ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2022 October 19; 12(10): 1268-1312

Published by Baishideng Publishing Group Inc

WJP World Journal of Psychiatry

Contents

Monthly Volume 12 Number 10 October 19, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Observational Study

World Journal of Psychiatry

Monthly Volume 12 Number 10 October 19, 2022

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Xin-Qiao Liu, PhD, Associate Professor, School of Education, Tianjin University, Tianjin 300350, China. xinqiaoliu@pku.edu.cn

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, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJP* as 3.500; IF without journal self cites: 3.313; 5-year IF: 7.380; Journal Citation Indicator: 0.62; Ranking: 89 among 155 journals in psychiatry; and Quartile category: Q3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Psychiatry

ISSN
ISSN 2220-3206 (online)

LAUNCH DATE
December 31, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE
October 19, 2022

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Psychiatry

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

World J Psychiatry 2022 October 19; 12(10): 1268-1286

DOI: 10.5498/wjp.v12.i10.1268

ISSN 2220-3206 (online)

REVIEW

Substance use and substance use disorders in Africa: An epidemiological approach to the review of existing literature

Olakunle James Onaolapo, Anthony Tope Olofinnade, Foluso Olamide Ojo, Olufunto Adeleye, Joshua Falade, Adejoke Yetunde Onaolapo

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, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kar SK, India; Liu XQ, China; Setiawati Y, Indonesia

Received: March 4, 2022
Peer-review started: March 4, 2022
First decision: April 18, 2022
Revised: May 1, 2022
Accepted: September 7, 2022
Article in press: September 7, 2022
Published online: October 19, 2022

Olakunle James Onaolapo, Behavioral Neuroscience Unit, Neuropharmacology Subdivision, Department of Pharmacology, Ladoke Akintola University of Technology, Ogbomoso 210214 Oyo, Nigeria

Anthony Tope Olofinnade, Department of Pharmacology, Therapeutics and Toxicology, Lagos State University, Ikeja 100001, Lagos, Nigeria

Foluso Olamide Ojo, Olufunto Adeleye, Department of Anatomy, Ladoke Akintola University of Technology, Ogbomoso 210214, Oyo, Nigeria

Joshua Falade, Department of Mental Health, Afe Babalola University, Ado-Ekiti 360282, Ekiti, Nigeria

Adejoke Yetunde Onaolapo, Behavioral Neuroscience Unit, Neurobiology Subdivision, Department of Anatomy, Ladoke Akintola University of Technology, Ogbomoso 210214, Oyo, Nigeria

Corresponding author: Adejoke Yetunde Onaolapo, MBBS, MSc, PhD, Reader (Associate Professor), Behavioral Neuroscience Unit, Neurobiology Subdivision, Department of Anatomy, Ladoke Akintola University of Technology, Old Oyo/Ilorin Road Ogbomoso P.M.B 4000, Ogbomoso 210214, Oyo, Nigeria. adegbayibiy@yahoo.com

Abstract

The relationship between man and substances that have abuse potentials, and whose use has been associated with the development or progression of substance use disorders has continued to evolve in terms of geography, economic implications, and time. History shows that local plants with psychoactive constituents can get exported worldwide through global travel, commerce, or even conquest. Time and globalization also change people's relationship with substances of abuse; hence, an area that was initially alien to certain substances might evolve to becoming a trafficking hub, and then a destination. A case in point is Africa where a rapidly increasing prevalence of substance use/abuse and substance use disorder among adolescents and young adults is putting enormous strain on the economy, healthcare system, and society at large. However, there appears to be a paucity of scientific literature and data on the epidemiology, risk assessment, and contributing factors to substance use and the development of substance use disorders across Africa. In this narrative review, we examine extant literature (PubMed, Google scholar, Medline) for information on the prevalence, trends, and

influencers of substance use and the development of substance use disorders. This is with a view of understanding the determinants of substance use and factors that influence the development of substance use disorders in the region, and how this information can be channeled towards developing a comprehensive intervention and treatment program.

Key Words: Addiction; Cannabis; Catha edulis; Datura metal; Drug dependence; Novel psychoactive substances

Core Tip: Substance use for medicinal and recreational purposes dates back centuries; however, in recent times, substance use is increasingly becoming a global public health crisis. In Africa, there is a consensus that substance use is emerging as a public health crise, but there appears to be a paucity of data on the epidemiology, risk assessment, and contributing factors to substance use and the development of substance use disorders across Africa. Here, we examined the extant literature for information on the prevalence, trends, and influencers of substance use and substance use disorders as it relates to Africa.

Citation: Onaolapo OJ, Olofinnade AT, Ojo FO, Adeleye O, Falade J, Onaolapo AY. Substance use and substance use disorders in Africa: An epidemiological approach to the review of existing literature. *World J Psychiatry* 2022; 12(10): 1268-1286
URL: https://www.wjgnet.com/2220-3206/full/v12/i10/1268.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i10.1268

INTRODUCTION

Substance use and substance use disorders are increasingly becoming a global public health crisis, largely due to their increasing prevalence, worsening disability-adjusted life years, and high socioeconomic burden[1]. According to the World Drug Report, 2021[2], approximately 275 million people used drugs worldwide in the preceding year, with another 36 million persