotic experiences are associated with poorer global functioning throughout adolescence and into early adulthood. *Acta Psychiatr Scand* 2018; **138**: 26-34 [PMID: 29855047 DOI: 10.1111/acps.12907]
85 **Niles HF**, Walsh BC, Woods SW, Powers AR 3rd. Does hallucination perceptual modality impact psychosis risk? *Acta Psychiatr Scand* 2019; **140**: 360-370 [PMID: 31355420 DOI: 10.1111/acps.13078]
86 **Lehembre-Shiah E**, Leong W, Brucato G, Abi-Dargham A, Lieberman JA, Horga G, Girgis RR. Distinct Relationships Between Visual and Auditory Perceptual Abnormalities and Conversion to Psychosis in a Clinical High-Risk Population. *JAMA Psychiatry* 2017; **74**: 104-106 [PMID: 27851840 DOI: 10.1001/jamapsychiatry.2016.3055]
87 **Ciarleglio AJ**, Brucato G, Masucci MD, Altschuler R, Colibazzi T, Corcoran CM, Crump FM, Horga G, Lehembre-Shiah E, Leong W, Schobel SA, Wall MM, Yang LH, Lieberman JA, Girgis RR. A predictive model for conversion to psychosis in clinical high-risk patients. *Psychol Med* 2019; **49**: 1128-1137 [PMID: 29950184 DOI: 10.1017/S003329171800171X]
88 **Zielasek J**, Gaebel W. [Schizophrenia and other primary psychotic disorders in ICD-11]. *Fortschr Neurol Psychiatr* 2018; **86**: 178-183 [PMID: 29621821 DOI: 10.1055/s-0044-101832]
89 **Klosterkötter J**. The meaning of basic symptoms for the genesis of the schizophrenic nuclear syndrome. *Jpn J Psychiatry Neurol* 1992; **46**: 609-630 [PMID: 1487845 DOI: 10.1111/j.1440-1819.1992.tb00535.x]
90 **Campion J**, Bhui K, Bhugra D; European Psychiatric Association. European Psychiatric Association (EPA) guidance on prevention of mental disorders. *Eur Psychiatry* 2012; **27**: 68-80 [PMID: 22285092 DOI: 10.1016/j.eurpsy.2011.10.004]
91 **Kirkbride JB**, Fearon P, Morgan C, Dazzan P, Morgan K, Tarrant J, Lloyd T, Holloway J, Hutchinson G, Leff JP, Mallett RM, Harrison GL, Murray RM, Jones PB. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Arch Gen Psychiatry* 2006; **63**: 250-258 [PMID: 16520429 DOI: 10.1001/archpsyc.63.3.250]
92 **Schultze-Lutter F**, Schimmelmann BG, Michel C. Clinical high-risk of and conversion to psychosis in the community: A 3-year follow-up of a cohort study. *Schizophr Res* 2021; **228**: 616-618 [PMID: 33234428 DOI: 10.1016/j.schres.2020.11.032]
93 **Carpenter WT**. Attenuated psychosis syndrome: need for debate on a new disorder. *Psychopathology* 2014; **47**: 287-291 [PMID: 25060627 DOI: 10.1159/000365221]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 450-469

DOI: 10.5498/wjp.v12.i3.450

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Sergio E Starkstein, Ricardo E Jorge, Jessica Aloisi, Marcelo L Berthier, Guadalupe Dávila

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Azocar I, Lin SK

Received: June 30, 2021
Peer-review started: June 30, 2021
First decision: July 28, 2021
Revised: August 13, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 19, 2022

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Guadalupe Dávila, Department of Psychobiology and Methodology of Behavioral Science, Faculty of Psychology and Speech Therapy, University of Malaga, Malaga 29071, Spain

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Jessica Aloisi, Marcelo L Berthier, Guadalupe Dávila, Cognitive Neurology and Aphasia Unit, Centro de Investigaciones Médico-Sanitarias, University of Malaga, Malaga 29010, Spain

Lisa Edelkraut, Diana López-Barroso, María José Torres-Prioris, Marcelo L Berthier, Guadalupe Dávila, Instituto de Investigación Biomédica de Málaga, University of Malaga, Malaga 29010, Spain

Sergio E Starkstein, School of Psychiatry and Neurosciences, The University of Western Australia, Perth 6009, Australia

Ricardo E Jorge, Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX 77030, United States

Corresponding author: Guadalupe Dávila, PhD, Associate Professor, Department of Psychobiology and Methodology of Behavioral Science, Faculty of Psychology and Speech Therapy, University of Malaga, Campus de Teatinos, s/n, Malaga 29071, Spain.
mgdavila@uma.es

Abstract

BACKGROUND

Neuropsychiatric symptoms (NPS) have been insufficiently examined in persons with aphasia (PWA) because most previous studies exclude participants with language and communication disorders.

AIM

To report a two-part study consisting of a literature review and an observational study on NPS in post-stroke aphasia.

METHODS

Study 1 reviewed articles obtained from PubMed, PsycINFO, Google Scholar and Cochrane databases after cross-referencing key words of post-stroke aphasia to NPS and disorders. Study 2 examined language deficits and activities of daily

living in 20 PWA (median age: 58, range: 28-65 years; 13 men) with the Western Aphasia Battery-Revised and the Barthel Index, respectively. Informants of these 20 PWA were proxy-evaluated with the Neuropsychiatric Inventory and domain-specific scales, including the Stroke Aphasia Depression Questionnaire-10 item version and the Starkstein Apathy Scale. In addition, an adapted version of the Hospital Anxiety and Depression Scale was directly administered to the PWA themselves. This observational study is based on the baseline assessment of an intervention clinical trial (EudraCT: 2017-002858-36; ClinicalTrials.gov identifier: NCT04134416).

RESULTS

The literature review revealed a broad spectrum of NPS in PWA, including depression, anxiety, apathy, agitation/aggression, eating and sleep disorders, psychosis, and hypomania/mania. These findings alert to the need for improving assessment and treatment approaches of NPS taking into consideration their frequent occurrence in PWA. Study 2 showed that the 20 participants had mild- to-moderate aphasia severity and were functionally independent. A wide range of comorbid NPS was found in the post-stroke aphasic population (median number of NPS: 5, range: 1-8). The majority of PWA (75%) had depressive symptoms, followed by agitation/aggression (70%), irritability (70%), anxiety (65%) and appetite/eating symptoms (65%). Half of them also presented symptoms of apathy, whereas euphoria and psychotic symptoms were rare (5%). Domain-specific scales revealed that 45% of participants had apathy and 30% were diagnosed with depression and anxiety.

CONCLUSION

Concurrent NPS are frequent in the chronic period of post-stroke aphasia. Therefore, further research on reliable and valid assessment tools and treatment for this aphasic population is strongly warranted.

Key Words: Aphasia; Stroke; Neuropsychiatric symptoms; Anxiety; Apathy; Depression

Core Tip: The literature on neuropsychiatric disorders in persons with aphasia (PWA) is limited, given that this population is usually excluded from neuropsychiatric evaluations. This article provides a state-of-art analysis on the prevalence, nature, pathophysiology, assessment, and treatment of neuropsychiatric symptoms (NPS) in PWA. We also report findings from a proof-of-concept observational study that included 20 PWA after chronic left hemisphere lesions which identified a spectrum of NPS, primarily depression, irritability, agitation, anxiety, and apathy.

Citation: Edelkraut L, López-Barroso D, Torres-Prioris MJ, Starkstein SE, Jorge RE, Aloisi J, Berthier ML, Dávila G. Spectrum of neuropsychiatric symptoms in chronic post-stroke aphasia. *World J Psychiatry* 2022; 12(3): 450-469

URL: https://www.wjgnet.com/2220-3206/full/v12/i3/450.htm

DOI: https://dx.doi.org/10.5498/wjp.v12.i3.450

INTRODUCTION

Aphasia, defined as the partial or complete loss of language caused by brain damage is one of the most frequent and devastating sequelae of stroke[1-3]. In fact, about 21% to 38% of acute stroke individuals have aphasia[1] and 25% to 50% of them still show residual language and communication deficits in the chronic period[4]. Before focusing on neuropsychiatric symptoms (NPS) associated with post-stroke aphasia (PSA), below we present a brief overview on the impact of aphasia in the acute and chronic stroke periods as well as the traditional and emerging evaluation approaches used to classify language deficits and to implements adequate therapies.

Overview on PSA

PSA may be associated with worse outcomes in acute/subacute (onset to week 12), chronic (week 13-week 52) and very chronic (week 53 onwards) periods than strokes unassociated with aphasia[5,6]. This is the consequence of the increased length of hospital stay and inpatient medical complications, including those caused by the neurological disability itself. The course of aphasia during the sub-acute and chronic stroke periods may also be complicated by reduced functional independence, longer stays

in rehabilitation settings, reduced adherence to aphasia therapy, particularly in older people, and poorer quality of life and activities of daily living[1,5,6].

Stroke lesions causing aphasia usually affect the left hemisphere (dominant for language in most right handed individuals) in the distribution of the middle cerebral artery territory with damage to the perisylvian language core and its subcortical structures (basal ganglia, internal capsule and white matter). The resulting syndromes are chiefly characterized by impaired repetition in the context of impaired spontaneous speech, and variable deficits in auditory comprehension and naming. These syndromes are known as the "classical" or "perisylvian" aphasias (Broca's, Wernicke's, conduction and global) which roughly account for 80% of all cases and have poorer prognosis than other types of aphasias[7]. The rest of post-stroke aphasic syndromes, representing 20% of all cases, are associated with infarctions in arterial "borderzone" vascular territories (*i.e.*, the junction between anterior and middle cerebral arteries). These aphasias (motor, sensory and mixed transcorticals and anomic) are characterized by preserved repetition and echolalia with variable deficits in other language domains (spontaneous speech, comprehension and naming) and usually have better long-term prognosis than perisylvian aphasias[8]. Whereas infarctions account for around 80% of cases, hemorrhages are less frequent[1]. The clinical profile of acute and chronic PSA is heterogeneous with a variable degree of involvement of phonology, semantics, fluency and connected speech production. Traditional classifications of aphasia dichotomically separate syndromes (*e.g.*, Broca's, Wernicke's, transcortical) on the basis of differences in surface language deficits (fluent/nonfluent speech, impaired/preserved comprehension). In spite of this coarse division, the syndrome-based approach (*e.g.*, Broca's aphasia) is still retained in clinical practice to predict prognosis, manage recovery in acute clinical settings, and inform patients and relatives[1]. However, using this approach the aphasia profile in more than a quarter of stroke patients is unclassifiable and there is no clear-cut correspondence between lesion location and aphasia profile particularly in chronic cases. Even more important is that clinical labels (*e.g.*, Broca's aphasia) provide little information on the underlying language and cognitive deficits and knowing the status of these deficits is crucial to select adequate model-based therapies. Therefore, since understanding the neural mechanisms underpinning language processing is important for diagnosis and treatment, current accounts use data-driven approaches for aphasia classification and lesion-based predictions of recovery[9,10]. Moreover, it is well known that persons with aphasia (PWA) have an increased incidence of NPS compared to patients with other chronic diseases[2,11], greatly influencing rehabilitation responses, quality of life, and long-term functional outcomes[12-15]. In general, NPS are a frequent and challenging consequence of stroke, derived from the crossroad of lesion-related brain factors and psychological distress related to the event and its functional impact in daily life[16,17]. Several comprehensive reviews dealing with NPS in post-stroke patients have been reported[18-22] and a recent original study evaluating 518 non-aphasic stroke patients found that half of the sample presented at least one NPS based on Neuropsychiatric Inventory (NPI)[23,24]. However, one relevant limitation of the above studies is that they exclude aphasic participants due to the inherent linguistic-assessment difficulties[25-29]. The aims of the present study were thus twofold. In study 1 the objective was to carry out a narrative review on NPS in PSA, covering data of prevalence, risk factors, assessment tools, pathophysiology, and treatment options. Study 2 reports original data from 20 PWA in the chronic phase after suffering a left hemisphere lesion who were evaluated with the NPI and domain-specific psychiatric scales to examine the frequency and severity of NPS.

MATERIALS AND METHODS

Study 1: Literature review

Search strategy: The authors conducted a literature search on Medline/PubMed, PsycINFO, Google Scholar and Cochrane databases from inception to June 2021. Key search terms for NPS or disorders were cross-referenced to PSA. The following terms were included: "aphasia" or "PSA" or "acquired language impairment" or "acquired language disorder" or "post-stroke linguistic disorder" or "post-stroke linguistic impairment" AND "neuropsychiatric*" or "neuropsychiatry" "psychy*" or "neurobehav*" or "behavio[u]r*" or "emotion*" or "mood" or "affect*" or "depression" or "depressive" or "dysthym*" or "distress" or "apathy" or "apathetic" or "motivat*" or "drive" or "indifferen*" or "anxiety" or "anxious*" or "stress" or "phobia" or "fear" "catastrophic reaction" or "disinhibit*" or "impulsiv*" or "agitat*" or "aggress*" or "anger" or "irritab*" or "psycho*" or "hallucination" or "delusion" or "delusive" or "prodrom* or "sleep" or "appetite" or "eating" or "elation" or "pathological laugh*" or "euphoria" or "mania" or "bipolar" or "quality of life". Articles including the terms "stroke" or "post-stroke" or "cerebrovascular" AND "neuropsychy*" or "neurobehav*" or "emotion" or "depression" were also screened for aphasia terms within its full text and considered for inclusion. This search strategy was analogous to other published reviews on post-stroke depression[30,31].

Titles, abstracts, and full texts were reviewed by 2 independent observers (MB and LE) to assess inclusion criteria and read the selected articles for final incorporation. In addition, references of all

selected articles were searched for studies that could also meet inclusion criteria. Possible investigator divergences were compared and resolved through discussion. A third observer (GD) was available for an appeal if disagreements existed. Studies were included if: (1) Participants had a clear assessment of aphasia and presented a single or multiple NPS or disorders; (2) NPS or disorders were assessed with validated scales or through clearly defined criteria; (3) participants were adults (*i.e.*, 18 years or older); (4) participants were only affected by cerebrovascular lesions; and (5) articles were written in English.

This narrative review prioritized manuscripts in the following order: (1) Meta-analysis or systematic reviews; (2) randomized clinical trials; (3) cohort studies; and (4) case-reports. When only case-reports were retrieved, articles including neuroimaging measures were prioritized. Studies including participants with pre-stroke neurodegenerative (*e.g.*, primary progressive aphasia, dementia) or premorbid psychiatric disorders that would make differential diagnoses difficult were excluded from the search.

Study 2: A proof-of-concept study of neuropsychiatric symptoms in chronic post-stroke aphasia

Study design and subject selection: The focus of this study was the assessment of the frequency of NPS at baseline of an intervention trial in PWA after stroke (EudraCT:2017-002858-36; ClinicalTrials.gov identifier: NCT04134416). The study included 20 chronic PWA (median age of participants: 58, range: 28-65 years; 13 men) evaluated at the Unit of Cognitive Neurology and Aphasia at the University of Malaga, Spain. A consecutive series of participants meeting the following criteria were included: (1) Age between 18 and 70 years; (2) right handedness (80 points in the Edinburgh handedness inventory)[32]; (3) Spanish as native language; (4) left-hemisphere stroke lesions; and (5) diagnosis of aphasia established by a score in the aphasia quotient (AQ) of the Western Aphasia Battery-Revised (WAB-R) ≤ 93.8 points[33]. Exclusion criteria were: (1) Dysarthria without aphasia; (2) bilateral lesions; (3) increased risk of a new stroke or unstable neurological condition (*e.g.*, transient ischemic attacks); (4) history of pre-stroke dementia and/or psychiatric disorders (schizophrenia, major depression, bipolar disorder, anxiety disorders); (5) alcohol and substance use or abuse; or (6) coexistence of aphasia with post-stroke dementia. Table 1 shows the demographic and clinical characteristics of the group. Participants with aphasia also underwent comprehensive neurological, neuropsychological, and neuroradiological assessments. Participants who were taking psychotropic drugs (antidepressants or tranquillizers) and/or antiepileptics were not excluded, but all prescribed medications were maintained stable during the study. Written informed consent was obtained from all participants and informants after providing detailed descriptions of the study. None of the participants or informants refused to take part in the investigation. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethical Research of Drugs Committee Provincial of Malaga, Spain and the Spanish Drug and Healthcare Products Agency.

Functional evaluation: The Barthel Index was employed to measure the degree of assistance required by each person on 10 items of mobility and self-care regarding activities of daily living. A higher score (maximum: 100 points) reflects a better competence to function independently[34].

Language evaluation: The type and severity of aphasia were evaluated with the WAB-R[33]. The profile of aphasia was made according to the taxonomic criteria of the WAB-R and aphasia severity was rated according to the scoring of the AQ of WAB-R. Lower AQ scores indicate more severe aphasia.

Multidomain neuropsychiatric evaluation: Relatives in close contact with participants were interviewed using the NPI[24]. Although this semi-structured interview was originally developed to evaluate the spectrum of NPS in patients with dementia, its use has later been expanded to assess people with stroke and other neurological conditions[23,35-37]. The NPI assesses the frequency and severity of psychological and behavioral symptoms grouped into 12 categories: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor behavior, appetite, and sleep/nighttime disturbances. The questions pertain to changes in the patient's behavior since the onset of the stroke and, if so, whether the altered behavior was present during the last month. For the purpose of this study, the presence of symptoms was determined by the number of patients with scores > 0 in the respective symptom[23]. Frequency scores range from 1 to 4 (where 1= occasionally, less than once per week; 4 = very frequently, once, or more per day or continuously). Severity scores range from 1 to 3 (where 1 = mild, 2 = moderate, 3 = severe). Each domain´s final composite score is the product of the frequency times the severity, with a maximum score of 12 points.

Domain-specific neuropsychiatric evaluation: Since the NPI does not provide specific cut-off scores for neuropsychiatric diagnoses, domain-specific scales that specifically assessed depression, anxiety, and apathy disorders were also used. These scales were selected because all of them have previously been used in patients with stroke[38-40]. After data interpretation, neuropsychiatric diagnoses were blindly assessed by an expert behavioral neurologist who was blinded to the outcome goals of this study.

Hospital Anxiety and Depression Scale: The Hospital anxiety and depression scale (HADS) is a 14-item instrument evaluating both anxiety and depression (seven items for each subscale)[39]. For each

Table 1 Demographic and clinical characteristics of persons with aphasia

Patient	Sex/handedness	Age (yr)	Education (yr)	Stroke duration (mo)	Barthel index[1]	Lesion volume (cm^3)	Aphasia type[2]	Antidepressants
1	F/R	50	12	80	80	113.33	Conduction	Sertraline
2	M/R	61	14	103	90	163.02	Broca	Citalopram
3	M/R	49	17	61	90	210.38	Broca	No
4	M/R	42	11	45	100	99.31	Anomic	Citalopram
5	M/R	63	8	11	85	23.16	Conduction	No
6	F/R	58	12	126	95	188.76	Anomic	No
7	M/R	60	12	45	60	44.96	Anomic	No
8	M/R	54	14	44	90	66.97	Anomic	No
9	M/R	51	13	7	80	225.69	Anomic	Amitriptyline
10	M/R	54	10	19	90	282.59	Wernicke	No
11	F/R	58	15	66	95	98.84	Broca	No
12	F/R	61	12	17	45	4.47	Anomic	Sertraline
13	M/R	32	18	10	100	34.01	Wernicke	Sertraline
14	M/R	49	8	13	80	17.45	Anomic	No
15	F/R	28	8	6	100	51.26	Anomic	No
16	F/R	65	17	13	100	26.10	Wernicke	No
17	M/R	64	17	120	100	157.58	Anomic	No
18	F/R	65	17	13	75	158.25	Broca	No
19	M/R	58	8	17	100	69.66	Wernicke	No
20	M/R	63	17	10	100	50.43	Wernicke	Fluoxetine
Median		58	12.5	18	90	84.25		

[1]Barthel Index measures participant´s independence in activities of daily living;
[2]Type of aphasia was obtained from fluency, comprehension, and repetition subtest of the Western Aphasia Battery-Revised.
F: Female; M: Male; R: Right-handed.

statement, the participant chooses one of four responses (*e.g.*, 'definitely as much', 'not quite as much', 'only a little', 'hardly at all')[39]. Scores for each subscale range from 0 to 21 points and a cut-off scores of 8 points are used for each scale. In the present study, the HADS was directly administered to the PWA. To overcome comprehension deficits of participants, each question together with the alternative responses were printed in large font letters on individual pages and the items were read aloud by the examiner who then scored a reliable answer. Cronbach's alpha for HADS-Anxiety varies from 0.68-0.93 and for HADS-Depression from 0.67-0.90[41].

Starkstein Apathy Scale: This scale was developed to assess apathy in patients with neurological diseases including stroke[40,42]. Informants of the participants were requested to answer the Starkstein Apathy Scale (SAS)'s 14 items, each of which scores on a 0–3 scale[40]. The cut-off score of the SAS is 14 (maximum score 42) and higher scores indicate more severe apathy. The scale has an excellent Cronbach's α of 0.939[43].

Stroke Aphasia Depression Questionnaire: The stroke aphasia depression questionnaire (SADQ)-10 was developed to assess depressed mood in patients with aphasia[38]. It contains 10 items answered on a 0-3 scale by the principal informant on behalf of the PWA. The cut-off score of the SADQ-10 is 14 points (maximum score 30)[44]. Participants are classified as having depression when they score ≥ 14 points[38], or classified with subthreshold depression[45] when the SADQ-10 score is ≥ 6[46]. The questionnaire has an excellent internal consistency, with a Cronbach's alpha of 0.80 and split-half reliability of $r = 0.81$[44].

Statistical analysis

We computed descriptive statistics for demographic and clinical data. In addition, non-parametrical two-tailed Spearman's correlations on NPI scores and domain-specific instruments (AS, HADS and SAQ21) were performed. Statistical analysis regarding the number of NPS based on demographic and clinical variables were obtained with non-parametric independent samples Mann-Whitney U test and Kruskal-Wallis test. All statistical tests were two-tailed, and the significance threshold was set at $P < 0.05$. Analyses were carried out using SPSS v.21 and JASP (2020) software.

Lesion overlap

For the purpose of the current study, only T_1-weighted magnetic resonance images (MRI) were acquired at the baseline assessment to delineate the lesion of each participant with aphasia. The MRI sequence was acquired on a 3-T MRI scanner (Philips Intera, Amsterdam, The Netherlands), Release 3.2.3.4, with a MASTER gradient system (nominal maximum gradient strength = 30 mT/m, maximum slew rate = 150 mT/m/ms), equipped with a six-channel Philips SENSE head coil. Lesions were manually drawn in native space by DL-B and MJT-P, who were blind to all clinical data outcomes at the moment of the lesion delineation. Lesion maps were drawn by using Mricron software[47] on a slice-by-slice basis. Lesion overlap maps were created as follow: first, individual lesion maps and T_1-weighted images were reoriented according to the anterior commisure. To achieve optimal normalization of the lesions and the T_1-weighted images, cost function masking was applied during the preprocessing[48]. T_1-weighted images after masking out individual lesions were segmented into different tissues and the resulting parameters were used to normalize both the T_1-weighted images and the lesion masks to Montreal Neurological Institute space. Normalized lesion masks were smoothed with a 3 mm FWHM kernel and binarised. The overlap of the resulting binarised masks was performed with ImCalc. All these processing steps were performed with SPM12 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm12).

RESULTS

Study 1: Literature review

One hundred fourteen articles covering PSA and NPS (disorders) were included in this narrative review. The studied publications focused primarily on assessment/diagnosis of depression and anxiety (n = 34/29.8%) and on intervention approaches (n = 24/20.5%). Few articles covered prevalence data of NPS in PWA (n = 6/5.2%), risk factors (n = 5/4.2%) or pathophysiological mechanisms (n = 7/6.1%). Over half of all articles covered depression (n = 60/52.6%), 21 articles (18.4%) examined anxiety, and 12 articles (10.5%) referred to quality of life in PWA. Systematic reviews and meta-analysis accounted for 16.6% of all included articles (n = 19). Below, we present the synthesis of published data on depression, anxiety, apathy, agitation/aggression, mania, and psychosis.

Depression: The co-occurrence of stroke and aphasia is a stressful life event resulting in mood alterations and depression[11]. In fact, post-stroke depression has been identified as one of the most frequent and long-term sequela of PWA[11,26,49,50]. The disorder is categorized in the diagnostic and statistical manual for mental disorder-fifth edition (DSM-5) as "mood disorders due to another medical condition" such as stroke with depressive features, major depressive-like episode, or mixed-mood features (simultaneous depression and manic features)[30,51]. A diagnosis of major depression includes depressed mood and/or anhedonia/Loss of interest alongside four other symptoms (weight loss/gain, insomnia/hypersomnia, psychomotor agitation/retardation, fatigue, feelings of worthlessness, diminished concentration, and suicidal ideation) lasting for two or more weeks, and having an impact on daily functioning[51].

Depressive symptoms are associated with communication impairments following stroke, but the prevalence of depression in PWA is seldomly reported[26,28,45,52]. However, if any NPS are reported in PWA it is usually depression. Prevalence of this disorder ranges from 52%[53] to 62%[54] of PWA one year post-stroke, and this incidence is higher than in the overall stroke population[53-56]. As for risk factors, the presence of aphasia augments the chance of developing depressive symptoms[21,29,53,54]. Moreover, depressive symptoms may account for a significant variance in functional communication after acquired aphasia[57] and persons with Broca's aphasia (non-fluent verbal production with mild impairment in comprehension) are almost 9 times more likely to suffer depression compared to Wernicke's patients (fluent speech with impaired auditory and reading comprehension)[58]. Regarding aphasia evolution, Herrmann *et al*[59] compared single left-sided acute to chronic PWA and depression and found no significant between-group differences on depression sum-scores, age, sex, or severity of hemiparesis. On the other hand, Kauhanen *et al*[60] stated that aphasia increases the risk of developing depression in the chronic phase of stroke (> 6 mo of evolution)[60].

In the absence of suitable biological markers, the assessment and diagnosis of depression must rely on the results of clinical evaluations and psychometric testing[61]. To date, only a handful of instruments for the assessment of clinical depression in PWA have been proposed[26,62,63]. Among the

most common are the SADQ-21 and its shortened version (SADQ-10)[38], the Aphasic Depression Rating Scale[64], the Signs of Depression scale[65], or the Depression Intensity Scale Circles[66]. Non-verbal measurements, such as the Dynamic Visual Analogue Mood Scale[67] represent an important step forward in assessing mood in people with language impairments[68] while objective acoustic measures related to affective state change in the speech of PWA are also being developed[69]. On the other hand, the ROMA consensus statements highlight the general health questionnaire-12 for the assessment of emotional wellbeing in PWA[70] In addition, in PWA showing mild deficits in auditory comprehension, it is feasible to use well-known testing scales (*e.g.*, Beck Depression Inventory, the Hamilton Depression Rating Scale or the HADS[27,71-73]).

Causal factors of depression after stroke are probably multifactorial. Alterations in monoamine neurotransmitter systems, higher levels of glutamate in the synaptic cleft, hypothalamic–pituitary–adrenal axis abnormalities, anomalous neurotrophic responses, and an excess of proinflammatory cytokines have all been linked to the pathogenesis of depression after stroke[26,31,74]. The idea that the risk of depression after stroke is influenced by lesion location is still controversial[75]. The hypothesis was first proposed over 30 years ago by Robinson's group reporting that left-hemisphere strokes, especially in frontal region, were associated with depressive disorders[76,77]. Many replication studies have been carried out since then, but results remain inconclusive. Systematic reviews performed by Carson *et al*[78] and Wei *et al*[79] found no support for a higher frequency of depression in frontal left-hemisphere stroke lesions. As Wei *et al*[79] discuss, most patients with severe aphasia are excluded from studies, and the frequency of depression in left-hemisphere patients may be underestimated. However, a multivariate lesion-symptom mapping study found a significant association between the severity of depression scores and lesions affecting the left dorsolateral prefrontal cortex in 39 PWA and chronic stroke[80]. Therefore, a coherent explanatory model, able to integrate the underlying pathophysiological mechanisms of depression in PWA, still remains to be formulated.

Therapeutic interventions to alleviate depression in PWA are still scarce[81]. In fact, less than one percent of PWA receive direct treatment for psychological distress[82]. In a systematic review of rehabilitation interventions for the prevention and treatment of depression in PWA Baker *et al*[83] highlight that PWA with mild depression may benefit from psychosocial-type treatments, whereas no evidence was found for the treatment of moderate to severe depression. A systematic review by Wray *et al*[84] for self-management interventions (*i.e.*, decision-making, problem solving, goal setting) could also not clarify whether these approaches were suitable for PWA, especially with moderate or severe aphasia. More recent reports show that the employment of two weeks of Intensive Language-Action Therapy has proven effective in reducing not only language deficits but also low mood in persons with fluent and non-fluent aphasias[71,85]. This is in line with Baker *et al*[83]'s statement, who suggested that treatment strategies for the improvement of physical, cognitive and communication functions can have a beneficial effect on both rehabilitation and depression outcomes in PWA. A randomized controlled trial for PWA, comparing behavioral therapy and usual care with a usual care control, showed significant improvement of affective symptomatology in the experimental group at three and six months post-intervention[86]. The development of solution-focused psychotherapy approaches, in addition to behavioral activation therapies, specifically tailored for PWA are also under way[82,87,88]. No studies have been published about the pharmacological treatment of depressed PWA. Neuromodulation techniques, such as transcranial direct current stimulation or repetitive transcranial magnetic stimulation have shown promise for the treatment of depression in PWA[89-91].

Anxiety: Adult anxiety comprises a class of conditions that includes generalized anxiety disorder, panic disorder, and phobias[51,92]. In the context of PWA, the DSM-5 classifies these conditions as anxiety disorders due to another medical condition[51] and clinical criteria are disproportionate fear, apprehension of danger, restlessness and day-to-day distress[93-95]. PWA regularly report feeling anxious when employing language to communicate[96]. In some patients, anxiety during language testing can escalate quickly to frustration, transient bursts of tears, eventually leading to requests of interrupting testing (catastrophic reactions)[97-99]. Such reactions are usually associated to non-fluent aphasias due to anterior left-hemisphere or basal ganglia lesions[100,101]. It is noteworthy that anxiety has received comparatively less attention in PWA than depression[94,101]. Impairments in the ability to communicate is one the most significant sources of stress for PWA[102,103]. To date, the prevalence of anxiety among PWA is estimated to be around 44%, in contrast to the 18%-25% of stroke survivors without language disorders[94,104,105]. Schöttke *et al*[106] however, find a slightly lower prevalence of both anxiety (29%) and depression (38%) in acute PWA and people with post-stroke anomia. As for risk factors, Pompon *et al*[107] indicates that PWA are at higher risk for experiencing chronic stress, which, in turn, is associated with increases in depression and anxiety.

Cahana-Amitay and colleagues (2011) coined the term "linguistic anxiety", to describe a person in whom the deliberate, laborious production of language precipitates the apprehension of committing an error, with the anticipation of linguistic failure serving as the trigger[96,108]. Even in mild aphasia, language-based anxiety can interfere with task performance[108]. Indeed, stress reactivity is considerably higher during linguistic in comparison to non-linguistic tasks[55,94,103] and higher anxiety and stress responses are related to non-fluent aphasias[96,102]. PWA also show heightened physiological arousal and anxiety scores in general compared to stroke patients without aphasia[94,109].

Post-stroke anxiety is assessed *via* questionnaires and/or clinical interviews and PWA are ordinarily excluded from anxiety evaluations[94,104] as scales to assess post-stroke anxiety in aphasia have not yet been developed and validated[104]. Usually, modified versions of the Behavioural Outcomes of Anxiety Scale[110], the HADS[39], the Generalized Anxiety Disorder-7[111], or the Burden of Stroke Scale[112] are employed to rate anxiety in PWA. In addition, the NPI can be proxy-administered[35].

One potential psychological mechanism underlying linguistic anxiety is the overfocus on the language testing (area of worry), coupled with reduced attentional functions. The patient's fixation on his/her impaired language performance reduces the ability to follow language assignments, which is signaled by heightened physiological stress responses such as heart rate and skin conductance[96,108]. Premorbid personality traits (self-demand attitude, perfectionism) may also favor the emergence of anxiety in PWA[103]. The pathophysiological mechanisms involved in post-stroke anxiety in PWA remain unknown as there are few studies that explore the physiological stress responses in PWA during language examination[96]. An extended cortical and subcortical network was proposed to be involved in the regulation of stress and anxiety responses, including the reticular system of the brainstem, limbic structures (amygdala), and the frontal lobe, activating both the autonomic nervous system and the hypothalamus-pituitary-adrenal axis[96,108]. However, a recent meta-analysis studying post-stroke anxiety and lesion location found no strong associations[104]. Recently, Ryan *et al*[113] reported a systematic review of non-pharmacological treatment interventions for anxiety in PWA. The authors did find 10 studies (5 randomized controlled studies) and none of them showed significant improvement of anxiety outcomes in PWA[113]. Torres-Prioris *et al*[103], stressed the usefulness of including adequately trained laypersons/carers in the evaluation and treatment of PWA to overlook the "white coat" effect. Affected individuals usually show reduced anxiety levels towards familiar people in both evaluation and rehabilitation[103]. A beneficial role of the β-blocker agent propranolol in naming has been suggested[114,115]. It is possible that this agent improves anomia by exerting its anxiolytic effects[115, 116].

Apathy: Apathy is defined as a multidimensional syndrome of diminished goal-directed behavior, emotion and cognition resulting in a loss of initiative, decreased interaction with their environment, and interest in social life[117-119]. However, the DMS-5 does not categorize apathy as an independent mental illness but as an incipient symptom in other psychiatric and neurocognitive disorders (*e.g.*, energy loss in major depressive disorder)[51]. The prevalence of apathy in PWA is currently unknown as a previous meta-analysis covering post-stroke apathy could not provide any specific data for the aphasic population[120]. However, Kennedy *et al*[121] evaluated 19 acute PWA with the Apathy Inventory-Clinical Scale[122] and found that 53% of the sample was apathetic[121]. In fact, during the acute post-stroke phase, aphasia correlates with apathy severity and PWA are also less likely to show resolution of such motivation deficits[121]. Apathy is usually proxy-assessed through the SAS[40], the Apathy Evaluation Scale[123], the Apathy Inventory-Clinical Scale[122] or the Dimensional Apathy Scale[124] in addition to the NPI[24]. Actigraphy records from an unaffected arm may serve to measure poststroke apathy in PWA, but should not be used alone[125]. Crucial brain structures for motivated behavior in healthy people include fronto-striatal circuits (including the nucleus accumbens), the dorsal anterior cingulate and the orbitofrontal cortex[126,127]. On the other hand, Starkstein *et al*[128] recently reviewed the neuroimaging literature and found that lesions of the basal ganglia are the most common correlates of apathy in stroke. However, no studies have specifically evaluated the neuroimaging correlates of apathy in PWA. In addition, there is a lack of high-quality evidence to guide management of post-stroke apathy[117,120,129] and only one case report described the improvement of apathy and behavioral disinhibition with transcranial direct current stimulation combined with speech-language therapy in patient with severe non-fluent aphasia[91]. The recent Canadian Stroke Best Practice Recommendations specifically endorses to offer nonpharmacological interventions, such as exercise and music therapy, to stroke patients with marked apathy (with or without clinical depression), but not special recommendation were given for PWA[130]. Ideally, treatment would begin soon after stroke, as apathy limits the patients' ability to participate in the intensive rehabilitation programs.

Agitation and aggression: Agitation, inability to control anger and aggression are observed symptoms in PWA[22,36,131]. Anger represents an emotional reaction, whereas aggressiveness is understood as the subsequent behavioral reaction[132]. As everyday functional communication is reduced in PWA, they can become frustrated, less tolerant and irritable, getting easily angry regarding trivial matters [133]. The study of aggression in PWA has traditionally been difficult, and only few articles have been published[132,134-137]. However, it seems that aphasia is associated with higher levels of anger, as well as loneliness and social isolation[131,132]. Angelelli *et al*[36] observed three times more risk of agitation in PWA and four times more risk of being irritable than those with normal language. Another study evaluating anger in acute stroke patients found that 31% of participants with aphasia (n = 26) were irritable and aggressive[134]. A more recent study, evaluating anger in acute stroke, found that half of PWA (n = 26) and 10 dysarthric participants (n = 44) displayed anger[135]. On studying mild post-stroke aphasia, Choi-Kwon *et al*[138] found that lesion location was not related to anger. However, participants with moderate to severe aphasia were excluded, thus biasing the results. There are no validated questionnaires for the assessment of anger in PWA. Instruments employed to evaluate anger in non-aphasic population include the state-trait anger expression inventory-2 or the modified Spielberger trait

anger scale[139]. In addition, there are no studies targeting the pathophysiology or treatment of agitation and irritability in PWA.

Hypomania/mania: Elevated mood, hypomania and mania are seldomly reported in PWA, except in aphasic patients with posterior left hemisphere strokes[140]. Mania is defined as an abnormally and persistently raised expansive or irritable mood, thought and speech acceleration, lack of insight, overactivity, and social disinhibition[141]. In the context of PWA, the DSM-5 classifies these conditions as bipolar and related disorders due to another medical condition[51]. In a study conducted by Signers *et al*[140], one-fifth of participants with chronic fluent aphasia and posterior left hemisphere lesions were elated (a state of extreme happiness or excitement[142]) and unaware of their language impairment[140]. By contrast, elation has not been described among patients with non-fluent aphasia [143], except in a case of mixed transcortical aphasia associated with hypermusia, musicophilia, and compulsive whistling[144]. It seems that mania after left hemisphere damage is rare and according to the sparse published information it is difficult to describe its demographic, clinical and prognostic characteristics[141]. To date, only case reports have been published on mania in PWA[145-147]. These studies suggest that the onset of mania may be delayed up to two years post-stroke[148]. Manic states following stroke are often difficult to treat as brain damage and comorbidities enhance adverse effects and impair efficacy of some antimanic agents[149]. Case reports of post-stroke mania in non-aphasic stroke patients have found lithium, anticonvulsant mood stabilizers (valproate or carbamazepine), atypical antipsychotic drugs (olanzapine, aripiprazole, risperidone), clonazepam and clonidine to be effective[150,151]. However, there are no studies of treatment of hypomania and mania in PWA.

Psychosis: Delusions and hallucinations: Post-stroke psychosis involves the presence of delusions and/or hallucinations[152]. Within the context of PWA, the DSM-5 classifies this conditions as psychotic disorder due to another medical condition[51]. The development of psychosis is considered to be among the most devastating post-stroke syndromes[153]. Delusions in PWA are not rare. Shehata *et al*[55] evaluated 30 PWA and 31 non-aphasic stroke patients with the Eysenck Personality Questionnaire and found that psychosis was more prominent in PWA. Another study found that 28 PWA out of 61 chronic participants developed delusions, being mostly of persecutory nature[140]. The symptoms were found to be more common with posterior left hemisphere lesions[140], particularly in patients with Wernicke´s aphasia[154], who are more paranoid and aggressive[19,155,156] than patients with anterior lesions who instead may become more frustrated and depressed[133,140]. A detailed language evaluation of Wernicke's aphasia is desirable because characterization of speech and language deficits can be misinterpreted as psychotic speech disorder[157-159]. Potential explanations for this relationship may include auditory comprehension deficits with misinterpretation of information, in addition to anosognosia for aphasia and psychosis. Up to now, the pathophysiological mechanisms underlying psychosis in PWA are unknown, in part, because these patients are excluded from stroke studies on NPS[25,152]. Treatment approaches for psychosis in PWA are also not currently known. Antipsychotic medication is the main treatment for stroke patients[152] as poststroke and primary psychosis may likely reflect a common mechanism[152,160] but further research is strongly needed for PWA.

Study 2: A proof-of-concept study of neuropsychiatric symptoms in chronic post-stroke aphasia

Demographic and clinical data: Demographic and clinical data of participants are shown in Table 1. The Barthel Index indicated that most PWA were functionally independent, with a median score of 90 points (range: 45-100). Only one participant (subject 12) with anomic aphasia and a dense right hemiparesis showed high dependency regarding activities of daily living (Barthel Index: 45 points). All participants were in the chronic phase of stroke evolution with a median duration of 18 mo (range: 7-126). Results indicate that 9 patients were diagnosed with anomic aphasia (77.3 ± 6.2 points on the AQ of WAB-R), 5 with Wernicke´s (55.4 ± 15.9 points), 4 with Broca´s (55.7 ± 9.2 points) and 2 with conduction aphasia (64.8 ± 14.9 points). Table 2 displays the number and composite score of NPS in our sample based on the NPI. As can be seen, there was a significant presence of comorbid NPS. In fact, all 20 participants were rated by their informants as exhibiting more than one NPS, except in one participant (subject 15), a female of 28 years of age with mild aphasia, who only showed a high NPI score in changes in appetite/eating behavior. On average, each PWA yielded a median number of 5 NPS (range: 1-8), with a mean composite score of 2 points (range: 1-6), indicating symptoms of mild severity in the chronic phase of stroke evolution.

Based on the result of the NPI, the majority of PWA (75%) had depressive symptoms, followed by agitation and irritability (70%), anxiety and appetite/eating disorders (65%). Half of the sample also showed symptoms of apathy, while sleep disturbances were also relatively frequent (40%). Euphoria and psychotic disorders were rare. The most severe symptoms were apathy, depression, anxiety, agitation, and irritability (see Table 2). Regarding sexes, women had a median number of 6 NPS while men presented 5 NPS. Mann-Whitney U tests showed that there were no statistically significant sex differences concerning the number of NPS (P = 0.841). Antidepressants were taken by 7 patients. Median results showed that participants taking antidepressants were rated with a relatively similar number of NPS (6) compared to the participants without antidepressant intake (5), (P = 0.496). When analyzing the median number of NPS based on aphasia type, participants with Broca´s aphasia

Table 2 Incidence and composite score of neuropsychiatric symptoms based on the domain-general neuropsychiatric inventory evaluation

NPI symptom	No. of PWA with NPS (max. 20)	Percentage of PWA with NPS (%)	Composite NPI score[1]
Depression	15	75	4
Irritability	14	70	2
Agitation	14	70	2
Anxiety	13	65	2.5
Appetite/eating disorders	13	65	1
Apathy	10	50	4.5
Disinhibition	9	45	1
Sleep/nighttime disturbances	8	40	1.5
Euphoria	1	5	2
Aberrant motor behavior	1	5	2
Hallucinations	1	5	1
Delusions	0	0	0

[1]Neuropsychiatric inventory scores were calculated based on positive cases.

Incidence of symptom was determined by the number of persons with aphasia with frequency scores of > 0 of the respective symptom. PWA: Persons with aphasia; NPI: Neuropsychiatric Inventory; NPS: Neuropsychiatric symptoms.

presented the highest number of symptoms (6.5) followed by anomic participants (5), conduction aphasia (4.5) and Wernicke´s aphasia (3). However, non-parametric Kruskal-Wallis test showed no statistically significant differences (P = 0.508).

Specific-domain scales revealed that 30% of PWA were above the cut-off score for depression and anxiety (based on the SADQ-10, HADS-anxiety), 40% of patients were diagnosed with subthreshold depression (SADQ-10)[45,85] and 45% of participants had apathy (SAS) (see Table 3). However, percentages of diagnosis of the proxy-administered SADQ-10 stands in contrast to HADS-Depression results. Average scores of these domain-specific scales point into mild disorder severity. There were significant correlations between two domain-specific scales (SADQ-10 and SAS) and the most frequently reported NPI domains (e.g., depression, anxiety, apathy, agitation, and irritability) (see Table 4). No significant correlations were found between both neuropsychiatric scales (NPS and domain-specific scales) and aphasia severity (measured with the AQ of WAB-R), fluency, comprehension, or repetition scores.

Lesion size and location: The MRIs of participants showed a wide range of lesion volumes (Table 1). Lesion location showed that the maximum areas of overlap comprised regions of the long and the anterior segments of the arcuate fasciculus, the insula and the putamen in the left hemisphere. Involvement of different sectors of the left anterior cingulate gyrus were seen in six participants. The overlay of lesions is shown in Figure 1.

DISCUSSION

Study 2: A proof-of-concept study of neuropsychiatric symptoms in chronic post-stroke aphasia

Results of study 2 show that our participants presented mild-to-moderate aphasia severity and were functionally independent. We found a spectrum of comorbid NPS in all but one participant with mild anomic aphasia. On average PWA had a median number of 5 NPS (range: 1-8). The most frequent symptoms were depression, irritability, agitation/aggression, and anxiety, followed by appetite/eating disorders, apathy, and sleep disorders, whereas euphoria, delusions/hallucinations were rare. Apathy and depressive symptoms were rated as the most severe by their caregivers, followed by anxiety and agitation. There were no statistically significant differences regarding the number of NPS based on sex, antidepressant intake or aphasia type. When employing domain-specific scales that provide cut-off scores for diagnoses, 30% of participants had mild anxiety and depression, 45% showed subthreshold depression and 45% of participants had mild-to-moderate apathy.

The prevalence of depressive and anxiety symptoms based on the NPI was higher than the frequency of these disorders using the SADQ-10 and HADS. As mentioned, the NPI is an informant-based questionnaire developed to screen for the presence of symptoms, but not to establish diagnoses of

Table 3 Incidence and median score of neuropsychiatric diagnoses based on domain-specific scales

Domain-specific scale (range)	No. of PWA with diagnoses	Percentage of PWA with diagnosis (%)	Median score (range)
SADQ-10, depression (0-30)	6	30	15 (14-19)
SADQ-10, subthreshold depression (0-30)	9	45	14 (13-19)
SAS, apathy (0-42)	9	45	12 (1-35)
HADS, anxiety (0-21)	6	30	5 (0-12)
HADS, depression (0-21)	3	15	5.5 (1-14)

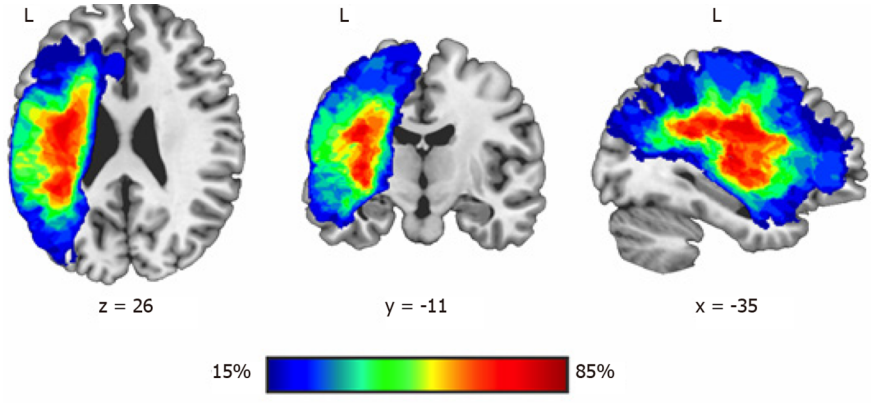
PWA: Persons with aphasia; SADQ-10: Stroke Aphasic Depression Questionnaire-version 10; SAS: Starkstein Apathy Scale; HADS: Hospital Anxiety and Depression Scale.

Table 4 Correlations between neuropsychiatric inventory-subdomains and domain-specific scales

Domain-specific scale	NPI-subdomains	Spearman correlation (rs)
SADQ-10	NPI-depression	0.67, $P < 0.001$[a]
	NPI-anxiety	0.60, $P < 0.005$[a]
	NPI-apathy	0.43, $P = 0.540$
	NPI-agitation	0.60, $P < 0.005$[a]
	NPI-irritability	0.63, $P < 0.003$[a]
HADS	NPI-depression	0.38, $P = 0.820$
	NPI-anxiety	0.27, $P = 0.240$
	NPI-apathy	0.27, $P = 0.243$
	NPI-agitation	0.14, $P = 0.540$
	NPI-irritability	0.11, $P = 0.620$
SAS	NPI-depression	0.50, $P < 0.023$[b]
	NPI-anxiety	0.30, $P = 0.192$
	NPI-apathy	0.58, $P < 0.006$[a]
	NPI-agitation	0.18, $P = 0.440$
	NPI-irritability	0.09, $P = 0.700$

[a]$P < 0.01$;
[b]$P < 0.05$.
NPI: Neuropsychiatric Inventory; SADQ-10: Stroke Aphasic Depression Questionnaire-version 10; SAS: Starkstein Apathy Scale; HADS: Hospital Anxiety and Depression Scale.

mental disorders. Thus, we expected to find a higher number of symptoms with the NPI in contrast to domain-specific scales. Results revealed a higher percentage of depression with the SADQ-10 than with the HADS, therefore showing a low level of congruency between these proxy and self-rated measures. Correlation analyses between NPI subdomains and domain-specific scales showed that the SADQ-10 correlated with a higher number NPI subdomains (depression, anxiety, irritability, and agitation) than the HADS (no associations found). The SAS, on the other hand, showed a significant correlation with NPI subdomains of apathy and depression. In general, it seems that proxy-rated neuropsychiatric instruments (*e.g.*, SADQ-10) are more sensitive to evaluate PWA than directly considering aphasic individuals themselves (*e.g.*, HADS) because of cognitive or communication problems. In support of these findings, outcome differences between proxy-based and directly administered instruments have also been described in other studies regarding PWA[161]. Moreover, family members have generally been found to be reliable informants in areas of emotions, daily activities, well-being, and overall quality of life[162]. In fact, Bourgeois *et al*[21] advise physicians to give credence to caregivers' testimonies about the behavior of PWA. Nevertheless, the opinion of informants should not jeopardize the autonomy and self-determination of PWA[163]. In general, more studies regarding the reliability and validity of neuropsychiatric proxy and self-measured instruments in PWA are strongly needed. Lastly, we found a lack of correlation between neuropsychiatric assessment tools (NPI and domain-



DOI: 10.5498/wjp.v12.i3.450

Figure 1 Lesion overlap map from the 20 participants overlaid on a brain template in Montreal Neurological Institute standard space. The maximum lesion overlap (red color) (85%, *n* = 17) involved regions comprising the left arcuate fasciculus (long and the anterior segments), the insula and the putamen. Different sectors of the left anterior cingulate gyrus were involved in six participants. L: left.

specific scales) and WAB-R. These results align with findings from another study showing no correlations between WAB-R and depression scores based on the SADQ-21 in PWA and chronic left hemisphere strokes[80].

Structural MRIs in our sample showed a wide range of lesion volumes. There was a predominant involvement of the left perisylvian language core and lesion overlap analysis showed that the region corresponding to the arcuate fasciculus, insula and putamen were affected in 17 participants (85%). The insular cortex together with the striatum and the anterior cingulate gyrus (affected in 6 participants) are intrinsic components of the Salience Network[164]. The Salience Network is composed of two major hubs, anterior insula and dorsal anterior cingulate cortex. It also included three interconnected subcortical hubs: amygdala, ventral striatum, and substantia nigra/ventral tegmental area[165]. This network, among others, contributes to complex brain functions such as communication, social behavior, and self-awareness, by means of integrating of sensory, emotional, and cognitive information[164,165]. Damage to the left Salience Network in our sample may have impaired self-regulation of cognition, behavior, emotion and autonomic arousal favoring the emergence of an array of NPS[164]. Moreover, lesions in the left arcuate fasciculus have been associated with affective symptoms and somatic depressive complaints[166] and preliminary findings show that the lesion load in the left arcuate fasciculus correlates with naming improvement in PWA treated with antidepressants[167]. In any case, the role of the arcuate fasciculus in the NPS of PWA requires further analysis.

Some limitations to the current study should be acknowledged. First, this was a relatively small sample including people with chronic PSA of mild to moderate severity, so that it is not representative of all PWA and stroke. Another limitation is that we only used three domain-specific scales, whereas the NPI assesses twelve NPS. Nevertheless, we have evaluated the three most prevalent neuropsychiatric disorders already found in stroke patients without aphasia. In any case, future studies may include further domain-specific scales targeting other neuropsychiatric disorders. A longitudinal study to evaluate the evolution of NPS from the acute to the chronic phase of stroke survivors is also warranted.

CONCLUSION

Study 1: Literature review

We did find that NPS in PWA are insufficiently investigated. Prevalence of NPS in PWA is unknown, hindering the development of assessment tools and treatment strategies. If reported, most researchers and clinicians tend to focus mostly on diagnosing depression to the extent that there are no reports on symptoms of disinhibition, aberrant motor behavior, appetite-eating disorders, or sleep disturbances, already identified in non-aphasic stroke patients using the NPI. In addition, no pharmacological randomized controlled trials have been published for the reviewed symptoms in PWA. Pharmacotherapy, neuromodulation and behavioral therapies have only been implemented for depression and/or anxiety. Therefore, further research on the prevalence, assessment, pathophysiology, and treatment of NPS in PSA is strongly needed.

General conclusions and directions for further research

The comorbidity of NPS in patients with chronic PSA is very frequent and seems to exceed the prevalence data reported in the non-aphasic stroke population. Therefore, more studies are necessary as NPS are still underdiagnosed in chronic PSA. Our study 1 shows the paucity of reports dealing with

NPS diagnosis, assessment, and treatment in PWA. In our study 2, we found high comorbidity of NPS among a small sample of PWA. Findings from study 2 suggest that the NPI may be used as a screening instrument and this assessment can be complemented with domain-specific psychiatric scales. Further aims must attempt to develop structured interviews and guidelines for the diagnosis, treatment, or prevention of comorbid NPS in PWA.

Many important questions regarding the neuropsychiatric spectrum in PWA remain unanswered or unaddressed. What is the frequency of NPS in acute aphasic stroke patients? Which are the best psychometric instruments to evaluate NPS? What is the best combination of self-rated and proxy-based measures depending on the severity of language impairment (production and/or comprehension deficits)? Which are the most important demographic variables that affect the occurrence of NPS in PWA? How do premorbid psychiatric conditions affect the occurrence and clinical phenomenology of NPS and language deficits after stroke? Is there any relationship between anosognosia for aphasia and NPS (hypomania/mania, psychosis)? How do NPS evolve or remit spontaneously? Are psychopharmacological agents including cognitive enhancing drugs useful? What kind of behavioral therapies should be applied for NPS in PWA? Does aphasia therapy positively influence psychiatric outcomes? Does the treatment of one NPS affect the outcome and comorbidity of other symptoms? Should biological treatments be prioritized over behavioral approaches, or should they be combined?

ARTICLE HIGHLIGHTS

Research background

Aphasia due to stroke is associated with worse outcomes than in non-aphasic stroke patients. Worse outcomes in post-stroke aphasia often result from the co-occurrence of neuropsychiatric symptoms (NPS) and disorders.

Research motivation

Persons with aphasia (PWA) are frequently excluded from studies on stroke related NPS because of their language and communication deficits. The exclusion of PWA and stroke hinders obtaining relevant information on prevalence, diagnosis, associated deficits (cognitive impairment, functional disability), assessment, neurobiological mechanisms, and treatment of NPS in this population.

Research objectives

We report a two-part study consisting of a literature review on NPS (study 1) and an observational study on NPS in chronic post-stroke aphasia (study 2).

Research methods

In study 1, we reviewed the databases after cross-referencing key words of post-stroke aphasia to NPS and disorders. In study 2, we evaluated aphasic deficits, activities of daily living and a spectrum of NPS and disorders using well-validated scales in 20 persons with chronic mild-to-moderate post-stroke aphasia associated with left hemisphere strokes. NPS were evaluated with the 12 symptom domains of the Neuropsychiatric Inventory and with three domain-specific scales for depression, anxiety, and apathy.

Research results

The literature review performed in study 1 revealed a spectrum of NPS in PSA including depression, anxiety, apathy, agitation/aggression, psychosis, and hypomania/mania. This broad spectrum of NPS was also found in observational study 2, since all but one PWA has more than one NPS (median number of NPS: 5, range: 1-8).

Research conclusions

A spectrum of NPS is highly prevalent in chronic PSA. Therefore, future comprehensive evaluations of NPS using multidomain and domain-specific scales will enable a better characterization of this broad spectrum favoring the design and implementation of adequate therapies.

Research perspectives

Since the spectrum of NPS in PWA and stroke is an underexplored research area, there are still many pending issues to be addressed. Essential areas of inquiry include knowing the incidence in acute and chronic stroke periods, risk factors (family and personal history of psychiatric disorders), clinical features, assessment instruments devised to test language and communication impaired patients, impact on quality of life, neurobiological correlates, short- and long-term outcomes, and response to psychological and biological interventions.

FOOTNOTES

Author contributions: Dávila G, Berthier ML, Edelkraut L, López-Barroso D and Torres-Prioris MJ were involved in the acquisition of the original data; Dávila G, Berthier ML and Edelkraut L conceived and designed the manuscript; D ávila G, Berthier ML and Edelkraut L reviewed the literature; López-Barroso D, Torres-Prioris MJ, Aloisi J, Starkstein SE and Jorge RE analyzed the language and neuropsychiatric original data; López-Barroso D and Torres-Prioris MJ analyzed neuroimaging data and created the figure; Dávila G, Berthier ML, López-Barroso D, Torres-Prioris MJ, Starkstein SE, Jorge RE and Edelkraut L wrote the manuscript; all authors gave final approval of the current version of the article to be published.

Supported by Ministerio de Economía, Industria y Competitividad, Instituto de Salud Carlos III, Madrid, Spain, No. PI16/01514.

Institutional review board statement: The study was approved by the Ethical Research of Drugs Committee Provincial of Malaga and the Spanish Drug and Healthcare Products Agency, Spain (Approval No. FIM-DON-2017-01).

Informed consent statement: All study participants, and their legal guardians, provided informed written consent prior to study enrolment.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: Spain

ORCID number: Lisa Edelkraut 0000-0001-7444-2686; Diana López-Barroso 0000-0002-8938-1959; María José Torres-Prioris 0000-0003-3795-8151; Sergio E Starkstein 0000-0002-9716-1614; Ricardo E Jorge 0000-0002-1711-5416; Jessica Aloisi 0000-0002-8406-7012; Marcelo L Berthier 0000-0002-6393-3487; Guadalupe Dávila 0000-0002-3297-4243.

S-Editor: Zhang H
L-Editor: A
P-Editor: Zhang H

REFERENCES

1 **Berthier ML**. Poststroke aphasia: epidemiology, pathophysiology and treatment. *Drugs Aging* 2005; **22**: 163-182 [PMID: 15733022 DOI: 10.2165/00002512-200522020-00006]
2 **Hilari K**, Needle JJ, Harrison KL. What are the important factors in health-related quality of life for people with aphasia? *Arch Phys Med Rehabil* 2012; **93**: S86-S95 [PMID: 22119074 DOI: 10.1016/j.apmr.2011.05.028]
3 **Code C**, Hemsley G, Herrmann M. The emotional impact of aphasia. *Semin Speech Lang* 1999; **20**: 19-31 [PMID: 10100374 DOI: 10.1055/s-2008-1064006]
4 **Flowers HL**, Skoretz SA, Silver FL, Rochon E, Fang J, Flamand-Roze C, Martino R. Poststroke Aphasia Frequency, Recovery, and Outcomes: A Systematic Review and Meta-Analysis. *Arch Phys Med Rehabil* 2016; **97**: 2188-2201.e8 [PMID: 27063364 DOI: 10.1016/j.apmr.2016.03.006]
5 **Lazar RM**, Boehme AK. Aphasia As a Predictor of Stroke Outcome. *Curr Neurol Neurosci Rep* 2017; **17**: 83 [PMID: 28929424 DOI: 10.1007/s11910-017-0797-z]
6 **Berthier ML**, Dávila G, García-Casares N, Moreno-Torres I. Post-stroke Aphasia. In: Schweizer TA, Macdonald RL. The Behavioral Consequences of Stroke. New York: Springer, 2014: 95-118
7 **Gleichgerrcht E**, Kocher M, Nesland T, Rorden C, Fridriksson J, Bonilha L. Preservation of structural brain network hubs is associated with less severe post-stroke aphasia. *Restor Neurol Neurosci* 2016; **34**: 19-28 [PMID: 26599472 DOI: 10.3233/RNN-150511]
8 **Flamand-Roze C**, Cauquil-Michon C, Roze E, Souillard-Scemama R, Maintigneux L, Ducreux D, Adams D, Denier C. Aphasia in border-zone infarcts has a specific initial pattern and good long-term prognosis. *Eur J Neurol* 2011; **18**: 1397-1401 [PMID: 21554494 DOI: 10.1111/j.1468-1331.2011.03422.x]
9 **Landrigan JF**, Zhang F, Mirman D. A data-driven approach to post-stroke aphasia classification and lesion-based prediction. *Brain* 2021; **144**: 1372-1383 [PMID: 34046670 DOI: 10.1093/brain/awab010]
10 **Halai AD**, Woollams AM, Lambon Ralph MA. Using principal component analysis to capture individual differences within a unified neuropsychological model of chronic post-stroke aphasia: Revealing the unique neural correlates of

speech fluency, phonology and semantics. *Cortex* 2017; **86**: 275-289 [PMID: 27216359 DOI: 10.1016/j.cortex.2016.04.016]

11 **Baker C**, Worrall L, Rose M, Ryan B. 'It was really dark': the experiences and preferences of people with aphasia to manage mood changes and depression. *Aphasiology* 2020; **34**: 19-46 [DOI: 10.1080/02687038.2019.1673304]

12 **Worrall LE**, Hudson K, Khan A, Ryan B, Simmons-Mackie N. Determinants of living Well With Aphasia in the First Year Poststroke: A Prospective Cohort Study. *Arch Phys Med Rehabil* 2017; **98**: 235-240 [PMID: 27457540 DOI: 10.1016/j.apmr.2016.06.020]

13 **Code C**, Herrmann M. The relevance of emotional and psychosocial factors in aphasia to rehabilitation. *Neuropsychol Rehabil* 2003; **13**: 109-132 [PMID: 21854330 DOI: 10.1080/09602010244000291]

14 **Manning M**, MacFarlane A, Hickey A, Franklin S. Perspectives of people with aphasia post-stroke towards personal recovery and living successfully: A systematic review and thematic synthesis. *PLoS One* 2019; **14**: e0214200 [PMID: 30901359 DOI: 10.1371/journal.pone.0214200]

15 **Lam JM**, Wodchis WP. The relationship of 60 disease diagnoses and 15 conditions to preference-based health-related quality of life in Ontario hospital-based long-term care residents. *Med Care* 2010; **48**: 380-387 [PMID: 20220536 DOI: 10.1097/MLR.0b013e3181ca2647]

16 **Nemani K**, Gurin L. Neuropsychiatric Complications after Stroke. *Semin Neurol* 2021; **41**: 85-100 [PMID: 33511605 DOI: 10.1055/s-0040-1722723]

17 **Bullier B**, Cassoudesalle H, Villain M, Cogné M, Mollo C, De Gabory I, Dehail P, Joseph PA, Sibon I, Glize B. New factors that affect quality of life in patients with aphasia. *Ann Phys Rehabil Med* 2020; **63**: 33-37 [PMID: 31352062 DOI: 10.1016/j.rehab.2019.06.015]

18 **Hackett ML**, Köhler S, O'Brien JT, Mead GE. Neuropsychiatric outcomes of stroke. *Lancet Neurol* 2014; **13**: 525-534 [PMID: 24685278 DOI: 10.1016/S1474-4422(14)70016-X]

19 **Ferro JM**, Caeiro L, Figueira ML. Neuropsychiatric sequelae of stroke. *Nat Rev Neurol* 2016; **12**: 269-280 [PMID: 27063107 DOI: 10.1038/nrneurol.2016.46]

20 **Zhang S**, Xu M, Liu ZJ, Feng J, Ma Y. Neuropsychiatric issues after stroke: Clinical significance and therapeutic implications. *World J Psychiatry* 2020; **10**: 125-138 [PMID: 32742946 DOI: 10.5498/wjp.v10.i6.125]

21 **Bourgeois JA**, Hilty DM, Chang CH, Wineinger MA, Servis ME. Poststroke Neuropsychiatric Illness: An Integrated Approach to Diagnosis and Management. *Curr Treat Options Neurol* 2004; **6**: 403-420 [PMID: 15279761 DOI: 10.1007/s11940-996-0031-9]

22 **Ferro JM**, Santos AC. Emotions after stroke: A narrative update. *Int J Stroke* 2020; **15**: 256-267 [PMID: 31581930 DOI: 10.1177/1747493019879662]

23 **Wong A**, Lau AY, Yang J, Wang Z, Liu W, Lam BY, Au L, Shi L, Wang D, Chu WC, Xiong YY, Lo ES, Law LS, Leung TW, Lam LC, Chan AY, Soo YO, Leung EY, Wong LK, Mok VC. Neuropsychiatric Symptom Clusters in Stroke and Transient Ischemic Attack by Cognitive Status and Stroke Subtype: Frequency and Relationships with Vascular Lesions, Brain Atrophy and Amyloid. *PLoS One* 2016; **11**: e0162846 [PMID: 27632159 DOI: 10.1371/journal.pone.0162846]

24 **Cummings JL**, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994; **44**: 2308-2314 [PMID: 7991117 DOI: 10.1212/wnl.44.12.2308]

25 **Townend E**, Brady M, McLaughlan K. Exclusion and inclusion criteria for people with aphasia in studies of depression after stroke: a systematic review and future recommendations. *Neuroepidemiology* 2007; **29**: 1-17 [PMID: 17898519 DOI: 10.1159/000108913]

26 **Laures-Gore JS**, Dotson VM, Belagaje S. Depression in Poststroke Aphasia. *Am J Speech Lang Pathol* 2020; **29**: 1798-1810 [PMID: 33181048 DOI: 10.1044/2020_AJSLP-20-00040]

27 **Døli H**, Helland T, Helland WA. Self-reported symptoms of anxiety and depression in chronic stroke patients with and without aphasia. *Aphasiology* 2017; **31**: 1392-1409 [DOI: 10.1080/02687038.2017.1280595]

28 **Brady MC**, Fredrick A, Williams B. People with aphasia: capacity to consent, research participation and intervention inequalities. *Int J Stroke* 2013; **8**: 193-196 [PMID: 23130972 DOI: 10.1111/j.1747-4949.2012.00900.x]

29 **Perrain R**, Mekaoui L, Calvet D, Mas JL, Gorwood P. A meta-analysis of poststroke depression risk factors comparing depressive-related factors versus others. *Int Psychogeriatr* 2020; **32**: 1331-1344 [PMID: 32014074 DOI: 10.1017/S1041610219002187]

30 **Robinson RG**, Jorge RE. Post-Stroke Depression: A Review. *Am J Psychiatry* 2016; **173**: 221-231 [PMID: 26684921 DOI: 10.1176/appi.ajp.2015.15030363]

31 **Medeiros GC**, Roy D, Kontos N, Beach SR. Post-stroke depression: A 2020 updated review. *Gen Hosp Psychiatry* 2020; **66**: 70-80 [PMID: 32717644 DOI: 10.1016/j.genhosppsych.2020.06.011]

32 **Oldfield RC**. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; **9**: 97-113 [PMID: 5146491 DOI: 10.1016/0028-3932(71)90067-4]

33 **Kertesz A**, Raven JC. Western Aphasia Battery Revised. San Antonio: PsychCorp, 2007

34 **Mahoney FI**, Barthel DW. Functional Evaluation: The Barthel Index. *Md State Med J* 1965; **14**: 61-65 [PMID: 14258950]

35 **Frey KL**, Newman JK, Arciniegas DB, Anderson CA, Ramsberger G. Assessing neuropsychiatric disturbances associated with post-stroke aphasia. *J Neuropsychiatry Clin Neurosci* 2011; **23**: E4-E5 [PMID: 22231346 DOI: 10.1176/jnp.23.4.jnpe4]

36 **Angelelli P**, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, Antonucci G, Fasotti L, Di Santantonio A, Grasso MG, Pizzamiglio L. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. *Acta Psychiatr Scand* 2004; **110**: 55-63 [PMID: 15180780 DOI: 10.1111/j.1600-0447.2004.00297.x]

37 **Knutson KM**, Dal Monte O, Schintu S, Wassermann EM, Raymont V, Grafman J, Krueger F. Areas of Brain Damage Underlying Increased Reports of Behavioral Disinhibition. *J Neuropsychiatry Clin Neurosci* 2015; **27**: 193-198 [PMID: 25959040 DOI: 10.1176/appi.neuropsych.14060126]

38 **Sutcliffe LM**, Lincoln NB. The assessment of depression in aphasic stroke patients: the development of the Stroke

Aphasic Depression Questionnaire. *Clin Rehabil* 1998; **12**: 506-513 [PMID: 9869254 DOI: 10.1191/026921598672167702]
39 **Zigmond AS**, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**: 361-370 [PMID: 6880820 DOI: 10.1111/j.1600-0447.1983.tb09716.x]
40 **Starkstein SE**, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci* 1992; **4**: 134-139 [PMID: 1627973 DOI: 10.1176/jnp.4.2.134]
41 **Bjelland I**, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; **52**: 69-77 [PMID: 11832252 DOI: 10.1016/s0022-3999(01)00296-3]
42 **Starkstein SE**, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. *Stroke* 1993; **24**: 1625-1630 [PMID: 8236333 DOI: 10.1161/01.str.24.11.1625]
43 **Morita H**, Kannari K. Reliability and validity assessment of an apathy scale for home-care patients with Parkinson's disease: a structural equation modeling analysis. *J Phys Ther Sci* 2016; **28**: 1724-1727 [PMID: 27390403 DOI: 10.1589/jpts.28.1724]
44 **Leeds L**, Meara RJ, Hobson JP. The utility of the Stroke Aphasia Depression Questionnaire (SADQ) in a stroke rehabilitation unit. *Clin Rehabil* 2004; **18**: 228-231 [PMID: 15053133 DOI: 10.1191/0269215504cr685oa]
45 **Ashaie SA**, Hurwitz R, Cherney LR. Depression and Subthreshold Depression in Stroke-Related Aphasia. *Arch Phys Med Rehabil* 2019; **100**: 1294-1299 [PMID: 30831094 DOI: 10.1016/j.apmr.2019.01.024]
46 **Bennett HE**, Thomas SA, Austen R, Morris AM, Lincoln NB. Validation of screening measures for assessing mood in stroke patients. *Br J Clin Psychol* 2006; **45**: 367-376 [PMID: 17147102 DOI: 10.1348/014466505x58277]
47 **Rorden C**, Brett M. Stereotaxic display of brain lesions. *Behav Neurol* 2000; **12**: 191-200 [PMID: 11568431 DOI: 10.1155/2000/421719]
48 **Brett M**, Leff AP, Rorden C, Ashburner J. Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage* 2001; **14**: 486-500 [PMID: 11467921 DOI: 10.1006/nimg.2001.0845]
49 **Wipprecht M**, Grötzbach H. Poststroke Depression bei Aphasie: Diagnose und Behandlungsmöglichkeiten. *Neuro Geriatrie* 2013; **10**: 149-159 [DOI: 10.1007/978-3-662-45890-7_10]
50 **Baker C**, Worrall L, Rose M, Ryan B. Experiences of mood changes and depression after post-stroke aphasia. *Aphasiology* 2018; **32**: 11-12 [DOI: 10.1080/02687038.2018.1486384]
51 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders (5th ed.). Arlington, VA, 2013
52 **Hilari K**. The impact of stroke: are people with aphasia different to those without? *Disabil Rehabil* 2011; **33**: 211-218 [PMID: 20712416 DOI: 10.3109/09638288.2010.508829]
53 **Mitchell AJ**, Sheth B, Gill J, Yadegarfar M, Stubbs B, Meader N. Prevalence and predictors of post-stroke mood disorders: A meta-analysis and meta-regression of depression, anxiety and adjustment disorder. *Gen Hosp Psychiatry* 2017; **47**: 48-60 [PMID: 28807138 DOI: 10.1016/j.genhosppsych.2017.04.001]
54 **Kauhanen ML**, Korpelainen JT, Hiltunen P, Määttä R, Mononen H, Brusin E, Sotaniemi KA, Myllylä VV. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. *Cerebrovasc Dis* 2000; **10**: 455-461 [PMID: 11070376 DOI: 10.1159/000016107]
55 **Shehata GA**, El Mistikawi T, Risha AS, Hassan HS. The effect of aphasia upon personality traits, depression and anxiety among stroke patients. *J Affect Disord* 2015; **172**: 312-314 [PMID: 25451431 DOI: 10.1016/j.jad.2014.10.027]
56 **Cruice M**, Worrall L, Hickson L. Health-related quality of life in people with aphasia: implications for fluency disorders quality of life research. *J Fluency Disord* 2010; **35**: 173-189 [PMID: 20831966 DOI: 10.1016/j.jfludis.2010.05.008]
57 **Fucetola R**, Connor LT, Perry J, Leo P, Tucker F, Corbetta M. Aphasia severity, semantics, and depression predict functional communication in acquired aphasia. *Aphasiology* 2006; **20**: 449-461 [DOI: 10.1080/02687030500390177]
58 **Robinson RG**, Boston JD, Starkstein SE, Price TR. Comparison of mania and depression after brain injury: causal factors. *Am J Psychiatry* 1988; **145**: 172-178 [PMID: 3341462 DOI: 10.1176/ajp.145.2.172]
59 **Herrmann M**, Bartels C, Wallesch CW. Depression in acute and chronic aphasia: symptoms, pathoanatomical-clinical correlations and functional implications. *J Neurol Neurosurg Psychiatry* 1993; **56**: 672-678 [PMID: 8509782 DOI: 10.1136/jnnp.56.6.672]
60 **Kauhanen M**, Korpelainen JT, Hiltunen P, Brusin E, Mononen H, Määttä R, Nieminen P, Sotaniemi KA, Myllylä VV. Poststroke depression correlates with cognitive impairment and neurological deficits. *Stroke* 1999; **30**: 1875-1880 [PMID: 10471439 DOI: 10.1161/01.str.30.9.1875]
61 **Carota A**, Staub F, Bogousslavsky J. Emotions, behaviours and mood changes in stroke. *Curr Opin Neurol* 2002; **15**: 57-69 [PMID: 11796952 DOI: 10.1097/00019052-200202000-00010]
62 **Townend E**, Brady M, McLaughlan K. A systematic evaluation of the adaptation of depression diagnostic methods for stroke survivors who have aphasia. *Stroke* 2007; **38**: 3076-3083 [PMID: 17932334 DOI: 10.1161/STROKEAHA.107.484238]
63 **van Dijk MJ**, de Man-van Ginkel JM, Hafsteinsdóttir TB, Schuurmans MJ. Identifying depression post-stroke in patients with aphasia: a systematic review of the reliability, validity and feasibility of available instruments. *Clin Rehabil* 2016; **30**: 795-810 [PMID: 26292693 DOI: 10.1177/0269215515599665]
64 **Benaim C**, Cailly B, Perennou D, Pelissier J. Validation of the aphasic depression rating scale. *Stroke* 2004; **35**: 1692-1696 [PMID: 15143288 DOI: 10.1161/01.STR.0000130591.95710.20]
65 **Hammond MF**, O'Keeffe ST, Barer DH. Development and validation of a brief observer-rated screening scale for depression in elderly medical patients. *Age Ageing* 2000; **29**: 511-515 [PMID: 11191243 DOI: 10.1093/ageing/29.6.511]
66 **Turner-Stokes L**, Kalmus M, Hirani D, Clegg F. The Depression Intensity Scale Circles (DISCs): a first evaluation of a simple assessment tool for depression in the context of brain injury. *J Neurol Neurosurg Psychiatry* 2005; **76**: 1273-1278 [PMID: 16107367 DOI: 10.1136/jnnp.2004.050096]
67 **Barrows PD**, Thomas SA. Assessment of mood in aphasia following stroke: validation of the Dynamic Visual Analogue Mood Scales (D-VAMS). *Clin Rehabil* 2018; **32**: 94-102 [PMID: 28653547 DOI: 10.1177/0269215517714590]
68 **Barrows PD**, Thomas SA, Van Gordon W. Assessing Self-Reported Mood in Aphasia Following Stroke: Challenges,

Innovations and Future Directions. *J Stroke Cerebrovasc Dis* 2021; **30**: 105425 [PMID: 33161350 DOI: 10.1016/j.jstrokecerebrovasdis.2020.105425]

69 **Gillespie S**, Laures-Gore J, Moore E, Farina M, Russell S, Haaland B. Identification of Affective State Change in Adults With Aphasia Using Speech Acoustics. *J Speech Lang Hear Res* 2018; **61**: 2906-2916 [PMID: 30481797 DOI: 10.1044/2018_JSLHR-S-17-0057]

70 **Wallace SJ**, Worrall L, Rose T, Dorze G, Le Breitenstein C, Hilari K, Babbitt E, Bose A, Brady M, Cherney LR, Copland D, Cruice M, Enderby P, Hersh D, Howe T, Kelly H, Kiran S, Rochon E. A core outcome set for aphasia treatment research : The ROMA consensus statement. Int. J. Stroke 2019 14, 180–185 [PMID: 30303810 DOI: 10.1177/1747493018806200]

71 **Mohr B**, Stahl B, Berthier ML, Pulvermüller F. Intensive Communicative Therapy Reduces Symptoms of Depression in Chronic Nonfluent Aphasia. *Neurorehabil Neural Repair* 2017; **31**: 1053-1062 [PMID: 29192534 DOI: 10.1177/1545968317744275]

72 **Wallace SJ**, Worrall L, Le Dorze G, Brandenburg C, Foulkes J, Rose TA. Many ways of measuring: A scoping review of measurement instruments for use with people with aphasia. *Aphasiology* 2020; 1-66 [DOI: 10.1080/02687038.2020.1836318]

73 **Berg A**, Lönnqvist J, Palomäki H, Kaste M. Assessment of depression after stroke: a comparison of different screening instruments. *Stroke* 2009; **40**: 523-529 [PMID: 19074478 DOI: 10.1161/STROKEAHA.108.527705]

74 **Murakami T**, Hama S, Yamashita H, Onoda K, Kobayashi M, Kanazawa J, Yamawaki S, Kurisu K. Neuroanatomic pathways associated with poststroke affective and apathetic depression. *Am J Geriatr Psychiatry* 2013; **21**: 840-847 [PMID: 23567364 DOI: 10.1016/j.jagp.2013.01.057]

75 **Feng C**, Fang M, Liu XY. The neurobiological pathogenesis of poststroke depression. *ScientificWorldJournal* 2014; **2014**: 521349 [PMID: 24744682 DOI: 10.1155/2014/521349]

76 **Robinson RG**, Starkstein SE. Current research in affective disorders following stroke. *J Neuropsychiatry Clin Neurosci* 1990; **2**: 1-14 [PMID: 2136055 DOI: 10.1176/jnp.2.1.1]

77 **Robinson RG**, Kubos KL, Starr LB, Rao K, Price TR. Mood changes in stroke patients: relationship to lesion location. *Compr Psychiatry* 1983; **24**: 555-566 [PMID: 6653097 DOI: 10.1016/0010-440x(83)90024-x]

78 **Carson AJ**, MacHale S, Allen K, Lawrie SM, Dennis M, House A, Sharpe M. Depression after stroke and lesion location: a systematic review. *Lancet* 2000; **356**: 122-126 [PMID: 10963248 DOI: 10.1016/S0140-6736(00)02448-X]

79 **Wei N**, Yong W, Li X, Zhou Y, Deng M, Zhu H, Jin H. Post-stroke depression and lesion location: a systematic review. *J Neurol* 2015; **262**: 81-90 [PMID: 25308633 DOI: 10.1007/s00415-014-7534-1]

80 **Grajny K**, Pyata H, Spiegel K, Lacey EH, Xing S, Brophy C, Turkeltaub PE. Depression Symptoms in Chronic Left Hemisphere Stroke Are Related to Dorsolateral Prefrontal Cortex Damage. *J Neuropsychiatry Clin Neurosci* 2016; **28**: 292-298 [PMID: 27255855 DOI: 10.1176/appi.neuropsych.16010004]

81 **Allida S**, Cox KL, Hsieh CF, Lang H, House A, Hackett ML. Pharmacological, Psychological, and Noninvasive Brain Stimulation Interventions for Treating Depression After Stroke. *Stroke* 2020; **51**: e259-e260 [PMID: 32660351 DOI: 10.1161/STROKEAHA.120.029239]

82 **Santo Pietro MJ**, Marks DR, Mullen A. When Words Fail: Providing Effective Psychological Treatment for Depression in Persons with Aphasia. *J Clin Psychol Med Settings* 2019; **26**: 483-494 [PMID: 30778804 DOI: 10.1007/s10880-019-09608-4]

83 **Baker C**, Worrall L, Rose M, Hudson K, Ryan B, O'Byrne L. A systematic review of rehabilitation interventions to prevent and treat depression in post-stroke aphasia. *Disabil Rehabil* 2018; **40**: 1870-1892 [PMID: 28420284 DOI: 10.1080/09638288.2017.1315181]

84 **Wray F**, Clarke D, Forster A. Post-stroke self-management interventions: a systematic review of effectiveness and investigation of the inclusion of stroke survivors with aphasia. *Disabil Rehabil* 2018; **40**: 1237-1251 [PMID: 28271913 DOI: 10.1080/09638288.2017.1294206]

85 **Berthier ML**, Edelkraut L, Mohr B, Pulvermüller F, Starkstein SE, Green-Heredia C, Dávila G. Intensive aphasia therapy improves low mood in fluent post-stroke aphasia: Evidence from a case-controlled study. *Neuropsychol Rehabil* 2022; **32**: 148-163 [PMID: 32867571 DOI: 10.1080/09602011.2020.1809463]

86 **Thomas SA**, Walker MF, Macniven JA, Haworth H, Lincoln NB. Communication and Low Mood (CALM): a randomized controlled trial of behavioural therapy for stroke patients with aphasia. *Clin Rehabil* 2013; **27**: 398-408 [PMID: 23059701 DOI: 10.1177/0269215512462227]

87 **Northcott S**, Thomas S, James K, Simpson A, Hirani S, Barnard R, Hilari K. Solution Focused Brief Therapy in Post-Stroke Aphasia (SOFIA): feasibility and acceptability results of a feasibility randomised wait-list controlled trial. *BMJ Open* 2021; **11**: e050308 [PMID: 34408055 DOI: 10.1136/bmjopen-2021-050308]

88 **Campanella W**, Pedrini R, Vestito L, Marinelli L, Trompetto C, Mori L. Transcranial Direct Current Stimulation in the Treatment of Subacute Post-Stroke Thalamic Aphasia. *Eur J Case Rep Intern Med* 2020; **7**: 001794 [PMID: 33194851 DOI: 10.12890/2020_001794]

89 **Northcott S**, Burns K, Simpson A, Hilari K. 'Living with Aphasia the Best Way I Can': A Feasibility Study Exploring Solution-Focused Brief Therapy for People with Aphasia. *Folia Phoniatr Logop* 2015; **67**: 156-167 [PMID: 26789122 DOI: 10.1159/000439217]

90 **Khedr EM**, Abo El-Fetoh N, Ali AM, El-Hammady DH, Khalifa H, Atta H, Karim AA. Dual-hemisphere repetitive transcranial magnetic stimulation for rehabilitation of poststroke aphasia: a randomized, double-blind clinical trial. *Neurorehabil Neural Repair* 2014; **28**: 740-750 [PMID: 24503205 DOI: 10.1177/1545968314521009]

91 **Valiengo L**, Casati R, Bolognini N, Lotufo PA, Benseñor IM, Goulart AC, Brunoni AR. Transcranial direct current stimulation for the treatment of post-stroke depression in aphasic patients: a case series. *Neurocase* 2016; **22**: 225-228 [PMID: 26743441 DOI: 10.1080/13554794.2015.1130231]

92 **Rafsten L**, Danielsson A, Sunnerhagen KS. Anxiety after stroke: A systematic review and meta-analysis. *J. Rehabil. Med.* **50**: , 769-778 [PMID: 30184240 DOI: 10.2340/16501977-2384]

93 **Naghavi FS**, Koffman EE, Lin B, Du J. Post-stroke neuronal circuits and mental illnesses. *Int J Physiol Pathophysiol*

Pharmacol 2019; **11**: 1-11 [PMID: 30911356]
94 **Morris R**, Eccles A, Ryan B, Kneebone II. Prevalence of anxiety in people with aphasia after stroke. *Aphasiology* 2017; **31**: 1410-1415 [DOI: 10.1080/02687038.2017.1304633]
95 **Kim JS**. Post-stroke Mood and Emotional Disturbances: Pharmacological Therapy Based on Mechanisms. *J Stroke* 2016; **18**: 244-255 [PMID: 27733031 DOI: 10.5853/jos.2016.01144]
96 **Cahana-Amitay D**, Albert ML, Pyun SB, Westwood A, Jenkins T, Wolford S, Finley M. Language as a Stressor in Aphasia. *Aphasiology* 2011; **25**: 593-614 [PMID: 22701271 DOI: 10.1080/02687038.2010.541469]
97 **Carota A**, Rossetti AO, Karapanayiotides T, Bogousslavsky J. Catastrophic reaction in acute stroke: a reflex behavior in aphasic patients. *Neurology* 2001; **57**: 1902-1905 [PMID: 11723287 DOI: 10.1212/wnl.57.10.1902]
98 **Berthier ML**, Starkstein SE. Catastrophic reaction in crossed aphasia. *Aphasiology* 1994; **8**: 89-95 [DOI: 10.1080/02687039408248643]
99 **Auerbach S**, Karow CM. Neurobehavioral assessment of mood and affect in patients with neurological disorders. *Semin Speech Lang* 2003; **24**: 131-143 [PMID: 12709886 DOI: 10.1055/s-2003-38904]
100 **Starkstein SE**, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Catastrophic reaction after cerebrovascular lesions: frequency, correlates, and validation of a scale. *J Neuropsychiatry Clin Neurosci* 1993; **5**: 189-194 [PMID: 8508037 DOI: 10.1176/jnp.5.2.189]
101 **Sagen U**, Finset A, Moum T, Mørland T, Vik TG, Nagy T, Dammen T. Early detection of patients at risk for anxiety, depression and apathy after stroke. *Gen Hosp Psychiatry* 2010; **32**: 80-85 [PMID: 20114132 DOI: 10.1016/j.genhosppsych.2009.10.001]
102 **Laures-Gore JS**, Buchanan TW. Aphasia and the neuropsychobiology of stress. *J Clin Exp Neuropsychol* 2015; **37**: 688-700 [PMID: 26299187 DOI: 10.1080/13803395.2015.1042839]
103 **Torres-Prioris MJ**, López-Barroso D, Paredes-Pacheco J, Roé-Vellvé N, Dawid-Milner MS, Berthier ML. Language as a Threat: Multimodal Evaluation and Interventions for Overwhelming Linguistic Anxiety in Severe Aphasia. *Front Psychol* 2019; **10**: 678 [PMID: 31133908 DOI: 10.3389/fpsyg.2019.00678]
104 **Campbell Burton CA**, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. *Int J Stroke* 2013; **8**: 545-559 [PMID: 23013268 DOI: 10.1111/j.1747-4949.2012.00906.x]
105 **Knapp P**, Dunn-Roberts A, Sahib N, Cook L, Astin F, Kontou E, Thomas SA. Frequency of anxiety after stroke: An updated systematic review and meta-analysis of observational studies. *Int J Stroke* 2020; **15**: 244-255 [PMID: 31980004 DOI: 10.1177/1747493019896958]
106 **Schöttke H**, Giabbiconi CM. Post-stroke depression and post-stroke anxiety: prevalence and predictors. *Int Psychogeriatr* 2015; **27**: 1805-1812 [PMID: 26178418 DOI: 10.1017/S1041610215000988]
107 **Hunting-Pompon R**, Smith AN, Baylor C, Kendall D. Exploring associations between a biological marker of chronic stress and reported depression and anxiety in people with aphasia. *J Speech Lang Hear Res* 2019; **62**: 4119-4130 [PMID: 31652403 DOI: 10.1044/2019_JSLHR-L-19-0111]
108 **Cahana-Amitay D**, Oveis AC, Sayers JT, Pineles SL, Spiro A 3rd, Albert ML. Biomarkers of "Linguistic Anxiety" in aphasia: a proof-of-concept case study. *Clin Linguist Phon* 2015; **29**: 401-413 [PMID: 25815438 DOI: 10.3109/02699206.2015.1014572]
109 **Ayerbe L**, Ayis SA, Crichton S, Wolfe CD, Rudd AG. Natural history, predictors and associated outcomes of anxiety up to 10 years after stroke: the South London Stroke Register. *Age Ageing* 2014; **43**: 542-547 [PMID: 24375225 DOI: 10.1093/ageing/aft208]
110 **Linley-Adams B**, Morris R, Kneebone I. The Behavioural Outcomes of Anxiety scale (BOA): a preliminary validation in stroke survivors. *Br J Clin Psychol* 2014; **53**: 451-467 [PMID: 24837000 DOI: 10.1111/bjc.12056]
111 **Spitzer RL**, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**: 1092-1097 [PMID: 16717171 DOI: 10.1001/archinte.166.10.1092]
112 **Doyle PJ**, McNeil MR, Mikolic JM, Prieto L, Hula WD, Lustig AP, Ross K, Wambaugh JL, Gonzalez-Rothi LJ, Elman RJ. The Burden of Stroke Scale (BOSS) provides valid and reliable score estimates of functioning and well-being in stroke survivors with and without communication disorders. *J Clin Epidemiol* 2004; **57**: 997-1007 [PMID: 15528050 DOI: 10.1016/j.jclinepi.2003.11.016]
113 **Ryan BJ**, Clunne SM, Baker CJ, Shiggins C, Rose ML, Kneebone II. A systematic review of non-drug interventions to prevent and treat anxiety in people with aphasia after stroke. *Disabil Rehabil* 2021; 1-10 [PMID: 34116603 DOI: 10.1080/09638288.2021.1925752]
114 **Tanaka Y**, Cahana-Amitay D, Añbert M, Fujita K, Chieko N. Miyazaki, M. Treatment of anxiety in aphasia. *Procedia Soc Behav Sci* 2010; **6**: 252-253 [DOI: 10.1016/j.sbspro.2010.08.126]
115 **Beversdorf DQ**, Sharma UK, Phillips NN, Notestine MA, Slivka AP, Friedman NM, Schneider SL, Nagaraja HN, Hillier A. Effect of propranolol on naming in chronic Broca's aphasia with anomia. *Neurocase* 2007; **13**: 256-259 [PMID: 17886000 DOI: 10.1080/13554790701595471]
116 **Cahana-Amitay D**, Albert ML, Oveis A. Psycholinguistics of Aphasia Pharmacotherapy: Asking the Right Questions. *Aphasiology* 2014; **28**: 133-154 [PMID: 24489425 DOI: 10.1080/02687038.2013.818099]
117 **Tay J**, Morris RG, Markus HS. Apathy after stroke: Diagnosis, mechanisms, consequences, and treatment. *Int J Stroke* 2021; **16**: 510-518 [PMID: 33527880 DOI: 10.1177/1747493021990906]
118 **Jorge RE**, Starkstein SE, Robinson RG. Apathy following stroke. *Can J Psychiatry* 2010; **55**: 350-354 [PMID: 20540829 DOI: 10.1177/070674371005500603]
119 **Starkstein SE**, Manes F. Apathy and depression following stroke. *CNS Spectr* 2000; **5**: 43-50 [PMID: 18277328 DOI: 10.1017/s1092852900012955]
120 **Caeiro L**, Ferro JM, Costa J. Apathy secondary to stroke: a systematic review and meta-analysis. *Cerebrovasc Dis* 2013; **35**: 23-39 [PMID: 23428994 DOI: 10.1159/000346076]
121 **Kennedy JM**, Granato DA, Goldfine AM. Natural History of Poststroke Apathy During Acute Rehabilitation. *J Neuropsychiatry Clin Neurosci* 2015; **27**: 333-338 [PMID: 26185903 DOI: 10.1176/appi.neuropsych.15010001]

122 **Robert PH**, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, Caci H, Borg M, Brocker P, Bedoucha P. The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry* 2002; **17**: 1099-1105 [PMID: 12461757 DOI: 10.1002/gps.755]

123 **Marin RS**, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res* 1991; **38**: 143-162 [PMID: 1754629 DOI: 10.1016/0165-1781(91)90040-v]

124 **Quang H**, Wong S, Husain M, Piguet O, Hodges JR, Irish M, Kumfor F. Beyond language impairment: Profiles of apathy in primary progressive aphasia. *Cortex* 2021; **139**: 73-85 [PMID: 33836304 DOI: 10.1016/j.cortex.2021.02.028]

125 **Goldfine AM**, Dehbandi B, Kennedy JM, Sabot B, Semper C, Putrino D. Quantifying Poststroke Apathy With Actimeters. *J Neuropsychiatry Clin Neurosci* 2016; **28**: 199-204 [PMID: 26900735 DOI: 10.1176/appi.neuropsych.15090235]

126 **Husain M**, Roiser JP. Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nat Rev Neurosci* 2018; **19**: 470-484 [PMID: 29946157 DOI: 10.1038/s41583-018-0029-9]

127 **Le Heron C**, Apps MAJ, Husain M. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia* 2018; **118**: 54-67 [PMID: 28689673 DOI: 10.1016/j.neuropsychologia.2017.07.003]

128 **Starkstein SE**, Brockman S. The neuroimaging basis of apathy: Empirical findings and conceptual challenges. *Neuropsychologia* 2018; **118**: 48-53 [PMID: 29410070 DOI: 10.1016/j.neuropsychologia.2018.01.042]

129 **van Dalen JW**, Moll van Charante EP, Nederkoorn PJ, van Gool WA, Richard E. Poststroke apathy. *Stroke* 2013; **44**: 851-860 [PMID: 23362076 DOI: 10.1161/STROKEAHA.112.674614]

130 **Lanctôt KL**, Lindsay MP, Smith EE, Sahlas DJ, Foley N, Gubitz G, Austin M, Ball K, Bhogal S, Blake T, Herrmann N, Hogan D, Khan A, Longman S, King A, Leonard C, Shoniker T, Taylor T, Teed M, de Jong A, Mountain A, Casaubon LK, Dowlatshahi D, Swartz RH; Management of Mood, Cognition and Fatigue Following Stroke Best Practice Writing Group, the Heart & Stroke Canadian Stroke Best Practices and Quality Advisory Committee; in collaboration with the Canadian Stroke Consortium. *Canadian Stroke Best Practice Recommendations*: Mood, Cognition and Fatigue following Stroke, 6th edition update 2019. *Int J Stroke* 2020; **15**: 668-688 [PMID: 31221036 DOI: 10.1177/1747493019847334]

131 **Osa García A**, Brambati SM, Brisebois A, Désilets-Barnabé M, Houzé B, Bedetti C, Rochon E, Leonard C, Desautels A, Marcotte K. Predicting Early Post-stroke Aphasia Outcome From Initial Aphasia Severity. *Front Neurol* 2020; **11**: 120 [PMID: 32153496 DOI: 10.3389/fneur.2020.00120]

132 **Ramos-Perdigués S**, Mané-Santacana A, Pintor-Pérez L. [Prevalence and associated factors of anger post stroke: a systematic review]. *Rev Neurol* 2015; **60**: 481-489 [PMID: 26005071]

133 **Benson DF**. Psychiatric aspects of aphasia. *Br J Psychiatry* 1973; **123**: 555-566 [PMID: 4766654 DOI: 10.1192/bjp.123.5.555]

134 **Santos CO**, Caeiro L, Ferro JM, Albuquerque R, Luísa Figueira M. Anger, hostility and aggression in the first days of acute stroke. *Eur J Neurol* 2006; **13**: 351-358 [PMID: 16643312 DOI: 10.1111/j.1468-1331.2006.01242.x]

135 **Santos AC**, Ferro JM. Profile of Anger in Acute Stroke: A Multifactorial Model of Anger Determinants. *J Neuropsychiatry Clin Neurosci* 2019; **31**: 159-164 [PMID: 30458665 DOI: 10.1176/appi.neuropsych.18030037]

136 **Kim JS**, Choi S, Kwon SU, Seo YS. Inability to control anger or aggression after stroke. *Neurology* 2002; **58**: 1106-1108 [PMID: 11940703 DOI: 10.1212/wnl.58.7.1106]

137 **Chan KL**, Campayo A, Moser DJ, Arndt S, Robinson RG. Aggressive behavior in patients with stroke: association with psychopathology and results of antidepressant treatment on aggression. *Arch Phys Med Rehabil* 2006; **87**: 793-798 [PMID: 16731214 DOI: 10.1016/j.apmr.2006.02.016]

138 **Choi-Kwon S**, Han K, Cho KH, Choi S, Suh M, Nah HW, Kim JS. Factors associated with post-stroke anger proneness in ischaemic stroke patients. *Eur J Neurol* 2013; **20**: 1305-1310 [PMID: 23692152 DOI: 10.1111/ene.12199]

139 **Spielberger CD**, Reheiser EC, Sydeman SJ. Measuring the experience, expression and control of anger. *Issues Compr. Pediatr. Nurs.***18**: , 207-232 [PMID: 8707652 DOI: 10.3109/01460869509087271]

140 **Signer S**, Cummings JL, Benson DF. Delusions and mood disorders in patients with chronic aphasia. *J Neuropsychiatry Clin Neurosci* 1989; **1**: 40-45 [PMID: 2535428 DOI: 10.1176/jnp.1.1.40]

141 **Santos CO**, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: a systematic review. *Cerebrovasc Dis* 2011; **32**: 11-21 [PMID: 21576938 DOI: 10.1159/000327032]

142 Cambridge University Press. Elation: a state of extreme happiness or excitement. Cambridge International Dictionary of English. [cited 23 June 2021]. Available from: https://dictionary.cambridge.org/dictionary/english/elation

143 **Code C**. Catastrophic reaction and anosognosia in anterior-posterior and left-right models of the cerebral control of emotion. *Psychol Res* 1986; **48**: 53-55 [PMID: 3714933 DOI: 10.1007/BF00309279]

144 **Jacome DE**. Aphasia with elation, hypermusia, musicophilia and compulsive whistling. *J Neurol Neurosurg Psychiatry* 1984; **47**: 308-310 [PMID: 6707680 DOI: 10.1136/jnnp.47.3.308]

145 **Liu CY**, Wang SJ, Fuh JL, Yang YY, Liu HC. Bipolar disorder following a stroke involving the left hemisphere. *Aust N Z J Psychiatry* 1996; **30**: 688-691 [PMID: 8902178 DOI: 10.3109/00048679609062667]

146 **Ahmed AI**. A manic episode in a 64-year-old man: an adverse effect of varenicline. *Gen Hosp Psychiatry* 2011; **33**: 200.e9-200.e11 [PMID: 21596218 DOI: 10.1016/j.genhosppsych.2010.11.005]

147 **Jampala VC**, Abrams R. Mania secondary to left and right hemisphere damage. *Am J Psychiatry* 1983; **140**: 1197-1199 [PMID: 6614229 DOI: 10.1176/ajp.140.9.1197]

148 **Ferreira M**, Machado C, Machado Á, Santos B. Clinical difficulties in post-stroke mania. *Rev Psiquiatr Clin* 2016; **43**: 17 [DOI: 10.1590/0101-60830000000074]

149 **Thomas P**. Delusion, mania, and personality changes. In: Godefroy O. The Behavioral and Cognitive Neurology of Stroke. Cambridge: Cambridge Univerisy Press, 2013; 351–362

150 **Huffman J**, Stern TA. Acute psychiatric manifestations of stroke: a clinical case conference. *Psychosomatics* 2003; **44**: 65-75 [PMID: 12515840 DOI: 10.1176/appi.psy.44.1.65]

151 **Starkstein SE**, Fedoroff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. *Biol Psychiatry* 1991; **29**: 149-158 [PMID: 1995084 DOI: 10.1016/0006-3223(91)90043-l]

152 **Stangeland H**, Orgeta V, Bell V. Poststroke psychosis: a systematic review. *J Neurol Neurosurg Psychiatry* 2018; **89**: 879-885 [PMID: 29332009 DOI: 10.1136/jnnp-2017-317327]

153 **Torrisi M**, De Luca R, Pollicino P, Leonardi S, Marino S, Maresca G, Maggio MG, Piccolo A, Bramanti P, Calabrò RS. Poststroke delusions: What about the neuroanatomical and neurofunctional basis? *Appl Neuropsychol Adult* 2019; **26**: 392-396 [PMID: 29351402 DOI: 10.1080/23279095.2017.1421536]

154 **Ross ED**. Acute agitation and other behaviors associated with Wernicke aphasia and their possible neurological bases. *Cogn Behav Neurol* 1993; **6**: 9-18

155 **Braun CM**, Suffren S. A general neuropsychological model of delusion. *Cogn Neuropsychiatry* 2011; **16**: 1-39 [PMID: 20198522 DOI: 10.1080/13546800903442314]

156 **Capron DJ**. Retentissement psychiatrique de l'AVC. The psychiatric consequences of stroke. *Neurol Psychiatr Geriatr* 2015; **15**: 353-358 [DOI: 10.1016/j.npg.2015.04.003]

157 **Sambunaris A**, Hyde TM. Stroke-related aphasias mistaken for psychotic speech: two case reports. *J Geriatr Psychiatry Neurol* 1994; **7**: 144-147 [PMID: 7916937 DOI: 10.1177/089198879400700303]

158 **Burch EA Jr**, Groene BM. Aphasic syndromes and "psychiatric" symptoms: diagnostic dilemmas. *South Med J* 1986; **79**: 1234-1237 [PMID: 3764519 DOI: 10.1097/00007611-198610000-00010]

159 **Jilani AQ**, Agarwal A, Bharti S, Srivastava S. Psychosis or Wernicke's aphasia, and response of speech therapy in wernicke's aphasia: A case report. *ERA's J Med Res* 2019; **6**: 1-3 [DOI: 10.24041/ejmr2019.151]

160 **Joyce EM**. Organic psychosis: The pathobiology and treatment of delusions. *CNS Neurosci Ther* 2018; **24**: 598-603 [PMID: 29766653 DOI: 10.1111/cns.12973]

161 **Hilari K**, Owen S, Farrelly SJ. Proxy and self-report agreement on the Stroke and Aphasia Quality of Life Scale-39. *J Neurol Neurosurg Psychiatry* 2007; **78**: 1072-1075 [PMID: 17259351 DOI: 10.1136/jnnp.2006.111476]

162 **Cruice M**, Worrall L, Hickson L, Murison R. Measuring quality of life: Comparing family members' and friends' ratings with those of their aphasic partners. *Aphasiology* 2005; **19**: 111-119 [DOI: 10.1080/02687030444000651]

163 **Nicholas M**, Jennelle L, Connor LT, Haynes C, Zipse L. Do caregiver proxy reports and congruence of client-proxy activity participation goals relate to quality of life in people with aphasia? *Int J Lang Commun Disord* 2020; **55**: 373-386 [PMID: 32056341 DOI: 10.1111/1460-6984.12524]

164 **Peters SK**, Dunlop K, Downar J. Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. *Front Syst Neurosci* 2016; **10**: 104 [PMID: 28082874 DOI: 10.3389/fnsys.2016.00104]

165 **Menon V**. Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci* 2011; **15**: 483-506 [PMID: 21908230 DOI: 10.1016/j.tics.2011.08.003]

166 **Pujol J**, Bello J, Deus J, Cardoner N, Martí-Vilalta JL, Capdevila A. Beck Depression Inventory factors related to demyelinating lesions of the left arcuate fasciculus region. *Psychiatry Res* 2000; **99**: 151-159 [PMID: 11068196 DOI: 10.1016/s0925-4927(00)00061-5]

167 **Fridriksson J**, den Ouden DB, Hillis AE, Hickok G, Rorden C, Basilakos A, Yourganov G, Bonilha L. Anatomy of aphasia revisited. *Brain* 2018; **141**: 848-862 [PMID: 29360947 DOI: 10.1093/brain/awx363]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 470-482

DOI: 10.5498/wjp.v12.i3.470

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Studying the relationship between clinical features and mental health among late-onset myasthenia gravis patients

Lu Yu, Li Qiu, Hao Ran, Qian Ma, Ya-Ru Lu, Wei-Bin Liu

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Goh KK, Setiawati Y

Received: August 1, 2021
Peer-review started: August 1, 2021
First decision: December 4, 2021
Revised: November 26, 2021
Accepted: February 22, 2022
Article in press: February 22, 2022
Published online: March 19, 2022

Lu Yu, Li Qiu, Qian Ma, Ya-Ru Lu, Wei-Bin Liu, Department of Neurology, National Key Clinical Department and Key Discipline of Neurology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong Province, China

Hao Ran, School of Pharmaceutical Science, Sun Yat-sen University, Guangzhou 510006, Guangdong Province, China

Corresponding author: Wei-Bin Liu, MD, Chief Physician, Professor, Department of Neurology, National Key Clinical Department and Key Discipline of Neurology, the First Affiliated Hospital of Sun Yat-sen University, No. 58 Zhongshan 2nd Road, Guangzhou 510080, Guangdong, China. liuwb@mail.sysu.edu.cn

Abstract

BACKGROUND

Mental disorders are common comorbidities among individuals with neurological diseases, and the prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high. There have been few studies on the mental health of patients with late-onset myasthenia gravis (MG).

AIM

To examine the relationship between clinical features and the mental health symptoms within late-onset MG patients.

METHODS

A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021. Patients were classified into two groups: early-onset MG (age at onset < 50 years, n = 63) and late-onset MG (age at onset ≥ 50 years, n = 42). Social demographic data and information about marital status, education level, clinical symptoms, serum antibody levels, and therapies used were collected for all participants. Participants were also evaluated using the Myasthenia Gravis Composite scale, the Myasthenia Gravis Activities of Daily Living scale, the Myasthenia Gravis Quality of Life 15 (MG-QOL-15) questionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A). The relationship between clinical features and mental health in late-onset MG patients was examined using multivariate logistic regression analyses.

RESULTS

Late-onset MG patients were more prone to dyspnea, had higher levels of serum anti-acetylcholine receptor antibodies, and higher total scores on the MG-QOL-15, HAM-D, and HAM-A questionnaires, than early-onset MG patients had ($P < 0.05$). Among those with late-onset MG, female patients had higher total HAM-D and HAM-A scores than male patients had ($P < 0.05$). High scores on the QOL-15 questionnaire were associated with higher incidences of anxiety and depression, and the association was found to be independent after adjusting for confounding risk factors. In the late-onset subgroup, the areas under the receiver operating characteristic curves for the MG-QOL-15 score-based diagnostic accuracy for anxiety and depression state were 0.816 ($P = 0.001$) and 0.983 ($P < 0.001$), respectively.

CONCLUSION

Higher MG-QOL-15 scores were a risk factor for anxiety and depression in late-onset MG, and women with late-onset MG were more likely to have anxiety and depression than men were.

Key Words: Mental health; Late-onset myasthenia gravis; Anxiety; Depression

Core tip: Mental disorders are the common comorbidities among myasthenia gravis (MG) patients in older age. In this study, we found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher scores on the Myasthenia Gravis Quality of Life 15 questionnaire were an independent risk factor for anxiety and depression in patients with late-onset MG. This is the first report detailing the relationship between clinical features and mental health in the subgroup of MG patients with late disease onset.

Citation: Yu L, Qiu L, Ran H, Ma Q, Lu YR, Liu WB. Studying the relationship between clinical features and mental health among late-onset myasthenia gravis patients. *World J Psychiatry* 2022; 12(3): 470-482
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/470.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.470

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder that is mainly caused by autoantibodies binding to nicotinic acetylcholine receptors (AChRs) at muscle endplates, and is characterized by skeletal muscle fatigability and weakness[1,2]. MG is also associated with emotional, cognitive, and behavioral symptoms[3].

Mental disorders are the most common comorbidities among individuals with neurological diseases, and the prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high[4]. MG is an autoimmune disease that can lead to disability. The global prevalence of MG is roughly 40-180 cases per 1 million individuals[5]. However, there are limited data on the relationship between mental disorders and MG, especially in patients with late-onset forms of the disease. Furthermore, because myasthenic symptoms of MG may overlap with somatic symptoms of depression and anxiety[6], such as fatigue or shortness of breath, which are also common in mental disorders, and facial weakness and blepharoptosis generally convey an impression of depression and apathy[7], comorbidities accompanied by mental and myasthenic symptoms may be misdiagnosed, thus the need to focus on both mental and physical therapies has been highlighted[8,9].

Mental disorders have often been reported; the incidence is up to 59% of MG patients, with depression being the most common disorder, followed by anxiety and hypochondria[10]. The unpredictable progression, chronic course and long-term treatment for MG can lead to limitations and reductions in quality of life (QOL)[11-13], which were found to predispose to psychological stress[7]. There is a questionnaire specifically aimed at assessing QOL among MG patients (Myasthenia Gravis Quality of Life 15-item (MG-QOL-15) scale, including 15 test items that address MG-specific social functioning and uses five response options, based on which QOL can be effectively rated[14,15]. The measures of MG-QOL-15 try to capture patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal, and higher scores on the MG-QOL-15 questionnaire were indicative of more severe clinical cases to some extent[13].

Longer disease duration, severity of disease, and MG-induced respiratory failure may contribute to the increased rates of depression[16,17]. Compromised swallowing and communication abilities, unpredictable and fluctuating nature of respiratory dysfunction suggests concerning risk factors for

developing anxiety among MG patients[7,16-18]. Fewer work restrictions could be protective factors for developing mental disorders in the limited observational studies[19]. Late-onset MG occurring in older adults is more difficult to manage mainly because of the multiple comorbidities[20,21] and MG with late disease onset is on the rise in recent years[22]. Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms[23], awareness of the occurrence of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. To this end, this cross-sectional study aimed to investigate the relationship between clinical features and mental health in patients with late-onset MG.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted in The First Affiliated Hospital of the Sun Yat-sen University, in Guangzhou, China. A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021. Clinical data were collected, and scores on clinical scales were procured through face-to-face evaluations with professional neurologists. This study was approved by the Ethics Committee of The First Affiliated Hospital of the Sun Yat-sen University. We obtained informed consent from all patients prior to the scale-based clinical examinations.

Inclusion and exclusion criteria

All participants were diagnosed with MG according to international consensus-based guidelines[24]. This study included patients who met the following criteria: (1) Diagnosed with MG; (2) aged ≥ 16 years; and (3) ability to fully cooperate during clinical scale-based evaluations. Patients were excluded if they: (1) Were under treatment with antianxiety and/or antidepressant drugs; and (2) had incomplete data.

Clinical data and scales

We collected data on sociodemographic characteristics, inducing factors, comorbidities, specific clinical features (*i.e.*, disease duration, Myasthenia Gravis Foundation of America Classification, symptoms at first evaluation, and mental status), details of serum antibodies levels [*i.e.*, levels of anti-AChR/muscle-specific tyrosine kinase (MuSK) antibodies], and immunotherapy history. Patients were independently examined using the Myasthenia Gravis Composite (MGC) scale, the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale, the MG-QOL-15 questionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D), and the Hamilton Anxiety Rating Scale (HAM-A) by two neurologists (both of whom were qualified to perform these evaluations).

The MGC scale[25] is composed of 10 items that measure symptoms and signs of MG, with a maximum score of 50 points, the reliability coefficient of the MGC scale was 98%, indicating excellent test-retest reliability. The MG-ADL scale[26] is composed of eight questions, aims to assess disability of ocular (2 items), bulbar (3 items), respiratory (1 item), and limb (2 items), with each response graded from 0 (normal) to 3 (most severe), and the total score ranges from 0 to 24, reliability coefficient was 93.7%. The MG-QOL-15 consists of 15 items: mobility (9 items), symptoms (3 items), general contentment (1 item), and emotional well-being (2 items)[27], with each response graded from 0 (not at all) to 4 (very much), and total scores of up to 60 points, the Chinese MG-QOL-15 had excellent internal consistency (Cronbach's $\alpha = 0.928$). Higher scores on MGC, MG-ADL, or MG-QOL-15 scales were indicative of more severe clinical cases. The HAM-A and HAM-D scales consist of 14 and 17 items, respectively, and are used to measure mental health symptoms[28,29]. The total scores are 56 (for the HAM-A) and 53 (for the HAM-D), and total HAM-A scores were classified as no (< 7), potential (7-13), assured (14-29), and severe (> 29) anxiety. Total HAM-D scores were classified as no (< 7), potential (7-17), assured (17-24), and severe (> 24) depression, the Cronbach's coefficient of them was > 0.8, indicating good internal consistency. The above questionnaires and scales were administered in the Chinese language, and are all reliable, valid, and widely used[30-33].

Groups

Participants were categorized into the following subgroups according to their age at disease onset[34]: early-onset MG (age at onset < 50 years, $n = 63$) and late-onset MG (age at onset ≥ 50 years, $n = 42$). HAM-A scores ≥ 7 and HAM-A scores < 7 were considered to be indicative of anxiety and nonanxiety states, while HAM-D scores ≥ 7 and HAM-D scores < 7 were classified to be depressive and nondepressive states, respectively[35,36]. Patients were considered seropositive for anti-AChR antibodies if their titers were > 0.45 nmol/L on ELISA. They were deemed seropositive for anti-MuSK antibodies if their titers were > 0.05 nmol/L on a radioimmunoassay. All test reagents were purchased from RSR Ltd. (Cardiff, United Kingdom.

Statistical analysis

Statistical analyses were performed using SPSS version 25 software (IBM, Chicago, United States) and GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA). Categorical data were presented as counts and percentages, and were analyzed using Fisher's exact test or χ^2 test. Numerical data were presented as medians and interquartile ranges (partial distribution), and compared using the Mann-Whitney *U* test. Correlations were estimated with Pearson or Spearman correlation coefficients. Clinical determinants of anxiety and depression were used in multivariate logistic regression analyses, while gender, age at onset, body mass index (BMI), anti-AChR antibody levels, and MG-QOL15 scores were considered confounding risk factors. Receiver operating characteristic (ROC) curves were drawn to evaluate the value of MG-QOL-15 scores for diagnosing anxiety and depression. Significance was accepted if *P* values were < 0.05, and are denoted as $^{a}P < 0.05$, $^{b}P < 0.01$, and $^{c}P < 0.001$.

RESULTS

Baseline characteristics

Patients with late-onset MG (age at onset ≥ 50 years) accounted for 40.0% (n = 42) of the 105 patients, and those with early-onset MG (age < 50 years) accounted for 60.0% (n = 63). Among the patients with late-onset MG, 45.24% were women, and 54.76% were men. Among the early-onset MG patients, 58.73% were women, and 41.27% were men.

The medians (interquartile ranges) of HAM-A scores were 5 (5.5) in early-onset patients and 8.5 (7.5) in late-onset patients. These scores were significantly different between the two groups (P < 0.001; Figure 1A). The HAM-D scores were 7 (8) and 10.5 (7.75) in early-onset and late-onset patient groups, respectively, and there was a significant difference between the two groups (P = 0.018; Figure 1B). There were also significant differences in BMI, disease duration, dyspnea symptoms, anti-AChR antibody levels, and MG-QOL-15 scores between the two groups (P < 0.05). HAM-A and HAM-D scores were significantly higher in female patients with late-onset MG than in those with early-onset MG (P < 0.001 and P = 0.001, respectively), but no significant differences were observed when only male patients were considered in these analyses (P = 0.192 and P = 0.731, respectively; Figure 2A and B). Baseline characteristics of the early-onset and late-onset groups are shown in Table 1.

Correlation between clinical features and age at onset, assessed using Pearson or Spearman correlation analysis

There was a positive correlation between age at onset and BMI (r = 0.41, P < 0.001), anti-AChR antibody levels (r = 0.31, P = 0.001), MG-QOL-15 scores (r = 0.32, P = 0.001), HAM-A scores (r = 0.41, P < 0.001), and HAM-D scores (r = 0.26, P = 0.007). However, there was a negative correlation between age at onset and disease duration (r = 0.59, P < 0.001). Correlations between all clinical features and age at onset are detailed in Table 2.

Clinical determinants of anxiety and depression in MG patients, measured using logistic analysis

Based on results from univariate analyses as well as previous literature[14-19], variables that may be relevant for mental health outcomes (gender, age at onset, BMI, anti-AChR antibody levels, and MG-QOL-15 scores) were included in a logistic regression model. No multicollinearity amongst the variables was found (variance inflation ranged from 1.072 to 1.536; tolerance ranged from 0.651 to 0.933) (Supplementary Table 1).

When the incidence of anxiety and depression were included as independent variables in the logistic analysis, they were associated with age at onset and MG-QOL-15 when other confounders were not considered. However, only MG-QOL15 scores were found to be independently associated with an increased risk of anxiety [odds ratio (OR) 1.10, 95%CI 1.04-1.15, P < 0.001) after adjusting for possible confounds (including gender, age at onset, BMI, and anti-AChR antibody levels). MG-QOL-15 scores were also significantly associated with the incidence of depression in MG patients (OR 1.20, 95%CI: 1.10-1.30, P < 0.001) (Table 3).

Diagnostic value of MG-QOL15 scores for examining mental health in late-onset MG patients

When multivariate analysis was performed after adjusting for related confounds, MG-QOL-15 scores were found to be independent risk factors for anxiety and depression. In patients with late-onset MG, the median (interquartile ranges) MG-QOL-15 scores in the nonanxiety and anxiety groups were 8 (10.5) and 20 (17), respectively, and there were significant differences between the two groups (P < 0.001). Similarly, MG-QOL-15 scores were significantly different between the depression and nondepression groups (P < 0.001; Supplementary Figures 1A and 2A). We also examined whether MG-QOL-15 scores could help to diagnose or predict anxiety/depression state in late-onset MG patients using ROC curves [the larger the area under the ROC curve (AUC), the higher the diagnostic accuracy], and the smallest point that maximizes the value of (sensitivity + specificity 1) is calculated as the cut-off value, which would lead to the maximum degree of classification for anxiety/depression state. In our study, the AUC

Table 1 Comparison between early-onset and late-onset groups

	Total patients (*n* = 105)	Early-onset (*n* = 63)	Late-onset (*n* = 42)	*P* value
Gender (*n*, %)[1]				
Male	49 (46.67)	26 (41.27)	23 (54.76)	
Female	56 (53.34)	37 (58.73)	19 (45.24)	0.231
Marital status (*n*, %)[2]				
Married	63 (60.0)	33 (52.38)	30 (71.43)	0.067
Single (unmarried/divorced/widowed)	42 (40.0)	30 (47.62)	12 (28.57)	
Education (*n*, %)[2]				
Primary school and below	26 (24.76)	12 (19.05)	14 (33.33)	0.073
Secondary school	44 (41.90)	25 (39.68)	19 (45.24)	
College and above	35 (33.33)	26 (41.27)	9 (21.43)	
Career change due to illness (*n*, %)[2]				0.955
No change	69 (65.71)	41 (65.08)	28 (66.67)	
Leave of absence	24 (22.86)	15 (23.81)	9 (21.43)	
Transfer/unemployment	12 (11.43)	7 (11.11)	5 (11.90)	
BMI (kg/m^2)[3]	21.71 (5.77)	20.51 (4.21)	24.36 (4.53)	< 0.001[c]
Disease duration (mo)[3]	5.00(12.21)	7.00(13.34)	4.00(8.50)	0.016[a]
MGFA classification at evaluating (*n*, %)[1]				
I	28 (26.67)	21 (33.33)	7 (16.67)	
II	40 (38.10)	22 (34.92)	18 (42.86)	
III	31 (29.52)	16 (25.40)	15 (35.71)	
IV	6 (5.71)	4 (6.35)	2 (4.76)	0.255
Thymectomy (*n*, %)[2]	44 (41.90)	28 (44.44)	16 (38.10)	0.551
Comorbidities (*n*, %)[2]	49 (46.67)	32 (50.79)	17 (40.48)	0.299
Inducing factor (*n*, %)[1]				
Respiratory infection	12 (11.43)	6 (9.52)	6 (14.29)	
Overfatigue	3 (2.86)	1 (1.59)	2 (4.76)	
No triggers	90 (85.71)	56 (88.89)	34 (80.95)	0.470
Clinical features				
Onset symptom				
Blepharoptosis (*n*, %)[2]	97 (92.38)	59 (93.65)	38 (90.48)	0.711
Dysphagia (*n*, %)[2]	50 (47.62)	29 (46.03)	21 (50.00)	0.842
Limb muscle weakness (*n*, %)[2]	55 (52.38)	31 (49.21)	24 (57.14)	0.550
Dyspnea (*n*, %)[2]	15 (14.29)	5 (7.94)	10 (23.81)	0.043[a]
Serum antibody (nmol/L) [3]				
Anti-AChR Ab	9.54 (25.98)	3.11 (17.98)	17.51 (27.45)	0.002[b]
Anti-MuSK Ab	0 (1.13)	0.31 (2.17)	0 (0)	0.098
Seronegative (*n*, %)[2]	16 (15.24)	11 (17.46)	5 (11.90)	0.582
Immunotherapy at evaluating				
Glucocorticoids (*n*, %)[2]	76 (72.38)	49 (77.78)	27 (64.29)	0.181
Azathioprine (*n*, %)[2]	31 (29.52)	19 (30.16)	12 (28.57)	0.861
Tacrolimus (*n*, %)[2]	8 (7.62)	3 (4.76)	5 (11.90)	0.262

Leflunomide (*n*, %)[2]	22 (20.95)	13 (20.63)	9 (21.43)	0.922
No immunotherapy (*n*, %)[2]	53 (50.48)	32 (50.79)	21 (50.00)	0.936
Neuropsychological scales				
MGC[3]	6.00 (6.50)	6.00 (6.00)	7.00 (7.00)	0.103
ADL[3]	3.00 (3.00)	3.00 (4.00)	3.00 (2.00)	0.960
QOL-15[3]	14.00 (15.00)	12.00 (13.50)	16.00 (20.00)	0.027[a]
HAM-A[3]	6.00 (7.00)	5.00 (5.50)	8.50 (7.50)	< 0.001[c]
HAM-D[3]	8.00 (7.00)	7.00 (8.00)	10.50 (7.75)	0.018[a]

[1]*n* (%), Fisher's exact test.
[2]*n* (%), Pearson's χ^2 test.
[3]Median (25%Q, 75%Q), Mann-Whitney *U* test.
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index; ADL: Activities of daily living scale; MGC: Myasthenia Gravis Composite scale; MG-QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

Table 2 Correlation between clinical features and age at onset

Clinical features	Correlation	95%CI	*t*	*P* value
Disease duration	-0.59	-0.70, -0.446	-7.370	< 0.001[c]
BMI	0.41	0.233, 0.555	4.520	< 0.001[c]
Anti-AChR Ab	0.31	0.128, 0.475	3.335	0.001[b]
QOL-15	0.32	0.133, 0.479	3.383	0.001[b]
HAM-A	0.41	0.236, 0.557	4.548	< 0.001[c]
HAM-D	0.26	0.074, 0.432	2.759	0.007[b]

[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
BMI: Body mass index; MG-QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale.

for MG-QOL-15 scores at a cut-off value of 14.5 in the anxiety group was 0.816 (P = 0.001), and the sensitivity-specificity was 75.86% and 84.62%, respectively (Supplementary Figure 1B). The AUC for MG-QOL-15 scores at a cut-off value of 14.5 in the depression group was 0.983 (P < 0.001), and the sensitivity-specificity were 70.59% and 100%, respectively (Supplementary Figure 2B).

DISCUSSION

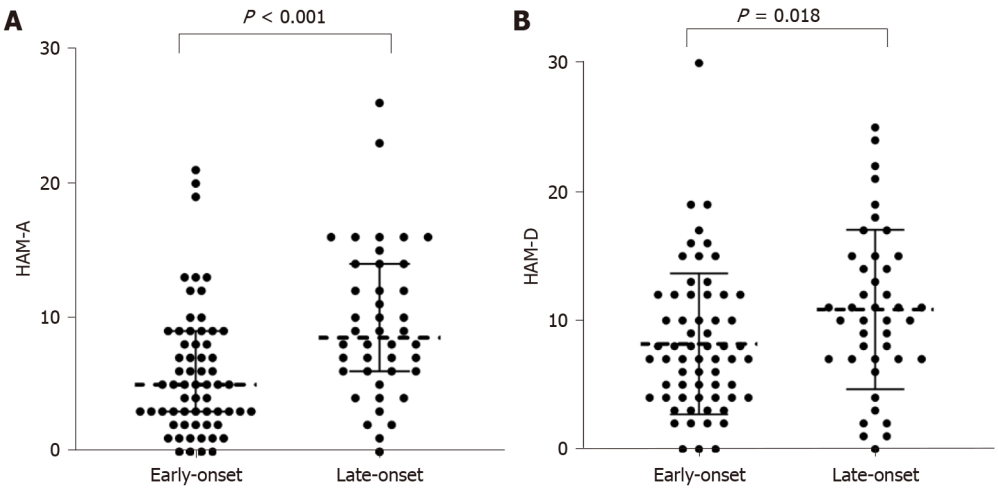
In the current study, late-onset MG patients had higher total scores on the MG-QOL-15, HAM-A, and HAM-D scales compared with early-onset group MG patients, and there was a positive linear correlation between age at onset and MG-QOL-15 scores, HAM-A scores, and HAM-D scores. These results support the idea that late-onset MG is correlated with more severe impairments to patients' QOL and mental state. MG has previously been demonstrated to affect QOL, as well as mental and physical health[37]. Factors that influence QOL in MG include trouble with eyesight, skeletal muscle weakness, activity limitations, and unhealthy mental state[38,39]. MG-QOL-15 scales have also previously been applied to assess MG-related dysfunction[40]. Several studies reported that MG-QOL-15 scores in MG patients are highly and positively correlated with scores on the HAM-A and HAM-D scales[38,41,42]. These findings supported the notion that low QOL correlates with poor mental health in MG patients.

We also found that female patients with late-onset MG were more susceptible to anxiety and depression. It is important to examine what factors are related to the mental health of patients with late-onset MG and why there are sex-related differences. The prevalence of depression and anxiety is higher among women than men. This difference in mental disorders is the result of a complex interplay

Table 3 Multivariate logistic model of the clinical determinants of anxiety/depression in myasthenia gravis patients

Variables	Model 1		Model 2	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Anxiety				
Gender	0.96 (0.45-2.07)	0.917	0.65 (0.25-1.68)	0.372
Age at onset	1.04 (1.02-1.07)	0.002[b]	1.02 (0.99-1.05)	0.305
Disease duration	0.93 (0.88-0.98)	0.070	0.97 (0.90-1.04)	0.414
BMI	1.10 (0.99-1.23)	0.075	1.05 (0.92-1.21)	0.485
Anti-AChR Ab	1.02 (1.00-1.05)	0.092	1.02 (0.99-1.05)	0.274
QOL-15	1.10 (1.05-1.16)	< 0.001[c]	1.10 (1.04-1.15)	< 0.001[c]
Depression				
Gender	0.82 (0.36-1.82)	0.636	0.56 (0.19-1.64)	0.293
Age at onset	1.03 (1.00-1.06)	0.022[a]	1.03 (0.99-1.06)	0.162
Disease duration	0.98 (0.93-1.03)	0.418	1.06 (0.98-1.15)	0.172
BMI	1.05 (0.93-1.17)	0.440	0.97 (0.83-1.13)	0.678
Anti-AChR Ab	1.10 (0.99-1.04)	0.387	1.01 (0.97-1.05)	0.582
QOL-15	1.19 (1.10-1.28)	< 0.001[c]	1.20 (1.10-1.30)	< 0.001[c]

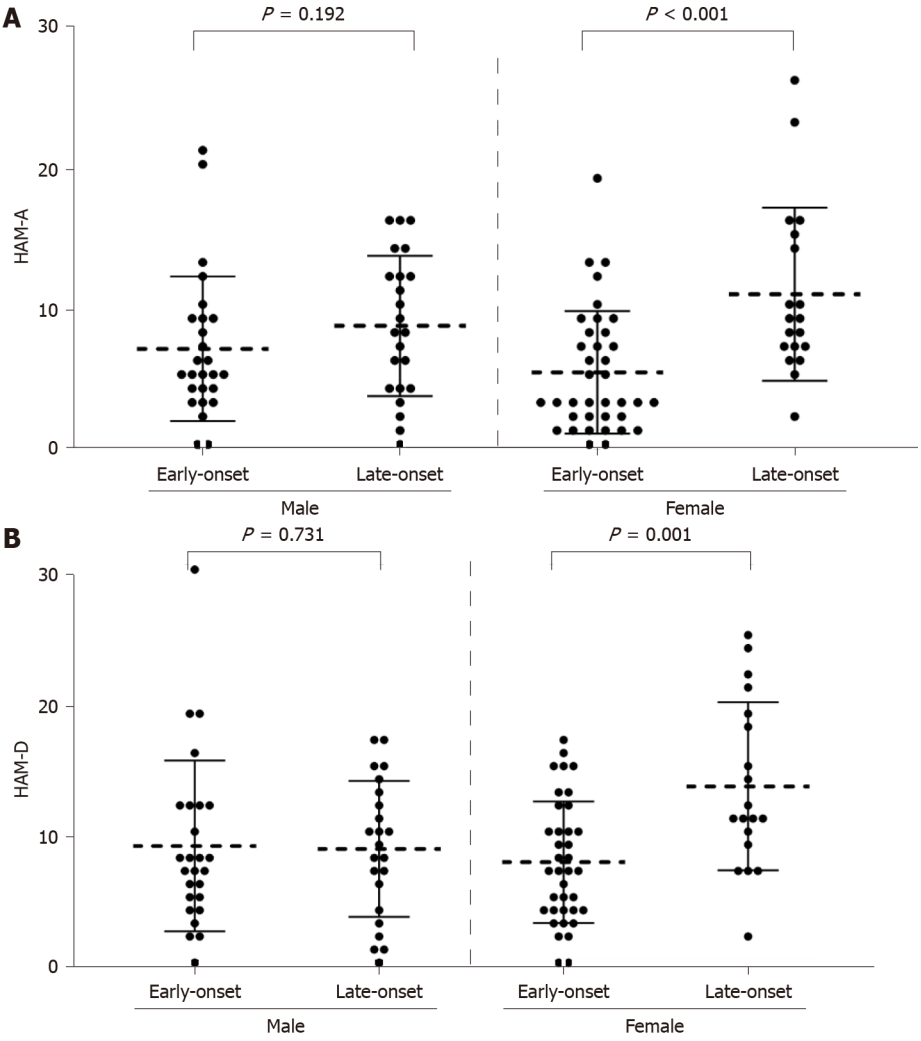
[a]*P* < 0.05.
[b]*P* < 0.01.
[c]*P* < 0.001.
Model 1: Unadjusted; Model 2: Adjusted for possible confounders including gender, age at onset, body mass index, and anti-acetylcholine receptor antibody. BMI: Body mass index; QOL-15: Myasthenia Gravis Quality of Life 15 questionnaire; OR = exp (β).



DOI: 10.5498/wjp.v12.i3.470

Figure 1 Hamilton anxiety rating and the Hamilton depression rating scores according to age of onset. A: The median (interquartile range) of Hamilton anxiety rating (HAM-A scale scores in early-onset and late-onset groups were 5 (5.5) and 8.5 (7.5), respectively. The HAM-A scale score was significantly higher in the late-onset group than early-onset group (*P* < 0.001); B: The Hamilton depression rating (HAM-D) score levels in early-onset and late-onset groups were 7 (8) and 10.5 (7.75), respectively. The HAM-D scale score was significantly higher in the late-onset group than early-onset group (*P* = 0.018). *P* value was calculated using Mann-Whitney *U* test.

between genetic, hormonal and psychosocial factors[43-45]. Some studies have shown that women rather than men carrying the SS genotype of serotonin transporter gene-linked promoter region (5-HTTLPR) more easily develop depressive symptoms under a negative environment[46,47]. Female patients with MG tend to have more severe cases of the disease, and may also be affected by hormonal changes associated with menstruation, pregnancy, and/or postpartum fluctuations in hormone levels [48-50]. Previous studies have reported that the use of glucocorticoids is associated with changes in



DOI: 10.5498/wjp.v12.i3.470

Figure 2 Hamilton anxiety rating and the Hamilton depression rating scores according to age of onset and sex. A: The median (interquartile range) of Hamilton anxiety rating (HAM-A scale levels in late-onset groups were 3 (6), and 9 (8), respectively, and HAM-A scale scores were significantly higher in late-onset group than early-onset group in women ($P < 0.001$); B: The Hamilton depression rating (HAM-D) score levels in early-onset and late-onset groups were 7 (7) and 11 (10), respectively, and HAM-D scale score was significantly higher in late-onset group than early-onset group in women ($P = 0.001$). There were no significant differences in men for both HAM-A and HAM-D scale scores. *P* value was calculated using Mann-Whitney *U* test.

physical appearances, leading to conditions such as moon face and/or central obesity, which may have greater negative sociopsychological effects on women with MG than men. Moreover, some patients with late-onset MG do not have positive responses to medication, and some are intolerant to treatment, which can result in refractory conditions[51]. Female patients with late-onset MG may endure the adverse effects of comorbidities longer than their male counterparts, which would contribute to poorer QOL[52]. These factors could explain why female MG patients had higher susceptibility to anxiety and depression than male patients.

Our study showed that MG-QOL-15 scores were independently associated with an increased risk of anxiety and depression when gender, age at onset, BMI, and anti-AChR antibody levels were adjusted for in a multivariate analysis. We found that the ORs (95%CIs) of MG-QOL-15 scores for the anxiety and depression groups were 1.10 (1.04-1.15, $P < 0.001$) and 1.20 (1.10-1.30, $P < 0.001$), respectively, indicating that under the same conditions of gender, age at onset, and other factors, the odds of anxiety state increased by 10% and depression state increased by 20% for each increase in MG-QOL-15 scores, and high MG-QOL-15 scores were indeed a risk factor for anxiety/depression state. Previous studies have demonstrated that lower perceived QOL is highly correlated with mental impairment in MG patients[9,53,54]. In late-onset groups, the areas under the ROC curves for MG-QOL-15 scores at a cutoff value of 14.5 in the anxiety and depression groups were 0.816 and 0.983, respectively, which suggested that MG-QOL-15 scores had good diagnostic accuracy for the mental disorders, at least among late-onset MG patients. Our data revealed that MG-QOL-15 score cutoff of 14.5 could be a good indicator for poor mental health in need of attention among late-onset MG patients. Further research is needed for fine-tuning this threshold.

Some research has also reported that patients with MG who received thymectomy or proper immunosuppressive therapy had improved physical health and decreased disability symptoms, which indirectly improved mental health[55,56]. However, our study found that the rate of thymectomy and immunosuppressive treatment was comparable between early-onset and late-onset groups, but that late-onset MG patients had significantly higher levels of serum anti-AChR antibodies and were more prone to dyspnea. The proportion of overweight patients in the late-onset group was greater than that in the early-onset group. This pattern could be related to older age, which contributes to reductions in physical activity and possibly susceptibility to the adverse effects of glucocorticoids[57]. Compared to early-onset MG patients, higher anti-AChR antibody titers were reported in late-onset MG patients[57,58], which may partly be due to immune dysregulation, including age-related decreases in immunocompetence and increases in the production of autoantibodies[59,60]. Bulbar[23] and ocular symptoms [61] have been previously reported to be more common in late-onset MG patients. However, we found no differences in extraocular or limb muscle involvement between the two groups. Genetic factors may influence these results, since a similar study that reported a higher occurrence of ocular symptoms in late-onset patients also reported a higher proportion of women in the late-onset group[62].

There were some limitations to our study. First, limits in our sampling method make it difficult to draw firm conclusions. Second, our study had a prospective design, so further follow-up and particularly studies that include healthy control groups are needed to validate the results. However, our study had some advantages. For example, all included patients were enrolled from the same neuromuscular outpatient clinic. Thus, they received prompt and high-quality clinical scale evaluations that were performed by well-qualified and trained professionals, which ensured the integrity and authenticity of the data.

CONCLUSION

Our research showed that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher MG-QOL-15 scores were an independent risk factor for anxiety and depression in patients with late-onset MG. To our knowledge, this is the first report detailing the relationship between MG-QOL-15 scores and mental health in the subgroup of MG patients with late disease onset. Thus, this association warrants further exploration in future research.

ARTICLE HIGHLIGHTS

Research background

The prevalence of depressive and anxiety-related symptoms in newly referred patients at neurology outpatient clinics is high, and mental state of myasthenia gravis (MG) patients were seldom assessed by mental scales routinely, so little is known about the exact relationship between MG and mental disorders that often accompany it.

Research motivation

Due to the frequent occurrence of comorbidities in older people that might be confused with MG symptoms, awareness of mental disorders in older age groups of MG is needed for earlier intervention and thus a better outcome. In the present, there have been few studies on the mental health of patients with late-onset MG, so we conducted this study to assess the related factors for developing mental disorders in the subgroup of MG patients.

Research objectives

This study aimed to investigate the relationship between clinical features and mental health in patients with late-onset MG, in addition to treating physical symptoms, attention should also be paid to mental disorders in late-onset MG patients.

Research methods

A total of 105 patients diagnosed with MG were recruited consecutively from a neuromuscular outpatient clinic between December 2020 and February 2021 in our hospital. Clinical data including sociodemographic, neurological and mental information were collected, and scores on clinical scales were procured through face-to-face evaluations with professional neurologists. The relationship between clinical features and mental health in late-onset MG patients was examined using multivariate logistic regression analyses.

Research results

Late-onset MG patients had higher total scores on the MG Quality of Life 15 (MG-QOL-15) quest-

ionnaire, the 17-item version of the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) compared with early-onset group MG patients. Female patients had higher total HAM-D and HAM-A scores than male patients among late-onset MG ($P < 0.05$), and high scores on the MG-QOL-15 questionnaire were independently associated with higher incidences of anxiety and depression. In late-onset groups, the areas under the receiver operating characteristic curves for MG-QOL-15 scores at a cutoff value of 14.5 in the anxiety and depression groups were 0.816 and 0.983, respectively.

Research conclusions

We found that female patients with late-onset MG were more susceptible to anxiety and depression than their male counterparts, and that higher MG-QOL-15 scores were an independent risk factor for anxiety and depression in patients with late-onset MG. An MG-QOL-15 score cutoff of 14.5 could be a good indicator for poor mental health in need of attention among late-onset MG patients.

Research perspectives

In the future, we will seek to determine protective factors against developing mental disorders among late-onset MG. Further follow-up and particularly studies that include healthy control groups are needed to validate the results.

FOOTNOTES

Author contributions: Liu WB was the guarantor and contributed to the conception of the study; Yu L and Qiu L participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; Ran H, Ma Q, Lu YR revised the article critically for important intellectual content.

Supported by the National Natural Science Foundation of China, No. 81873772 and 81971754; National Natural Science Foundation Key International (Regional) Cooperation Research Project, No. 81620108010; Clinical Study of 5010 Planned Project Sun Yat-sen University, No. 2010003; Guangdong Provincial Key Laboratory of Diagnosis and Treatment of Major Neurological Diseases, No. 2020B1212060017; Guangdong Provincial Clinical Research Center for Neurological Diseases, No. 2020B1111170002; the Southern China International Cooperation Base for Early Intervention and Functional Rehabilitation of Neurological Diseases, No. 2015B050501003 and 2020A0505020004.

Institutional review board statement: This study was reviewed and approved by the ethics committee of The First Affiliated Hospital of the Sun Yat-sen University.

Informed consent statement: All study participants provided informed written consent prior to the scale-based clinical examinations.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: China

ORCID number: Lu Yu 0000-0002-1271-126X; Li Qiu 0000-0002-7889-8514; Hao Ran 0000-0003-4837-504X; Qian Ma 0000-0001-6588-6904; Ya-Ru Lu 0000-0003-3581-3733; Wei-Bin Liu 0000-0003-1909-4898.

S-Editor: Zhang H
L-Editor: Kerr C
P-Editor: Zhang H

REFERENCES

1 **Romi F**, Hong Y, Gilhus NE. Pathophysiology and immunological profile of myasthenia gravis and its subgroups. *Curr*

Opin Immunol 2017; **49**: 9-13 [PMID: 28780294 DOI: 10.1016/j.coi.2017.07.006]
2 **Gilhus NE**, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. *Nat Rev Dis Primers* 2019; **5**: 30 [PMID: 31048702 DOI: 10.1038/s41572-019-0079-y]
3 **Tong O**, Delfiner L, Herskovitz S. Pain, Headache, and Other Non-motor Symptoms in Myasthenia Gravis. *Curr Pain Headache Rep* 2018; **22**: 39 [PMID: 29725917 DOI: 10.1007/s11916-018-0687-3]
4 **Li Z**, Hao Y, Han Y, Wu S, Zhu D, Liu M, Dong Q, Wang X, Guan Y. Prevalence and associated physical symptoms of depressive and anxiety symptoms in neurology outpatient clinic. *J Neurol Neurosurg Psychiatry* 2019; **90**: 1286-1287 [PMID: 30760642 DOI: 10.1136/jnnp-2018-320130]
5 **Carr AS**, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in Myasthenia Gravis. *BMC Neurol* 2010; **10**: 46 [PMID: 20565885 DOI: 10.1186/1471-2377-10-46]
6 **Li Z**, Ruan M, Chen J, Fang Y. Major Depressive Disorder: Advances in Neuroscience Research and Translational Applications. *Neurosci Bull* 2021; **37**: 863-880 [PMID: 33582959 DOI: 10.1007/s12264-021-00638-3]
7 **Kulaksizoglu IB**. Mood and anxiety disorders in patients with myasthenia gravis: aetiology, diagnosis and treatment. *CNS Drugs* 2007; **21**: 473-481 [PMID: 17521227 DOI: 10.2165/00023210-200721060-00004]
8 **Raggi A**, Leonardi M, Antozzi C, Confalonieri P, Maggi L, Cornelio F, Mantegazza R. Concordance between severity of disease, disability and health-related quality of life in myasthenia gravis. *Neurol Sci* 2010; **31**: 41-45 [PMID: 19816655 DOI: 10.1007/s10072-009-0167-y]
9 **Leonardi M**, Raggi A, Antozzi C, Confalonieri P, Maggi L, Cornelio F, Mantegazza R. The relationship between health, disability and quality of life in myasthenia gravis: results from an Italian study. *J Neurol* 2010; **257**: 98-102 [PMID: 19669388 DOI: 10.1007/s00415-009-5279-z]
10 **Doering S**, Henze T, Schüssler G. Coping with myasthenia gravis and implications for psychotherapy. *Arch Neurol* 1993; **50**: 617-620 [PMID: 8503799 DOI: 10.1001/archneur.1993.00540060055018]
11 **Mullins LL**, Carpentier MY, Paul RH, Sanders DB; Muscle Study Group. Disease-specific measure of quality of life for myasthenia gravis. *Muscle Nerve* 2008; **38**: 947-956 [PMID: 18697209 DOI: 10.1002/mus.21016]
12 **Padua L**, Evoli A, Aprile I, Caliandro P, Mazza S, Padua R, Tonali P. Health-related quality of life in patients with myasthenia gravis and the relationship between patient-oriented assessment and conventional measurements. *Neurol Sci* 2001; **22**: 363-369 [PMID: 11917973 DOI: 10.1007/s100720100066]
13 **Yang Y**, Zhang M, Guo J, Ma S, Fan L, Wang X, Li C, Guo P, Wang J, Li H, Li Z. Quality of life in 188 patients with myasthenia gravis in China. *Int J Neurosci* 2016; **126**: 455-462 [PMID: 26000922 DOI: 10.3109/00207454.2015.1038712]
14 **Burns TM**, Grouse CK, Conaway MR, Sanders DB; mg composite and mg-qol15 study group. Construct and concurrent validation of the MG-QOL15 in the practice setting. *Muscle Nerve* 2010; **41**: 219-226 [PMID: 19941339 DOI: 10.1002/mus.21609]
15 **Burns TM**, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, Bril V, Barnett C, Guptill JT, Sanders DB, Hobson-Webb L, Juel VC, Massey J, Gable KL, Silvestri NJ, Wolfe G, Cutter G, Nagane Y, Murai H, Masuda M, Farrugia ME, Carmichael C, Birnbaum S, Hogrel JY, Nafissi S, Fatehi F, Ou C, Liu W, Conaway M. International clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r. *Muscle Nerve* 2016; **54**: 1015-1022 [PMID: 27220659 DOI: 10.1002/mus.25198]
16 **Ybarra MI**, Kummer A, Frota ER, Oliveira JT, Gomez RS, Teixeira AL. Psychiatric disorders in myasthenia gravis. *Arq Neuropsiquiatr* 2011; **69**: 176-179 [PMID: 21537555 DOI: 10.1590/s0004-282x2011000200006]
17 **Paul RH**, Cohen RA, Goldstein JM, Gilchrist JM. Severity of mood, self-evaluative, and vegetative symptoms of depression in myasthenia gravis. *J Neuropsychiatry Clin Neurosci* 2000; **12**: 499-501 [PMID: 11083168 DOI: 10.1176/jnp.12.4.499]
18 **Law C**, Flaherty CV, Bandyopadhyay S. A Review of Psychiatric Comorbidity in Myasthenia Gravis. *Cureus* 2020; **12**: e9184 [PMID: 32802619 DOI: 10.7759/cureus.9184]
19 **Blum S**, Lee D, Gillis D, McEniery DF, Reddel S, McCombe P. Clinical features and impact of myasthenia gravis disease in Australian patients. *J Clin Neurosci* 2015; **22**: 1164-1169 [PMID: 26021730 DOI: 10.1016/j.jocn.2015.01.022]
20 **Deymeer F**. Myasthenia gravis: MuSK MG, late-onset MG and ocular MG. *Acta Myol* 2020; **39**: 345-352 [PMID: 33458590 DOI: 10.36185/2532-1900-038]
21 **Aarli JA**. Myasthenia gravis in the elderly: Is it different? *Ann N Y Acad Sci* 2008; **1132**: 238-243 [PMID: 18567874 DOI: 10.1196/annals.1405.040]
22 **Alkhawajah NM**, Oger J. Late-onset myasthenia gravis: a review when incidence in older adults keeps increasing. *Muscle Nerve* 2013; **48**: 705-710 [PMID: 23893883 DOI: 10.1002/mus.23964]
23 **Gilhus NE**, Nacu A, Andersen JB, Owe JF. Myasthenia gravis and risks for comorbidity. *Eur J Neurol* 2015; **22**: 17-23 [PMID: 25354676 DOI: 10.1111/ene.12599]
24 **Sanders DB**, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, Kuntz N, Massey JM, Melms A, Murai H, Nicolle M, Palace J, Richman DP, Verschuuren J, Narayanaswami P. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology* 2016; **87**: 419-425 [PMID: 27358333 DOI: 10.1212/WNL.0000000000002790]
25 **Burns TM**, Conaway M, Sanders DB; MG Composite and MG-QOL15 Study Group. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. *Neurology* 2010; **74**: 1434-1440 [PMID: 20439845 DOI: 10.1212/WNL.0b013e3181dc1b1e]
26 **Wolfe GI**, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology* 1999; **52**: 1487-1489 [PMID: 10227640 DOI: 10.1212/wnl.52.7.1487]
27 **Burns TM**, Conaway MR, Cutter GR, Sanders DB; Muscle Study Group. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. *Muscle Nerve* 2008; **38**: 957-963 [PMID: 18642357 DOI: 10.1002/mus.21053]
28 **HAMILTON M**. The assessment of anxiety states by rating. *Br J Med Psychol* 1959; **32**: 50-55 [PMID: 13638508 DOI: 10.1111/j.2044-8341.1959.tb00467.x]
29 **HAMILTON M**. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; **23**: 56-62 [PMID: 14399272 DOI: 10.1136/jnnp.23.1.56]

30 **Miao X**, Lian Z, Liu J, Chen H, Shi Z, Li M, Zhou H, Hu X, Yang R. Translation, cross-cultural adaptation, and validation of the chinese version of the 15-item myasthenia gravis quality of life questionnaire. *Muscle Nerve* 2019; **59**: 95-99 [PMID: 30055010 DOI: 10.1002/mus.26313]

31 **Zheng YP**, Zhao JP, Phillips M, Liu JB, Cai MF, Sun SQ, Huang MF. Validity and reliability of the Chinese Hamilton Depression Rating Scale. *Br J Psychiatry* 1988; **152**: 660-664 [PMID: 3167442 DOI: 10.1192/bjp.152.5.660]

32 **Bagby RM**, Ryder AG, Schuller DR, Marshall MB. The Hamilton Depression Rating Scale: has the gold standard become a lead weight? *Am J Psychiatry* 2004; **161**: 2163-2177 [PMID: 15569884 DOI: 10.1176/appi.ajp.161.12.2163]

33 **Leung CM**, Wing YK, Kwong PK, Lo A, Shum K. Validation of the Chinese-Cantonese version of the hospital anxiety and depression scale and comparison with the Hamilton Rating Scale of Depression. *Acta Psychiatr Scand* 1999; **100**: 456-461 [PMID: 10626925 DOI: 10.1111/j.1600-0447.1999.tb10897.x]

34 **Gilhus NE**, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. *Lancet Neurol* 2015; **14**: 1023-1036 [PMID: 26376969 DOI: 10.1016/S1474-4422(15)00145-3]

35 **Thompson E**. Hamilton Rating Scale for Anxiety (HAM-A). *Occup Med (Lond)* 2015; **65**: 601 [PMID: 26370845 DOI: 10.1093/occmed/kqv054]

36 **Zimmerman M**, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. *J Affect Disord* 2013; **150**: 384-388 [PMID: 23759278 DOI: 10.1016/j.jad.2013.04.028]

37 **Winter Y**, Schepelmann K, Spottke AE, Claus D, Grothe C, Schröder R, Heuss D, Vielhaber S, Tackenberg B, Mylius V, Reese JP, Kiefer R, Schrank B, Oertel WH, Dodel R. Health-related quality of life in ALS, myasthenia gravis and facioscapulohumeral muscular dystrophy. *J Neurol* 2010; **257**: 1473-1481 [PMID: 20383521 DOI: 10.1007/s00415-010-5549-9]

38 **Braz NFT**, Rocha NP, Vieira ÉLM, Barbosa IG, Gomez RS, Kakehasi AM, Teixeira AL. Muscle strength and psychiatric symptoms influence health-related quality of life in patients with myasthenia gravis. *J Clin Neurosci* 2018; **50**: 41-44 [PMID: 29396072 DOI: 10.1016/j.jocn.2018.01.011]

39 **Alanazy MH**, Binabbad RS, Alromaih NI, Almansour RA, Alanazi SN, Alhamdi MF, Alazwary N, Muayqil T. Severity and depression can impact quality of life in patients with myasthenia gravis. *Muscle Nerve* 2020; **61**: 69-73 [PMID: 31573094 DOI: 10.1002/mus.26719]

40 **Burns TM**, Grouse CK, Wolfe GI, Conaway MR, Sanders DB; MG Composite and MG-OL15 Study Group. The MG-QOL15 for following the health-related quality of life of patients with myasthenia gravis. *Muscle Nerve* 2011; **43**: 14-18 [PMID: 21082698 DOI: 10.1002/mus.21883]

41 **Stojanov A**, Milošević V, Đorđević G, Stojanov J. Quality of Life of Myasthenia Gravis Patients in Regard to Epidemiological and Clinical Characteristics of the Disease. *Neurologist* 2019; **24**: 115-120 [PMID: 31246720 DOI: 10.1097/NRL.0000000000000238]

42 **Masuda M**, Utsugisawa K, Suzuki S, Nagane Y, Kabasawa C, Suzuki Y, Shimizu Y, Utsumi H, Fujihara K, Uchiyama S, Suzuki N. The MG-QOL15 Japanese version: validation and associations with clinical factors. *Muscle Nerve* 2012; **46**: 166-173 [PMID: 22806364 DOI: 10.1002/mus.23398]

43 **Green T**, Flash S, Reiss AL. Sex differences in psychiatric disorders: what we can learn from sex chromosome aneuploidies. *Neuropsychopharmacology* 2019; **44**: 9-21 [PMID: 30127341 DOI: 10.1038/s41386-018-0153-2]

44 **Gobinath AR**, Choleris E, Galea LA. Sex, hormones, and genotype interact to influence psychiatric disease, treatment, and behavioral research. *J Neurosci Res* 2017; **95**: 50-64 [PMID: 27870452 DOI: 10.1002/jnr.23872]

45 **Bangasser DA**, Valentino RJ. Sex differences in stress-related psychiatric disorders: neurobiological perspectives. *Front Neuroendocrinol* 2014; **35**: 303-319 [PMID: 24726661 DOI: 10.1016/j.yfrne.2014.03.008]

46 **Hammen C**, Brennan PA, Keenan-Miller D, Hazel NA, Najman JM. Chronic and acute stress, gender, and serotonin transporter gene-environment interactions predicting depression symptoms in youth. *J Child Psychol Psychiatry* 2010; **51**: 180-187 [PMID: 19811586 DOI: 10.1111/j.1469-7610.2009.02177.x]

47 **Ming QS**, Zhang Y, Chai QL, Chen HY, Hou CJ, Wang MC, Wang YP, Cai L, Zhu XZ, Yi JY, Yao SQ. Interaction between a serotonin transporter gene promoter region polymorphism and stress predicts depressive symptoms in Chinese adolescents: a multi-wave longitudinal study. *BMC Psychiatry* 2013; **13**: 142 [PMID: 23683292 DOI: 10.1186/1471-244X-13-142]

48 **Dong D**, Chong MK, Wu Y, Kaminski H, Cutter G, Xu X, Li H, Zhao C, Yin J, Yu S, Zhu J. Gender differences in quality of life among patients with myasthenia gravis in China. *Health Qual Life Outcomes* 2020; **18**: 296 [PMID: 32883289 DOI: 10.1186/s12955-020-01549-z]

49 **Boldingh MI**, Maniaol AH, Brunborg C, Weedon-Fekjær H, Verschuuren JJ, Tallaksen CM. Increased risk for clinical onset of myasthenia gravis during the postpartum period. *Neurology* 2016; **87**: 2139-2145 [PMID: 27770065 DOI: 10.1212/WNL.0000000000003339]

50 **Leker RR**, Karni A, Abramsky O. Exacerbation of myasthenia gravis during the menstrual period. *J Neurol Sci* 1998; **156**: 107-111 [PMID: 9559997 DOI: 10.1016/s0022-510x(98)00031-8]

51 **Schneider-Gold C**, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. *Ther Adv Neurol Disord* 2019; **12**: 1756286419832242 [PMID: 30854027 DOI: 10.1177/1756286419832242]

52 **Lee I**, Kaminski HJ, McPherson T, Feese M, Cutter G. Gender differences in prednisone adverse effects: Survey result from the MG registry. *Neurol Neuroimmunol Neuroinflamm* 2018; **5**: e507 [PMID: 30345333 DOI: 10.1212/NXI.0000000000000507]

53 **Kulkantrakorn K**, Sawanyawisuth K, Tiamkao S. Factors correlating quality of life in patients with myasthenia gravis. *Neurol Sci* 2010; **31**: 571-573 [PMID: 20461430 DOI: 10.1007/s10072-010-0285-6]

54 **Rostedt A**, Padua L, Stålberg EV. Correlation between regional myasthenic weakness and mental aspects of quality of life. *Eur J Neurol* 2006; **13**: 191-193 [PMID: 16490052 DOI: 10.1111/j.1468-1331.2006.01149.x]

55 **Wolfe GI**, Kaminski HJ, Sonnett JR, Aban IB, Kuo HC, Cutter GR. Randomized trial of thymectomy in myasthenia gravis. *J Thorac Dis* 2016; **8**: E1782-E1783 [PMID: 28149641 DOI: 10.21037/jtd.2016.12.80]

56 **Wang L**, Huan X, Xi JY, Wu H, Zhou L, Lu JH, Zhang TS, Zhao CB. Immunosuppressive and monoclonal antibody treatment for myasthenia gravis: A network meta-analysis. *CNS Neurosci Ther* 2019; **25**: 647-658 [PMID: 30809966 DOI:

10.1111/cns.13110]
57 **Szczudlik P**, Sobieszczuk E, Szyluk B, Lipowska M, Kubiszewska J, Kostera-Pruszczyk A. Determinants of Quality of Life in Myasthenia Gravis Patients. *Front Neurol* 2020; **11**: 553626 [PMID: 33071942 DOI: 10.3389/fneur.2020.553626]
58 **Zivković SA**, Clemens PR, Lacomis D. Characteristics of late-onset myasthenia gravis. *J Neurol* 2012; **259**: 2167-2171 [PMID: 22476514 DOI: 10.1007/s00415-012-6478-6]
59 **Stacy S**, Williams EL, Standifer NE, Pasquali A, Krolick KA, Infante AJ, Kraig E. Maintenance of immune tolerance to a neo-self acetylcholine receptor antigen with aging: implications for late-onset autoimmunity. *J Immunol* 2010; **184**: 6067-6075 [PMID: 20435934 DOI: 10.4049/jimmunol.0901618]
60 **Watad A**, Bragazzi NL, Adawi M, Amital H, Toubi E, Porat BS, Shoenfeld Y. Autoimmunity in the Elderly: Insights from Basic Science and Clinics - A Mini-Review. *Gerontology* 2017; **63**: 515-523 [PMID: 28768257 DOI: 10.1159/000478012]
61 **Suzuki S**, Utsugisawa K, Nagane Y, Satoh T, Kuwana M, Suzuki N. Clinical and immunological differences between early and late-onset myasthenia gravis in Japan. *J Neuroimmunol* 2011; **230**: 148-152 [PMID: 21074862 DOI: 10.1016/j.jneuroim.2010.10.023]
62 **Hellmann MA**, Mosberg-Galili R, Steiner I. Myasthenia gravis in the elderly. *J Neurol Sci* 2013; **325**: 1-5 [PMID: 23218585 DOI: 10.1016/j.jns.2012.10.028]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 483-493

DOI: 10.5498/wjp.v12.i3.483

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Childhood maltreatment and suicide ideation: A possible mediation of social support

Roland Donald Ahouanse, Wei Chang, Hai-Liang Ran, Die Fang, Yu-San Che, Wen-Hang Deng, Si-Fan Wang, Jun-Wei Peng, Lin Chen, Yuan-Yuan Xiao

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kotzalidis GD

Received: August 9, 2021
Peer-review started: August 17, 2021
First decision: October 17, 2021
Revised: October 23, 2021
Accepted: February 19, 2022
Article in press: February 19, 2022
Published online: March 19, 2022

Roland Donald Ahouanse, Wei Chang, Hai-Liang Ran, Die Fang, Yu-San Che, Wen-Hang Deng, Si-Fan Wang, Jun-Wei Peng, Lin Chen, Yuan-Yuan Xiao, Department of Epidemiology and Health Statistics, School of Public Health, Kunming Medical University, Kunming 650500, Yunnan Province, China

Corresponding author: Yuan-Yuan Xiao, PhD, Professor, Department of Epidemiology and Health Statistics, School of Public Health, Kunming Medical University, No. 1168 West Chunrong Road, Yuhua Street, Chenggong District, Kunming 650500, Yunnan Province, China. 33225647@qq.com

Abstract

BACKGROUND

Existing literature suggests a positive link between childhood maltreatment (CM) and suicide ideation (SI). Nevertheless, whether social support significantly mediates this association remains unknown.

AIM

To investigate whether social support significantly mediates the association between CM and SI.

METHODS

In this cross-sectional study of 4732 adolescents from southwest China, we intended to discuss the association between CM and multiple types of SI. In addition, the mediation of major types of social support in this association was also investigated. A self-administrated questionnaire was used to collect the data. A series of multivariate logistic regression models were employed to estimate the association between different types of CM, social support, and SI. The possible mediation of social support in the association between CM and SI was assessed using the path model.

RESULTS

Based on the cutoffs for subscales of Childhood Trauma Questionnaire, 928 (19.61%), 1269 (26.82%), 595 (12.57%), 2337 (49.39%), and 3067 (64.81%) respondents reported physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect, respectively. Among all the social sources, parental support presented as a significant mediator in the association between emotional

maltreatment, both abuse and neglect, and all three types of SI: 1-wk, 1-year, and lifetime. Parental social support mediated 5.31% and 29.23%, 4.80% and 24.50%, and 7.04% and 44.42% of the overall emotional abuse-SI and emotional neglect-SI associations, respectively.

CONCLUSION

Our findings suggest that improving parental social support might be effective in preventing suicidal risk related to childhood emotional maltreatment in adolescents.

Key Words: Adolescent; Childhood maltreatment; Suicide ideation; Mediation; Social support

Core Tip: Childhood maltreatment (CM) is associated with suicide ideation (SI). In the current study, we investigated the mediating role of social support in the association between CM and SI in a large sample (4732) of Chinese children and adolescents. Our results revealed a strong association between emotional CM and SI. In addition, only parental social support has been presented as a significant mediator in the association between emotional maltreatment and SI. The current study highlighted the intervention relevance of parental social support in emotional CM associated with suicidal risk. Rebuilding the parent-child relationship may be a promising way in preventing emotional CM-related suicide.

Citation: Ahouanse RD, Chang W, Ran HL, Fang D, Che YS, Deng WH, Wang SF, Peng JW, Chen L, Xiao YY. Childhood maltreatment and suicide ideation: A possible mediation of social support. *World J Psychiatry* 2022; 12(3): 483-493

URL: https://www.wjgnet.com/2220-3206/full/v12/i3/483.htm

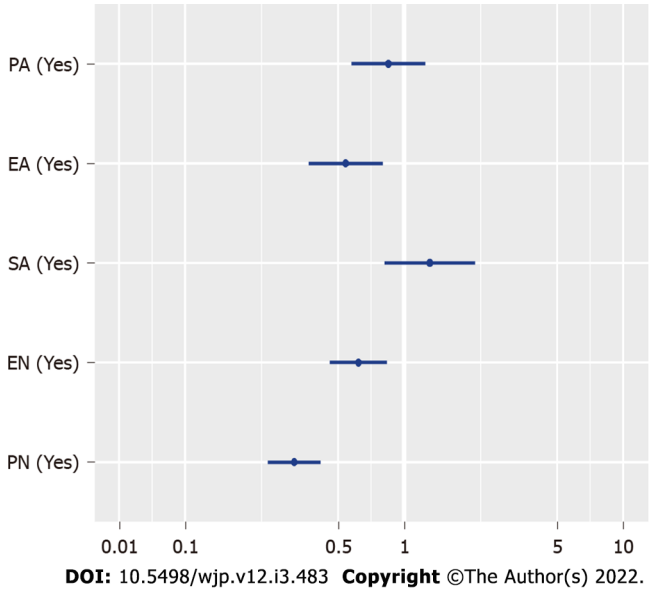
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.483

INTRODUCTION

Suicide represents a serious threat worldwide and has become the second leading cause of death among adolescents[1]. The theory of suicidality defines suicidal behavior as a continuous process that begins from suicide ideation (SI) and ends at completed suicide[2]. It has been estimated that more than 1.5 million individuals died of suicide worldwide in 2020[3]. A meta-analysis including 686672 children and adolescents across the world has estimated the lifetime and 1-year suicide prevalence rates in children and adolescents between 1989 and 2018 were 18.0% and 14.2%, respectively[4]. In China, according to a large sample cross-sectional study, about 32% of children and adolescents reported SI[5]. SI stands as a relevant indicator of acute suicidal risk because it generally leads to suicidal attempts during the 1st year of the ideation[6,7]. Thus, effective intervention on SI can be a plausible strategy to reduce suicidal risk.

Childhood maltreatment (CM) is an adverse life event that immediately influences the mental health of the children and may compromise their long-term physical and psychological health[7-9]. Normally, CM can be categorized into: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN), and emotional neglect (EN)[10]. In China, the estimated prevalence rates of CM were 26.6%, 19.6%, 8.7%, and 26.0% for PA, EA, SA, PN, and EN in 2015[11]. A recent meta-analysis reported a high prevalence rate of CM among Chinese primary and middle school students (PA: 20%, EA: 30%, SA: 12%, PN: 47%, EN: 44%)[12]. It has been reported that CM has a lasting negative influence on the mental health of the victims[13,14]. Children who had been exposed to any kind of CM may present several emotional and behavioral problems such as depression symptoms, anxiety, impulsivity, social isolation, misconduct, aggressivity, delinquency, and hyperactivity[14]. These problems may lead to SI according to the Stress-Diathesis Theory of Suicidality[15]. Additionally, Li *et al*[16] disclosed that CM history increased the risk of major depressive disorder, an intimate risk factor of SI. From this perspective, a positive connection between CM and SI should exist.

Interpersonal psychological theory of suicidal behavior believes that isolation increases the desire to commit suicide[17]. Perceived social support protects against isolation. Malecki *et al*[18] defined social support as getting supportive behavior that boosts individual functioning or buffers them from negative outcomes. Social support comes from different sources; therefore, disparities may exist in the associations between different sources of social support and SI. Numerous studies have found that social support from family and friends was negatively associated with SI[19]. However, Hetrick *et al*[20] found that neither of them showed a significant relationship with suicidal behavior in a clinical sample of young adolescents diagnosed with depressive disorder. More recently, a large cross-sectional study reported that social support from relatives, friends, and parents were all negatively associated with SI among 2899 Chinese rural left-behind children; however, social support from teachers was insignificant



DOI: 10.5498/wjp.v12.i3.483

Figure 1 Adjusted odds ratios with 95%CIs for the associations between different childhood abuse and parental social support. ORs: Odds ratios; EA: Emotional abuse; EN: Emotional neglect; PA: Physical abuse; PN: Physical neglect; SA: Sexual abuse.

[21]. All the existing literature in the field suggests that social support may play a buffering role in SI and suicidal behaviors among youngsters. Nevertheless, controversies remain to be further investigated, especially for different sources of social support.

Moreover, studies have suggested a positive and reciprocal association between CM and social support. On one hand, CM may generate social isolation, behavior disorder, and harmful interaction, which may cause decreased social support[18]. On the other hand, lower social support was also associated with the occurrence of CM[22]. In psychological research, moderation and mediation are two important concepts to understand the association between two variables of study interest. The mediation model assumes that there is a third variable, which sits in the association path between the two variables. In contrast, the moderation model specifies that a third variable modifies the strength of the association between the two variables[23]. Combine all existing evidence together, it is reasonable to suspect that social support may play a mediation role in the association between CM and SI. With this regard, in the current study, we aim to investigate this hypothesis by using a large population-representative sample of Chinese children and adolescents. We put forward the assumption that social support significantly mediates the association between CM and SI. In addition, social support of different sources showed discordant mediation in this association.

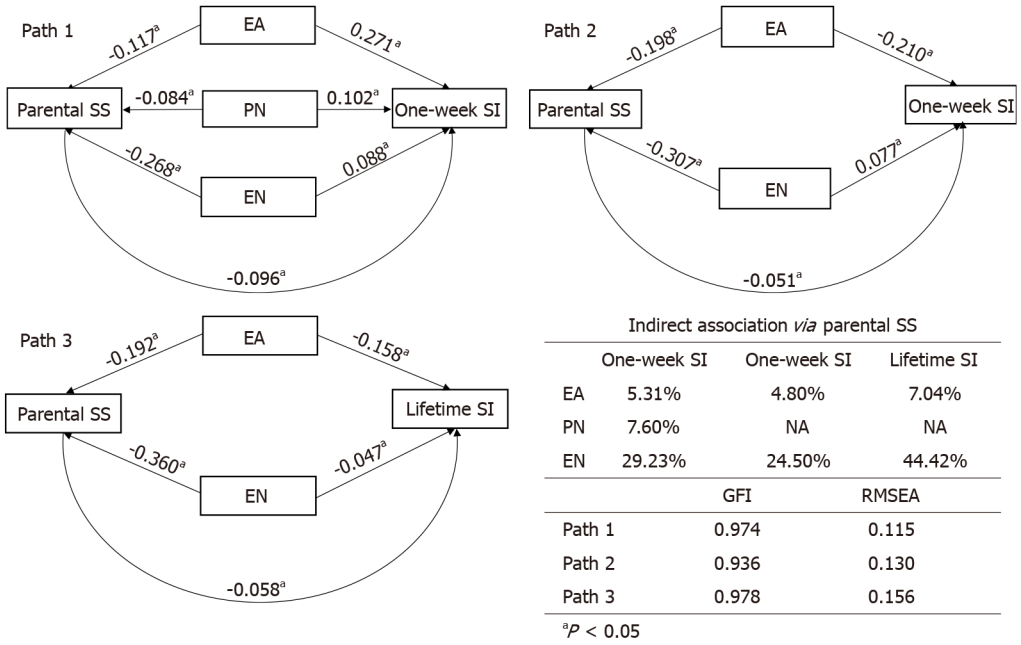
MATERIALS AND METHODS

Participants

We implemented a sampling survey in Kaiyuan, southwestern China Yunnan province between October 19 and November 3, 2020. A two-stage simple random cluster sampling method with probability proportionate to sample size design was used to determine study participants. In the first stage, among all primary, junior high, and senior high schools in Kaiyuan, 19 were randomly selected; in the second stage, based on the required sample size, several classes (4-6) within the chosen school were selected. All eligible students within the chosen class were preliminarily included. Students were further excluded if they were: (1) Aged below 10 years or above 18 years; (2) Reported serious mental or physical illnesses; (3) Had difficulties in hearing or speaking; and (4) Refused to participate. Before the survey, the study protocol was reviewed and approved by the Ethics Committee of Kunming Medical University.

Measures

After written informed consents from the legal guardians were provided, a self-administered questionnaire survey was conducted in each sampling school. The quality of the finished questionnaire was checked on the site immediately by pretrained quality control personnel, who were either graduate students who majored in psychology or public health or health professionals recruited locally. The questionnaire was comprehensive and self-developed and contained the following sections: general characteristics, CM, perceived social support, SI, resilience, sexual harassment behavior, depression, and anxiety, *etc.* Except for the general characteristics, all the information was measured by using well-



Indirect association *via* parental SS

	One-week SI	One-week SI	Lifetime SI
EA	5.31%	4.80%	7.04%
PN	7.60%	NA	NA
EN	29.23%	24.50%	44.42%

	GFI	RMSEA
Path 1	0.974	0.115
Path 2	0.936	0.130
Path 3	0.978	0.156

$^aP < 0.05$

DOI: 10.5498/wjp.v12.i3.483

Figure 2 Path models and fitting results for direct and indirect associations between childhood maltreatment and different types of suicide ideation with the mediation of parent social support. EA: Emotional abuse; EN: Emotional neglect; GFI: Goodness-of-fit index; NA: Not available; PN: Physical neglect; RMSEA: Root mean square error of approximation; SI: Suicide ideation; SS: Social support.

established instruments.

CM: The 28-item Childhood Trauma Questionnaire (CTQ) Short form represents one of the best self-report tools that retrospectively screens for five types of CM (PA, EA, SA, PN, EN)[10]. Each item uses a 5-point Likert style rating: never (1 point), occasionally (2 points), sometimes (3 points), frequently (4 points), and always (5 points). The whole questionnaire can be divided into 5 dimensions; each dimension contains five separate questions and measures one specific type of CM. Therefore, the score of each dimension varies from 5 to 25 points, and the total score of CTQ-Short form ranges from 25 to 125. The cutoffs of 8, 9, 6, 8, and 10 for PA, EA, SA, PN, and EA, respectively, were recommended[24]. In this study, we have followed the same cutoffs to dichotomize different types of CM. The Chinese version of CTQ presented a good internal consistency (Cronbach's α: 0.78-0.90) and test-retest reliability (Kappa: 0.79-0.88)[25]. The Cronbach α of CTQ in the current study was 0.84 (bootstrap 95%CI: 0.84-0.85).

Perceived social support: In the current study, we used the Chinese version of Child and Adolescent Social Support Scale (CASSS) for perceived social support[18]. The 40-item CASSS is a well-validated instrument that measures perceived social support from four sources: parents, teachers, classmates, and close friends. Each source includes 10 items with 5 responses that can be assigned a score from 1 (never) to 5 (always). Consequently, the combined score for every source ranges from 5 to 50 points. In the current study, we dichotomized different sources of social support by using the medians. The Cronbach α of CASSS in the current study was 0.92 (bootstrap 95%CI: 0.92-0.93).

SI: One-week and lifetime SI were assessed using the Chinese version of the Beck Scale for Suicide Ideation (BSSI). BSSI represents one of the best self-report inventories designed to evaluate the intensity of suicide thoughts and intentions. It is composed of 19 items, each graded from 0 to 2 by intensity. A higher total score of BSSI indicates more severe SI[26]. The Cronbach α of the BSSI in the current study was 0.88 (bootstrap 95%CI: 0.87-0.88). One-year SI was determined using a single question: how many times in the past year have you seriously considered ending your life? The responses include: never (0 times), rarely (only once), sometimes (twice), often (3-4 times), and very often (5 times or more). Participants who reported considered ending their own lives at least once were deemed positive.

Depression and anxiety: Depression and anxiety were examined using the Chinese version of The Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7). PHQ-9 includes 9 questions scored from 0 to 3 based on the intensity of the symptom asked[27]. A recent study recommended a cutoff of 10 or above to screen for major depression whatever the age[28]. In this study, we adopted a threshold of 12 (the median of PHQ-9) to dichotomize study subjects. The Cronbach α of PHQ-9 in the current study was 0.88 (bootstrap 95%CI: 0.88-0.89). For GAD-7, a cutoff score between 7 and 10 can be used to efficiently screen for anxiety[29]. In our study, we used a cutoff of 9 following the

median of the combined score. The Cronbach α of GAD-7 in the current study was 0.91 (bootstrap 95%CI: 0.90-0.91).

Statistical analysis

We performed a descriptive analysis to feature the main characteristics of the participants. The results of the multivariate binary logistic regression models led us to path analysis to determine the direct association between CM and SI, together with their possible indirect association meditated by different sources of social support. Associated factors of SI, childhood abuse, and social support identified from the multivariate logistic regression models were simultaneously incorporated into the hypothesized path model to control for possible confounding. We performed data analysis using the R software (Version 4.0.4). Considering the unequal probability sampling method used in this study, we mainly used the "survey" package to perform descriptive, univariate, and multivariate analyses. Path analysis was executed using the "lavaan" package.

RESULTS

Major characteristics of the participants

The main characteristics of our study subjects have been summarized in Table 1. Initially, 4858 eligible students were surveyed. Among them, 4732 with complete required information were included in our final analysis. Based on the cutoffs for subscales of CTQ, 928 (19.61%), 1269 (26.82%), 595 (12.57%), 2337 (49.39%), and 3067 (64.81%) were PA, EA, SA, PN and EN victims, respectively. The medians for different dimensions of CASSS were 37 [interquartile range (IQR): 9] for parent's support, 42 (IQR: 8) for teacher's support, 37 (IQR: 9) for classmate's support, and 39 (IQR: 9) for close friend's support. The prevalence rates of 1-wk, 1-year, and lifetime SI were 26.85% (95%CI: 24.30%-30.00%), 34.99% (95%CI: 30.60%-40.00%), and 55.69% (95%CI: 51.50%-60.00%), respectively.

Associations between CM, social support, and SI

We have used a series of binary univariate logistic regression models to screen for possible influencing factors of different types of SI. Based on the univariate analysis results, a group of multivariate logistic regression was further fitted, and the results were collectively displayed in Table 2. After adjusting for potential covariates, especially depression and anxiety, different types of CM, EA, PN, and EN were consistently associated with elevated odds ratios (ORs) of 1-wk, 1-year, and lifetime SI. For social support of different sources, only the support from parents was inversely associated with SI. Adjusted ORs for 1-wk, 1-year, and lifetime SI were 0.67 (95%CI: 0.55-0.83), 0.64 (95%CI: 0.53-0.77), and 0.63 (95%CI: 0.52-0.77), respectively.

We further analyzed the adjusted associations between CM and parental social support. For all five types of child abuse, EA, PN, and EN were prominently and inversely related to parental social support (Figure 1).

Path analysis

Based on the aforementioned analytical results, we proposed three different path models to illustrate the direct associations between CM and SI, together with their possible indirect associations mediated by parental social support. Standardized path coefficients, together with their statistical test results and model fitting indexes were jointly illustrated in Figure 2. Goodness-of-fit index and root mean square error of approximation indicated ideal model fitting for all three path models. The fitting results revealed that parental social support presented as a significant mediator in the association between emotional maltreatment, both abuse and neglect, and all three types of SI: 1-wk, 1-year, and lifetime. Parental social support mediated 5.31% and 29.23%, 4.80% and 24.50%, and 7.04% and 44.42% of the overall EA-SI and EN-SI associations, respectively.

DISCUSSION

The current study investigated the association between CM and SI by using a large representative sample of 4732 Chinese children and adolescents. Particularly, we estimated the possible mediation of social support in this association. Our analysis results were in general supportive of the hypotheses: social support could be a prominent mediator in the association between CM and SI. In addition, different sources of social support discordantly mediated the associations between different types of CM and SI. These findings may suggest that to reduce suicidal risk among youngsters who have experienced CM, rebuilding or consolidating social support might be an effective strategy.

We found that among all types of CM, only EN and EA showed a strong association with SI. Previous studies in a Chinese adolescent population also reported a prominent association between EN, EA, and

Table 1 General characteristics of study participants

Characteristic	mean ± SD[1]/median (IQR)[2]	*n* (%)
Age	13.46 ± 1.95[1]	
Mother's age	39.00 ± 5.76[1]	
Male sex		2359 (49.85)
Ethnicity		
Han majority		1312 (27.73)
Minorities		3420 (72.27)
Grade		
Primary school		1617 (34.17)
Junior high school		2544 (53.76)
Senior high school		571 (12.07)
Residence		
Urban		1581 (33.41)
Rural		3151 (66.59)
Childhood maltreatment		
Physical abuse (yes)		928 (19.61)
Emotional abuse (yes)		1269 (26.82)
Sexual abuse (yes)		595 (12.57)
Physical neglect (yes)		2337 (49.39)
Emotional neglect (yes)		3067 (64.81)
Boarding students (yes)		2373 (50.14)
Single child (yes)		1061 (22.42)
Living situation		
With both parents		3272 (69.15)
With single parent		618 (13.06)
With others		1460 (17.79)
Perceived social support (CASS score)		
Parents	37 (9)[2]	
Teachers	42 (8)[2]	
Classmates	37 (9)[2]	
Close friends	39 (9)[2]	
Suicide ideation (yes)		
1-wk		1271 (26.85)
1-yr		1656 (34.99)
Lifetime		2639 (55.69)
Depression (PQH ≥ 12)		2488 (52.57)
Anxiety (GAD-7 ≥ 9)		2413 (50.99)

[1]mean ± SD.
[2]Median (interquartile range).
IQR: Interquartile range; CASS: Child and Adolescent Social Support; PQH: Patient Health Questionnaire; GAD-7: Generalized Anxiety Disorder-7.

Table 2 Multivariate logistic regression results for associated factors of different suicide ideation

Covariates	1-wk SI		1-yr SI		Lifetime SI	
	Multivariate 1	Multivariate 2	Multivariate 1	Multivariate 2	Multivariate 1	Multivariate 2
Sex (Ref: Male): Female	1.49 (1.31-1.66)	1.36 (1.20-1.55)	2.08 (1.75-2.47)	1.41 (1.12-1.77)	1.70 (1.42-2.03)	1.41 (1.12-1.77)
Age: + 1 yr			1.01 (0.93-1.10)	0.87 (0.79-0.96)	0.95 (0.88-1.03)	0.87 (0.81-0.95)
Ethnicity (Ref: Han majority): Minorities			0.93 (0.76-1.10)	1.07 (0.92-1.24)		
Grade (Ref: Primary school)						
Junior high School			1.14 (0.75-1.72)	1.17 (0.87-1.57)	1.31 (0.99-1.73)	1.13 (0.84-1.52)
Senior high school			0.83 (0.50-1.38)	0.80 (0.49-1.29)	1.18 (0.79-1.75)	0.74 (0.44-1.25)
Residence (Ref: Urban): Rural	1.19 (1.03-1.37)	1.20 (0.99-1.44)	0.90 (0.73-1.11)	1.39 (1.10-1.76)		
Boarding students (Ref: No): Yes			0.70 (0.56-0.88)	0.72 (0.55-0.92)		
Single child (Ref: No): Yes			1.03 (0.92-1.16)	0.69 (0.54-0.88)		
Childhood abuse (Ref: No)						
PA: Yes	1.39 (1.17-1.65)		1.09 (0.86-1.38)		1.32 (1.04-1.68)	
EA: Yes	1.99 (1.77-2.26)		2.79 (2.19-3.56)		2.08 (1.66-2.60)	
SA: Yes	1.50 (1.20-1.87)		1.07 (0.79-1.43)		1.16 (0.85-1.59)	
PN: Yes	1.54 (1.33-1.77)		1.30 (1.06-1.59)		1.25 (1.07-1.47)	
EN: Yes	2.28 (1.94-2.67)		1.63 (1.36-1.97)		1.47 (1.29-1.68)	
Perceived social support (CASS)						
Parent support (Ref: < 37): ≥ 37		0.66 (0.55-0.83)		0.63 (0.52-0.77)		0.63 (0.52-0.77)
Teacher support (Ref : < 42): ≥ 42		0.94 (0.77-1.12)		0.97 (0.82-1.14)		0.97 (0.83-1.14)
Classmate support (Ref : < 37): ≥ 37		0.88 (0.77-1.00)		0.91 (0.73-1.14)		0.90 (0.72-1.13)
Close friend support (Ref : < 39): ≥ 39		0.80 (0.69-0.93)		0.80 (0.64-1.00)		0.80 (0.64-1.00)
Depression (Ref PQH < 12): Yes	1.15 (0.90-1.48)	1.35 (1.06-1.72)	2.94 (2.15-4.03)	1.88 (1.32-2.68)	2.12 (1.65-2.73)	1.86 (1.31-2.64)
Anxiety (Ref: GAD-7 < 9): Yes	1.75 (1.46-2.08)	2.06 (1.72-2.48)	1.85 (1.35-2.54)	1.98 (1.62-2.43)	2.23 (1.84-2.69)	1.99 (1.61-2.46)

CASS: Child and Adolescent Social Support; EA: Emotional abuse; EN: Emotional neglect; GAD-7: Generalized Anxiety Disorder-7; PA: Physical abuse; PN: Physical neglect; PQH: Patient Health Questionnaire; SA: Sexual abuse; SI: Suicide ideation.

SI[30,31]. EA and EN are related to a range of poor mental health outcomes[32,33]. Although physical and sexual CM have also been linked to SI, a longitudinal study has found that emotional maltreatment was the strongest predictor of SI[34]. Emotional maltreatment has been found to be a strong predictor of internal psychopathology development and may interrupt the psychosocial well-being during children's growth. Thus, it represents a source of lifetime depression[35]. A meta-analysis revealed that emotional maltreatment was strongly associated with major depression in an adolescent population [36]. These findings highlight the important role of emotional abuse in adolescent suicidal risk.

An important finding of our study is that among all sources of social support only parental social support presented as a significant mediator in the association between emotional maltreatment and SI. This finding is consistent with some previous studies, which have proven that parental support buffered the harmful effect of past stressful events on mental health among adolescents[36,37]. Moreover, some studies have revealed that social support from parents is a principal mediator in the association between depression and SI[37,38]. Parents exert an important impact during adolescence mainly through emotional assistance and positive relationships[39]. Studies have shown a protective effect of parental social support as the pivotal factor in the stress-buffering model[40,41]. Under this situation, supportive parents may protect adolescents against mental disorders even if they have been exposed to a stressful environment. Therefore, intervention measures concentrating on improving or rebuilding the parent-child relationship could be effective in reducing emotional maltreatment associated with suicidal risk

among youngsters.

Another interesting finding would be that although parental social support presented as a statistically significant mediator in their associations with SI for both EA and EN, the proportion of parental social support mediation was several folds higher in EN-SI association than in EA-SI association. As the two major types of CM, neglect and abuse have disparate influences on children: in the context of neglect, children could grow up with a lower level of belongingness and acceptance[24], whereas EA victims have experienced an insecure attachment relationship with their parents[42]. Many studies have shown that insecurely attached children are at an elevated risk of mental health problems[43]. In a newly published meta-analysis, the authors concluded that insecure attachment may be a predictor of depression among children and adolescents[44]. Considering the fact that depression is the single strongest risk factor of suicide, it is possible that for emotionally abused adolescents the EA-SI association is in essence the association between depression, which originated from insecure attachment and SI. As adolescent depression is hard to intervene directly, the consolidation of parental social support can only exhibit a very limited effect. Therefore, for adolescents who had experienced childhood emotional maltreatment, when implementing parental social support intervention measures to antagonize suicide risk, priority should be given to neglect victims.

The current study emphasized the role of parental social support in emotional maltreatment associated with suicide risk among Chinese adolescents. Family-based interventions, like family therapy [45] and attachment-based family therapy (ABFT)[46], probably can be used to restore and improve secure parent-child relationships. Prior studies on Chinese adolescents have proven that family therapy can effectively decrease depression symptoms and increase parental social support[47,48]. Meanwhile, the efficacy of attachment-based family therapy in reducing depressive symptoms and SI has also been documented in adolescents[49].

Some limitations of the current study should be noticed. First, our study did not investigate the source of CM in the sample. Second, our analysis was based on cross-sectional data. Therefore, causal inference cannot be reached, and the mediation we identified should be further corroborated by longitudinal studies. Third, all information was collected by self-reporting measures, which are prone to information bias. Finally, the extrapolation of study results to the general adolescent population in China should be made cautiously since our study sample was drawn from a localized region in southwest China.

CONCLUSION

The current findings provide support for the previous studies regarding the strong relationship between CM and SI. Moreover, a prominent mediation of parental social support has been identified in the association between emotional CM and SI. Our major findings highlight the promising and intervenable role of parental support in antagonizing emotional CM associated with suicide risk. For emotionally maltreated children and adolescents, rebuilding the parent-child relationship might be effective in suicide prevention.

ARTICLE HIGHLIGHTS

Research background

Suicide represents a major public health problem among the child and adolescent populations worldwide. Suicide ideation (SI) is the percussor of suicidal behavior. In China, over 32% of children and adolescents have reported SI. Adverse lifetime events such as childhood maltreatment (CM) increase the risk of SI. Meanwhile, social support protects against SI. Thus, a pathway between CM and SI *via* social support may exist.

Research motivation

Although the mediation of social support in the association between CM and SI seems plausible, this hypothesis has not been discussed. The motivation of our study is to investigate the mediation role of social support.

Research objectives

To investigate whether social support significantly mediates the association between CM and SI.

Research methods

A large representative sample of 4732 adolescents from southwest China Yunnan province was surveyed. CM was defined into five types according to the 28-items Childhood Trauma Questionnaire (CTQ) Short-form: physical abuse (PA), emotional abuse (EA), sexual abuse (SA), physical neglect (PN),

and emotional neglect (EN). The Chinese version of the Beck Scale for Suicide Ideation, the Child and Adolescent Social Support Scale, the Patient Health Questionnaire, and the 7-item anxiety scale were used to measure suicide ideation, social support, depression, and anxiety, respectively. We performed logistic regression and path analysis to evaluate the mediation of social support.

Research results

The prevalence rates of 1-wk, 1-year, and lifetime SI were 26.85% (95%CI: 24.30%-30.00%), 34.99% (95%CI: 30.60%-40.00%), and 55.69% (95%CI: 51.50%-60.00%), respectively. In addition, based on the cutoffs for subscales of CTQ, 928 (19.61%), 1269 (26.82%), 595 (12.57%), 2337 (49.39%), and 3067 (64.81%) were PA, EA, SA, PN and EN victims. According to the multivariate logistic regression, EA, PN and EN were consistently associated with SI. In addition, parental social support was inversely associated with SI. Following the multivariate analysis results, we performed path analysis. Parent social support presented as a significant mediator in the associations between emotional maltreatment (EA and EN) and SI.

Research conclusions

The current study suggests that parental social support may be considered as a potential mediator in the relationship between CM and SI. Intervention to rebuild the parent-child relationship may help to intervene CM-associated suicide risk.

Research perspectives

Future longitudinal studies are needed to verify the mediation of parental social support in the association between CM and SI.

FOOTNOTES

Author contributions: Ahouanse RD and Chang W contributed equally as joint first authors; Xiao YY designed the study; Ahouanse RD, Chang W, Ran HL, Fang D, Che YS, Deng WH, Wang SF, Peng JW, and Chen L collected and verified the data; Ahouanse RD and Xiao YY performed data analysis; Ahouanse RD and Chang W drafted the manuscript; Xiao YY provided critical revision of the manuscript for important intellectual content; all authors have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 82060601; Top Young Talents of Yunnan Ten Thousand Talents Plan, No. YNWR-QNBJ-2018-286; and Innovative Research Team of Yunnan Province, No. 202005AE160002.

Institutional review board statement: Before the survey, study protocol was reviewed and approved by the Ethics Committee of Kunming Medical University.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The database of the current study is available from the corresponding author upon reasonable request.

Country/Territory of origin: China

ORCID number: Roland Donald AHOUANSE 0000-0003-0894-1174; Wei Chang 0000-0001-8098-4422; Hailiang Ran 0000-0001-7290-3880; Die Fang 0000-0001-5995-7729; Yusan Che 0000-0002-8366-6937; Wenhang Deng 0000-0001-8456-496X; Sifan Wang 0000-0001-9252-8504; Junwei Peng 0000-0002-0973-6191; Lin Chen 0000-0002-9298-5972; Yuanyuan Xiao 0000-0003-2441-7209.

S-Editor: Zhang H
L-Editor: Filipodia CL
P-Editor: Zhang H

REFERENCES

1 **Patton GC**, Coffey C, Sawyer SM, Viner RM, Haller DM, Bose K, Vos T, Ferguson J, Mathers CD. Global patterns of mortality in young people: a systematic analysis of population health data. *Lancet* 2009; **374**: 881-892 [PMID: 19748397 DOI: 10.1016/S0140-6736(09)60741-8]

2 **Krug EG**, Mercy JA, Dahlberg LL, Zwi AB. The world report on violence and health. *Lancet* 2002; **360**: 1083-1088 [PMID: 12384003 DOI: 10.1016/S0140-6736(02)11133-0]

3 **Bertolote JM**, Fleischmann A. A global perspective in the epidemiology of suicide. *Suicid* 2002; **7**: 6-8 [DOI: 10.5617/suicidologi.2330]

4 **Lim KS**, Wong CH, McIntyre RS, Wang J, Zhang Z, Tran BX, Tan W, Ho CS, Ho RC. Global Lifetime and 12-Month Prevalence of Suicidal Behavior, Deliberate Self-Harm and Non-Suicidal Self-Injury in Children and Adolescents between 1989 and 2018: A Meta-Analysis. *Int J Environ Res Public Health* 2019; **16** [PMID: 31752375 DOI: 10.3390/ijerph16224581]

5 **Tan L**, Xia T, Reece C. Social and individual risk factors for suicide ideation among Chinese children and adolescents: A multilevel analysis. *Int J Psychol* 2018; **53**: 117-125 [PMID: 27090061 DOI: 10.1002/ijop.12273]

6 **Nock MK**, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, Borges G, Bromet E, Bruffaerts R, de Girolamo G, de Graaf R, Florescu S, Gureje O, Haro JM, Hu C, Huang Y, Karam EG, Kawakami N, Kovess V, Levinson D, Posada-Villa J, Sagar R, Tomov T, Viana MC, Williams DR. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. *PLoS Med* 2009; **6**: e1000123 [PMID: 19668361 DOI: 10.1371/journal.pmed.1000123]

7 **Klonsky ED**, Saffer BY, Bryan CJ. Ideation-to-action theories of suicide: a conceptual and empirical update. *Curr Opin Psychol* 2018; **22**: 38-43 [PMID: 30122276 DOI: 10.1016/j.copsyc.2017.07.020]

8 **Chapman DP**, Liu Y, Presley-Cantrell LR, Edwards VJ, Wheaton AG, Perry GS, Croft JB. Adverse childhood experiences and frequent insufficient sleep in 5 U.S. States, 2009: a retrospective cohort study. *BMC Public Health* 2013; **13**: 3 [PMID: 23286392 DOI: 10.1186/1471-2458-13-3]

9 **Dhakal S**, Niraula S, Sharma NP, Sthapit S, Bennett E, Vaswani A, Pandey R, Kumari V, Lau JY. History of abuse and neglect and their associations with mental health in rescued child labourers in Nepal. *Aust N Z J Psychiatry* 2019; **53**: 1199-1207 [PMID: 31185738 DOI: 10.1177/0004867419853882]

10 **Bernstein DP**, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, Stokes J, Handelsman L, Medrano M, Desmond D, Zule W. Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse Negl* 2003; **27**: 169-190 [PMID: 12615092 DOI: 10.1016/s0145-2134(02)00541-0]

11 **Fang X**, Fry DA, Ji K, Finkelhor D, Chen J, Lannen P, Dunne MP. The burden of child maltreatment in China: a systematic review. *Bull World Health Organ* 2015; **93**: 176-85C [PMID: 25838613 DOI: 10.2471/BLT.14.140970]

12 **Wang L**, Cheng H, Qu Y, Zhang Y, Cui Q, Zou H. The prevalence of child maltreatment among Chinese primary and middle school students: a systematic review and meta-analysis. *Soc Psychiatry Psychiatr Epidemiol* 2020; **55**: 1105-1119 [PMID: 32632599 DOI: 10.1007/s00127-020-01916-7]

13 **Chandan JS**, Thomas T, Gokhale KM, Bandyopadhyay S, Taylor J, Nirantharakumar K. The burden of mental ill health associated with childhood maltreatment in the UK, using The Health Improvement Network database: a population-based retrospective cohort study. *Lancet Psychiatry* 2019; **6**: 926-934 [PMID: 31564467 DOI: 10.1016/S2215-0366(19)30369-4]

14 **Springer KW**, Sheridan J, Kuo D, Carnes M. Long-term physical and mental health consequences of childhood physical abuse: results from a large population-based sample of men and women. *Child Abuse Negl* 2007; **31**: 517-530 [PMID: 17532465 DOI: 10.1016/j.chiabu.2007.01.003]

15 **van Heeringen K**, Mann JJ. The neurobiology of suicide. *Lancet Psychiatry* 2014; **1**: 63-72 [PMID: 26360403 DOI: 10.1016/S2215-0366(14)70220-2]

16 **Li M**, D'Arcy C, Meng X. Maltreatment in childhood substantially increases the risk of adult depression and anxiety in prospective cohort studies: systematic review, meta-analysis, and proportional attributable fractions. *Psychol Med* 2016; **46**: 717-730 [PMID: 26708271 DOI: 10.1017/S0033291715002743]

17 **Joiner TE**, Van Orden KA, Witte TK, Selby EA, Ribeiro JD, Lewis R, Rudd MD. Main predictions of the interpersonal-psychological theory of suicidal behavior: empirical tests in two samples of young adults. *J Abnorm Psychol* 2009; **118**: 634-646 [PMID: 19685959 DOI: 10.1037/a0016500]

18 **Malecki CK**, Demary MK. Measuring perceived social support: Development of the child and adolescent social support scale (CASSS). *Psychol Schools* 2002; **39**: 1-18 [DOI: 10.1002/pits.10004]

19 **King CA**, Merchant CR. Social and interpersonal factors relating to adolescent suicidality: a review of the literature. *Arch Suicide Res* 2008; **12**: 181-196 [PMID: 18576200 DOI: 10.1080/13811110802101203]

20 **Hetrick SE**, Parker AG, Robinson J, Hall N, Vance A. Predicting suicidal risk in a cohort of depressed children and adolescents. *Crisis* 2012; **33**: 13-20 [PMID: 21940241 DOI: 10.1027/0227-5910/a000095]

21 **Xiao Y**, Chen Y, Chang W, Pu Y, Chen X, Guo J, Li Y, Yin F. Perceived social support and suicide ideation in Chinese rural left-behind children: A possible mediating role of depression. *J Affect Disord* 2020; **261**: 198-203 [PMID: 31634679 DOI: 10.1016/j.jad.2019.09.081]

22 **Kim J**, Cicchetti D. Longitudinal pathways linking child maltreatment, emotion regulation, peer relations, and psychopathology. *J Child Psychol Psychiatry* 2010; **51**: 706-716 [PMID: 20050965 DOI: 10.1111/j.1469-7610.2009.02202.x]

23 **Cohen J**, Cohen P, West SG, Aiken LS. Applied multiple regression/correlation analysis for the behavioral sciences. 3rd ed. Mahwah: Lawrence Erlbaum Associates Publishers, 2003

24 **Bernstein D**, Fink L. Manual for the childhood trauma questionnaire. New York: The Psychological Corporation, 1998

25 **Han A**, Wang G, Xu G, Su P. A self-harm series and its relationship with childhood adversity among adolescents in mainland China: a cross-sectional study. *BMC Psychiatry* 2018; **18**: 28 [PMID: 29390995 DOI: 10.1186/s12888-018-1607-0]

26 **Beck AT**, Kovacs M, Weissman A. Assessment of suicidal intention: the Scale for Suicide Ideation. *J Consult Clin Psychol*

1979; **47**: 343-352 [PMID: 469082 DOI: 10.1037//0022-006x.47.2.343]
27 **Kroenke K**, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606-613 [PMID: 11556941 DOI: 10.1046/j.1525-1497.2001.016009606.x]
28 **Levis B**, Benedetti A, Thombs BD; DEPRESSion Screening Data (DEPRESSD) Collaboration. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ* 2019; **365**: l1476 [PMID: 30967483 DOI: 10.1136/bmj.l1476]
29 **Plummer F**, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry* 2016; **39**: 24-31 [PMID: 26719105 DOI: 10.1016/j.genhosppsych.2015.11.005]
30 **Li X**, You J, Ren Y, Zhou J, Sun R, Liu X, Leung F. A longitudinal study testing the role of psychache in the association between emotional abuse and suicidal ideation. *J Clin Psychol* 2019; **75**: 2284-2292 [PMID: 31468529 DOI: 10.1002/jclp.22847]
31 **Gong M**, Zhang S, Li W, Wang W, Wu R, Guo L, Lu C. Association between Childhood Maltreatment and Suicidal Ideation and Suicide Attempts among Chinese Adolescents: The Moderating Role of Depressive Symptoms. *Int J Environ Res Public Health* 2020; **17** [PMID: 32824995 DOI: 10.3390/ijerph17176025]
32 **Kumari V**. Emotional abuse and neglect: time to focus on prevention and mental health consequences. *Br J Psychiatry* 2020; **217**: 597-599 [PMID: 32892766 DOI: 10.1192/bjp.2020.154]
33 **Janiri D**, De Rossi P, Kotzalidis GD, Girardi P, Koukopoulos AE, Reginaldi D, Dotto F, Manfredi G, Jollant F, Gorwood P, Pompili M, Sani G. Psychopathological characteristics and adverse childhood events are differentially associated with suicidal ideation and suicidal acts in mood disorders. *Eur Psychiatry* 2018; **53**: 31-36 [PMID: 29879623 DOI: 10.1016/j.eurpsy.2018.05.009]
34 **Miller AB**, Jenness JL, Oppenheimer CW, Gottlieb AL, Young JF, Hankin BL. Childhood Emotional Maltreatment as a Robust Predictor of Suicidal Ideation: A 3-Year Multi-Wave, Prospective Investigation. *J Abnorm Child Psychol* 2017; **45**: 105-116 [PMID: 27032784 DOI: 10.1007/s10802-016-0150-z]
35 **LeMoult J**, Humphreys KL, Tracy A, Hoffmeister JA, Ip E, Gotlib IH. Meta-analysis: Exposure to Early Life Stress and Risk for Depression in Childhood and Adolescence. *J Am Acad Child Adolesc Psychiatry* 2020; **59**: 842-855 [PMID: 31676392 DOI: 10.1016/j.jaac.2019.10.011]
36 **Infurna MR**, Reichl C, Parzer P, Schimmenti A, Bifulco A, Kaess M. Associations between depression and specific childhood experiences of abuse and neglect: A meta-analysis. *J Affect Disord* 2016; **190**: 47-55 [PMID: 26480211 DOI: 10.1016/j.jad.2015.09.006]
37 **Ge X**, Natsuaki MN, Neiderhiser JM, Reiss D. The longitudinal effects of stressful life events on adolescent depression are buffered by parent-child closeness. *Dev Psychopathol* 2009; **21**: 621-635 [PMID: 19338701 DOI: 10.1017/S0954579409000339]
38 **Fredrick SS**, Demaray MK, Malecki CK, Dorio NB. Can social support buffer the association between depression and suicidal ideation in adolescent boys and girls? *Psychol Schools* 2018; **55**: 490-505 [DOI: 10.1002/pits.22125]
39 **Au AC**, Lau S, Lee MT. Suicide ideation and depression: the moderation effects of family cohesion and social self-concept. *Adolescence* 2009; **44**: 851-868 [PMID: 20432604]
40 **Holahan CJ**, Valentiner DP, Moos RH. Parental support and psychological adjustment during the transition to young adulthood in a college sample. *J Fam Psychol* 1994; **8**: 215-223 [DOI: 10.1037/0893-3200.8.2.215]
41 **Hazel NA**, Oppenheimer CW, Technow JR, Young JF, Hankin BL. Parent relationship quality buffers against the effect of peer stressors on depressive symptoms from middle childhood to adolescence. *Dev Psychol* 2014; **50**: 2115-2123 [PMID: 24932722 DOI: 10.1037/a0037192]
42 **Baer JC**, Martinez CD. Child maltreatment and insecure attachment: a meta-analysis. *J Rep and Infant Psychol* 2006; **24**: 187-197 [DOI: 10.1080/02646830600821231]
43 **Madigan S**, Brumariu LE, Villani V, Atkinson L, Lyons-Ruth K. Representational and questionnaire measures of attachment: A meta-analysis of relations to child internalizing and externalizing problems. *Psychol Bull* 2016; **142**: 367-399 [PMID: 26619212 DOI: 10.1037/bul0000029]
44 **Spruit A**, Goos L, Weenink N, Rodenburg R, Niemeyer H, Stams GJ, Colonnesi C. The Relation Between Attachment and Depression in Children and Adolescents: A Multilevel Meta-Analysis. *Clin Child Fam Psychol Rev* 2020; **23**: 54-69 [PMID: 31392452 DOI: 10.1007/s10567-019-00299-9]
45 **Pote H**, Stratton P, Cottrell D, Shapiro D, Boston P. Systemic family therapy can be manualized: research process and finding. *J Fam Therapy* 2003; **25**: 236-262 [DOI: 10.1111/1467-6427.00247]
46 **Diamond GM**. Attachment-based family therapy interventions. *Psychotherapy (Chic)* 2014; **51**: 15-19 [PMID: 24059739 DOI: 10.1037/a0032689]
47 **Zhang S**, Dong J. Improvement of family therapy on the efficacy and social performance of adolescent depression. *Zhonghua Xingwei Yixue Yu Naokexue Zazhi* 2013; **22**: 417-439 [DOI: 10.3760/cma.j.issn.1674-6554.2013.05.011]
48 **Li J**, Wang X, Meng H, Zeng K, Quan F, Liu F. Systemic Family Therapy of Comorbidity of Anxiety and Depression with Epilepsy in Adolescents. *Psychiatry Investig* 2016; **13**: 305-310 [DOI: 10.4306/pi.2016.13.3.305]
49 **Diamond GS**, Kobak RR, Krauthamer Ewing ES, Levy SA, Herres JL, Russon JM, Gallop RJ. A Randomized Controlled Trial: Attachment-Based Family and Nondirective Supportive Treatments for Youth Who Are Suicidal. *J Am Acad Child Adolesc Psychiatry* 2019; **58**: 721-731 [PMID: 30768418 DOI: 10.1016/j.jaac.2018.10.006]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 494-504

DOI: 10.5498/wjp.v12.i3.494

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Personality traits and self-harm behaviors among Chinese children and adolescents: The mediating effect of psychological resilience

Xue-Yang Jiao, Chuan-Zhi Xu, Ying Chen, Qing-Lan Peng, Hai-Liang Ran, Yu-San Che, Die Fang, Jun-Wei Peng, Lin Chen, Si-Fan Wang, Yuan-Yuan Xiao

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cotez CM, Hosak L, Vyshka G

Received: September 6, 2021
Peer-review started: September 6, 2021
First decision: December 27, 2021
Revised: January 5, 2022
Accepted: February 16, 2022
Article in press: February 16, 2022
Published online: March 19, 2022

Xue-Yang Jiao, Chuan-Zhi Xu, Ying Chen, Qing-Lan Peng, Hai-Liang Ran, Yu-San Che, Die Fang, Jun-Wei Peng, Lin Chen, Si-Fan Wang, Yuan-Yuan Xiao, School of Public Health, Kunming Medical University, Kunming 650500, Yunnan Province, China

Corresponding author: Yuan-Yuan Xiao, PhD, Professor, School of Public Health, Kunming Medical University, No. 1168 Chunrong West Road, Kunming 650500, Yunnan Province, China. 33225647@qq.com

Abstract

BACKGROUND

Previous studies have shown that personality traits are associated with self-harm (SH) in adolescents. However, the role of resilience in this association remains unclear. Our research aims to explore the hypothesized mediation effect of resilience in the relationship between personality traits and SH in Chinese children and adolescents.

AIM

To evaluate resilience as a mediator of the association between personality traits and SH.

METHODS

A population-based cross-sectional survey involving 4471 children and adolescents in Yunnan province in southwestern China was carried out. Relevant data were collected by self-reporting questionnaires. Univariate and multivariate logistic regression models were employed to identify associated factors of SH. A path model was used to assess the mediation effect of resilience with respect to personality traits and SH association.

RESULTS

Among the 4471 subjects, 1795 reported SH, with a prevalence of 40.1% (95%CI: 34.4%-46.0%). All dimensions of personality traits were significantly associated with SH prevalence. Resilience significantly mediated the associations between three dimensions of personality (extroversion, neuroticism, psychoticism) and SH, accounting for 21.5%, 4.53%, and 9.65%, respectively, of the total associations. Among all dimensions of resilience, only emotional regulation played a significant mediation role.

CONCLUSION
The results of the study suggest that improving emotion regulation ability might be effective in preventing personality-associated SH among Chinese children and adolescents.

Key Words: Adolescents; Emotion regulation; Mediation; Personality traits; Resilience; Self-harm

Core Tip: In children and adolescents, personality traits are closely related to self-harm (SH) behaviors. In this cross-sectional study of 4471 Chinese children and adolescents, we detected a significant role of resilience in the association between personality traits and SH. Further, among all dimensions of resilience, only emotion regulation mediated the association between personality and SH. Improving emotion regulation ability could reduce the occurrence of SH in Chinese children and adolescents.

Citation: Jiao XY, Xu CZ, Chen Y, Peng QL, Ran HL, Che YS, Fang D, Peng JW, Chen L, Wang SF, Xiao YY. Personality traits and self-harm behaviors among Chinese children and adolescents: The mediating effect of psychological resilience. *World J Psychiatry* 2022; 12(3): 494-504
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/494.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.494

INTRODUCTION

Self-harm (SH) refers to the behavior of harming one's own body with or without the intention of suicide[1]. SH is a global health concern. Among all age groups, the highest risk of SH has been reported in the adolescent population, and the lifetime prevalence of SH in non-Western countries was found to be higher than that in Western countries[2]. A meta-analysis found that the prevalence of SH among Chinese adolescents has reached 22.37%[3]. SH is the most prominent risk factor of future suicide[4]. Considering the high prevalence of SH among adolescents, together with the intimate relationship between SH and suicide, proactively preventing SH can be an effective way to reduce suicidal risk among teenagers.

Identifying the influencing factors of SH is crucial for SH prevention. In recent years, the positive link between poor mental health and SH has been repeatedly reported in adolescent populations: Impulsivity, anger dysregulation, and low self-esteem are the identified risk factors for SH in adolescents[5,6]. Personality traits are also significantly associated with adolescent SH. A study on Norwegian adolescents found that neuroticism was a risk factor that contributed to SH in youth[7]. Similarly, among Italian middle school students, those with more impulsive and aggressive personalities were more likely to report SH[8]. A domestic study in Chinese college students suggested that, those with higher extraversion scores (E scores) in the Eysenck personality questionnaire were at higher risk of SH[9]. In addition, a cross-sectional study with a large sample size showed that susceptible personality traits were significantly related to SH consciousness[10].

As a long-lasting and stable feature of an individual, personality is hard to intervene directly. Therefore, exploring modifiable factors which lie along the pathway between personality and SH would be more practicable in preventing personality-associated SH among adolescents. In recent years, some studies have found that mental resilience plays a beneficial role in protecting adolescents from SH[11-13]. Psychological resilience refers to the ability of an individual to adjust to changes when experiencing a traumatic, or negative, or frustrating event[14]. Many studies have shown that personality traits are significantly associated with resilience: For instance, extroversion, conscientiousness, and openness have been shown to be positively correlated with resilience, whereas emotionality has shown a negative association[15,16]. All of these findings suggest that resilience may play a mediating role in the association between personality traits and SH; however, this hypothesis has never been thoroughly investigated.

Aiming to address this shortcoming, the current study used a large representative sample of Chinese children and adolescents to examine the relationship between personality traits and SH, and more importantly, the possible mediation effect of resilience on personality-associated SH.

MATERIALS AND METHODS

Study design

The data used for analysis in this study were obtained from the Mental Health Survey of Children and Adolescents in Kaiyuan. A cross-sectional survey was carried out in Kaiyuan, Yunnan province in southwest China, from October 27 to November 4, 2020. The survey used a population-based two-stage simple random cluster sampling method with probability proportionate to sample size (PPS) design. It was carried out in two stages: In stage one, eight primary schools, nine junior high schools and two senior high schools were randomly selected from all schools in Kaiyuan; in stage two, 3–4 classes were randomly selected from each chosen school, and all students within the chosen classes who met the inclusion criteria were included.

Based on the literature, we set a conservative SH prevalence of 20%, and an acceptable error rate of 2% was determined. According to the simple random sampling sample size calculation method, we reached a preliminary required sample size of 1600. Considering that the sampling error in the cluster samples would inevitably be higher than that in random samples, we used a design effect of '2' to further adjust for the required sample size, and the final calculated sample size was 3200.

In this study, except for personality, SH, and resilience, we also measured suicide ideation among the respondents. Since children under the age of 10 cannot fully understand the definition and consequences of suicide[17], we only included adolescents aged 10 years old and above. Subjects were further excluded if at least one of the following exclusion criteria was satisfied: (1) Unable to complete the questionnaire due to severe psychological or physical illnesses; (2) Having a speech disorder, communication disorder or reading comprehension disorder; and (3) Refused to participate. Before the survey, the written informed consent of the respondents was obtained from their legal guardians. In addition, when the survey was underway, verbal consent was also obtained from the respondents themselves.

The study protocol was reviewed and approved by the Ethics Review Board of Kunming Medical University, No. KMMU2020MEC047.

Measurements

A structured questionnaire was used to collect information from the participants. This questionnaire mainly measures demographics, personality traits, anxiety and depression, SH behaviors, psychological resilience, suicide ideation, and parenting styles. The demographics section consisted of factual questions, and validated instruments were used for all of the other sections. In the current study, we used the following sections to perform the data analysis: General characteristics, SH behavior, psychological resilience, personality traits, depression, and anxiety.

SH behaviors: The modified version of the Adolescents Self-Harm Scale (MASHS) developed by Feng [18] was used to measure lifetime SH behaviors[18]. The MASHS includes 18 items measuring frequency (never, 1 time; 2–4 times, 5 times and above) and severity (non-observable, mild, moderate, severe, devastating) of the 18 most common SH behaviors in Chinese adolescents.

Personality traits: The children's version of the Eysenck Personality Questionnaire developed by Eysenck and other researchers in 1975 was used to assess personality traits[19]. The questionnaire consists of 88 items, divided into four subscales: Neuroticism (N); psychoticism (P); E; lie (L). The first three scales represent the three dimensions of the personality structure and are independent of each other. The L scale is a measure of effectiveness and represents the personality traits related to false trust. Each question is scored '1' or '0', and finally converted into a normal standard T score. For the L scale, a T score greater than 61.5 was taken to indicate a lack of authenticity. The T scores for N, P, and E scales were collectively used to classify subjects into five levels. E (extraversion) was divided into: Typical introversion ($T \leq 38.5$), introversion ($38.5 < T \leq 43.3$), extraversion intermediate ($43.3 < T \leq 56.7$), extroversion ($56.7 < T \leq 61.5$), and typical extroversion ($T > 61.5$). N was divided into: Typical non-neuroticism ($T \leq 38.5$), non-neuroticism ($38.5 < T \leq 43.3$), neuroticism intermediate ($43.3 < T \leq 56.7$), neuroticism ($56.7 < T \leq 61.5$), and typical neuroticism ($T > 61.5$). P was divided into: Typical non-psychoticism ($T \leq 38.5$), non-psychoticism ($38.5 < T \leq 43.3$), psychoticism intermediate ($43.3 < T \leq 56.7$), psychoticism ($56.7 < T \leq 61.5$), and typical psychoticism ($T > 61.5$)[9,20]. The Cronbach's α was 0.891 (Bootstrap 95%CI: 0.886-0.896).

Depression and anxiety: The Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) were used to assess the subjects' experience of depression and anxiety in the past two weeks. There are nine items on the PHQ-9, which correspond to the nine diagnostic criteria for depression (interest in doing things, mood fluctuations, sleep quality, vitality, appetite, self-evaluation, concentration on things, speed of movement, thoughts of suicide)[21]. The GAD-7 contains seven items, which measure nervousness, anxiety, uncontrollable worry, excessive worry, inability to relax, inability to sit still, irritability, and ominous premonition[22]. Each item on the PHQ-9 and GAD-7 is divided into four levels by severity of the scenario: Not at all (0 point), several days (1 point), more than half of the days (2 points), almost every day (3 points). A higher combined score was taken to indicate more severe symptoms of depression or anxiety[23]. The Cronbach's α for the PHQ-9 and GAD-7 were 0.883 (Bootstrap 95%CI: 0.874-0.890) and 0.909 (Bootstrap 95%CI: 0.902-0.915).

Resilience: The Resilience Scale for Chinese Adolescents (RSCA) compiled by Hu and Gan[24] was used. It contains 27 items, including two dimensions of personal strength and support. The personal strength dimension is divided into three factors: Goal concentration, emotion regulation, and positive perception. The support dimension is divided into two factors: Family support and interpersonal assistance. The questionnaire is scored using a five-point scale (1-totally disagree, 2-disagree, 3-not sure, 4-agree, 5-totally agree), with a higher total score representing a higher level of mental resilience[24]. The Cronbach's α was 0.846 (Bootstrap 95%CI: 0.837-0.855).

Statistical analysis

We used the R software (Version 4.0.3, The R Foundation for Statistical Computing, Vienna, Austria) to perform the statistical analysis, and the "Survey" package has been mainly used to adjust for unequal sampling probability. Descriptive statistics are presented to describe the general characteristics of the survey subjects, t tests, chi-squared tests, and rank-based non-parametric tests were carried out to compare the differences between subgroups as appropriate to variable type. Univariate and multivariate binary unconditional logistic regression models were used to explore the crude and adjusted associations between personality traits and SH (prevalence, repetition, severity). A series of path models were fitted to examine psychological resilience as a mediator of the associations between personality and SH prevalence, SH severity, and SH repetition. Except for the univariate logistic regression models which adopted a lower significance level of 0.10 to screen for possible covariates, the significance level for all of the other statistical analyses was set as 0.05 (two-tailed).

RESULTS

General characteristics

A total of 4780 children and adolescents met the inclusion criteria, of whom 57 were excluded because of incomplete information. A further 252 respondents were defined as untrustworthy because their EPQ-L scores were greater than 61.5. In the end, 4471 subjects were included in the analysis, and the effective response rate was 93.5%. Among all analyzed participants, 1795 reported SH behaviors, accounting for 40.1% (95%CI: 34.4%-46.0%). In respect to the general characteristics listed in Table 1, except for sex and ethnicity, statistically significant differences were found between respondents who self-harmed and those who did not SH. The T sores for the E, N, and P dimensions of personality traits were also different between the two groups. Compared with SH subjects, subjects who did not SH reported a consistently higher level of resilience, either in general, or on the five specific dimensions.

Associated factors of SH

Based on univariate logistic regression analysis, age, gender, grade, anxiety, depression, resilience, and all of the personality trait dimensions (extraversion, neuroticism, psychoticism) were included into the subsequent multivariate logistic regression models: Model 1 represented the adjusted associations between the three dimensions of personality traits and SH; Model 2 revealed the adjusted association between resilience and SH; in Model 3, personality traits and resilience were simultaneously incorporated into the model, and the results indicated that typical introverted personality types (E ≤ 38.5) were associated with an increased risk of SH (OR = 1.46, 95%CI: 1.14-1.87), whereas a more stable mood (a lower N score) (OR = 0.19, 95%CI: 0.13-0.26) and a lower psychotic score (P ≤ 56.7) (OR = 0.29, 95%CI: 0.17-0.51) were associated with a decreased risk of SH (Table 2).

Mediation of resilience

Based on the results of the multivariate logistic regression models, we constructed a possible path model to illustrate resilience as a mediator of the associations between the three personality trait dimensions and SH prevalence. The analytical results showed that the mediation effect of resilience for all of the three personality trait dimensions was significant: The standardized path coefficients were -0.0301 (0.494 × -0.061), 0.0225 (-0.369 × -0.061), and 0.0145 (-0.238 × -0.061), which accounted for 21.5%, 4.53%, and 9.65% of the total associations, respectively (Figure 1). We further dissected this association based on the five dimensions of resilience. The path model suggested that among the three significant dimensions of resilience identified by a prior multivariate logistic regression model (the results are summarized in Supplementary Table 1), only emotion regulation was identified as a prominent mediator (Figure 2).

We intended to further analyze the possible mediation effect of emotion regulation in terms of the associations between personality traits and SH repetition, as well as SH severity. However, the preliminary multivariate analysis revealed that the adjusted associations between emotion regulation and SH repetition/severity were all insignificant (Supplementary Table 2); thus, the suspected mediation effect was not found.

Table 1 General features of 4471 adolescents, Kaiyuan, Yunnan, China, 2020

Features	Total (*n* = 4471)	SH (*n* = 1795)	Non-SH (*n* = 2676)	Test statistic	*P* value
Demographics					
Age (X bar ± S)	13.01 (0.40)	13.42 (0.34)	12.73 (0.43)	-11.99[1]	0.01
Sex, *n*, (%): Boys	2184 (48.8)	824 (45.9)	1360 (50.8)	3.17[2]	0.09
Ethnicity, *n*, (%)				0.37[2]	0.67
Han	1242 (27.8)	504 (28.1)	738 (27.6)		
Yi	1788 (40.0)	693 (38.6)	1095 (40.9)		
Others	1441 (32.2)	598 (33.3)	843 (31.5)		
Grade, *n*, (%)				32.24[2]	0.01
Primary school	1472 (32.9)	374 (20.8)	1098 (41.0)		
Junior high school	2442 (54.6)	1157 (64.5)	1285 (48.0)		
Senior high school	557 (12.5)	264 (14.7)	293 (10.9)		
Mental health					
Depression, *n*, (%): Yes (PHQ9 ≥ 10)	501 (11.2)	411 (22.9)	90 (3.4)	176.27[2]	0.01
Anxiety, *n*, (%): Yes (GAD7 ≥ 7)	778 (17.4)	570 (31.8)	208 (7.8)	244.43[2]	0.01
Personality traits					
EPQ-E, *n*, (%)				3.54[3]	0.01
Typical extroversion: Score E > 61.5	1024 (22.9)	357 (19.9)	667 (24.9)		
Extroversion: 56.7 < score E ≤ 61.5	740 (16.6)	270 (15.0)	470 (17.6)		
Intermediate: 43.3 < score E ≤ 56.7	1825 (40.8)	763 (42.5)	1062 (39.7)		
Introversion: 38.5 < score E ≤ 43.3	419 (9.4)	191 (10.6)	228 (8.5)		
Typical introversion: score E ≤ 38.5	463 (10.4)	214 (11.9)	249 (9.3)		
EPQ-N, *n*, (%)				-18.10[3]	0.01
Typical neuroticism: Score N > 61.5	646 (14.4)	510 (28.4)	136 (5.1)		
Neuroticism: 56.7 < score N ≤ 61.5	323 (7.2)	197 (11.0)	126 (4.7)		
Intermediate: 43.3 < score N ≤ 56.7	1227 (27.4)	574 (32.0)	653 (24.4)		
Non-neuroticism: 38.5 < score N ≤ 43.3 N ≤ 43.3	552 (12.3)	189 (10.5)	363 (13.6)		
Typical non-neuroticism: Score N ≤ 38.5 NN ≤ 38.5	1723 (38.5)	325 (18.1)	1398 (52.2)		
EPQ-P, *n*, (%)				-11.02[3]	0.01
Typical psychoticism: score P > 61.5	422 (9.4)	289 (16.1)	133 (5.0)		
Psychoticism: 56.7 < score P ≤ 61.5	518 (11.6)	308 (17.2)	210 (7.8)		
Intermediate: 43.3 < score P ≤ 56.7	2335 (52.2)	967 (53.9)	1368 (51.1)		
Non-psychoticism: 38.5 < score P ≤ 43.3	1026 (22.9)	211 (11.8)	815 (30.5)		
Typical non-psychoticism: Score P ≤ 38.5	170 (3.8)	20 (1.1)	150 (5.6)		
Resilience (Median, IQR)					
Combined score	89 (19)	84 (16)	93 (20)	-15.98[3]	0.01
Goal concentration	17 (6)	16 (6)	18 (6)	-11.17[3]	0.01
Emotion regulation	20 (7)	18 (7)	21 (6)	-13.26[3]	0.01
Positive perception	14 (5)	13 (5)	14 (5)	-2.68[3]	0.02
Family support	21 (6)	19 (5)	22 (5)	-10.27[3]	0.01
Interpersonal assistance	20 (6)	18 (6)	21 (6)	-10.93[3]	0.01

[1]*t* test.
[2]Chi-squared test.
[3]Wilcoxon rank-sum test.
SH: Self-harm; E: Extraversion; N: Neuroticism; P: Psychoticism.

DISCUSSION

In the current study, we discussed the relationship between personality traits and SH in a large representative sample of Chinese children and adolescents. The analysis of the results showed that all personality trait dimensions were significantly related to the prevalence of SH after adjusting for other covariates. Resilience played a noticeable mediating role in terms of the associations between different dimensions of personality (E, N, P) and SH, accounting for 21.5%, 4.53%, and 9.65% of the total associations, respectively. Further analysis revealed that, for different dimensions of resilience, only emotion regulation was identified as a prominent mediator in this association. The current study could provide valuable evidence for personality-associated SH prevention in children and adolescents.

A high lifetime prevalence of SH (40.1%) was found in our study sample, and this prevalence was much higher than that previously reported. For example, two previously published meta-analysis papers found a lifetime SH prevalence of 13.7% (95%CI: 11.0%-17.0%) and 16.9% (95%CI: 15.1%-18.9%) among children and adolescents globally[2,25]. Another meta-analysis found that the prevalence of SH among Chinese adolescents was 22.37%[3], which is comparable to our previous study involving children and adolescents who were randomly chosen from another city (Lincang) of Yunnan province, with a reported lifetime prevalence of SH of 47%[12]. These prominent differences in the lifetime prevalence of SH can likely be attributed to heterogeneity in SH instruments and definitions, which prevent a direct comparison of the studies involving different children and adolescent populations.

An important finding of our study is that personality traits were significantly associated with SH prevalence: Higher E scores were correlated with lower SH odds, whereas higher N and P scores were associated with an increased risk of SH. These associations were well supported by existing literature. First of all, introverts may find it more difficult to integrate into society, although no pertinent studies have been published to elaborate upon the influence of introversion on SH, and a higher risk of future suicide has been reported among introverted college students[26]. The positive association that was identified in the current study between neuroticism and SH is in line with the results published by Hafferty *et al*[27]. Another meta-analysis on neuroticism and suicide ideation showed that neuroticism was also a significant risk factor for suicide ideation and is of great significance for suicide prevention [28]. The positive connection between psychoticism and SH can also be justified. Studies have found that high psychoticism individuals exhibited higher levels of impulsivity and aggressiveness, which are known risk factors for SH[29,30].

The path analysis results indicated that resilience was a significant mediator of the association between all personality trait dimensions and SH. In general, resilience is related to positive personality traits such as optimism, persistence, cooperation, maturity, and responsibility[31]. A study on American college students also found that neuroticism in personality traits was negatively correlated with resilience, while conscientiousness and extroversion were positively correlated with resilience[16,32]. In addition, existing studies have shown that resilience has a protective effect on the occurrence of SH in adolescents, and adolescents with higher levels of resilience were less likely to develop SH[11]. In the relationship between personality and SH, resilience-mediated associations accounted for over one-fifth (21.5%) of the total association for the extraversion dimension, which was the highest among all of the three dimensions. This finding probably suggests that, for introverted children and adolescents, building up resilience might be an effective way to prevent personality-related SH.

Resilience is a composite definition. Our further analysis revealed that, among the five dimensions of resilience, only emotion regulation was a significant mediator of the association between personality traits and SH. Emotion regulation refers to the ability to respond to the ongoing demands of experience with a range of emotions in a socially tolerable manner[33]. A newly published study found that poor emotion regulation was an important cause of SH[34]. In addition, a retrospective study has also indicated that there were differences in the ability to control emotions among individuals with different personalities[35]. Therefore, among all dimensions of resilience, improving emotion regulation ability could be regarded as the priority in antagonizing personality-associated SH among children and adolescents. Currently, some effective intervention methods in improving emotion regulation ability have already been proposed. Since SH has a high prevalence in children and adolescents, group-based therapy should be prioritized when considering interventions. Acceptance-based emotion regulation group therapy had a good effect on improving emotion regulation ability and reducing SH: It focuses on controlling behavior when emotions are present, rather than controlling emotions themselves[36-38]. Domestic studies have also shown that acceptance-commitment therapy has a positive effect on the acceptance of bad emotions and feelings, as well as on the rational use of emotion regulation strategies in patients with bipolar disorder[39]. Moreover, although studies on emotion regulation intervention strategies were also published recently in China, they mainly focused on clinical populations, such as

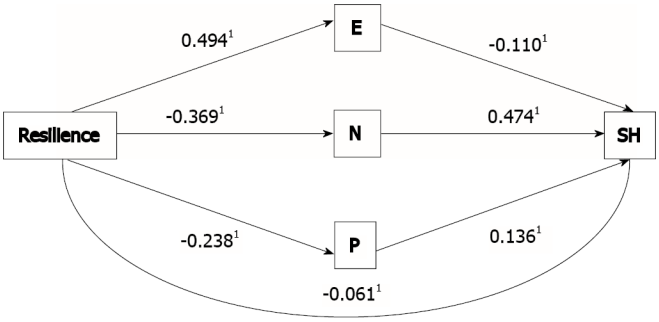
Table 2 Univariate and multivariate logistic regression fitting results for associated factors of self-harm

Variable	Univariate model; Crude OR (90%CI)	Multivariate model 1; Adjusted OR (95%CI)	Multivariate model 2; Adjusted OR (95%CI)	Multivariate model 3; Adjusted OR (95%CI)
Age: +1 yr	1.20 (1.14-1.27)	1.00 (0.93-1.08)	1.03 (0.95-1.11)	1.01 (0.94-1.09)
Sex (Ref: Boys): Girls	1.22 (1.01-1.46)	0.98 (0.75-1.28)	1.09 (0.89-1.34)	0.98 (0.76-1.27)
Grade (Ref: Primary school)				
Junior high school	2.64 (2.11-3.31)	1.81 (1.23-2.67)	2.18 (1.49-3.19)	1.82 (1.24-2.69)
Senior high school	2.65 (2.01-3.48)	1.43 (0.89-2.30)	2.12 (1.29-3.49)	1.51 (0.93-2.46)
Depression (Ref: PHQ9 < 10): PHQ9 ≥ 10	8.53 (6.29-11.59)	2.21 (1.49-3.27)	3.30 (2.56-4.82)	2.18 (1.47-3.23)
Anxiety (Ref: GAD7 < 7): GAD7 ≥ 7	5.52 (4.55-6.69)	1.43 (1.14-1.78)	2.28 (1.84-2.83)	1.37 (1.10-1.70)
Personality traits				
EPQ-E (Ref: Typical extroversion, score E > 61.5)				
Extroversion (56.7 < score E ≤ 61.5)	1.07 (0.94-1.22)	1.10 (0.90-1.34)		1.05 (0.85-1.29)
Intermediate (43.3 < score E ≤ 56.7)	1.34 (1.16-1.55)	1.29 (1.06-1.57)		1.13 (0.92-1.40)
Introversion (38.5 < score E ≤ 43.3)	1.57 (1.26-1.95)	1.50 (1.17-1.91)		1.21 (0.94-1.54)
Typical introversion (score E ≤ 38.5)	1.61 (1.26-2.04)	1.90 (1.41-2.56)		1.46 (1.14-1.87)
EPQ-N (Ref: Typical neuroticism, score N > 61.5)				
Neuroticism (56.7 < score N ≤ 61.5)	0.42 (0.33-0.52)	0.63 (0.45-0.88)		0.64 (0.45-0.91)
Intermediate (43.3 < score N ≤ 56.7)	0.23 (0.20-0.27)	0.45 (0.34-0.60)		0.50 (0.37-0.67)
Non-neuroticism (38.5 < score N ≤ 43.3)	0.14 (0.11-0.18)	0.31 (0.21-0.46)		0.36 (0.24-0.54)
Typical non-neuroticism (score N ≤ 38.5)	0.06 (0.05-0.08)	0.16 (0.11-0.22)		0.19 (0.13-0.26)
EPQ-P (Ref: Typical psychoticism, score P > 61.5)				
Psychoticism (56.7 < score P ≤ 61.5)	0.67 (0.51-0.90)	0.83 (0.61-1.13)		0.86 (0.62-1.19)
Intermediate (43.3 < score P ≤ 56.7)	0.33 (0.24-0.44)	0.66 (0.47-0.93)		0.73 (0.51-1.03)
Non-psychoticism (38.5 < score P ≤ 43.3)	0.12 (0.09-0.17)	0.36 (0.26-0.50)		0.42 (0.30-0.58)
Typical non-psychoticism (score P ≤ 38.5)	0.06 (0.04-0.09)	0.25 (0.14-0.42)		0.29 (0.17-0.51)
Resilience (Ref: RSCA < 89): RSCA ≥ 89	0.32 (0.27-0.36)		0.42 (0.36-0.50)	0.63 (0.52-0.77)

SH: Self-harm; E: Extraversion; N: Neuroticism; P: Psychoticism; RSCA: Resilience Scale for Chinese Adolescents.

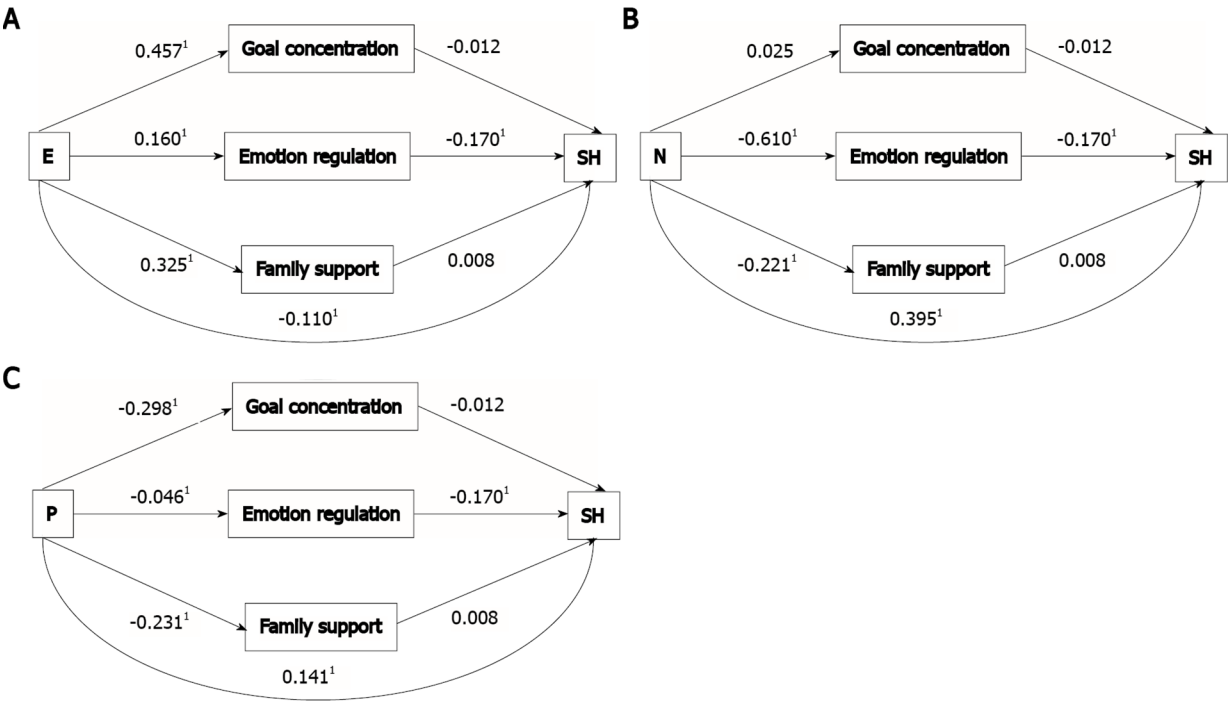
depressed teenagers[40]. Therefore, the usefulness and effectiveness of available emotion regulation intervention methods for the general child and adolescent population in China are yet to be corroborated.

The major advantages of the current research are that it involved a large population-based representative sample of Chinese children and adolescents, and the study design and implementation were scientific and rigorous. However, two limitations should be noted. First, due to the cross-sectional design, causal inferences were impossible. Second, the entire study sample was chosen from a single



DOI: 10.5498/wjp.v12.i3.494

Figure 1 The path model of resilience, personality traits, and self-harm. [1]Statistically significant. SH: Self-harm.



DOI: 10.5498/wjp.v12.i3.494

Figure 2 The path model of different dimensions of resilience, personality traits, and self-harm. A: The mediation of resilience in personality traits E and self-harm (SH); B: The mediation of resilience in N and SH; C: The mediation of resilience in P and SH. [1]Statistically significant. SH: Self-harm; E: Extraversion; N: Neuroticism; P: Psychoticism.

province in southwest China; therefore, the results cannot be generalized to the entire Chinese child and adolescent population.

CONCLUSION

In this cross-sectional study, we discussed the relationship between personality traits and SH in a large sample of Chinese children and adolescents. More importantly, we thoroughly examined the mediating role of resilience in this relationship. We found that personality traits were significantly associated with SH, and resilience was identified as a prominent mediator. Further analysis revealed that, for all the dimensions of resilience, emotion regulation was the only noticeable mediator. The major findings of our study are of significance in preventing seemingly unchangeable personality-associated SH among children and adolescents: For introverted individuals, interventions that focus on reinforcing resilience might be a promising strategy. This hypothesis should be further corroborated by future intervention studies.

ARTICLE HIGHLIGHTS

Research background

Children and adolescents are at increased risk of self-harm (SH), an established indicator of future suicide. Published studies support a positive relationship between personality traits and SH. There is a possibility that resilience may play a mediating role in the association between personality traits and SH; however, this hypothesis has never been thoroughly investigated.

Research motivation

The current study aimed to provide valuable evidence for identifying personality traits that are associated with SH in children and adolescents.

Research objectives

To investigate resilience as a mediator of the association between personality traits and SH among a large representative sample of Chinese children and adolescents.

Research methods

We surveyed 4780 children and adolescents from Kaiyuan City, Honghe Prefecture, Yunnan province, China. The children's version of the Eysenck Personality Questionnaire was used to assess the personality traits. The Chinese Youth psychological resilience scale was used to measure the level of resilience. The revised version of the Adolescent Self-harm Scale was used to measure the lifetime prevalence of SH among the survey subjects. We used univariate and multivariate logistic regression models and path analysis to evaluate resilience as a mediator.

Research results

Among the 4471 subjects included into the final analysis, the prevalence of SH was 40.1% (95%CI: 34.4%-46.0%). For different dimensions of personality traits, higher E-dimension scores and lower N- and P-dimension scores were associated with a lower SH prevalence. Resilience was identified as an obvious mediator of the associations between the three dimensions of personality and SH, accounting for 21.5%, 4.53%, and 9.65%, respectively, of the total associations. In addition, we found that, among the five dimensions of resilience, only emotion regulation was identified as a significant mediator.

Research conclusions

According to the current research results, we found that resilience was a significant mediator of the association between personality traits and SH, especially the dimension of emotion regulation. Intervention measures which aim to improve resilience may be effective in preventing personality traits that are associated with SH in Chinese children and adolescents.

Research perspectives

Future interventional studies are warranted to further corroborate our major findings.

FOOTNOTES

Author contributions: Xiao YY conceived the study; Jiao XY, Xu CZ, Chen Y, Peng QL, Ran HL, Che YS, Fang D, Peng JW, Chen L, and Wang SF collected, verified, and analyzed the data; Jiao XY and Xu CZ drafted the manuscript; all authors provided critical revision of the manuscript for important intellectual content.

Supported by National Natural Science Foundation of China, No. 82060601; Top Young Talents of Yunnan Ten Thousand Talents Plan, No. YNWR-QNBJ-2018-286; and the Innovative Research Team of Yunnan Province, No. 202005AE160002.

Institutional review board statement: The study protocol was reviewed and approved by the Ethics Review Board of Kunming Medical University, No. KMMU2020MEC047.

Conflict-of-interest statement: The authors declare no conflict of interest.

Data sharing statement: The analytical dataset of the current study can be obtained from the corresponding author under reasonable request.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Country/Territory of origin: China

ORCID number: Xue-Yang Jiao 0000-0003-0496-2429; Chuan-Zhi Xu 0000-0001-5469-7112; Ying Chen 0000-0001-8147-3798; Qing-Lan Peng 0000-0003-0508-2319; Hai-Liang Ran 0000-0001-7290-3880; Yu-San Che 0000-0002-8366-6937; Die Fang 0000-0001-5995-7729; Jun-Wei Peng 0000-0002-0973-6191; Lin Chen 0000-0002-9298-5972; Si-Fan Wang 0000-0001-9252-8504; Yuan-Yuan Xiao 0000-0003-2441-7209.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Hawton K**, Hall S, Simkin S, Bale L, Bond A, Codd S, Stewart A. Deliberate self-harm in adolescents: a study of characteristics and trends in Oxford, 1990-2000. *J Child Psychol Psychiatry* 2003; **44**: 1191-1198 [PMID: 14626459 DOI: 10.1111/1469-7610.00200]
2 **Lim KS**, Wong CH, McIntyre RS, Wang J, Zhang Z, Tran BX, Tan W, Ho CS, Ho RC. Global Lifetime and 12-Month Prevalence of Suicidal Behavior, Deliberate Self-Harm and Non-Suicidal Self-Injury in Children and Adolescents between 1989 and 2018: A Meta-Analysis. *Int J Environ Res Public Health* 2019; **16** [PMID: 31752375 DOI: 10.3390/ijerph16224581]
3 **Lang J**, Yao Y. Prevalence of nonsuicidal self-injury in chinese middle school and high school students: A meta-analysis. *Medicine (Baltimore)* 2018; **97**: e12916 [PMID: 30335024 DOI: 10.1097/MD.0000000000012916]
4 **Whitlock J**, Muehlenkamp J, Eckenrode J, Purington A, Baral Abrams G, Barreira P, Kress V. Nonsuicidal self-injury as a gateway to suicide in young adults. *J Adolesc Health* 2013; **52**: 486-492 [PMID: 23298982 DOI: 10.1016/j.jadohealth.2012.09.010]
5 **Lockwood J**, Daley D, Townsend E, Sayal K. Impulsivity and self-harm in adolescence: a systematic review. *Eur Child Adolesc Psychiatry* 2017; **26**: 387-402 [PMID: 27815757 DOI: 10.1007/s00787-016-0915-5]
6 **Chang SH**, Hall WA, Campbell S, Lee L. Experiences of Chinese immigrant women following "Zuo Yue Zi" in British Columbia. *J Clin Nurs* 2018; **27**: e1385-e1394 [PMID: 29266549 DOI: 10.1111/jocn.14236]
7 **Junker A**, Nordahl HM, Bjørngaard JH, Bjerkeset O. Adolescent personality traits, low self-esteem and self-harm hospitalisation: a 15-year follow-up of the Norwegian Young-HUNT1 cohort. *Eur Child Adolesc Psychiatry* 2019; **28**: 329-339 [PMID: 30027416 DOI: 10.1007/s00787-018-1197-x]
8 **Di Pierro R**, Sarno I, Perego S, Gallucci M, Madeddu F. Adolescent nonsuicidal self-injury: the effects of personality traits, family relationships and maltreatment on the presence and severity of behaviours. *Eur Child Adolesc Psychiatry* 2012; **21**: 511-520 [PMID: 22722662 DOI: 10.1007/s00787-012-0289-2]
9 **Chen F**, Huang J, Zhang LS. Influencing factors of self-injury behavior among undergraduates by two-level binary Logistic regression model. *Chinese J Dis Cont Preven* 2017; **21**: 387-390
10 **Kuang L**, Wang W, Huang Y, Chen X, Lv Z, Cao J, Ai M, Chen J. Relationship between Internet addiction, susceptible personality traits, and suicidal and self-harm ideation in Chinese adolescent students. *J Behav Addict* 2020; **9**: 676-685 [PMID: 32750031 DOI: 10.1556/2006.2020.00032]
11 **Xiao Y**, He L, Chen Y, Wang Y, Chang W, Yu Z. Depression and deliberate self-harm among Chinese left-behind adolescents: A dual role of resilience. *Asian J Psychiatr* 2020; **48**: 101883 [PMID: 31786362 DOI: 10.1016/j.ajp.2019.101883]
12 **Ran H**, Cai L, He X, Jiang L, Wang T, Yang R, Xu X, Lu J, Xiao Y. Resilience mediates the association between school bullying victimization and self-harm in Chinese adolescents. *J Affect Disord* 2020; **277**: 115-120 [PMID: 32810666 DOI: 10.1016/j.jad.2020.07.136]
13 **Tian X**, Chang W, Meng Q, Chen Y, Yu Z, He L, Xiao Y. Resilience and self-harm among left-behind children in Yunnan, China: a community-based survey. *BMC Public Health* 2019; **19**: 1728 [PMID: 31870359 DOI: 10.1186/s12889-019-8075-4]
14 **Xu MJ**, Wan PY, Yang XG. Positive cognitive emotion regulation and psychological resilience on suicide ideation among left-behind adolescents. *Modern Preven Med* 2016; **43**: 4143-4146
15 **Nakaya M**, Oshio A, Kaneko H. Correlations for Adolescent Resilience Scale with big five personality traits. *Psychol Rep* 2006; **98**: 927-930 [PMID: 16933700 DOI: 10.2466/pr0.98.3.927-930]
16 **Campbell-Sills L**, Cohan SL, Stein MB. Relationship of resilience to personality, coping, and psychiatric symptoms in young adults. *Behav Res Ther* 2006; **44**: 585-599 [PMID: 15998508 DOI: 10.1016/j.brat.2005.05.001]
17 **Mishara BL**. Conceptions of death and suicide in children ages 6-12 and their implications for suicide prevention. *Suicide Life Threat Behav* 1999; **29**: 105-118 [PMID: 10407964]
18 **Feng Y**. The relationship of adolecents'self-harm behaviors, individual emotion characteristics and family environment factors. *Cent China Normal Uni* 2008
19 **Gong YX**. Revision of Eysenck Personality Questionnaire in China. *J Psy Sci* 1984; **4**: 13-20
20 **Zhang Y**. Investigation on Depressive State of Cadet Pilots and Analysis of Eysenck Personality Questionnaire. *Pract Pre*

Med 2009; **16**: 378-379
21 Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ* 2019; **365**: l1781 [PMID: 30979729 DOI: 10.1136/bmj.l1781]
22 **Plummer F**, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic metaanalysis. *Gen Hosp Psychiatry* 2016; **39**: 24-31 [PMID: 26719105 DOI: 10.1016/j.genhosppsych.2015.11.005]
23 **Spitzer RL**, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; **282**: 1737-1744 [PMID: 10568646 DOI: 10.1001/jama.282.18.1737]
24 **Hu YQ**, Gan YQ. Development and Psychometric Validity of the Resilience Scale for Chinese Adolescents: Development and Psychometric Validity of the Resilience Scale for Chinese Adolescents. *Acta Psychologica Sinica* 2008; **8**: 902-912
25 **Gillies D**, Christou MA, Dixon AC, Featherston OJ, Rapti I, Garcia-Anguita A, Villasis-Keever M, Reebye P, Christou E, Al Kabir N, Christou PA. Prevalence and Characteristics of Self-Harm in Adolescents: Meta-Analyses of Community-Based Studies 1990-2015. *J Am Acad Child Adolesc Psychiatry* 2018; **57**: 733-741 [PMID: 30274648 DOI: 10.1016/j.jaac.2018.06.018]
26 **Mars B**, Heron J, Klonsky ED, Moran P, O'Connor RC, Tilling K, Wilkinson P, Gunnell D. Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: a population-based birth cohort study. *Lancet Psychiatry* 2019; **6**: 327-337 [PMID: 30879972 DOI: 10.1016/S2215-0366(19)30030-6]
27 **Hafferty JD**, Navrady LB, Adams MJ, Howard DM, Campbell AI, Whalley HC, Lawrie SM, Nicodemus KK, Porteous DJ, Deary IJ, McIntosh AM. The role of neuroticism in self-harm and suicidal ideation: results from two UK population-based cohorts. *Soc Psychiatry Psychiatr Epidemiol* 2019; **54**: 1505-1518 [PMID: 31123787 DOI: 10.1007/s00127-019-01725-7]
28 **Garcia HA**, Sanchez-Meca J, Alvarez MF, Rubio-Aparicio M, Navarro-Mateu F. [Neuroticism and suicidal thoughts: a meta-analytic study]. *Rev Esp Salud Publica* 2018; **92**: e201808049
29 **Lockwood J**, Townsend E, Daley D, Sayal K. Impulsivity as a predictor of self-harm onset and maintenance in young adolescents: a longitudinal prospective study. *J Affect Disord* 2020; **274**: 583-592 [PMID: 32663991 DOI: 10.1016/j.jad.2020.05.021]
30 **O'Donnell O**, House A, Waterman M. The co-occurrence of aggression and self-harm: systematic literature review. *J Affect Disord* 2015; **175**: 325-350 [PMID: 25665494 DOI: 10.1016/j.jad.2014.12.051]
31 **Eley DS**, Cloninger CR, Walters L, Laurence C, Synnott R, Wilkinson D. The relationship between resilience and personality traits in doctors: implications for enhancing well being. *PeerJ* 2013; **1**: e216 [PMID: 24282675 DOI: 10.7717/peerj.216]
32 **Shi M**, Liu L, Wang ZY, Wang L. The mediating role of resilience in the relationship between big five personality and anxiety among Chinese medical students: a cross-sectional study. *PLoS One* 2015; **10**: e0119916 [PMID: 25794003 DOI: 10.1371/journal.pone.0119916]
33 **Cole PM**, Michel MK, Teti LO. The development of emotion regulation and dysregulation: a clinical perspective. *Monogr Soc Res Child Dev* 1994; **59**: 73-100 [PMID: 7984169 DOI: 10.2307/1166139]
34 **Brereton A**, McGlinchey E. Self-harm, Emotion Regulation, and Experiential Avoidance: A Systematic Review. *Arch Suicide Res* 2020; **24**: 1-24 [PMID: 30636566 DOI: 10.1080/13811118.2018.1563575]
35 **Hughes DJ**, Kratsiotis IK, Niven K, Holman D. Personality traits and emotion regulation: A targeted review and recommendations. *Emotion* 2020; **20**: 63-67 [PMID: 31961180 DOI: 10.1037/emo0000644]
36 **Gratz KL**, Gunderson JG. Preliminary data on an acceptance-based emotion regulation group intervention for deliberate self-harm among women with borderline personality disorder. *Behav Ther* 2006; **37**: 25-35 [PMID: 16942958 DOI: 10.1016/j.beth.2005.03.002]
37 **Gratz KL**, Tull MT. Extending research on the utility of an adjunctive emotion regulation group therapy for deliberate self-harm among women with borderline personality pathology. *Personal Disord* 2011; **2**: 316-326 [PMID: 22448804 DOI: 10.1037/a0022144]
38 **Gratz KL**, Weiss NH, Tull MT. Examining Emotion Regulation as an Outcome, Mechanism, or Target of Psychological Treatments. *Curr Opin Psychol* 2015; **3**: 85-90 [PMID: 25859561 DOI: 10.1016/j.copsyc.2015.02.010]
39 **Li M**, Shi JY, Feng G, Shi YQ, Sun LL, Li L, Wang BH. The Intervention of Group Acceptance and Commitment Therapy (ACT) for Emotion Regulation of Patients with Bipolar Disorder (BD). *World Latest Med Infor* 2019; **19**: 23-24+27
40 **Ding HQ**, Yan F, He XJ. Effect of emotional regulation strategy on non-suicidal self-injury behavior of adolescents with depressive disorder. *J Nur Sci* 2021; **36**: 62-65

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 505-520

DOI: 10.5498/wjp.v12.i3.505

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Trends in suicide by hanging, strangulation, and suffocation in Serbia, 1991-2020: A joinpoint regression and age-period-cohort analysis

Milena Ilic, Irena Ilic

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kotzalidis GD, Lyu J

Received: September 7, 2021
Peer-review started: September 7, 2021
First decision: November 8, 2021
Revised: November 18, 2021
Accepted: February 10, 2022
Article in press: February 10, 2022
Published online: March 19, 2022

Milena Ilic, Department of Epidemiology, Faculty of Medical Sciences, University of Kragujevac, Kragujevac 34000, Serbia

Irena Ilic, Faculty of Medicine, University of Belgrade, Belgrade 11000, Serbia

Corresponding author: Milena Ilic, MD, PhD, Professor, Department of Epidemiology, Faculty of Medical Sciences, University of Kragujevac, S. Markovica 69, Kragujevac 34000, Serbia. drmilenailic@yahoo.com

Abstract

BACKGROUND

Hanging is one of the most commonly used methods for suicide in both sexes worldwide. In a number of countries, hanging mortality has increased over the last decades. Nevertheless, there is a scarcity of studies that have explored the patterns and trends for mortality of suicide by hanging on global, regional and national levels, as most evaluations are limited to certain populations.

AIM

To assess the trends of suicide mortality by hanging, strangulation, and suffocation in Serbia, from 1991 to 2020.

METHODS

This nationwide study, with epidemiological descriptive study design, was carried out based on official data. The age-standardized rates (ASRs, expressed *per* 100000 persons) were calculated by direct standardization, using the World Standard Population. Mortality trends from suicide by hanging were assessed using the joinpoint regression analysis: The average annual percent change (AAPC) with the corresponding 95% confidence interval (95%CI) was calculated. Age-period-cohort analysis was performed to address the possible underlying reasons for the observed suicide trends.

RESULTS

Over the 30-year period studied, there were 24340 deaths by hanging (17750 males and 6590 females) in Serbia. In 2020, the ASR of deaths by hanging was 4.5 *per* 100000 persons in both sexes together (7.6 in males *vs* 1.7 in females). The trends of suicide mortality by hanging decreased significantly between 1991 and 2020 in

both males (AAPC = -1.7% *per* year; 95%CI: -2.0 to -1.4) and females (AAPC = - 3.5% *per* year; 95%CI: -3.9 to -3.1). Mortality rates of suicide by hanging had a continuously decreasing tendency in both sexes together in all age groups: The only exception was among males in 40-49 age group, with an increasing trend of suicide by hanging from 1991 to 2011 (by +0.3% *per* year).

CONCLUSION

The trends in suicide mortality by hanging have been decreasing in Serbia in the last three decades in both sexes, but this was more pronounced in women than in men. Despite the decreasing trends observed in mortality of suicide by hanging, further research is needed for better clarification of trends and help in suicide prevention in the future.

Key Words: Suicide; Hanging; Mortality; Trends; Joinpoint analysis

Core Tip: Although scarce, previous research showed disparities in mortality trends of suicide by hanging across the world. The mortality trends of suicide by hanging decreased significantly in Serbia in the last three decades in both sexes together, but it was more pronounced in women than in men. In 2020, the age-standardized rate of mortality by hanging was 4.5 *per* 100000 persons in both sexes together (7.6 in males *vs* 1.7 in females), the male-to-female ratio was almost 5. Further research will allow a clarification of trends and help in a more effective suicide prevention.

Citation: Ilic M, Ilic I. Trends in suicide by hanging, strangulation, and suffocation in Serbia, 1991-2020: A joinpoint regression and age-period-cohort analysis. *World J Psychiatry* 2022; 12(3): 505-520
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/505.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.505

INTRODUCTION

Suicide is a complex global public health issue[1-3]. According to the World Health Organization (WHO) 2000-2019 estimates, almost 800000 people die every year due to suicide across the world[4]. Previous research revealed that hanging was the predominant method of suicide in both sexes in most countries in the last decades[5,6]. Spicer and Miller[7] indicated that hanging, following firearms and drowning, was the most lethal method of suicide, while poisoning and cutting were the least lethal methods.

According to a systematic review and meta-analysis, the most common method of suicide in the Eastern Mediterranean Region of WHO was hanging (with a share of 39.7%, 95%CI: 26.8–52.7)[8]. Also, in almost all countries in Eastern Europe[4] and South Asia[9] hanging was the preferred method of suicide. During a 10-year period from 2004 to 2013 in India, poisoning as a method of suicide has declined in both genders aged 15-29 years, while hanging became the preferred method[10]. Based on the WHO mortality database, between 2000 and 2015 among 58 countries the age-standardized mortality rates of suicide by hanging among persons aged 15-64 were the highest both in males and females in Lithuania, while the highest rates among persons aged 65 years and older were both in males and females in Serbia[5]. The 20-year study (1997-2016) that examined suicides in South Africa, showed that mortality rates due to hanging increased by 3.9% *per* year in males and by 3.0% *per* year in females [11]. Similarly, over a period of 44 years (1969-2012) both sexes in Norway showed an upward trend for suicide by hanging, with a notably significant increase in men aged 15–24 years[12].

Previous studies[13-16] indicated that suicide rates were the highest among males, elderly, single individuals, those with less schooling, family disintegration, unemployment, poverty, living in rural areas, with mental illness (especially alcohol misuse). Some authors indicated that males more frequently use highly lethal methods of suicide, such as hanging or firearms, in comparison to females [17]. In people with substance use disorders in Norway, the most common cause of death in males was hanging, while in females it was poisoning[18]. A study of the effects of Greece's economic crisis during the years 2011 and 2012 recorded the strengthened seasonality of suicides, while a noteworthy suicide risk was revealed for males, persons aged 45 years or more and for suicides by hanging[19].

The 2030 Agenda for Sustainable Development adopted by the United Nations in 2015 includes a target to reduce suicide mortality by one third by 2030, and to promote mental health and wellbeing [20]. The coronavirus disease 2019 (COVID-19) pandemic has drastically changed social and daily life: Lockdown, business restrictions, school closures, social distancing policies in order to prevent the spread of the coronavirus infection, and possible delays in diagnoses of mental and other illnesses led to

increased mental stress globally, but how it is affecting the burden of suicide is not yet clear[21,22]. Nevertheless, there is a scarcity of studies that have explored the trends for mortality of suicide by hanging on global, regional and national levels, as most evaluations are limited to some populations[3,5,6].

Serbia is a country in southeastern Europe where the previous three decades marked its socio-political landscape from the end of the last to the beginning of this century, representing a time-frame of civil wars and global crisis; in addition to 1991-1999 civil wars, the break-up of Yugoslavia, influx of arrivals of more than a million refugees, devastating impact of the United Nations-imposed economic sanctions (1992-1995), a 78-d NATO's bombing in 1999, political changes and transition to democracy in 2000, and global financial crisis in 2008. As the result of dramatic socio-economic changes, the population of Serbia has experienced significant health problems[23,24]. This study aimed to evaluate the direction and magnitude of the national trends in mortality of suicide by hanging in Serbia from 1991 to 2020, with special emphasis on age, period and cohort effects.

MATERIALS AND METHODS

Study design

For this nationwide research, with epidemiological descriptive study design, we used data of annual underlying mortality causes in Serbia to describe mortality trends of suicide by hanging for the period 1991–2020.

Data sources

Official death certification data for suicide by hanging, strangulation and suffocation were obtained from the Statistical Office of the Republic of Serbia (unpublished data).

During the calendar period considered, different revisions of the international classification of diseases (ICD) were used in Serbia: From 1990 to 1996 data about the main cause of death were classified by 9th Revision (ICD-9), and since 1997 the data processing of mortality statistics is based on 10th Revision (ICD-10). Mortality data of suicide by hanging, strangulation and suffocation were covered by site code E953 by ICD-9[25] and code X70 based on ICD-10[26]. In this study, term "suicide by hanging" includes deaths from suicide by hanging, strangulation and suffocation. Besides this, "suicides" include deaths from self-inflicted injury or intentional self-harm, but not those that are of undetermined intent. In Serbia, according to the WHO guidelines, the definition of the underlying cause of death includes a disease or injury that has started a series of diseases or an injury that has triggered a series of disease states that directly led to death.

Death registration and certification of cause of death in Serbia is conducted by an authorized physician in a health care organization, a coroner, or a forensic physician. The procedure is consistent throughout the whole country and comprises several levels of control and verification by another trained medical doctor or specialist. The procedures of death certification and registration in Serbia are coordinated by the Ministry of Health and the Ministry of Internal Affairs. The standard practice with unnatural deaths is that the investigating judge orders an autopsy, including toxicological analyses. All data files are confidential. The completeness of the Serbian mortality database was 98% in 2000[27]. Also, the WHO evaluated national mortality data in Serbia as medium quality, based on criteria such as completeness reporting of > 90% and ill-defined causes and injury deaths with undetermined intent appear on < 10% of registrations[28].

Estimates of the resident population, based on the official censuses (1991, 2002 and 2011 censuses), were obtained from the same Serbian national statistical database. This study comprised the whole population of Serbia (approximately 7 million inhabitants). During the study period, as a consequence of wars in the former Yugoslavia during the 1990s, Serbia had the largest populations (nearly 1000000 persons) of refugees (from the former Socialist Federal Republic of Yugoslavia) and internally displaced persons (from Kosovo & Metohia), and ranked among the top countries in the world by the number of refugees[29]. During the following decades, after the wars in the former Yugoslavia, Serbia remained at the top of the list of European countries in terms of forced migration, as well as one of the five countries in the world facing a prolonged refugee crisis[30]. The last census in 2011 showed there are nearly 300000 forced migrants living in Serbia, equaling 3.9% of the total population. Data for refugees were included in the Serbian population in the present study and could not be set aside as a special contingent.

Statistical analysis

In this study, two types of death rates (expressed *per* 100000 persons) of suicide by hanging in Serbia were calculated: Specific (age- and sex-specific) and age-standardized. The age-standardized rates (ASRs) were calculated by the direct standardization method, using the World standard population[31] as a reference population.

The temporal trends for mortality of suicide by hanging were assessed using the joinpoint regression analysis (Joinpoint regression software, Version 4.5.0.1–June 2017, available through the Surveillance Research Program of the United States National Cancer Institute), proposed by Kim *et al*[32]. Joinpoint regression analysis was used to identify point(s), the so-called "joinpoints", where a significant change (increases or decreases) in the linear slope of the trend occurred, and to estimate annual percent change (APC) based on the trend within each segment[32]. Finally, the average annual percent change (AAPC) over the entire considered period was calculated; for each annual percent estimate, the corresponding 95% confidence interval (95%CI) was determined[33]. Due to difficulties in computing with small numbers (small number of cases reported in youngest age group), we restricted the analysis to the age group 10 years and over. Disparities in suicide mortality trends according to age and sex were tested by using a comparability test[34]. The objective of the comparability test was to designate whether the two regression mean functions were identical (test of coincidence) or parallel (test of parallelism). A P value of < 0.05 was considered statistically significant. In determining the direction of temporal trends, the terms "significant increase" or "significant decrease" were used, in order to signify that the slope of the trend was statistically significant (P < 0.05, on the basis of the statistical significance of the AAPC compared to zero). For non-statistically significant trends (P > 0.05, while AAPC with a 95%CI overlapping with zero), the terms "non-statistically significant increase" (for AAPC > 0.5%), and "non-statistically significant decrease" (for AAPC < -0.5%) were used, while the term "stable" was used for AAPC between -0.5% and 0.5%.

The age-period-cohort analysis was performed to examine the effects of age, period, and birth cohort on the observed temporal trends using the United States NCI web-based statistical tool, according to the method proposed by Rosenberg *et al*[35]. The parameters of the age-period-cohort analysis included longitudinal age curves (indicated the fitted longitudinal age-specific rates in the reference cohort, adjusted for period deviations), the period rate ratios (represent variations in mortality rates over time associated with all age groups simultaneously), the cohort rate ratios (associated with changes in mortality rates across groups of individuals with the same birth years, that is, for successive age groups in successive time periods), and local drifts (represent the annual percentage changes for each age group, generated from log-linear regressions) with net drift (represents the average annual percentage change in mortality *per* year of birth). Due to difficulties in computing due to unstable mortality rates, we omitted < 10 and 80+ age groups from the age-period-cohort analysis. The significance test used was a 1-df Wald test. Values of P less than 0.05 were considered statistically significant.

Ethics statement

This study is approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac (No. 01-14321).

RESULTS

In the period 1991-2020, a total of 24340 (17750 males and 6590 females) deaths of suicide by hanging in Serbia were reported (Table 1). The overall average annual ASR was 7.0 *per* 100000 in both sexes together (ranging from 9.1 *per* 100000 in 1991 to 4.5 *per* 100000 in 2020). The average annual ASR was 11.1 *per* 100000 in men and 3.3 *per* 100000 in women. Suicide by hanging was about 3.7 times more common in males than females in Serbia.

Trend for mortality of suicide by hanging was decreasing significantly in both sexes together by -2.1% yearly (95%CI: -2.4 to -1.8), from 1991 to onwards (Figure 1A and Table 2). Overall mortality of suicide by hanging peaked at 9.2 *per* 100000 in 1993, and declined thereafter to 4.5 *per* 100000 in 2020. Joinpoint regression analysis identified one joinpoint (in 2012), with consequent two trends: Both periods showed significantly decreasing trends, firstly with APC of -1.6% (95%CI: -1.9 to -1.2) and then with APC of -4.1% (95%CI: -5.6 to -2.6).

Suicide death rates by hanging increased with age both in males and females (Tables 2 and 3). In both sexes, suicide mortality rates were almost four times higher in people aged 70 or older than in people under 70. Age-specific suicide mortality rates in males were two times higher than rates in females in people under 70 and almost three times higher in people aged 70 or older. Suicide mortality rates were decreasing significantly in all age groups in both sexes from 1991 to 2020: The only exception was for males in age group 40-49, with an unfavorable trend of suicide mortality by hanging in 1991-2011 period, with APC = +0.3% *per* year (95%CI: -0.9 to +1.4). According to comparability test, mortality trends of suicide by hanging by age were parallel (P > 0.05) both in males and females.

Suicide mortality rates by hanging in males decreased from 14.1 *per* 100000 in 1991 to 7.6 *per* 100000 in the last year observed; AAPC = -1.7%, 95%CI: -2.0 to -1.4 (Figure 1B and Table 3). Joinpoint analyses of suicide mortality by hanging in males identified one joinpoint in the year 2012, with two trends: Both trends were decreasing significantly, with APC of -1.2% (95%CI: -1.6 to -0.9) and -3.7% (95%CI: -5.2 to -2.3). In females, suicide mortality rates by hanging decreased from 5.4 *per* 100000 in 1993 to 1.7 *per* 100000 in the last year observed. Trend of suicide mortality by hanging in females decreased significantly from 1991 to 2020 (AAPC = -3.5%, 95%CI: -3.9 to -3.1). According to the comparability test,

Table 1 Suicide mortality by hanging/strangulation/suffocation in Serbia, 1991-2020; number of cases and age standardized rate *per* 100000 (using World standard population)

Year	All		Males		Females	
	Number	ASR	Number	ASR	Number	ASR
1991	978	9.1	690	14.1	288	4.7
1992	1010	9.1	697	13.7	313	5.0
1993	1033	9.2	690	13.6	343	5.4
1994	948	8.5	679	13.3	269	4.3
1995	830	7.4	588	11.4	242	4.0
1996	909	8.3	638	12.6	271	4.5
1997	907	8.1	649	12.6	258	4.0
1998	857	7.6	594	11.6	263	4.2
1999	947	8.2	661	12.7	286	4.3
2000	919	7.7	646	12.1	273	3.9
2001	860	7.4	605	11.4	255	3.9
2002	876	7.4	644	12.0	232	3.3
2003	807	6.9	600	11.5	207	2.9
2004	836	7.1	623	11.6	213	3.2
2005	856	6.9	609	11.0	247	3.2
2006	881	7.3	640	11.7	241	3.3
2007	841	7.0	609	11.1	232	3.3
2008	804	6.9	572	10.6	232	3.4
2009	836	7.1	630	11.6	206	3.1
2010	745	5.9	562	9.7	183	2.4
2011	818	6.8	603	10.9	215	3.1
2012	807	6.7	616	11.1	191	2.7
2013	734	6.1	562	10.1	172	2.5
2014	720	5.9	558	9.9	162	2.2
2015	646	5.4	501	9.0	145	2.1
2016	603	5.2	451	8.4	152	2.2
2017	614	5.1	481	8.7	133	1.9
2018	586	4.8	466	8.2	120	1.7
2019	586	5.1	453	8.5	133	1.9
2020	546	4.5	433	7.6	113	1.7
Overall	24340	7.0	17750	11.1	6590	3.3

ASR: Age-standardized rate.

trends of suicide mortality by hanging in men and women were not parallel and not coincident ($P < 0.05$).

The risk of death from suicide by hanging increased continuously with age in both sexes together (Figure 2). The net drift was -1.8% (95%CI: -2.3 to -1.3) *per* year, and the curves of local drift values were under 0 in all age groups, with a few non-significant exceptions in the youngest age groups. Period rate ratios were significantly declining over the whole period studied, particularly after 2013. Cohort rate ratios showed significantly downward patterns, but these tendencies slowed down in recent cohorts, particularly for those born in 1951-1980 birth cohorts and after 1996. Results of Wald tests showed that the relative risk for suicide by hanging in Serbia had statistically significant ($P < 0.05$) cohort and period

Table 2 Joinpoint regression analysis[1] of suicide mortality by hanging/strangulation/suffocation in both sexes in Serbia, by age, 1991-2020

Age[2]	Year 1991		Year 2020		Number of joinpoints	AAPC	Lower 95%CI	Upper 95%CI
	No of cases	rates	No of cases	rates				
Age-specific rates[3]								
10-19	9	0.9	4	0.6	0	- 2.7[1]	-4.4	-1.1
20-29	56	5.8	20	2.5	0	- 1.5[1]	-2.4	-0.6
30-39	101	8.4	45	4.7	0	- 1.2[1]	-1.8	-0.6
40-49	133	14.1	69	7.1	0	- 1.5[1]	-2.2	-0.8
50-59	190	17.5	100	10.8	0	- 1.4[1]	-1.8	-1.1
60-69	219	23.7	123	12.4	0	- 2.8[1]	-3.1	-2.4
70-79	161	48.6	107	18.5	0	- 3.5[1]	-4.1	-2.9
80+	109	76.5	78	24.5	0	- 3.4[1]	-3.9	-3.0
Age-standardized rates[3]								
All ages	978	9.1	546	4.5	1	-2.1[1]	-2.4	-1.8

[1]Statistically significant trend.
[2]Joinpoint results are not shown for the subgroups aged < 10 yr, because during the observed period, a total of 2 cases of suicide by hanging/strangulation/suffocation deaths occurred in both sexes.
[3]*Per* 100000 people.
AAPC: Average annual percentage change; CI: Confidence interval.

effects, as well as the net drift and local drifts.

In Serbia in both males and females, the risk of death from suicide by hanging increased by age (Table 4). The period effects have showed a downward pattern since 2013 in males, while continuously decreasing in females. The risk of deaths by hanging decreased, in general, with birth cohort in both sexes in Serbia, with stable cohort effects for men and women born between 1946 and 1966. The local drift values were under zero in all age groups in both genders, while an insignificant value was observed in age groups < 50 in males and < 30 in females (data not shown). The net drift was −1.4% (95%CI: −1.9 to −0.9) in males, and in females it was −3.7% (95%CI: −5.1 to −2.2). The Wald test showed statistically significant period and cohort effects for both genders, as well as net drift, but the local drifts were not statistically significant ($P > 0.05$).

DISCUSSION

This study described mortality trends of suicide by hanging in Serbia over a 30-year period from 1991 to 2020. Male predominance in suicide rates by hanging was showed. Trends of suicide mortality by hanging have been decreasing in both sexes and all age groups, but it was more pronounced in women than in men. Furthermore, this population-based analysis revealed significant period and birth-cohort effects in mortality of suicide by hanging.

Unfortunately, national-level data on the suicide by hanging are quite limited[36]. In the WHO mortality database, only about one third of the WHO Member States reported data on methods of suicide, and that was mostly highly developed countries[5,36]. The data on global suicides mortality by hanging are much clearer for high-income countries, which account for 50% of all suicides by hanging in the world. Hanging was a common method of suicide in Europe between 1970 and 2009: Its prevalence in Poland was the highest, comprising 90% of all suicides, with the very high (7:1) male-to-female rate ratio[37], while lower prevalence of suicides by hanging with sex differentials was reported in Estonia [38], Germany[39], Austria[40], and Finland[41]. The earlier study on suicide-related mortality in Serbia indicated that hanging accounted for 61.2% of all suicides in the 1991-2014 period, with a 3:1 male-to-female rate ratio[24]. However, data on mortality rates of suicide by hanging at the national level are still very sparse.

This manuscript indicates an annual ASR of suicide by hanging of 4.5 *per* 100000 population in Serbia in 2020 (7.6 for males and 1.7 for females). In Canada in 2018 an ASR of hanging of 9.6 was recorded in males and 3.0 in females[42]. In Australia, from 1986 to 2005, ASR of hanging was 7.33 in males and 1.47 in females, with increasing trends[43]. In India in 2014, ASR of suicide by hanging was 6.1 among males and 2.6 among females[44]. Based on the WHO mortality database, among 58 countries in 2015, ASR of

Table 3 Joinpoint analysis: Trends[1] in age-specific suicide mortality rates (*per* 100000) by hanging/strangulation/suffocation in Serbia, by sexes, 1991-2020

Age[2]	Males		Females	
	Period	APC (95%CI)	Period	APC (95%CI)
10-19	1991-2020	-2.8[1] (-4.4 to -1.0)	[3]	
20-29	1991-2020	-1.2[1] (-2.1 to -0.3)	[3]	
30-39	1991-2014	-0.1 (-1.0 to +0.7)	1991-2020	-2.2[1] (-3.3 to -1.1)
	2014-2020	-7.7[1] (-13.5 to -1.5)		
	Full period[4]	-1.1[1] (-1.7 to -0.4)		
40-49	1991-2011	+0.3 (-0.9 to +1.4)	1991-2020	-3.2[1] (-4.4 to -2.1)
	2011-2020	-4.9[1] (-8.5 to -1.1)		
	Full period	-1.0[1] (-1.7 to -0.2)		
50-59	1991-2020	-0.8[1] (-1.3 to -0.4)	1991-2020	-3.2[1] (-4.0 to -2.5)
60-69	1991-2020	-2.3[1] (-2.8 to -1.8)	1991-2008	-2.2[1] (-3.8 to -0.6)
			2008-2020	-7.6[1] (-10.1 to -5.0)
			Full period	-4.3[1] (-5.1 to -3.5)
70-79	1991-2020	-3.1[1] (-3.6 to -2.5)	1991-2020	-4.7[1] (-5.5 to -3.9)
80+	1991-2020	-3.2[1] (-3.7 to -2.7)	1991-2020	-3.8[1] (-4.9 to -2.8)
All ages	1991-2012	-1.2[1] (-1.6 to -0.9)	1991-2020	-3.5[1] (-3.9 to -3.1)
	2012-2020	-3.7[1] (-5.2 to -2.3)		
	Full period	-1.7[1] (-2.0 to -1.4)		

[1]Statistically significant trend.
[2]Joinpoint results are not shown for the subgroups aged < 10 yr, because during the observed period, a total of 1 case of suicide by hanging/strangulation/suffocation deaths occurred in men and 1 case in women.
[3]Incalculable: Joinpoint results are not shown because fewer than 10 cases of suicide by hanging/strangulation/suffocation occurred in each of the decennium in any year.
[4]For full period presented average annual percent change.
APC: Annual percent change; CI: Confidence interval.

suicide by hanging among persons aged 15-44 was the highest both in males and females in Guyana (73.4 and 24.4, respectively), among persons aged 45-64 it was the highest in males in Lithuania (88.1) and in females in Belgium (18.0), while among persons aged 65 years and older rates were the highest in Republic of Korea (106.0 and 32.2, respectively)[5]. Variations in suicide rates can be attributed to many different factors, such as social, economic, personal factors, mental health[45,46]. Numerous studies confirmed association between unemployment rates and suicide rates by hanging[47]. In many countries (like Lithuania and other Eastern European countries, Brazil, the United States of America), mortality rates of suicide were linked to alcohol consumption[46,48,49]. The Serbian National health surveys (2000, 2006, 2013, 2019)[50] reported a lower prevalence of risk factors such as alcohol use and substance abuse in population of Serbia compared to most of the neighbouring countries and other countries in Europe[51]. Also, variations in mortality by hanging can be partly interpreted as the effects of availability of lethal methods, suicide prevention efforts, mental health diagnosis and treatment availability[52,53]. In India, more developed states with higher agricultural employment and higher literacy reported higher rates of suicide by hanging[44]. Although it is always a question whether the differences in suicide mortality rates are real or reflect variations in data quality worldwide, suicide by hanging is less likely to be misclassified as unintentional or undetermined death unlike other suicide methods[6].

Study about suicide mortality by hanging in 58 countries reported higher suicide mortality in males compared with females[5]. Similar to other countries, mortality rates of suicide by hanging were considerably higher (3.7:1) in men compared to women in Serbia, which might be because of the differences in alcohol use, substance abuse, mental health, marital status or unemployment between males and females. The 2019 Serbian National Health Survey determined that, in the last 12 months, 1.7% of Serbian population (3.2% of men and 0.3% of women) at least once a week drank risky on a single occasion of drinking (equivalent to 60 g of pure ethanol or more)[50]. Every month, 18.3% of men and

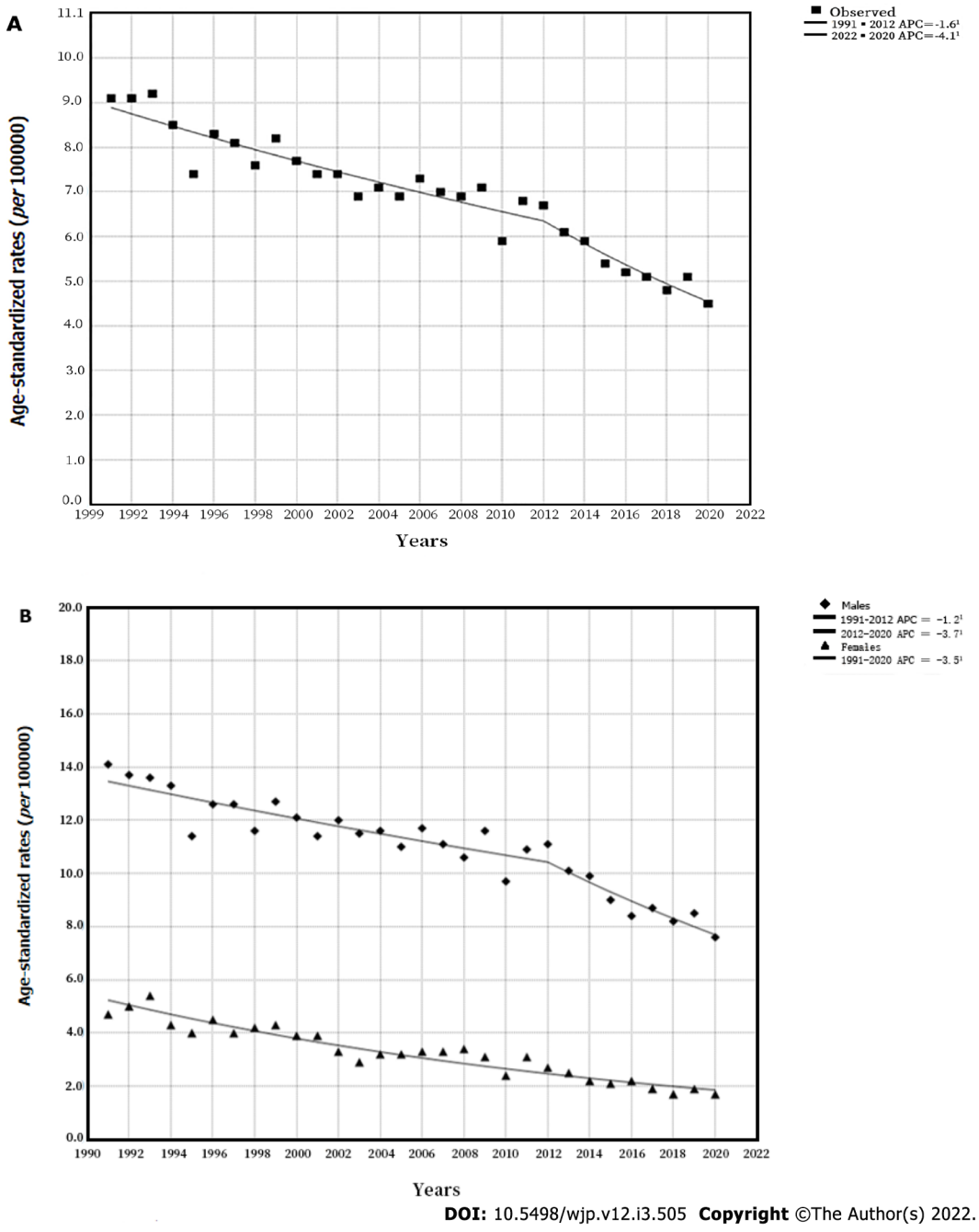
Table 4 Age, period, and cohort effects on suicide mortality by hanging/strangulation/suffocation in Serbia, by sexes, 1991-2020

Group		Males		Females	
		Effect	95%CI	Effect	95%CI
Age	10-14	1.7	0.9–3.1	0.8	0.2–3.1
	15-19	4.4	3.0–6.4	1.6	0.7–3.6
	20-24	8.4	6.3–11.3	2.9	1.6–5.2
	25-29	9.3	7.1–12.1	3.1	1.8–5.2
	30-34	10.8	8.7–13.5	3.7	2.5–5.5
	35-39	12.7	10.5–15.4	4.2	2.9–5.9
	40-44	15.3	12.9–18.2	4.2	3.1–5.9
	45-49	17.4	14.8–20.5	5.1	3.7–6.9
	50-54	21.1	17.1–23.7	5.2	3.8–7.1
	55-59	21.5	17.3–24.3	5.2	3.7–7.1
	60-64	21.4	17.7–25.8	5.2	3.7–7.3
	65-69	21.2	17.3–25.9	5.3	3.7–7.6
	70-74	25.1	20.3–31.0	5.5	3.8–8.0
	75-79	30.8	24.5–38.5	5.7	3.9–8.4
Period	1991-1995	1.1	0.9–1.2	1.3	1.1–1.7
	1996-2000	1.0	0.9–1.2	1.2	1.0–1.5
	2001-2005	1.0	1.0–1.0	1.0	1.0–1.0
	2006-2010	1.0	0.9–1.1	0.9	0.7–1.1
	2011-2015	0.9	0.8–1.0	0.7	0.5–0.9
	2016-2020	0.7	0.6–0.8	0.5	0.4–0.7
Cohort	1916–1920	2.9	2.0–4.3	6.4	3.6–11.3
	1921–1925	2.2	1.7–2.9	4.5	2.9–7.0
	1926–1930	1.9	1.5–2.4	3.3	2.2–4.9
	1931–1935	1.7	1.4–2.1	2.7	1.9–3.9
	1936–1940	1.4	1.2–1.7	2.3	1.6–3.3
	1941–1945	1.2	1.0–1.5	1.9	1.3–2.6
	1946–1950	1.1	0.9–1.3	1.4	1.0–2.0
	1951–1955	1.1	0.9–1.3	1.1	0.8–1.5
	1956–1960	1.1	0.9–1.3	1.1	0.8–1.6
	1961–1965	1.0	1.0–1.0	1.0	1.0–1.0
	1966–1970	0.9	0.8–1.1	0.8	0.5–1.2
	1971–1975	0.9	0.8–1.2	0.6	0.4–0.9
	1976–1980	0.9	0.7–1.1	0.7	0.4–1.1
	1981–1985	0.9	0.7–1.2	0.6	0.4–1.0
	1986–1990	0.8	0.6–1.1	0.4	0.2–0.8
	1991–1995	0.7	0.4–1.0	0.5	0.2–1.1
	1996–2000	0.7	0.4–1.1	0.2	0.1–1.0
	2001–2005	0.6	0.3–1.5	0.1	0.0–4.7
	2006–2010	0.4	0.0–2.9	0.1	0.0–49.4

Wald Chi-square tests for estimable functions, *P* value

Net drift	< 0.000	< 0.000
All period rate ratios	< 0.000	< 0.000
All cohort rate ratios	< 0.000	< 0.000
All local drifts	0.092	0.897

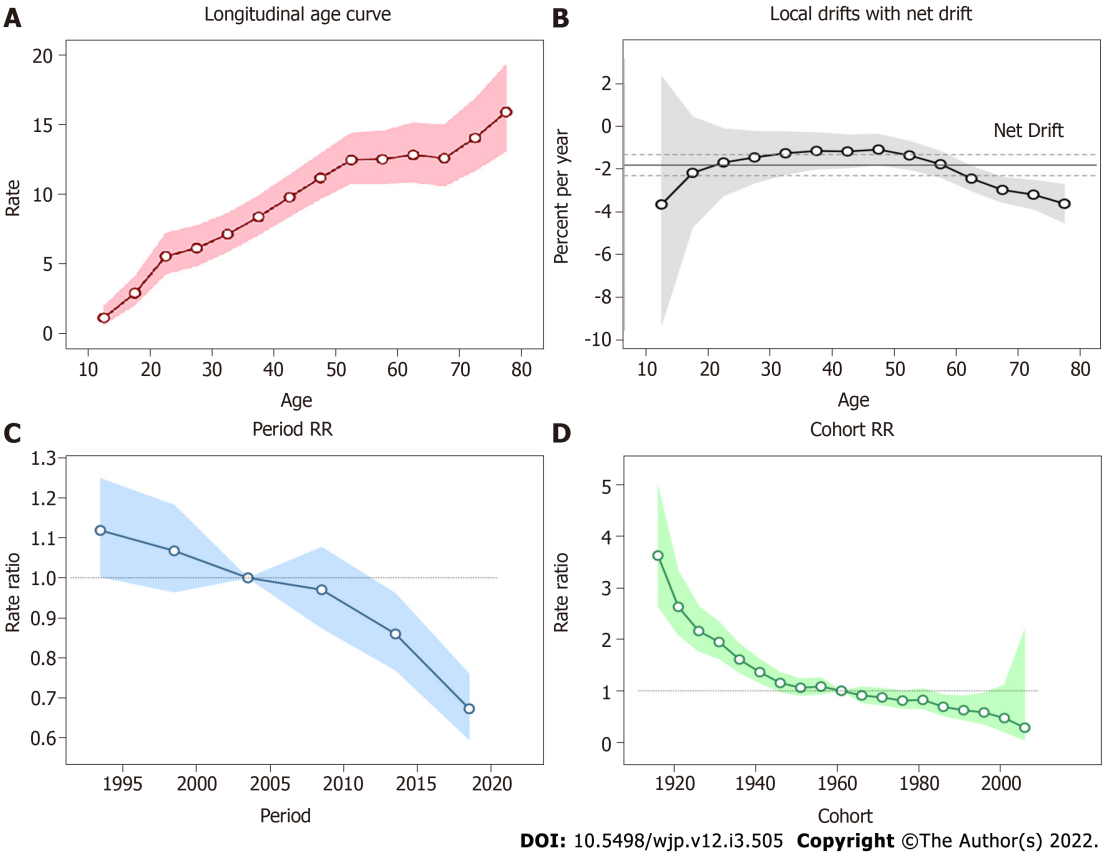
CI: Confidence interval.



DOI: 10.5498/wjp.v12.i3.505

Figure 1 Trend in suicide mortality by hanging/strangulation/suffocation in Serbia, 1991-2020. A: Joinpoint regression analysis; all: 1 Joinpoint; final selected model: 1 Joinpoint; B: By sex, 1991-2020; joinpoint analysis; Males: 1 Joinpoint *vs* Females: 0 Joinpoints. Final selected model: Males-1 Joinpoint, Females-0 Joinpoints. Rejected parallelism. [1]Indicates that the APC is significantly different from zero at the alpha = 0.05 level. APC: Average percentage change.

4.5% of women drank risky on a single occasion, which is a lower percentage than the European Union average[50,51]. By contrast, Serbian female population reported significantly more often the use of sedatives, sleep aids and painkillers (24.5%, 14.6%, and 44.8%, respectively) than males (11.3%, 10.4%, and 36.1%, respectively). Similar to the population in Europe, symptoms of depression were observed



DOI: 10.5498/wjp.v12.i3.505

Figure 2 Legend: Suicide mortality by hanging/strangulation/suffocation in Serbia, by sexes, 1991-2020: An age-period-cohort analysis. A: Longitudinal age curve of suicide by hanging mortality rates (*per* 100000 people) and 95% confidence intervals (the area colored in pink); B: Local drift value: age group-specific annual percent change (%) and 95% confidence intervals (the area colored in grey); C: Period effects for the suicide by hanging mortality rates and 95% confidence intervals (the area colored in blue); D: Cohort effects for the suicide by hanging mortality rates and 95% confidence intervals (the area colored in green). RR: Rate ratio.

more often in females (2.8%) than in males (1.5%) in Serbia in 2019. Similar to almost all countries in Eastern and Central Europe, poor social support was recorded in 15.4% of the population in Serbia, most often among residents with lower level of education, lower household income, who live in suburban settlements and the elderly[50,51].

In Serbia, mortality pattern of suicide by hanging was characterized by an initial decrease (by -1.6% *per* year) and followed by a sharp decline (by -4.1% *per* year) since 2012 (less pronounced declines observed in eldest men than in women during the study, although trends in males were parallel with trend in overall). In 2020 in Serbia, irrespective of more accelerated decreasing mortality trends of suicide by hanging in males in comparison to females in the recent decade, male-to-female rate ratio was almost 5:1, in relation to the beginning of the observed period when it was 3:1. Apart from Serbia, in both sexes together in those aged 15–65 years and above, decreasing rates of suicide by hanging have also been observed in Finland, Hungary and Switzerland from 2000 to 2015[5]. By contrast, significantly increasing death rates of suicide by hanging have been observed in some countries; for instance, in Canada by +1.1% *per* year from 1981 to 2018 for both sexes together[42], among Australians aged 10–24 years between 2004 and 2014[54], in the United States of America by +52% for all ages combined from 2000 to 2010[52], in Mexico by +11.89% from 2003 to 2012[55], in England and Wales over three decades [45], in South Korea[5,56]. Both sexes experienced an upward trend for suicide by hanging from 1969 to 2012 in Norway (by +1.5% *per* year in males and by +2.7% in females), with a particularly significant increase in 15–24 year old males[12]. The observed suicide mortality increase between 2000 and 2015 (*e.g.*, the Republic of Korea and the United States of America) could be explained by various factors, including financial crisis, increased unemployment and easy access to highly lethal methods such as hanging[5,45]. Also, the observed increase in suicide by hanging could possibly be explained by substitution with other methods, primarily of suicide by firearms or by poisoning, thanks to stricter gun control, control of pesticide use, prescription of drugs, *etc.*[57-60]. Significant differences in suicide mortality by sexes could be explained by different prevalence of the main risk factors (such as mental disorders, alcohol and drug abuse)[5]. Gender differences regarding suicidal behavior, also known as the "gender paradox of suicidal behavior", include several factors that have a gender-dependent impact on suicidal behavior, such as stressful life events, socio-demographical factors, socio-economical factors, sexual abuse, psychiatric (co)morbidity, attitude towards antidepressant treatment, choice of suicide

methods[17]. The 2019 Serbian National Health Survey recorded depressive symptoms in 2.1% of Serbian population, which is a decrease compared to 2013 (4.1%)[50]. Also, 49.3% of Serbian population consumed alcohol: 3.1% drank every day, which is lower than in 2013 (4.7%) and 2006 (3.4%). Although different revisions of the ICD were used in Serbia, from 1991 to 1996 and from 1997 to 2000, this could not have notably affected some of the trend changes observed during the period observed, both because the changes would be reflected in trends in both sexes and because the incidence of symptoms and insufficiently defined conditions in the structure of general mortality has not changed significantly[61]. Besides this, the implementation of national guidelines for suicide prevention only in some countries might, at least partly, explain the observed differences in suicide mortality rates and trends in the world [62].

Mortality from suicide by hanging in Serbia has been declining since 1991 in all age groups in both genders. The risk of death of suicide by hanging declined continuously in every subsequent birth cohort since 1916. In contrast, the earlier study on suicide-related mortality in Serbia showed non-significant declining mortality trends of suicide by hanging in males aged 20-59 in 1991-2014 period[24]. An increasing excess suicide rate in men was observed in Poland between 1970 and 2009, and the suicide rate peaked at ages 40-54 years[37]. In Canada, between 1981 and 2018, there was an increasing trend in suicide by hanging for both males and females aged 10-64, and a decreasing suicide trend at ages 65+ years[42]. In the United States of America, between 2000 and 2010, trends in suicide by hanging/suffocation increased for ages 15-69, and decreased at ages 70+ years[52]. In Japanese aged 15 or above, in 1990–2011, the trend for suicide by hanging in males increased by +2.4% *per* year, while in females it remained flat[61].

However, Serbia saw a non-significant increase in mortality of suicide by hanging in males aged 40-49 from 1991 to 2011. The possible explanations for this unfavorable trend during this period in males include the devastating effects of civil wars, the economic and political sanctions, the collapse of the economy, the hyperinflation of the national currency, the notable drop in general living standard, the poor quality of health services (shortage of drugs, medical equipment, together with a large number of wounded individuals, decreasing hospitalization rates, particularly for people aged ≥ 60 years), the influx of more than a million refugees and social disintegration all generated circumstances where suicide prevention and management presented a significant challenge in medical practice[63,64]. The autopsy protocols of all 44 suicides committed by war veterans in the capital Belgrade over the 1991-2000 period showed that 27.3% of veterans had posttraumatic stress disorder, 9.1% had major depression and 6.8% had schizophrenia, while most suicides (84.1%) were committed by recruits of the Yugoslav National Army who spent 3-8 mo in the zone of war operations[65]. Contrary, among migrants of the Balkan wars in Sweden during the 1991-2001 Balkan wars, in comparison to other European migrants in Sweden during the same period, the risk of death from somatic diseases and psychiatric disorders, particularly post-traumatic stress disorder, was elevated, while the risk of suicide was reduced[66]. The reason for decreased risk of suicide in migrants from the Balkan wars could possibly be because those people were not having mental health problems, maintained a high drive for survival despite adversity, and also had increased surveillance, such as more frequent health check-ups in Sweden.

But, the decline in the rates of deaths by hanging is not fully explained. Differences in the classification of causes of death and in postmortem examinations exist across countries[67]. Registration of autopsies in Serbia began in 2006, with stable autopsy rate of about 2% of all deaths from 2006 to 2015, so it is unlikely that this affected the coding of mortality from suicide by hanging[51]. Furthermore, some level of underreporting might exist[68,69]. International comparisons are also complicated by methodological differences between studies: *i.e.* some studies considering trends of suicide mortality, but not all, in analysis comprised code ICD-10 X70 together with the undetermined death (particularly codes ICD-10 Y20, Y87.0)[1-3,5,6]. However, the authors consider that the changes in trends of suicide mortality could not be explained by underreporting or misclassification alone[70].

The COVID-19 pandemic has brought other circumstances detrimental to mental health that were not seen during the economic downturns, such as fears of virus infection, social distancing, isolation at home and quarantine. Some authors indicated that quarantine was associated with negative psychological effects, such as symptoms of post-traumatic stress, depression and anxiety, observed in China and Canada during the 2003 outbreak of severe acute respiratory syndrome (SARS)[71,72]. In the context of COVID-19-related consequences, suicide prevention that must include joint measures such as financial provisions and social support programs, as well as timely access to mental healthcare and optimal treatment for mental disorders is urgently needed[73].

The changes in trends in suicide by hanging require attention from health authorities and indicate a need for innovations in approaches to suicide prevention. In order to take the right action, the understanding of the scale of the problem is critical for prevention. Recognizing changes in methods of suicide is important because preventive measures aimed toward this growing problem across certain countries are necessary (*e.g.* improving mental health literacy, less availability of the method, such as in certain hospitalized or incarcerated individuals, correctional facilities *etc.*). Further research is needed in order to allow a much better clarification of suicide trends and help in a more effective prevention of suicide by hanging[45,62].

Strengths and limitations

To the best of our knowledge, this is the first report which quantifies national mortality trends of suicide by hanging in Serbia from the year 1991 through 2020. Another strength is that it covers the whole population of Serbia using mortality data which is evaluated as medium quality based on the WHO criteria[28], with trends analyzed by both joinpoint and age-period-cohort analysis. Thus, the satisfactory reliability and validity of mortality statistics of suicide in Serbia enable international comparison. However, there were several limitations in this study. Of course, the question of data quality always exists due to a possibility of underreporting or misclassification of suicide. Although a longer study period might provide a more accurate assessment of mortality time trends, no data were available for a longer period in Serbia. There are no separate data on mortality among population of refugees and internally displaced persons, which might confound the pattern of suicide mortality in Serbia. Also, age-period-cohort analysis has inherent limitations (such as ecological fallacy or collinearity among age, period, and cohort effects). Besides this, although this study was population-based and could not investigate individual factors that contributed to the changes in trends of suicide mortality, this is a nationwide study that suggests strong period and birth cohort effects as determinants of changes in suicide by hanging in Serbia.

CONCLUSION

The trends in suicide mortality by hanging have been decreasing in Serbia in the last three decades in both sexes, but this was more pronounced in women than in men. Despite the decreasing trends observed in mortality of suicide by hanging, further research is needed for better clarification of trends and help in suicide prevention in the future.

ARTICLE HIGHLIGHTS

Research background

Hanging is one of the most commonly used methods for suicide in both sexes worldwide.

Research motivation

Although scarce, previous research showed disparities in mortality trends of suicide by hanging across the world.

Research objectives

The aim of this manuscript was to assess the trends of suicide mortality by hanging in Serbia, from 1991 to 2020.

Research methods

This population-based study was based on official data. The age-standardized rates (ASRs, expressed *per* 100000 persons) were calculated by direct standardization, using the World Standard Population. Mortality trends from suicide by hanging were assessed using the joinpoint regression analysis: The average annual percent change (AAPC) with the corresponding 95% confidence interval (95%CI) was calculated. In order to address the possible underlying reasons for observed suicide trends, an age-period-cohort analysis was performed.

Research results

Over the 30-year period studied, there were 24340 deaths by hanging (17750 males and 6590 females) in Serbia. In 2020, the ASR of deaths by hanging was 4.5 *per* 100000 persons in both sexes together (7.6 in males *vs* 1.7 in females). The trends of suicide mortality by hanging decreased significantly between 1991 and 2020 in both males (AAPC = -1.7% *per* year; 95%CI: -2.0 to -1.4) and females (AAPC = -3.5% *per* year; 95%CI: -3.9 to -3.1). The suicide by hanging rate was found to increase with increasing age in both sexes. Mortality rates of suicide by hanging had a continuously decreasing tendency in both sexes together in all age groups: The only exception was among males in 40-49 age group, with an increasing trend of suicide by hanging from 1991 to 2011 (by +0.3% *per* year).

Research conclusions

The trends in suicide mortality by hanging have been decreasing in Serbia in the last three decades in both sexes, but this was more pronounced in women than in men.

Research perspectives

Further research will allow a clarification of trends and help in a more effective suicide prevention.

FOOTNOTES

Author contributions: All authors equally contributed to this paper with conception and design of the study, data acquisition and analysis, drafting and critical revision and editing, and approval of the final version.

Supported by Ministry of Education, Science and Technological Development, Republic of Serbia, 2011–2020, No. 175042.

Institutional review board statement: This study is approved by the Ethics Committee of the Faculty of Medical Sciences, University of Kragujevac, No. 01-14321.

Informed consent statement: The data used for inputs and analysis were retrieved from the official database. Official data for deaths of suicide by hanging, strangulation and suffocation were obtained from the national statistical office (unpublished data). The data are fully aggregated, without any identification data. No patient approvals were sought nor required for this study. Our research question for estimating the trends of suicide mortality was based on the number of suicide mortality figures in Serbia from 1991 to 2020. However, as our model-based analysis used aggregated data, patients were not involved in the design, or conduct or reporting or dissemination plans of the research.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement–checklist of items, and the manuscript was prepared and revised according to the STROBE Statement–checklist of items.

Country/Territory of origin: Serbia

ORCID number: Milena Ilic 0000-0003-3229-4990; Irena Ilic 0000-0001-5347-3264.

S-Editor: Fan JR
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **World Health Organization**. Suicide worldwide in 2019: Global Health Estimates. Geneva, Switzerland: World Health Organization, 2021. [cited 02 July 2021]. Available from: https://www.who.int/publications/i/item/9789240026643
2 **Fazel S**, Runeson B. Suicide. *N Engl J Med* 2020; **382**: 266-274 [PMID: 31940700 DOI: 10.1056/NEJMra1902944]
3 **Naghavi M**; Global Burden of Disease Self-Harm Collaborators. Global, regional, and national burden of suicide mortality 1990 to 2016: systematic analysis for the Global Burden of Disease Study 2016. *BMJ* 2019; **364**: l94 [PMID: 31339847 DOI: 10.1136/bmj.l94]
4 **World Health Organization**. Mental Health and Substance Use. Suicide data. [cited 02 July 2021]. Available from: https://www.who.int/teams/mental-health-and-substance-use/suicide-data
5 **Wu Y**, Schwebel DC, Huang Y, Ning P, Cheng P, Hu G. Sex-specific and age-specific suicide mortality by method in 58 countries between 2000 and 2015. *Inj Prev* 2021; **27**: 61-70 [PMID: 32152194 DOI: 10.1136/injuryprev-2019-043601]
6 **Ajdacic-Gross V**, Weiss MG, Ring M, Hepp U, Bopp M, Gutzwiller F, Rössler W. Methods of suicide: international suicide patterns derived from the WHO mortality database. *Bull World Health Organ* 2008; **86**: 726-732 [PMID: 18797649 DOI: 10.2471/blt.07.043489]
7 **Spicer RS**, Miller TR. Suicide acts in 8 states: incidence and case fatality rates by demographics and method. *Am J Public Health* 2000; **90**: 1885-1891 [PMID: 11111261 DOI: 10.2105/ajph.90.12.1885]
8 **Morovatdar N**, Moradi-Lakeh M, Malakouti SK, Nojomi M. Most common methods of suicide in Eastern Mediterranean Region of WHO: a systematic review and meta-analysis. *Arch Suicide Res* 2013; **17**: 335-344 [PMID: 24224668 DOI: 10.1080/13811118.2013.801811]
9 **Arafat SMY**, Ali SA, Menon V, Hussain F, Ansari DS, Baminiwatta A, Saleem T, Singh R, Varadharajan N, Biyyala D,

Kar SK, Khan MM. Suicide methods in South Asia over two decades (2001-2020). *Int J Soc Psychiatry* 2021; **67**: 920-934 [PMID: 34027683 DOI: 10.1177/00207640211015700]
10 **Aggarwal S**. Suicide in India. *Br Med Bull* 2015; **114**: 127-134 [PMID: 25958380 DOI: 10.1093/bmb/ldv018]
11 **Kootbodien T**, Naicker N, Wilson KS, Ramesar R, London L. Trends in Suicide Mortality in South Africa, 1997 to 2016. *Int J Environ Res Public Health* 2020; **17** [PMID: 32178393 DOI: 10.3390/ijerph17061850]
12 **Puzo Q**, Qin P, Mehlum L. Long-term trends of suicide by choice of method in Norway: a joinpoint regression analysis of data from 1969 to 2012. *BMC Public Health* 2016; **16**: 255 [PMID: 26968155 DOI: 10.1186/s12889-016-2919-y]
13 **de Souza RSB**, de Oliveira JC, Alvares-Teodoro J, Teodoro MLM. [Suicide and indigenous populations in Brazil: systematic reviewEl suicidio y los pueblos indígenas brasileños: revisión sistemática]. *Rev Panam Salud Publica* 2020; **44**: e58 [PMID: 32612644 DOI: 10.26633/RPSP.2020.58]
14 **Li M**, Katikireddi SV. Urban-rural inequalities in suicide among elderly people in China: a systematic review and meta-analysis. *Int J Equity Health* 2019; **18**: 2 [PMID: 30606191 DOI: 10.1186/s12939-018-0881-2]
15 **Bitta MA**, Bakolis I, Kariuki SM, Nyutu G, Mochama G, Thornicroft G, Newton CRJC. Suicide in a rural area of coastal Kenya. *BMC Psychiatry* 2018; **18**: 267 [PMID: 30157796 DOI: 10.1186/s12888-018-1855-z]
16 **Roškar S**, Sedlar N, Furman L, Roškar M, Podlesek A. Association of Selected Area-Level Indicators With Suicide Mortality in Slovenian Municipalities. *Crisis* 2021; **42**: 441-447 [PMID: 33275051 DOI: 10.1027/0227-5910/a000742]
17 **Schrijvers DL**, Bollen J, Sabbe BG. The gender paradox in suicidal behavior and its impact on the suicidal process. *J Affect Disord* 2012; **138**: 19-26 [PMID: 21529962 DOI: 10.1016/j.jad.2011.03.050]
18 **Myhre MØ**, Kildahl AT, Walby FA. Suicide after contact with substance misuse services: a national registry study. *BJPsych Open* 2020; **6**: e45 [PMID: 32375917 DOI: 10.1192/bjo.2020.23]
19 **Christodoulou C**, Efstathiou V, Michopoulos I, Gkerekou M, Paraschakis A, Koutsaftis F, Douzenis A. The Economic Crisis in Greece and Its Impact on the Seasonality of Suicides in the Athens Greater Area. *Psychiatry Investig* 2017; **14**: 16-20 [PMID: 28096870 DOI: 10.4306/pi.2017.14.1.16]
20 **UN General Assembly**. Transforming our world: the 2030 Agenda for Sustainable Development, 21 October 2015, A/RES/70/1. [cited 02 July 2021]. Available from: http://www.refworld.org/docid/57b6e3e44.html
21 **Banerjee D**, Kosagisharaf JR, Sathyanarayana Rao TS. 'The dual pandemic' of suicide and COVID-19: A biopsychosocial narrative of risks and prevention. *Psychiatry Res* 2021; **295**: 113577 [PMID: 33229123 DOI: 10.1016/j.psychres.2020.113577]
22 **Ueda M**, Nordström R, Matsubayashi T. Suicide and mental health during the COVID-19 pandemic in Japan. *J Public Health (Oxf)* 2021 [PMID: 33855451 DOI: 10.1093/pubmed/fdab113]
23 **Ilic M**, Ilic I. Gender disparities in mortality from infectious diseases in Serbia, 1991-2014: a time of civil wars and global crisis. *Epidemiol Infect* 2016; **144**: 2473-2484 [PMID: 27483375 DOI: 10.1017/S0950268816001345]
24 **Ilic M**, Ilic I. Malignant lymphatic and hematopoietic neoplasms mortality in Serbia, 1991-2010: a joinpoint regression analysis. *PLoS One* 2014; **9**: e109379 [PMID: 25333862 DOI: 10.1371/journal.pone.0109379]
25 **World Health Organisation**. International classification of diseases, ninth revision (ICD-9). Geneva, Switzerland: World Health Organization, 1977. [cited 02 July 2021]. Available from: http://europepmc.org/article/MED/629506
26 **World Health Organisation**. International statistical classification of diseases and related health problems, tenth revision (ICD-10). Geneva, Switzerland: World Health Organization, 1992. [cited 02 July 2021]. Available from: https://apps.who.int/iris/handle/10665/246208
27 **Atanackovic-Markovic Z**, Bjegovic V, Jankovic S, Kocev N, Laaser U, Marinkovic J, Markovic-Denic Lj, Pejin-Stokic LJ, Penev G, Stanisavljevic D, Santric Milicevic M, Saulic A, Sipetic-Grujicic S, Terzic-Supic Z, Vlajinac H. The Burden of Disease and Injuries in Serbia. Belgrade, Serbia: Ministry of Health of the Republic of Serbia, 2003
28 **Mathers CD**, Fat DM, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from: an assessment of the global status of cause of death data. *Bull World Health Organ* 2005; **83**: 171-177 [PMID: 15798840]
29 **Vujadinović S**, Šabić D, Stojković S, and Milinčić M. Years of refugee life in serbia – challenges for a new beginning: stay or return home? *Trames* 2011; **3**: 235-258 [DOI: 10.3176/TR.2011.3.02]
30 **Government of the Republic of Serbia**. Refugees in Serbia. [cited 2 July 2021]. Available from: http://www.srbija.gov.rs/vesti/vest.php?id=64403
31 **Jensen OM**, Parkin DM, Lennan R, Muir CS, Skeet RG. Cancer registration. Principles and Methods. Lyon, France: International Agency for Research on Cancer, 1991
32 **Kim HJ**, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med* 2000; **19**: 335-351 [PMID: 10649300 DOI: 10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z]
33 **Clegg LX**, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. *Stat Med* 2009; **28**: 3670-3682 [PMID: 19856324 DOI: 10.1002/sim.3733]
34 **Kim HJ**, Fay MP, Yu B, Barrett MJ, Feuer EJ. Comparability of segmented line regression models. *Biometrics* 2004; **60**: 1005-1014 [PMID: 15606421 DOI: 10.1111/j.0006-341X.2004.00256.x]
35 **Rosenberg PS**, Check DP, Anderson WF. A web tool for age-period-cohort analysis of cancer incidence and mortality rates. *Cancer Epidemiol Biomarkers Prev* 2014; **23**: 2296-2302 [PMID: 25146089 DOI: 10.1158/1055-9965.EPI-14-0300]
36 **Fleischmann A**, Arensman E, Berman A, Carli V, De Leo D, Hadlaczky G, Howlader S, Vijayakumar L, Wasserman D, Saxena S. Overview evidence on interventions for population suicide with an eye to identifying best-supported strategies for LMICs. *Glob Ment Health (Camb)* 2016; **3**: e5 [PMID: 28596874 DOI: 10.1017/gmh.2015.27]
37 **Höfer P**, Rockett IR, Värnik P, Etzersdorfer E, Kapusta ND. Forty years of increasing suicide mortality in Poland: undercounting amidst a hanging epidemic? *BMC Public Health* 2012; **12**: 644 [PMID: 22883342 DOI: 10.1186/1471-2458-12-644]
38 **Värnik A**, Kõlves K, van der Feltz-Cornelis CM, Marusic A, Oskarsson H, Palmer A, Reisch T, Scheerder G, Arensman E, Aromaa E, Giupponi G, Gusmão R, Maxwell M, Pull C, Szekely A, Sola VP, Hegerl U. Suicide methods in Europe: a gender-specific analysis of countries participating in the "European Alliance Against Depression". *J Epidemiol Community Health* 2008; **62**: 545-551 [PMID: 18477754 DOI: 10.1136/jech.2007.065391]

39 **Baumert J**, Erazo N, Ruf E, Ladwig KH. Time trends in suicide mortality vary in choice of methods: an analysis of 145,865 fatal suicide cases in Germany 1991-2002. *Soc Psychiatry Psychiatr Epidemiol* 2008; **43**: 913-919 [PMID: 18560783 DOI: 10.1007/s00127-008-0380-7]

40 **Etzersdorfer E**, Voracek M, Kapusta N, Sonneck G. Epidemiology of suicide in Austria 1990-2000: general decrease, but increased suicide risk for old men. *Wien Klin Wochenschr* 2005; **117**: 31-35 [PMID: 15986588 DOI: 10.1007/s00508-004-0263-1]

41 **Räsänen P**, Hakko H, Jokelainen J, Tiihonen J. Seasonal variation in specific methods of suicide: a national register study of 20,234 Finnish people. *J Affect Disord* 2002; **71**: 51-59 [PMID: 12167501 DOI: 10.1016/s0165-0327(01)00411-6]

42 **Liu L**, Capaldi CA, Orpana HM, Kaplan MS, Tonmyr L. Changes over time in means of suicide in Canada: an analysis of mortality data from 1981 to 2018. *CMAJ* 2021; **193**: E331-E338 [PMID: 33685950 DOI: 10.1503/cmaj.202378]

43 **Qi X**, Hu W, Page A, Tong S. Dynamic pattern of suicide in Australia, 1986-2005: a descriptive-analytic study. *BMJ Open* 2014; **4**: e005311 [PMID: 25079935 DOI: 10.1136/bmjopen-2014-005311]

44 **Arya V**, Page A, Gunnell D, Dandona R, Mannan H, Eddleston M, Armstrong G. Suicide by hanging is a priority for suicide prevention: method specific suicide in India (2001-2014). *J Affect Disord* 2019; **257**: 1-9 [PMID: 31299398 DOI: 10.1016/j.jad.2019.07.005]

45 **Gunnell D**, Bennewith O, Hawton K, Simkin S, Kapur N. The epidemiology and prevention of suicide by hanging: a systematic review. *Int J Epidemiol* 2005; **34**: 433-442 [PMID: 15659471 DOI: 10.1093/ije/dyh398]

46 **Kõlves K**, Milner A, Värnik P. Suicide rates and socioeconomic factors in Eastern European countries after the collapse of the Soviet Union: trends between 1990 and 2008. *Sociol Health Illn* 2013; **35**: 956-970 [PMID: 23398609 DOI: 10.1111/1467-9566.12011]

47 **Milner A**, Page A, LaMontagne AD. Long-term unemployment and suicide: a systematic review and meta-analysis. *PLoS One* 2013; **8**: e51333 [PMID: 23341881 DOI: 10.1371/journal.pone.0051333]

48 **Zerbini T**, Ponce Jde C, Mayumi Sinagawa D, Barbosa Cintra R, Muñoz DR, Leyton V. Blood alcohol levels in suicide by hanging cases in the state of Sao Paulo, Brazil. *J Forensic Leg Med* 2012; **19**: 294-296 [PMID: 22687772 DOI: 10.1016/j.jflm.2012.02.022]

49 **Conner KR**, Huguet N, Caetano R, Giesbrecht N, McFarland BH, Nolte KB, Kaplan MS. Acute use of alcohol and methods of suicide in a US national sample. *Am J Public Health* 2014; **104**: 171-178 [PMID: 23678938 DOI: 10.2105/AJPH.2013.301352]

50 **Ministry of Health**, Republic of Serbia. National Health Survey, Serbia 2021. Belgrade, Serbia: Ministry of Health, Republic of Serbia, 2021.

51 **Harbers MM**, Verschuuren M, de Bruin A. Implementing the European Core Health Indicators (ECHI) in the Netherlands: an overview of data availability. *Arch Public Health* 2015; **73**: 9 [PMID: 25741441 DOI: 10.1186/s13690-014-0058-4]

52 **Baker SP**, Hu G, Wilcox HC, Baker TD. Increase in suicide by hanging/suffocation in the U.S., 2000-2010. *Am J Prev Med* 2013; **44**: 146-149 [PMID: 23332330 DOI: 10.1016/j.amepre.2012.10.010]

53 **Cuchara B**, Diaz FJ. An 8-Year Retrospective Study on Suicides in Washington, DC. *Am J Forensic Med Pathol* 2020; **41**: 18-26 [PMID: 32000223 DOI: 10.1097/PAF.0000000000000536]

54 **Stefanac N**, Hetrick S, Hulbert C, Spittal MJ, Witt K, Robinson J. Are young female suicides increasing? *BMC Public Health* 2019; **19**: 1389 [PMID: 31660926 DOI: 10.1186/s12889-019-7742-9]

55 **Hernández-Alvarado MM**, González-Castro TB, Tovilla-Zárate CA, Fresán A, Juárez-Rojop IE, López-Narváez ML, Villar-Soto M, Genis-Mendoza A. Increase in Suicide Rates by Hanging in the Population of Tabasco, Mexico between 2003 and 2012. *Int J Environ Res Public Health* 2016; **13** [PMID: 27258292 DOI: 10.3390/ijerph13060552]

56 **Park S**, Ahn MH, Lee A, Hong JP. Associations between changes in the pattern of suicide methods and rates in Korea, the US, and Finland. *Int J Ment Health Syst* 2014; **8**: 22 [PMID: 24949083 DOI: 10.1186/1752-4458-8-22]

57 **Reisch T**, Hartmann C, Hemmer A, Bartsch C. Suicide by hanging: Results from a national survey in Switzerland and its implications for suicide prevention. *PLoS One* 2019; **14**: e0220508 [PMID: 31532773 DOI: 10.1371/journal.pone.0220508]

58 **Marzano L**, Katsampa D, Mackenzie JM, Kruger I, El-Gharbawi N, Ffolkes-St-Helene D, Mohiddin H, Fields B. Patterns and motivations for method choices in suicidal thoughts and behaviour: qualitative content analysis of a large online survey. *BJPsych Open* 2021; **7**: e60 [PMID: 33622447 DOI: 10.1192/bjo.2021.15]

59 **Ibrahim S**, Hunt IM, Rahman MS, Shaw J, Appleby L, Kapur N. Recession, recovery and suicide in mental health patients in England: time trend analysis. *Br J Psychiatry* 2019; 1-7 [PMID: 31190654 DOI: 10.1192/bjp.2019.119]

60 **Martínez-Rives NL**, Dhungel B, Martin P, Gilmour S. Method-Specific Suicide Mortality Trends in Australian Men from 1978 to 2017. *Int J Environ Res Public Health* 2021; **18** [PMID: 33923084 DOI: 10.3390/ijerph18094557]

61 **Yoshioka E**, Hanley SJ, Kawanishi Y, Saijo Y. Time trends in method-specific suicide rates in Japan, 1990-2011. *Epidemiol Psychiatr Sci* 2016; **25**: 58-68 [PMID: 25373686 DOI: 10.1017/S2045796014000675]

62 **World Health Organization**. Live life: an implementation guide for suicide prevention in countries. Geneva, Switzerland: World Health Organization, 2021

63 **Statistical Office of the Republic of Serbia**. Demographic Yearbook in the Republic of Serbia, 1991–2014. Belgrade, Serbia: Statistical Office of the Republic of Serbia, 2015

64 **Kunitz SJ**. The making and breaking of Yugoslavia and its impact on health. *Am J Public Health* 2004; **94**: 1894-1904 [PMID: 15514224 DOI: 10.2105/ajph.94.11.1894]

65 **Mihailović Z**, Savić S, Damjanjuk I, Jovanović A, Vuković S. Suicides among Serbian War Veterans - An Autopsy Study. *Srp Arh Celok Lek* 2015; **143**: 590-594 [PMID: 26727868 DOI: 10.2298/sarh1510590m]

66 **Thordardottir EB**, Yin L, Hauksdottir A, Mittendorfer-Rutz E, Hollander AC, Hultman CM, Lichtenstein P, Ye W, Arnberg FK, Fang F, Holmes EA, Valdimarsdottir UA. Mortality and major disease risk among migrants of the 1991-2001 Balkan wars to Sweden: A register-based cohort study. *PLoS Med* 2020; **17**: e1003392 [PMID: 33259494 DOI: 10.1371/journal.pmed.1003392]

67 **Tøllefsen IM**, Hem E, Ekeberg Ø, Zahl PH, Helweg-Larsen K. Differing Procedures for Recording Mortality Statistics in Scandinavia. *Crisis* 2017; **38**: 123-130 [PMID: 27661262 DOI: 10.1027/0227-5910/a000425]

68 **Pritchard C**, Iqbal W, Dray R. Undetermined and accidental mortality rates as possible sources of underreported suicides:

population-based study comparing Islamic countries and traditionally religious Western countries. *BJPsych Open* 2020; **6**: e56 [PMID: 32482190 DOI: 10.1192/bjo.2020.38]

69 **Snowdon J**, Choi NG. Undercounting of suicides: Where suicide data lie hidden. *Glob Public Health* 2020; **15**: 1894-1901 [PMID: 32744898 DOI: 10.1080/17441692.2020.1801789]

70 **Chishti P**, Stone DH, Corcoran P, Williamson E, Petridou E; EUROSAVE Working Group. Suicide mortality in the European Union. *Eur J Public Health* 2003; **13**: 108-114 [PMID: 12803408 DOI: 10.1093/eurpub/13.2.108]

71 **Brooks SK**, Webster RK, Smith LE, Woodland L, Wessely S, Greenberg N, Rubin GJ. The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 2020; **395**: 912-920 [PMID: 32112714 DOI: 10.1016/S0140-6736(20)30460-8]

72 **Zortea TC**, Brenna CTA, Joyce M, McClelland H, Tippett M, Tran MM, Arensman E, Corcoran P, Hatcher S, Heise MJ, Links P, O'Connor RC, Edgar NE, Cha Y, Guaiana G, Williamson E, Sinyor M, Platt S. The Impact of Infectious Disease-Related Public Health Emergencies on Suicide, Suicidal Behavior, and Suicidal Thoughts. *Crisis* 2021; **42**: 474-487 [PMID: 33063542 DOI: 10.1027/0227-5910/a000753]

73 **McIntyre RS**, Lee Y. Projected increases in suicide in Canada as a consequence of COVID-19. *Psychiatry Res* 2020; **290**: 113104 [PMID: 32460184 DOI: 10.1016/j.psychres.2020.113104]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 521-532

DOI: 10.5498/wjp.v12.i3.521

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Prospective Study

Trajectories of response in schizophrenia-spectrum disorders: A one-year prospective cohort study of antipsychotic effectiveness

Petros Drosos, Erik Johnsen, Christoffer Andreas Bartz-Johannessen, Tor Ketil Larsen, Solveig Klæbo Reitan, Maria Rettenbacher, Rune Andreas Kroken

Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Ma H, Yelamanchi R

Received: September 22, 2021
Peer-review started: September 22, 2021
First decision: November 8, 2021
Revised: December 14, 2021
Accepted: January 29, 2022
Article in press: January 29, 2022
Published online: March 19, 2022

Petros Drosos, Tor Ketil Larsen, TIPS-Network for Clinical Research in Psychosis, Clinic For Adult Mental Health, Stavanger University Hospital, Stavanger 4011, Norway

Petros Drosos, Erik Johnsen, Christoffer Andreas Bartz-Johannessen, Rune Andreas Kroken, NORMENT, Division of Psychiatry, Haukeland University Hospital, Bergen 5036, Norway

Petros Drosos, Erik Johnsen, Tor Ketil Larsen, Rune Andreas Kroken, Department of Clinical Medicine, University of Bergen, Bergen 5007, Norway

Solveig Klæbo Reitan, Institute for Mental Health, St Olav's University Hospital, Trondheim 7030, Norway

Solveig Klæbo Reitan, Department of Mental Health, Norwegian University of Natural Science and Technology, Trondheim 7491, Norway

Maria Rettenbacher, Department of Psychiatry and Psychotherapy, Medical University Innsbruck, Innsbruck 6020, Austria

Corresponding author: Petros Drosos, MD, Doctor, Research Fellow, TIPS-Network for Clinical Research in Psychosis, Clinic For Adult Mental Health, Stavanger University Hospital, Jan Johnsens Gate 12, Stavanger 4011, Norway. petros.drosos@sus.no

Abstract

BACKGROUND

Antipsychotic drugs remain the mainstay of schizophrenia treatment; however, their effectiveness has been questioned, and it is not possible to predict the response to a specific antipsychotic drug in an individual patient. Thus, it is important to compare the effectiveness of the various antipsychotics and search for possible response predictors.

AIM

To investigate the effectiveness of antipsychotic drugs, we examined response trajectories and predictors for belonging to different trajectory groups.

METHODS

The Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) trial compared the effectiveness of three atypical antipsychotics-amisulpride, aripiprazole, and

olanzapine-in a prospective, semirandomized, rater-blind, head-to-head design. Adult participants with a schizophrenia spectrum disorder diagnosis, according to international classification of diseases, Tenth Revision (ICD-10) F20–29, were included. Participants were followed for a period of 12 mo, with assessments at baseline; after one, three and six weeks; and after three, six, nine and 12 mo. A latent class mixed model was fitted to our data. The three-trajectory model based on the Positive and Negative Syndrome Scale (PANSS) total score reduction was found to have adequate fit, and the study drugs, as well as various demographic and clinical parameters, were tested as predictors for belonging to the different trajectory groups.

RESULTS

Overall, 144 participants were included, and 41% completed the 12-mo study period. The largest trajectory group, consisting of 74% of participants, showed a PANSS total score reduction of 59% from baseline to 12 mo (Good response group). A trajectory group comprising 13% of participants had their PANSS total score reduced by 82.5% at 12 mo (Strong response group), while the last response trajectory group comprising 13% of the participants had a PANSS total score reduction of 13.6% (Slight response group). The largest part of the total reduction for the Good and Strong response groups occurred at six weeks of treatment, amounting to 45% and 48% reductions from baseline, respectively. The use of amisulpride predicted belonging to the Strong response group, while unemployment, depression, and negative psychotic symptoms at baseline increased the chance of belonging to the Slight response group, indicating a poor response to antipsychotic drug treatment.

CONCLUSION

Most of the participants (87%) had a good outcome after one year. Amisulpride users, more often than aripiprazole and olanzapine users, belonged to the response trajectory group with a strong response.

Key Words: Schizophrenia; Response; Trajectories; Treatment; Antipsychotic drugs

Core Tip: In this clinical trial of the three atypical antipsychotics amisulpride, aripiprazole, and olanzapine, we identified three trajectory groups of responses at the one-year follow-up. The majority of the study participants (87%) followed a trajectory of a good or strong response to antipsychotic drugs, while 13% showed a poor response. The use of amisulpride predicted belonging to the Strong response group. This antipsychotic should therefore be used more often in clinical practice. Unemployment, depression, and negative psychotic symptoms at baseline predicted nonresponse to antipsychotic drugs.

Citation: Drosos P, Johnsen E, Bartz-Johannessen CA, Larsen TK, Reitan SK, Rettenbacher M, Kroken RA. Trajectories of response in schizophrenia-spectrum disorders: A one-year prospective cohort study of antipsychotic effectiveness. *World J Psychiatry* 2022; 12(3): 521-532
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/521.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.521

INTRODUCTION

Antipsychotic drugs remain one of the most effective interventions for patients with schizophrenia-spectrum disorders[1], as recommended by the guidelines for schizophrenia treatment[2,3]. The choice of antipsychotic drug is based on its efficacy and side-effect profile, the patient's personal history of previous response to antipsychotics, and the clinician's experience with different types of antipsychotics [2,4]. Several studies exist on the efficacy of the various antipsychotic drugs in both multiple-episode and first-episode schizophrenia, including pairwise and network meta-analyses, which conclude that antipsychotic drugs are generally more efficacious than placebo[1,5,6]. However, the long-term use of antipsychotic drugs has been criticized because of the associated severe side effects, including brain structural changes[7] and metabolic abnormalities[8]. Moreover, a study showed that nonmedicated patients with schizophrenia performed better after the first three years of illness[9]. Many studies support, however, the effect of antipsychotic drugs on both symptom improvement and social function, as well as on the risk of hospitalization, mortality, and suicidality[10-12]. These results apply both to first-episode and multiple-episode treatment-resistant schizophrenia.

There are various ways to describe the effects of antipsychotic drug treatment on patients with schizophrenia. Important parameters include medication adherence and side effects, symptom improvement, and illness relapse. Clinicians and researchers in the field of schizophrenia frequently use the terms "treatment response", "symptom remission", and "recovery". However, not all of these concepts have been clearly defined, and it is of high importance to agree on their definitions and rating methods to enhance the quality of clinical practice and research in schizophrenia. The first step in the progress of schizophrenia treatment is the response to antipsychotic drugs, which provides an amelioration of mostly positive psychotic symptoms and helps patients maintain stability. The second step is the remission of symptoms, where a prolonged improvement of key schizophrenia symptoms can be seen. The last and most difficult stage to achieve is recovery, where the patient enjoys functional and social autonomy, with no symptoms of schizophrenia or mild symptoms over a long period.

There remains a lack of consensus on the definition of standardized response criteria. Researchers have used different criteria based on the reduction of the Positive and Negative Syndrome Scale (PANSS)[13] total score and the Brief Psychiatric Rating Scale (BPRS)[14] score from baseline[15,16]. Various cutoffs have been used in clinical trials, from at least 20% to 30%, 40%, or 50% of the baseline score. Another issue is the clinical significance of the measured response, and researchers have proposed solving this problem by linking the PANSS and BPRS scores to Clinical Global Impression (CGI) scales[17]. They concluded that it is useful to apply both PANSS and CGI, as they measure different dimensions, and that it is possible to link PANSS scores to CGI scores. For example, the importance of a 20% reduction in PANSS score varies from the perspective of treating refractory patients *vs* acutely ill, nonrefractory patients[18,19]. In a study of response to antipsychotics in drug-naive patients with schizophrenia, 71% responded to second-generation antipsychotics at the one-year follow-up, with a 50% drop in baseline PANSS total score[20]. A shorter duration of untreated psychosis, compliance with medication treatment, and alcohol and other substance use were important predictors influencing response but not remission.

The course of schizophrenia is highly heterogeneous, and it has not yet been possible to predict which patient will respond adequately to which antipsychotic drug. An important aim of current research is to define predictors of medication response. A novel way to examine response is to define trajectories that describe the timeframe of symptom change. Trajectories also provide better information about the course of schizophrenia than dichotomized measures of success or failure of treatment, as the latter does not capture the complexity of treatment response.

Aims of the study

In our study, the Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) study, we compared the efficacy of three antipsychotic drugs-amisulpride, aripiprazole, and olanzapine-after a 12-mo follow-up[21]. The primary aim of this study was to define trajectories for the pooled 12-mo response to treatment with three different antipsychotic drugs. We then wanted to identify possible predictors for belonging to a certain response trajectory in the studied cohort.

MATERIALS AND METHODS

Design and duration

This cohort study included participants in the BeSt InTro study, a 12-mo prospective, randomized, rater-blind, head-to-head comparison of amisulpride, aripiprazole, and olanzapine[21]. Each participant was randomized to a sequence of the examined antipsychotic drugs, for example amisulpride-olanzapine-aripiprazole or aripiprazole-amisulpride-olanzapine. The patient was offered the first drug in the randomized sequence, and this drug was the basis of the intention-to-treat (ITT) analyses. If the first drug could not be used because of previous inefficacy or tolerability issues, the patient was offered the next drug in the randomized sequence. The drug that was actually chosen was the basis of the preprotocol (PP) analyses.

Participants were followed over a period of 12 mo, and the assessment points were at baseline and then after one week, three weeks, six weeks, three months, six months, nine months, and 12 mo. The study medications were administered as oral tablets, and the dosing intervals were 50–1200 mg/d for amisulpride, 5–30 mg/d for aripiprazole, and 2.5–20 mg/d for olanzapine.

The participating study centers were in Bergen, Trondheim, and Stavanger in Norway in collaboration with the Schizophrenia Research Group in Innsbruck, Austria.

Study population

The inclusion criteria were 18 years of age or more and a diagnosis within the schizophrenia spectrum according to International Classification of Diseases, Tenth Revision (ICD-10) diagnoses F20–29. Participants should also have symptoms of ongoing psychosis as determined by a score of four or more on at least one of the following PANSS items: P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness/persecution), or G9 (unusual thought content).

Exclusion criteria were the inability to understand the native language, organic psychosis due to limbic encephalitis, pregnancy or breastfeeding, hypersensitivity to the active substance or any of the excipients of the study drugs, prolactin-dependent tumors, pheochromocytoma, lactation, combination with medications that could induce torsade de pointes, and patients with known risk of narrow-angle glaucoma.

Patients' clinical condition and capability of providing informed consent were confirmed by their attending physician or psychiatrist. All patients entering the study provided written informed consent. More information about randomization and concomitant medications can be found in the BeSt InTro primary outcome publication[21].

Outcome measures

The primary outcome measure was the change in PANSS total score during the one-year follow-up, which corresponded to the minimum recommended time of maintenance antipsychotic drug therapy after an acute psychotic episode in patients with schizophrenia[22,23]. To compute the percentage reduction in PANSS, we subtracted 30 points, as this is the minimum score possible. To calculate response rates, we used the following formula: [(PANSS baseline-30)-(PANSS followup-30)] × 100/(PANSS baseline-30)[15].

We used the Structured Clinical Interview for the PANSS. All investigators conducting assessments were trained and calibrated by the PANSS Institute (https://panss.org/) until satisfactory interrater reliability was achieved.

Other outcome measures included the Calgary Depression Scale for Schizophrenia (CDSS), the CGI-Severity of Illness scale (CGI-S), and the Global Assessment of Functioning scale (GAF) as the average of GAF function and GAF symptom scale score[24].

Data analyses/statistical methods

A latent class mixed model (LCMM) with PANSS total score as a dependent variable, time as an independent fixed variable, and subject as a random intercept was fit to our data. The model fitting was performed in R using the LCMM package[25]. Models with a different number of latent classes and with the time variable on different functional forms were investigated. The Bayesian information criterion (BIC) and entropy were used to select the best model. Lower BIC and higher entropy values indicate a better model fit. Differences between the latent classes obtained by the LCMM model were examined. The model with three latent classes and with time represented as visit number best fit the data. We labeled the three different response groups as "Strong response group", "Good response group" and "Slight response group". Comparisons between response groups were performed by analyzing categorical and continuous variables with the use of chi-square tests and one-way ANOVAs in IBM SPSS Statistics (version 24). In the case of significant ANOVA tests, post hoc pairwise analyses were performed using Tukey's test. In the antipsychotic drug use comparison among response groups, we divided the patients according to the ITT method, and post hoc pairwise analyses were conducted using Fisher's test.

The data were also analyzed by splitting the patients into two groups: The Good and Strong response groups were merged into the "Response group", and the Slight response group was labeled the "Nonresponse group".

Ethics and monitoring

The study was approved in Norway by the Regional Committees for Medical and Health Research Ethics and the Norwegian Medicines Agency and in Austria by the Ethical Committee of the Medical University of Innsbruck and the Austrian Federal Office for Safety in Health Care (BASG).

The Department of Research and Development in Haukeland University Hospital conducted clinical monitoring according to the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) in Norway; in Austria, this was performed by the Clinical Trial Centre at the Medical University of Innsbruck.

RESULTS

Subjects

Between October 20, 2011 and December 30, 2016, 359 participants were assessed for eligibility, and 144 were included and randomized to one of the study drugs. In total, 215 patients were excluded (107 did not meet the inclusion criteria, 82 declined to participate, and 26 for other reasons). Fifty-nine participants (41%) completed the 12-mo study period. The demographic and clinical characteristics for each response trajectory group are presented in Table 1.

In the cases of missing data, the total number of patients with data available for analysis was as follows: White: 134; Living alone: 137; Employed: 136; Smokers: 127; Alcohol abuse/dependence: 135; Drug abuse/dependence: 136; DUP: 65; Years of education: 127; GAF: 143; CDSS: 135.

Table 1 Baseline demographic and clinical characteristics in response trajectory analyses (mean ± SD)

	Strong response group (*n* = 19)	Good response group (*n* = 106)	Slight response group (*n* = 19)	Total (*n* = 144)	*P* value (3 groups)	*P* value (2 groups)
	n (%)	*n* (%)	*n* (%)	*n* (%)		
Men	13 (68.4)	70 (66)	10 (52.6)	93 (64.6)	0.495	0.242
White	14 (87.5)	87 (87.9)	17 (89.5)	118 (88.1)	0.978	0.837
Living alone	7 (38.9)	48 (48)	6 (31.6)	61 (44.5)	0.640	0.418
Employed	3 (17.6)	32 (32)	1 (5.3)	36 (26.5)	0.036	0.024
Smokers	13 (81.2)	58 (61.1)	13 (81.2)	84 (66.1)	0.113	0.172
Alcohol abuse/dependence	2 (13.3)	8 (7.9)	3 (15.8)	13 (9.6)	0.496	0.326
Drug abuse/dependence	4 (26.7)	19 (18.6)	4 (21.1)	27 (19.9)	0.759	0.888
AP-naive	5 (26.3)	45 (42.4)	6 (31.6)	56 (38.9)	0.323	0.483
Antipsychotic drug					0.046	0.023
Amisulpride	9 (47.4)	34 (32.1)	1 (5.3)	44 (30.6)		
Aripiprazole	4 (21.1)	37 (34.9)	7 (36.8)	48 (33.3)		
Olanzapine	6 (31.6)	35 (33)	11 (57.9)	52 (36.1)		
Diagnosis					0.226	0.428
Schizophrenia F20	15 (78.9)	56 (52.8)	13 (68.4)	84 (58.3)		
Schizotypal F21	0 (0)	1 (0.9)	1 (5.3)	2 (1.4)		
Delusional disorder F22	1 (5.3)	18 (17)	2 (10.5)	21 (14.6)		
Acute and transient F23	2 (10.5)	16 (15.1)	0 (0)	21 (14.6)		
Schizo-affective F25	1 (5.3)	7 (6.6)	2 (10.5)	10 (6.9)		
Other nonorganic F28	0 (0)	1 (0.9)	0 (0)	1 (0.7)		
Unspecified nonorganic F29	0 (0)	7 (6.6)	1 (5.3)	8 (5.5)		
Age	31.7 (12.3)	31.3 (12.7)	33.5 (13.9)	31.7 (12.7)	0.798	0.508
DUP						
Mean weeks	114 (207)	101.7 (261.6)	119 (163.1)	105.1 (244.2)	0.979	0.875
Median weeks	6	25	40	21	0.332	0.966
Duration of AP treatment (weeks)	21.1 (19.3)	19.8 (20.9)	16.2 (14.5)	19.5 (19.9)	0.716	0.436
Years of education	11.0 (1.6)	12.6 (2.9)	11.6 (2.3)	12.2 (2.7)	0.047	0.303
CGI-S	5.8 (0.6)	4.8 (0.8)	5.3 (0.7)	5.0 (0.8)	< 0.001	0.061
GAF	30.6 (10.7)	37.4 (8.7)	32.2 (8.0)	35.8 (9.3)	0.002	0.068
CDSS	8.1 (6.4)	6.0 (4.8)	9.0 (4.9)	6.7 (5.1)	0.035	0.038
PANSS total	94.7 (12.2)	72.3 (12.1)	85.4 (15.6)	78.4 (15.9)	< 0.001	0.023
PANSS positive	25.4 (5.2)	19.8 (4)	22.2 (4.1)	21.2 (4.8)	< 0.001	0.123
PANSS negative	20.8 (6.2)	16.2 (5.2)	21.4 (6.1)	17.8 (6.1)	< 0.001	0.006
PANSS general	48.4 (6.3)	36.3 (6.6)	41.8 (9)	39.4 (8.6)	< 0.001	0.172

Chi-square and ANOVAs were used. For the antipsychotic parameter, Fisher's test was used.

Smokers: Daily tobacco smokers; AP-naïve: No previous exposure to antipsychotic drugs; DUP: Duration of Untreated Psychosis; CGI-S: Clinical Global Impression severity of illness scale; GAF: Global Assessment of Functioning scale-split version, average of GAF function and GAF symptom scale score; CDSS: The Calgary Depression Scale for Schizophrenia total score; PANSS: Positive and Negative Syndrome Scale.

The number of patients with data available for analysis for DUP by group was as follows: Strong response group: 8; Good response group: 50; Slight response group: 7.

Trajectories of response

In total, participants had an average PANSS total score of 78.4 points at baseline, which was reduced by 56% after one year. In our three-trajectory model (Figure 1), a large group of patients (n = 106, 74%) (Good response group) had a 54% reduction in PANSS total score over the first 26 wk of follow-up and maintained it after one year, with a 59% total reduction (Table 2). The second group of patients (n = 19, 13%) showed the fastest response, with a 17% reduction after one week of antipsychotic treatment, and had the largest reduction in PANSS total score among the three groups, with 82.5% at one year (Strong response group). These two groups showed similar improvement of PANSS total score until the six-week follow-up (Good response group: 45% reduction, Strong response group: 48% reduction). However, after this, the Good response group had only a 15% further reduction until the one-year follow-up. In contrast, the Strong response group continued to show remarkable improvement until one year, with a 34% further reduction after the six-week follow-up. The third group of patients (n = 19, 13%) followed a trajectory of poor improvement, with a 13.6% reduction in PANSS total score over the one-year study period (Slight response group). The course of the PANSS total score in this group was quite stable throughout the entire follow-up period.

Patients in the three groups had different baseline average PANSS total scores. Patients in the Strong response group had the highest average PANSS total score (99.7 points), while patients in the Good response group had the lowest (73.3 points). The end point estimates, however, were quite similar, with the Strong response group ending at 42.2 points and the Good response group ending at 47.6 points. Patients in the Slight response group had an average PANSS total score of 86.1 at baseline but had a substantially higher PANSS total score than patients in both the other two groups at the six-week follow-up and until the end of the one-year follow-up (78.5 points).

Predictors of response

In our three-trajectory model and after conducting post hoc pairwise analyses, we did not find significant differences among the trajectory groups regarding years of education or CDSS score at baseline. Having a regular job was significantly more common among patients in the Good response group than in the Slight response group after the pairwise analyses. In post hoc pairwise analyses for the GAF score at baseline, patients in the Strong response group had significantly lower GAF scores than patients in the Good response group. For the CGI-S score, patients in the Good response group had a significantly lower score at baseline than patients in both other response groups. As expected, because the grouping was based on the PANSS total score data, the PANSS total, PANSS positive, and PANSS general average scores at baseline were significantly different in all the post hoc pairwise comparisons between response groups. Patients in the Strong response group had higher PANSS total, PANSS positive and PANSS general average scores at baseline than patients in both the other response groups. For the PANSS negative score, we found significant differences between the Good response and the Strong response group and between the Good response and the Slight response group. Patients in the Slight response group had the highest PANSS negative average score at baseline, while patients in the Good response group had the lowest.

When the Strong and Slight response groups were compared in the antipsychotic drug post hoc analyses, we found significantly more patients who used amisulpride in the Strong response group (47.4% *vs* 5.3%). The proportion of Slight response patients in each medication group was as follows: 1/44 for amisulpride, 7/48 for aripiprazole and 11/52 for olanzapine. When these proportions were compared pairwise, we did not find a significant difference between olanzapine and aripiprazole or between amisulpride and aripiprazole. There was a statistically significant difference between olanzapine and amisulpride (*i.e.*, a significantly higher proportion of Slight response participants in the olanzapine group than in the amisulpride group).

In the comparison between the Response and Nonresponse groups, there was a significant difference regarding employment status: More patients in the Response group had a regular job at baseline. The CDSS score at baseline was significantly higher in the Nonresponse group than in the Response group. The Nonresponse group had higher average scores in both PANSS total-86.1 *vs* 77.3 points-and PANSS negative-21.4 *vs* 17.3 points-at baseline. There was a significantly higher proportion of patients who used amisulpride in the Response group than in the Nonresponse group-43/125 compared to 1/18.

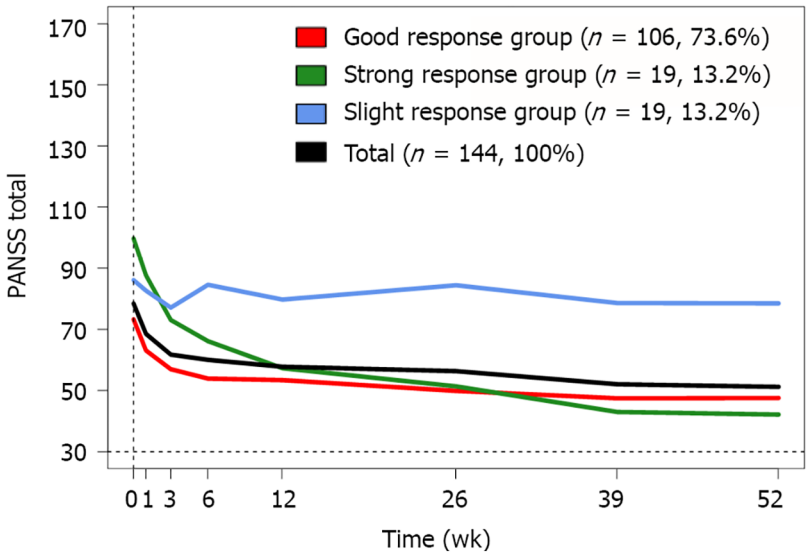
DISCUSSION

The key finding of our study is that 87% of participants followed a trajectory of good or strong response to antipsychotic drugs. This provides additional strong evidence of the efficacy of antipsychotic drugs, corresponding to current research and treatment guidelines for schizophrenia[1-3,5,6]. The largest group of patients, the Good response trajectory group, showed a 54% reduction in PANSS total score at the one-year follow-up. This percentage can be regarded as a good response to schizophrenia treatment, as

Table 2 Response measured as Positive and Negative Syndrome Scale total score improvement from baseline

	Baseline PANSS total score	1 wk[1]	3 wk[1]	6 wk[1]	12 wk[1]	26 wk[1]	39 wk[1]	52 wk[1]
Strong response group	99.7	12.0 (17.2%)	26.6 (38.2%)	33.5 (48.1%)	42.4 (60.8%)	48.3 (69.3%)	56.7 (81.3%)	57.5 (82.5%)
Good response group	73.3	10.2 (23.5%)	16.3 (37.6%)	19.3 (44.7%)	19.8 (45.8%)	23.4 (54%)	25.8 (59.6%)	25.7 (59.4%)
Slight response group	86.1	3.5 (6.2%)	9.0 (16%)	1.5 (2.7%)	6.4 (11.3%)	1.7 (3%)	7.5 (13.4%)	7.6 (13.6%)
Total	78.4	9.9 (20.5%)	16.7 (34.5%)	18.4 (38%)	20.7 (42.6%)	22.1 (45.6%)	26.4 (54.4%)	27.2 (56.2%)

[1]PANSS total baseline–PANSS total follow-up point. PANSS: Positive and Negative Syndrome Scale; %: Percentage of improvement from baseline score.



DOI: 10.5498/wjp.v12.i3.521

Figure 1 Response trajectories.

a cutoff of 20%, 30%, 40%, or 50% reduction in PANSS total score has been used in clinical studies[15]. The PANSS total change of 54% corresponds to a CGI-I (improvement scale) of "much improved"[19]. The Slight response group in our study included both antipsychotic-naive patients and patients with previous exposure to antipsychotics. We know from previous research that a group of patients (approximately 13%-25%) will not respond adequately after a trial of an antipsychotic drug in their first episode of psychosis[26-28], while approximately 30% of those with chronic schizophrenia will be regarded as treatment-resistant after two failed trials with antipsychotics[29].

Another key finding of this study is the importance of response in the first six weeks of treatment, which seems to predict further response to the antipsychotic drug. Participants in the Slight response group did not show any further improvement after the first six weeks of treatment. Both the current Norwegian guidelines and the National Institute for Health and Care Excellence (NICE) guidelines suggest a trial with medication at an optimum dosage for four to six weeks[2,30]. The Maudsley guidelines propose an assessment of the adjusted dosage over two to three weeks and an antipsychotic switch if there is no effect during this period. If a partial response is detected, the clinician should continue for at least four weeks before abandoning this treatment[3]. Our data could suggest that patients without a reduction in the PANSS total score of 30% from baseline to six weeks in treatment with nonclozapine antipsychotic drugs seldom achieve sufficient response, and switching to another antipsychotic drug should be considered. On the other hand, the results from the OPTiMiSE study, a multicenter three-phase switching study in first-episode schizophrenia, concluded that switching antipsychotics did not improve clinical outcomes in patients who had not reached symptomatic remission after their first antipsychotic trial compared to continuing treatment[31]. The authors suggested an algorithm of treatment with a single antipsychotic drug for up to 10 wk, followed by the use of clozapine in patients who did not reach symptomatic remission.

There were significant differences in the distribution of the examined antipsychotic drugs among the three response groups, and our findings indicate more favorable results for amisulpride. Interestingly, amisulpride is less frequently used than aripiprazole and olanzapine. In Norway, the use of amisulpride remained stable from 2014 to 2018, and in 2018, amisulpride was used 30 times less frequently than olanzapine and 9 times less frequently than aripiprazole[32]. In the United States, amisulpride is

registered for the treatment and prevention of postoperative nausea and vomiting[33] but not for schizophrenia treatment. Hence, one of the most effective drugs is not available for antipsychotic treatment. This is a strong reminder that different prescribing cultures among countries regarding the choice of drugs for schizophrenia treatment exist[4,34] and underlines the need for evidence-based clinical practice in schizophrenia treatment.

We found three variables that predicted nonresponse: Unemployment, depression, and negative psychotic symptoms. Previous studies have suggested that there may be a correlation between employment status and other types of outcomes. The causal direction, however, remains unclear[35,36]. In our study, we found that patients in the Slight response group had a significantly lower percentage of employment, both in the two-group and three-group analyses. Of the 36 participants with paid work at baseline, 35 belonged to the Response group and only one to the Nonresponse group, showing a strong predictive value of having paid work for a good symptom outcome over the 12-mo follow-up. We also found a higher level of symptoms of depression at baseline in the Nonresponse group. This corresponds with previous studies showing that depression in schizophrenia is common and associated with negative outcomes[37]. The Slight response group had the highest PANSS negative average score at baseline in both the two-group and three-group analyses. Negative psychotic symptoms are difficult to treat with the available antipsychotic drugs, which stresses the need for new therapeutic agents in schizophrenia treatment[38].

Strengths and limitations

Our study (BeSt InTro) is the first head-to-head comparison of amisulpride, aripiprazole and olanzapine in a randomized, pragmatic efficacy trial. This direct comparison of these agents provides some clear advantages compared to network meta-analyses. Moreover, our study was industry-independent and rater-blind. Another strength of the study was the frequent follow-up points, particularly in the first weeks of treatment, which are quite important, as demonstrated above. Our follow-up was relatively long (12 mo), which gave an advantage compared to other response studies that examined shorter periods with antipsychotic drugs. Finally, we used well-validated instruments to describe our main parameters, such as PANSS, CGI and CDSS.

Our study has also some limitations. First, there was no placebo control; therefore, we must interpret our results with caution. Second, there was a drop-out rate of 59%, which is comparable to that found in other large randomized antipsychotic drug trials, such as the CATIE study (74% before 18 mo)[39] and the EUFEST study (41.6% before 12 mo)[40]. Furthermore, further analyses of attrition indicated that the sample after 52 wk was representative of the sample at baseline. Finally, some of our participants entered the study having tried other antipsychotic(s) previously, while the rest were antipsychotic-naive. This could have brought some bias into the interpretation of our results. Last, the vast majority of the included patients were white Europeans (88%). Our results are therefore not generalizable to all human populations.

CONCLUSION

In summary, the vast majority of our study participants had a very good outcome during the 12-mo course. The response to antipsychotic drugs after the first six weeks of treatment predicted a further course during the first year, and the use of amisulpride indicated a better response. An antipsychotic switch should be considered in patients with inadequate response (less than 30% reduction in PANSS total from baseline) after six weeks of treatment. Unemployment, depression, and negative psychotic symptoms at baseline predicted nonresponse.

ARTICLE HIGHLIGHTS

Research background

It is important to compare the effectiveness of various antipsychotic agents in the treatment of schizophrenia. The Bergen-Stavanger-Innsbruck-Trondheim (BeSt InTro) study directly compared three antipsychotics (amisulpride, aripiprazole and olanzapine) in patients with schizophrenia-spectrum disorders between October 20, 2011 and December 30, 2016. The inclusion and follow-up of the patients are now completed, and the main findings have been published. In this substudy, we examined response trajectories and possible predictors for belonging to the different response groups.

Research motivation

Schizophrenia is a serious illness with a heterogeneous course. Pharmacological treatment with antipsychotic drugs remains the cornerstone in the treatment of schizophrenia, yet it is not possible to predict its effect on individual patients. Finding predictors of medication response can enhance the quality of schizophrenia treatment and the development of more personalized medicine.

Research objectives

The main objective of this substudy was to define response trajectories after a one-year follow-up for patients randomized to the three studied antipsychotics. The secondary objective was to define predictors of belonging to the different response trajectories. After realizing these objectives, we could present some suggestions for better clinical practice. We could also suggest further research on switching antipsychotics and on factors that predicted nonresponse, such as unemployment, depression, and negative psychotic symptoms.

Research methods

Our study was a cohort study with data from a clinical trial of three antipsychotics in a prospective, randomized, rater-blind design. We defined response trajectories by fitting a latent class mixed model with Positive and Negative Syndrome Scale (PANSS) total as a dependent variable, time as an independent fixed variable, and subject as a random intercept to our data. We used the Bayesian information criterion and entropy to select the best model, and the model with three latent classes and with time represented as visit number best fit the data. Response trajectories provide a better picture of the course of symptoms over time and are a relatively novel way of examining response in schizophrenia.

Research results

The finding that 87% of the participants had a good or strong response to antipsychotic treatment adds to the research evidence about the general effectiveness of antipsychotic drugs. The response after the first six weeks of treatment seems to indicate further response to antipsychotics. The results indicate the need for further research on switching antipsychotics in incomplete responders to avoid delays in treatment and to enhance the quality of treatment.

Research conclusions

Antipsychotic treatment has a good effect in a vast majority of schizophrenia-spectrum patients enrolled in a randomized drug trial. Furthermore, the six-week response seemed to predict the effects through the one-year follow-up. This can indicate an antipsychotic switch in patients without a reduction in the PANSS total score of 30% from baseline to six weeks in treatment with nonclozapine antipsychotics. Another important conclusion is the favorable results for amisulpride in comparison to aripiprazole and olanzapine, which could encourage more frequent use of this drug in schizophrenia treatment.

Research perspectives

Future research on schizophrenia treatment should be designed to develop more personalized medicine through the identification of response predictors.

ACKNOWLEDGEMENTS

The authors wish to thank all participants for their contribution to the study, as well as the staff of the study groups in Bergen, Trondheim, Stavanger and Innsbruck for their valuable contribution to the detection, inclusion and follow-up of participants.

FOOTNOTES

Author contributions: Johnsen E and Kroken RA designed the project; Bartz-Johannessen CA and Drosos P carried out the statistical analyses; Drosos P prepared the first draft; Johnsen E, Bartz-Johannessen CA, Larsen TK, Reitan SK and Rettenbacher M contributed to the manuscript; all authors have read and approved the final version of the manuscript.

Supported by Drosos P is a Research Fellow with a Grant From the Western Norway Regional Health Trust, No. 912140.

Institutional review board statement: The study was reviewed and approved by the Regional Committees for Medical and Health Research Ethics (REK), No. 2010/3387-6.

Clinical trial registration statement: This is a prospective cohort study using data from the randomized, controlled trial study, the Best Intro Study (ClinicalTrials.gov Identifier: NCT01446328).

Informed consent statement: All study participants, or their legal guardian, provided written informed consent prior to study enrollment.

Conflict-of-interest statement: The authors declare that they have no conflicts of interest.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: Norway

ORCID number: Petros Drosos 0000-0002-3532-7367; Erik Johnsen 0000-0003-0792-4436; Christoffer Andreas Bartz-Johannessen 0000-0002-9615-4551; Tor Ketil Larsen 0000-0001-7521-3834; Solveig Klæbo Reitan 0000-0002-3469-6822; Maria Rettenbacher 0000-0001-6544-2828; Rune Andreas Kroken 0000-0002-0903-3840.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Leucht S**, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, Samara M, Barbui C, Engel RR, Geddes JR, Kissling W, Stapf MP, Lässig B, Salanti G, Davis JM. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet* 2013; **382**: 951-962 [PMID: 23810019 DOI: 10.1016/S0140-6736(13)60733-3]
2 **NICE**. Psychosis and schizophrenia in adults: Prevention and management. In: National Institute for Health and Care Excellence NICE Clinical Guideline 178. London, 2014. [cited 10 August 2021]. Available from: https://www.nice.org.uk/guidance/cg178
3 **Taylor D**, Barnes T, Young A. The Maudsley Prescribing Guidelines in Psychiatry. 13th edition. UK: Wiley Blackwell, 2018.
4 **Papageorgiou G**, Cañas F, Zink M, Rossi A. Country differences in patient characteristics and treatment in schizophrenia: data from a physician-based survey in Europe. *Eur Psychiatry* 2011; **26**: 17-28 [PMID: 21440220 DOI: 10.1016/S0924-9338(11)71710-2]
5 **Huhn M**, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Backers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. Lancet 2019; 394: 939-951 [PMID: 31303314 DOI: 10.1016/S0140-6736(19)31135-3]
6 **Boter H**, Peuskens J, Libiger J, Fleischhacker WW, Davidson M, Galderisi S, Kahn RS; EUFEST study group. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). *Schizophr Res* 2009; **115**: 97-103 [PMID: 19819114 DOI: 10.1016/j.schres.2009.09.019]
7 **Fusar-Poli P**, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? *Neurosci Biobehav Rev* 2013; **37**: 1680-1691 [PMID: 23769814 DOI: 10.1016/j.neubiorev.2013.06.001]
8 **Rotella F**, Cassioli E, Calderani E, Lazzeretti L, Ragghianti B, Ricca V, Mannucci E. Long-term metabolic and cardiovascular effects of antipsychotic drugs. A meta-analysis of randomized controlled trials. *Eur Neuropsychopharmacol* 2020; **32**: 56-65 [PMID: 31917068 DOI: 10.1016/j.euroneuro.2019.12.118]
9 **Harrow M**, Jobe TH, Faull RN, Yang J. A 20-Year multi-followup longitudinal study assessing whether antipsychotic medications contribute to work functioning in schizophrenia. *Psychiatry Res* 2017; **256**: 267-274 [PMID: 28651219 DOI: 10.1016/j.psychres.2017.06.069]
10 **Zhang C**, Chen MJ, Wu GJ, Wang ZW, Rao SZ, Zhang Y, Yi ZH, Yang WM, Gao KM, Song LS. Effectiveness of Antipsychotic Drugs for 24-Month Maintenance Treatment in First-Episode Schizophrenia: Evidence From a Community-Based "Real-World" Study. *J Clin Psychiatry* 2016; **77**: e1460-e1466 [PMID: 28076667 DOI: 10.4088/JCP.15m10047]
11 **Taylor M**, Cavanagh J, Hodgson R, Tiihonen J. Examining the effectiveness of antipsychotic medication in first-episode psychosis. *J Psychopharmacol* 2012; **26**: 27-32 [PMID: 22337711 DOI: 10.1177/0269881112439252]
12 **Samara MT**, Dold M, Gianatsi M, Nikolakopoulou A, Helfer B, Salanti G, Leucht S. Efficacy, Acceptability, and Tolerability of Antipsychotics in Treatment-Resistant Schizophrenia: A Network Meta-analysis. *JAMA Psychiatry* 2016; **73**: 199-210 [PMID: 26842482 DOI: 10.1001/jamapsychiatry.2015.2955]
13 **Kay SR**, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261-276 [PMID: 3616518 DOI: 10.1093/schbul/13.2.261]
14 **Overall JE**, Gorham DR. The Brief psychiatric rating scale. *Psychol Rep* 1962; **10**: 799-812 [DOI: 10.2466/pr0.1962.10.3.799]
15 **Leucht S**, Davis JM, Engel RR, Kane JM, Wagenpfeil S. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology* 2007; **32**: 1903-1910 [PMID: 17287825 DOI: 10.1038/sj.npp.1301325]

16 **Leucht S**. Measurements of response, remission, and recovery in schizophrenia and examples for their clinical application. *J Clin Psychiatry* 2014; **75** Suppl 1: 8-14 [PMID: 24581453 DOI: 10.4088/JCP.13049su1c.02]

17 **Guy W**. Clinical global impressions. ECDEU assessment manual for psychopharmacology, revised (DHEW publ. No. ADM 76-338). National Institute of Mental Health, Rockville, 1976: 218-222

18 **Leucht S**, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res* 2005; **79**: 231-238 [PMID: 15982856 DOI: 10.1016/j.schres.2005.04.008]

19 **Levine SZ**, Rabinowitz J, Engel R, Etschel E, Leucht S. Extrapolation between measures of symptom severity and change: an examination of the PANSS and CGI. *Schizophr Res* 2008; **98**: 318-322 [PMID: 17949948 DOI: 10.1016/j.schres.2007.09.006]

20 **Zhang HX**, Shen XL, Zhou H, Yang XM, Wang HF, Jiang KD. Predictors of response to second generation antipsychotics in drug naïve patients with schizophrenia: a 1 year follow-up study in Shanghai. *Psychiatry Res* 2014; **215**: 20-25 [PMID: 24230993 DOI: 10.1016/j.psychres.2013.10.022]

21 **Johnsen E**, Kroken RA, Løberg EM, Rettenbacher M, Joa I, Larsen TK, Reitan SK, Walla B, Alisauskiene R, Anda LG, Bartz-Johannessen C, Berle JØ, Bjarke J, Fathian F, Hugdahl K, Kjelby E, Sinkeviciute I, Skrede S, Stabell L, Steen VM, Fleischhacker WW. Amisulpride, aripiprazole, and olanzapine in patients with schizophrenia-spectrum disorders (BeSt InTro): a pragmatic, rater-blind, semi-randomised trial. *Lancet Psychiatry* 2020; **7**: 945-954 [PMID: 33069317 DOI: 10.1016/S2215-0366(20)30341-2]

22 **Barnes TR**; Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 2011; **25**: 567-620 [PMID: 21292923 DOI: 10.1177/0269881110391123]

23 **Hasan A**, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, Thibaut F, Möller HJ; WFSBP Task force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. *World J Biol Psychiatry* 2013; **14**: 2-44 [PMID: 23216388 DOI: 10.3109/15622975.2012.739708]

24 **Karterud S**, Pedersen G, Løvdahl H, Friis S. Global assessment of Functioning-Split version. Background and scoring manual. Oslo, Norway. Ullevaal University Hospital, Department of Psychiatry, 1998.

25 **Rcore Team**. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing, 2020.

26 **Agid O**, Arenovich T, Sajeev G, Zipursky RB, Kapur S, Foussias G, Remington G. An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *J Clin Psychiatry* 2011; **72**: 1439-1444 [PMID: 21457676 DOI: 10.4088/JCP.09m05785yel]

27 **Carbon M**, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin Neurosci* 2014; **16**: 505-524 [PMID: 25733955 DOI: 10.31887/DCNS.2014.16.4/mcarbon]

28 **Robinson DG**, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, Chakos M, Mayerhoff D, Bilder R, Goldman R, Lieberman JA. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 1999; **156**: 544-549 [PMID: 10200732 DOI: 10.1176/ajp.156.4.544]

29 **Meltzer HY**. Treatment-resistant schizophrenia--the role of clozapine. *Curr Med Res Opin* 1997; **14**: 1-20 [PMID: 9524789 DOI: 10.1185/03007999709113338]

30 **Helsedirektoratet**. Nasjonal faglig retningslinje for utredning, behandling og oppfølging av personer med psykoselidelser (National guideline for assessment, treatment and follow-up of persons with psychotic disorders). Norwegian Directorate of Health. Oslo, 2013. [cited 10 August 2021]. Available from: https://helsedirektoratet.no/retningslinjer/nasjonal-faglig-retningslinje-for-utredning-behandling-og-oppfolging-av-personer-med-psykoselidelser

31 **Kahn RS**, Winter van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M, Arango C, Dazzan P, Drake R, Heres S, Díaz-Caneja CM, Rujescu D, Weiser M, Galderisi S, Glenthøj B, Eijkemans MJC, Fleischhacker WW, Kapur S, Sommer IE; OPTiMiSE study group. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry* 2018; **5**: 797-807 [PMID: 30115598 DOI: 10.1016/S2215-0366(18)30252-9]

32 **Norwegian Institute of Public Health**. Drug Consumption in Norway 2014–2018. Oslo. [cited 10 August 2021]. Available from: https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2019/Legemiddelforbruket-i-norge-2014-2018.pdf

33 **Ientile G**. Amisulpride injection now available in the US for postoperative nausea and vomiting. 2020. [cited 10 August 2021]. Available from: https://www.drugtopics.com/view/amisulpride-injection-now-available-in-the-us-for-postoperative-nausea-and-vomiting

34 **Taylor DM**, Werneke U. Ethnopharmacology†. *Nord J Psychiatry* 2018; **72**: S30-S32 [PMID: 30688173 DOI: 10.1080/08039488.2018.1525636]

35 **Marwaha S**, Johnson S. Schizophrenia and employment - a review. *Soc Psychiatry Psychiatr Epidemiol* 2004; **39**: 337-349 [PMID: 15133589 DOI: 10.1007/s00127-004-0762-4]

36 **Bell MD**, Lysaker PH, Milstein RM. Clinical benefits of paid work activity in schizophrenia. *Schizophr Bull* 1996; **22**: 51-67 [PMID: 8685664 DOI: 10.1093/schbul/22.1.51]

37 **Kjelby E**, Gjestad R, Sinkeviciute I, Kroken RA, Løberg EM, Jørgensen HA, Johnsen E. Trajectories of depressive symptoms in the acute phase of psychosis: Implications for treatment. *J Psychiatr Res* 2018; **103**: 219-228 [PMID: 29890508 DOI: 10.1016/j.jpsychires.2018.06.003]

38 **Möller HJ**, Czobor P. Pharmacological treatment of negative symptoms in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2015; **265**: 567-578 [PMID: 25895634 DOI: 10.1007/s00406-015-0596-y]

39 **Lieberman JA**, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; **353**: 1209-1223 [PMID: 16172203 DOI: 10.1056/NEJMoa051688]

40 **Kahn RS**, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, López-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rössler A, Grobbee DE; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet* 2008; **371**: 1085-1097 [PMID: 18374841 DOI: 10.1016/S0140-6736(08)60486-9]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 533-535

DOI: 10.5498/wjp.v12.i3.533

ISSN 2220-3206 (online)

LETTER TO THE EDITOR

Therapeutic use of melatonin in schizophrenia-more than meets the eye!

Ahmed Naguy

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: de Oliveira I, Mogulkoc R, Stoyanov D

Received: September 16, 2021
Peer-review started: September 16, 2021
First decision: November 8, 2021
Revised: November 8, 2021
Accepted: February 12, 2022
Article in press: February 12, 2022
Published online: March 19, 2022

Ahmed Naguy, Al-Manara CAP Centre, Kuwait Centre for Mental Health (KCMH), Shuwaikh 22094, Kuwait

Corresponding author: Ahmed Naguy, MBChB, MSc, Staff Physician, Al-Manara CAP Centre, Kuwait Centre for Mental Health (KCMH), Jamal Abdul-Nassir Street, Shuwaikh 22094, Kuwait. ahmednagy@hotmail.co.uk

Abstract

Adjunctive melatonin use in schizophrenia, as supported by a modicum of evidence, has multiple transcending chronobiotic actions, including fixing concurrent sleep problems to bona fide augmentative antipsychotic actions, mitigating the risk of tardive dyskinesias, curbing the drastic metabolic syndrome and ultimately providing neuroprotective actions. Its use is rather an art than science!

Key Words: Melatonin; Schizophrenia; Chronobiotic; Neuroprotectant; Antipsychotic; Tardive dyskinesia; Metabolic syndrome

Core Tip: Adjuventia melatonin use in schizophrenia is strongly recommended, although it is supported by a modicum of evidence. Its use has multiple transcending chronobiotic actions, rectifying sleep disturbance in schizophrenia to bona fide augmentative antipsychotic actions, mitigating the risk of relentless tardive dyskinesias, curbing the drastic cardio-metabolic syndrome and ultimately providing neuroprotective actions in the face of the neuroprogressive course of schizophrenia.

Citation: Naguy A. Therapeutic use of melatonin in schizophrenia-more than meets the eye!. *World J Psychiatry* 2022; 12(3): 533-535
URL: https://www.wjgnet.com/2220-3206/full/v12/i3/533.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i3.533

TO THE EDITOR

In a recent issue of the *World J Psychiatry*, Duan *et al*[1] conducted an interesting systematic review of melatonin use for schizophrenia. They concluded that add-on melatonin can help with sleep, might curtail metabolic risk and possibly mitigate tardive dyskinesia in patients with schizophrenia. We completely agree with authors, and we[2] have previously published on melatonin adjuventia in patients with bipolar mood disorders as well. Herein, we will try to expand a bit more on the therapeutic potential of melatonin in schizophrenia.

Sleep and circadian rhythm disturbances, as high as 80%, lie at the core of the etiopathogenesis of schizophrenia, as supported by both human studies and preclinical evidence in animal (mice) models with genetic mutations pertinent to schizophrenia[3]. Wide heterogeneity in phenotypes has been demonstrated. This includes, among other things, severe circadian misalignment, phase advances and delays, non-24 h rhythms that were not entrained by the light/dark cycle and disturbed sleep/wake cycle, perhaps reflecting the heterogeneity of the disease itself.

Melatonin secretion is reduced in schizophrenia. Therefore, it follows that melatonin (N-acetyl 5-methoxytryptamine) use addresses a core pathophysiology central to schizophrenia, beyond being a mere sleeping aid.

Moreover, it has been shown that melatonin might augment anti-psychotic efficacy by virtue of anti-inflammatory and anti-oxidant actions. Melatonin impacts tryptophan catabolic pathways *via* its effect on stress response and cortisol secretion, and this might impact cortex associated cognition, amygdala associated affect and striatal motivational processing. Melatonin in schizophrenia has been demonstrated to serve both as a biologic marker and as a treatment adjunct[4].

Melatonin mitigates risk of tardive dyskinesia, akin to similar use of vitamin E, given that melatonin is 6-10 times more potent than vitamin E. Moreover, it curbs metabolic syndrome. Mechanistically, melatonin regulates the photo-neuroendocrine axis. It has complex interactions with leptin, improves insulin resistance, and possesses cardio-protective actions.

Schizophrenia relapses are typified with neuroprogression leading to subcortical atrophy, ventriculomegaly and further white matter loss. This is chiefly mediated through microglial activation, neuroinflammation and oxidative/nitrosative stress. Mitochondrial dysfunction due to deficiency of the antioxidant glutathione also contributes[5]. Taken together, these findings make case for a role for melatonin in neuroprotection, owing to its anti-apoptotic actions and its regulation of adult hippocampal neurogenesis.

Quo Vadis? melatonin use in schizophrenia, as supported by a modicum of evidence base, has multiple transcending chronobiotic actions, including bona fide antipsychotic actions, mitigation of tardive dyskinesia, curbing metabolic syndrome and ultimately providing neuroprotective actions. Its use is rather an art than science!

ACKNOWLEDGEMENTS

Author extends his deepest gratitude to Dr. Bibi Alamiri, MD, ScD, ABPN for her invaluable scientific input to the manuscript.

FOOTNOTES

Author contributions: Naguy A wrote the manuscript.

Conflict-of-interest statement: Author declares no conflicts of interest or financial affiliations.

Country/Territory of origin: Kuwait

ORCID number: Ahmed Naguy 0000-0002-6465-456X.

S-Editor: Fan JR
L-Editor: Filipodia
P-Editor: Fan JR

REFERENCES

1 **Duan C**, Jenkins ZM, Castle D. Therapeutic use of melatonin in schizophrenia: A systematic review. *World J Psychiatry* 2021; **11**: 463-476 [PMID: 34513608 DOI: 10.5498/wjp.v11.i8.463]

2 **Naguy A**, Francis K. Melatonin: A new game-changer in juvenile bipolar disorders? *Psychiatry Res* 2019; **279**: 364-365 [PMID: 30812069 DOI: 10.1016/j.psychres.2016.04.052]

3 **Delorme TC**, Srivastava LK, Cermakian N. Are Circadian Disturbances a Core Pathophysiological Component of Schizophrenia? *J Biol Rhythms* 2020; **35**: 325-339 [PMID: 32498652 DOI: 10.1177/0748730420929448]

4 **Naguy A**, Al-Amiri B, Shoukry T. Melatonin Use in Psychiatry-Quo Vadis? *Am J Ther* 2020; **27**: e495-e499 [PMID: 30277908 DOI: 10.1097/MJT.0000000000000833]

5 **Naguy A**, Moodliar-Rensburg S, Alamiri B. The long-acting injectable atypical antipsychotics-merits and demerits! *CNS Spectr* 2021; **26**: 442-443 [PMID: 32641186 DOI: 10.1017/S1092852920001558]

World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2022 March 19; 12(3): 536-540

DOI: 10.5498/wjp.v12.i3.536

ISSN 2220-3206 (online)

LETTER TO THE EDITOR

Does COVID-19 increase the risk of neuropsychiatric sequelae? Evidence from a mendelian randomization approach

Alfonsina Tirozzi, Federica Santonastaso, Giovanni de Gaetano, Licia Iacoviello, Alessandro Gialluisi

Specialty type: Genetics and heredity

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Coelho AC, Yoshikawa M

Received: November 12, 2021
Peer-review started: November 12, 2021
First decision: December 12, 2021
Revised: January 3, 2022
Accepted: February 23, 2022
Article in press: February 23, 2022
Published online: March 19, 2022

Alfonsina Tirozzi, Giovanni de Gaetano, Licia Iacoviello, Alessandro Gialluisi, Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli 86077, Italy

Federica Santonastaso, Licia Iacoviello, Alessandro Gialluisi, Department of Medicine and Surgery, University of Insubria, Varese 21100, Italy

Corresponding author: Licia Iacoviello, MD, PhD, Professor, Department of Epidemiology and Prevention, IRCCS Istituto Neurologico Mediterraneo Neuromed, Via Atinense 18, Pozzilli 86077, Italy. licia.iacoviello@moli-sani.org

Abstract

Observational studies based on electronic health records (EHR) report an increased risk of neurological/neuropsychiatric sequelae for patients who have had coronavirus disease 2019 (COVID-19). However, these studies may suffer from biases such as unmeasured confounding, residual reverse causality, or lack of precision in EHR-based diagnoses. To rule out these biases, we tested causal links between COVID-19 and different potential neurological/neuropsychiatric sequelae through a two-sample Mendelian randomization analysis of summary statistics from large Genome-Wide Association Scans of susceptibility to COVID-19 and different neurological and neuropsychiatric disorders, including major depression, anxiety, schizophrenia, stroke, Parkinson's and Alzheimer's diseases. We found robust evidence suggesting that COVID-19 – notably the hospitalized and most severe forms – carries an increased risk of neuropsychiatric sequelae, particularly Alzheimer's disease, and to a lesser extent anxiety disorder. In line with a large longitudinal EHR-based study, this evidence was stronger for more severe COVID-19 forms. These results call for a targeted screening strategy to tackle the post-COVID neuropsychiatric pandemic.

Key Words: COVID-19; Sars-CoV-2; Neurological disorders; Neuropsychiatric disorders; Alzheimer's disease; Anxiety; Mendelian randomization

Core Tip: Inspired by suggestive findings of an increased incident risk of neurological and neuropsychiatric sequelae in people who have had coronavirus disease 2019 (COVID-19), we carried out a two-sample Mendelian randomization analysis to further investigate causality links and build evidence free of biases such as unmeasured confounding, residual reverse causality or lack of precision in electronic health record-based diagnoses. This analysis – typically applied to genetic associations from large genomic studies on the diseases of interest – indicated that the most severe forms of COVID-19 increased the risk of Alzheimer's disease and anxiety, further supporting the findings of large observational studies.

Citation: Tirozzi A, Santonastaso F, de Gaetano G, Iacoviello L, Gialluisi A. Does COVID-19 increase the risk of neuropsychiatric sequelae? Evidence from a mendelian randomization approach. *World J Psychiatry* 2022; 12(3): 536-540

URL: https://www.wjgnet.com/2220-3206/full/v12/i3/536.htm

DOI: https://dx.doi.org/10.5498/wjp.v12.i3.536

TO THE EDITOR

During the ongoing coronavirus disease 2019 (COVID-19) pandemic, increasing attention is being paid to the long-term sequelae of the acute disease, particularly neurological and neuropsychiatric[1,2]. A recent retrospective analysis in more than 236000 COVID-19 survivors reported a significant increase of neurological/psychiatric outcomes in the six months after diagnosis, particularly for those treated in hospital, in an intensive care unit, and those who suffered encephalopathy[3]. The risk of first diagnosis of such sequelae, which included dementia, cerebrovascular, psychotic, mood and anxiety disorders, was almost double in those with COVID-19 compared to patients who suffered other types of viral influenza or respiratory infections, suggesting a specific contribution of Sars-CoV-2 infection to these sequelae[3]. This observational study was based on electronic health records, which unavoidably lack the precision of neurological/neuropsychiatric diagnoses, and may be subject to unmeasured confounding or residual reverse causality biases; in fact, most of the reported disorders are themselves risk factors for COVID-19 infection, and their milder forms may go undetected.

To overcome these limitations and provide independent evidence of the observations, we carried out a two-sample Mendelian randomization (MR) analysis to test whether susceptibility to COVID-19 could predispose to an increase in the risk of different psychiatric/neurodegenerative disorders, including major depression, anxiety, schizophrenia, stroke, Parkinson's and Alzheimer's diseases, as already suggested in the literature[2,3].

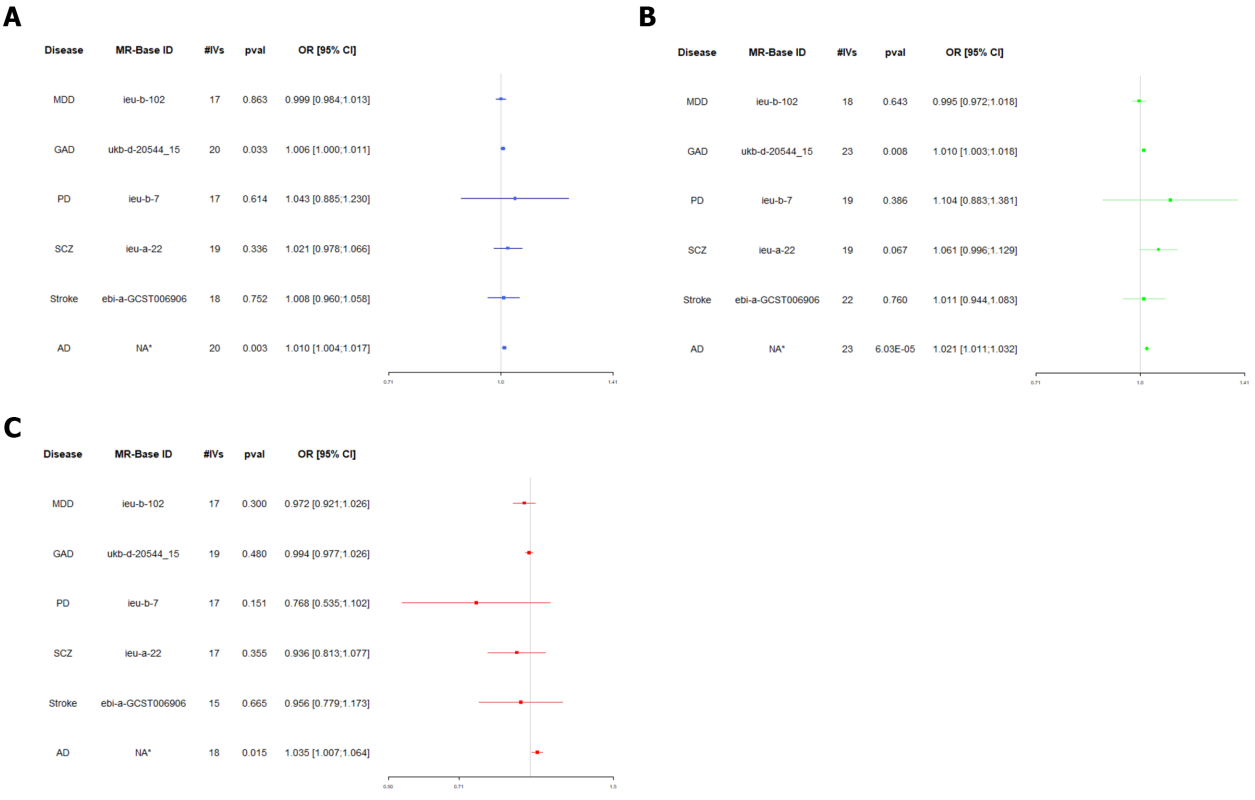
We employed summary statistics from large Genome-Wide Association Studies (GWAS) on COVID-19 susceptibility and all the disorders tested, through the MR-Base web app, or the equivalent R package TwoSampleMR v 0.5.6[4] when up-to-date summary statistics were not available in the MR-Base[5]. Since we detected no violation of the balanced horizontal pleiotropy assumption, we used Inverse variance weighted regression to model the relation between effects on exposure and outcome for each of the genetic instrumental variants (IVs). We selected the variants showing genome-wide significant associations with (COVID-19) exposure[6] ($P < 5 \times 10^{-8}$), removed palindromic variants, applied Linkage Disequilibrium (LD) clumping (r^2 cutoff 0.1 and clumping window 1000 kb), and retained only the variants that were also tested in the "outcome" study, resulting in 17-23 variants for each analysis.

MR analyses were repeated, testing variants associated with three different COVID-19 exposures, namely all (112612), hospitalized (24274) and severe cases (8779; namely, patients who required respiratory support, or whose death was related to COVID-19)[6], compared to population controls (> 1 million, see https://www.covid19hg.org/results/r6/).

This analysis indicated a significant causal link between severe and hospitalized COVID-19 and the risk of Alzheimer's disease and anxiety disorder (AD) (Figure 1), which survived Bonferroni correction for six different outcome conditions ($\alpha = 8.3 \times 10^{-3}$).

This evidence is closely aligned with that from a large observational study[3], where patients who were hospitalized and required intensive care had a steeper increase in incident neuropsychiatric sequelae in the six months after infection. However, the increases observed here in Alzheimer (1%-3%) and anxiety risk (0.5%-1%) were considerably smaller than those reported by Taquet *et al*[3], although measures of incident and prevalent risk and the different design and setting of the studies mean they are not directly comparable. This might be explained by the typically low effect size of the common variants detected in GWAS and used in MR analysis, and by the type of comparison in the original study on COVID-19[6], where population controls can include a number of undetected cases, reducing the power of the comparison.

Our analysis presents some limitations. First, the use of summary statistics from a meta-analysis of diverse ancestries may introduce a population stratification bias. Although no data based only on



DOI: 10.5498/wjp.v12.i3.536

Figure 1 Mendelian randomization analysis testing (A) severe, (B) hospitalized and (C) all Covid-19 forms against the risk of neuropsychiatric/neurological disorders. Odds ratios with 95% confidence intervals and *P* value from Mendelian randomization analyses are reported for each disorder tested as outcome against the three forms of coronavirus disease 2019 tested as exposure, with the number of instrumental variants (#IVs) analyzed. MR: Mendelian randomization; AD: Alzheimer's disease; GAD: Generalized anxiety disorder; OR: Odds ratios; CI: Confidence interval; NA: Not available. *Not available on MR-Base (see Data Availability statement or [5] for details).

European samples are available for the COVID-19 GWAS round 6 meta-analysis, we carried out a sensitivity analysis with the round 5 (European) meta-analysis results. This provided significant evidence of causality between hospitalized COVID-19 forms and increased AD risk (by 1.8%, $P < 0.05$), while only a trend of association was observed for increased AD risk *vs* the other COVID-19 exposures (Table 1). No significant evidence of causality was found for anxiety, although severe COVID-19 slightly increased the risk of GAD by 0.6% ($P = 0.09$). Overall, effect sizes between MR analysis using round 6 and round 5 (only EUR) data were very similar, corroborating the bounty of our main analysis. The lack of significance in most of the sensitivity MR analyses may be due to the notably smaller number of IVs used (from 3 to 10), implied by the smaller sample size and lower power of the round 5 meta-analysis. Therefore, caution is suggested in interpreting these data and further analyses are needed based on larger datasets, of European ancestry.

Second, partial sample overlap between the studies analyzed may introduce a type I error inflation bias which, however, does not apply to case-control outcomes when risk factor IVs are tested only in control participants[7]. While we do know the exact prevalence of Alzheimer and anxiety cases in the COVID-19 GWAS, the relatively low prevalence of these disorders in the general population (especially AD) suggests the real bias introduced by sample overlap may be very close to zero.

Last, although converging epidemiological and genetic evidence supports a causal effect of COVID-19 infection on neuropsychiatric/neurodegenerative disorders, the exact molecular mechanisms of this relationship remain to be clarified. The most convincing hypotheses so far involve the neurotropic action of the virus, dysregulation of the inflammatory response and of the vascular system, which in turn promote mechanisms that can affect mental health, like alteration of the blood-brain barrier and neuro-inflammation[2,8,9]. While deeper functional analyses will help clarify these aspects, the evidence presented here underlines the need for a targeted screening strategy to tackle the neuropsychiatric effects.

Table 1 Mendelian randomization analysis testing (A) severe, (B) hospitalized and (C) all COVID-19 forms against Alzheimer and anxiety risk in European ancestry

Disease	MR-Base ID	#IVs	*P* value	OR [95%CI]
(A)				
AD	NA[1]	8	0.193	1.006 [0.998; 1.014]
GAD	ukb-d-20544_15	5	0.090	1.006 [0.998; 1.014]
(B)				
AD	NA[1]	3	0.047	1.018 [1.000; 1.036]
GAD	ukb-d-20544_15	3	0.250	1.010 [0.994; 1.026]
(C)				
AD	NA[1]	10	0.169	1.014 [0.994; 1.034]
GAD	ukb-d-20544_15	5	0.580	1.006 [0.985; 1.028]

[1]Not available on MR-Base (see Data Availability statement or [5] for details).
Odds ratios with 95% confidence intervals and *P* value from Mendelian randomization analyses are reported for each disorder tested as outcome against the three forms of coronavirus disease 2019 tested as exposure, with the number of instrumental variants (#IVs) analyzed. MR: Mendelian randomization; AD: Alzheimer's disease; GAD: Generalized anxiety disorder; OR: Odds ratios; CI: Confidence interval; NA: Not available.

FOOTNOTES

Author contributions: Tirozzi A and Santonastaso F contributed equally to the present manuscript; Gialluisi A was responsible for conceptualization and analysis plan; Gialluisi A, Tirozzi A and Santonastaso F did the statistical analysis; Gialluisi A and Tirozzi A drafted the first manuscript; Iacoviello L and de Gaetano G were responsible for the manuscript reviewing and editing; Tirozzi A and Santonastaso F were in charge of figures; all co-authors did the data interpretation and literature search.

Supported by Fondazione Umberto Veronesi (to Gialluisi A).

Conflict-of-interest statement: The authors declare no competing financial interests.

Country/Territory of origin: Italy

ORCID number: Alfonsina Tirozzi 0000-0002-6052-1807; Federica Santonastaso 0000-0001-7105-7504; Giovanni de Gaetano 0000-0002-7823-1402; Licia Iacoviello 0000-0003-0514-5885; Alessandro Gialluisi 0000-0002-7388-4463.

S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

REFERENCES

1 **Gialluisi A**, de Gaetano G, Iacoviello L. New challenges from Covid-19 pandemic: an unexpected opportunity to enlighten the link between viral infections and brain disorders? *Neurol Sci* 2020; **41**: 1349-1350 [PMID: 32372197 DOI: 10.1007/s10072-020-04444-z]
2 **de Erausquin GA**, Snyder H, Carrillo M, Hosseini AA, Brugha TS, Seshadri S; CNS SARS-CoV-2 Consortium. The chronic neuropsychiatric sequelae of COVID-19: The need for a prospective study of viral impact on brain functioning. *Alzheimers Dement* 2021; **17**: 1056-1065 [PMID: 33399270 DOI: 10.1002/alz.12255]
3 **Taquet M**, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *The Lancet Psychiatry [Internet]* 2021; **8**: 416-427 [DOI: 10.1016/S2215-0366(21)00084-5]
4 **Hemani G**, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; **7** [PMID: 29846171 DOI:

10.7554/eLife.34408]

5 **Jansen IE**, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, Sealock J, Karlsson IK, Hägg S, Athanasiu L, Voyle N, Proitsi P, Witoelar A, Stringer S, Aarsland D, Almdahl IS, Andersen F, Bergh S, Bettella F, Bjornsson S, Brækhus A, Bråthen G, de Leeuw C, Desikan RS, Djurovic S, Dumitrescu L, Fladby T, Hohman TJ, Jonsson PV. , Kiddle SJ, Rongve A, Saltvedt I, Sando SB, Selbæk G, Shoai M, Skene NG, Snaedal J, Stordal E, Ulstein ID, Wang Y, White LR, Hardy J, Hjerling-Leffler J, Sullivan PF, van der Flier WM, Dobson R, Davis LK, Stefansson H, Stefansson K, Pedersen NL, Ripke S, Andreassen OA, Posthuma D. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet* 2019; **51**: 404-413 [PMID: 30617256 DOI: 10.1038/s41588-018-0311-9]

6 **COVID-19 Host Genetics Initiative**. Mapping the human genetic architecture of COVID-19. *Nature* 2021; **600**: 472-477 [PMID: 34237774 DOI: 10.1038/s41586-021-03767-x]

7 **Burgess S**, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. *Genet Epidemiol* 2016; **40**: 597-608 [PMID: 27625185 DOI: 10.1002/gepi.21998]

8 **Iadecola C**, Anrather J, Kamel H. Effects of COVID-19 on the Nervous System. *Cell* 2020; **183**: 16-27.e1 [PMID: 32882182 DOI: 10.1016/j.cell.2020.08.028]

9 **Boldrini M**, Canoll PD, Klein RS. How COVID-19 Affects the Brain. *JAMA Psychiatry* 2021; **78**: 682-683 [PMID: 33769431 DOI: 10.1001/jamapsychiatry.2021.0500]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com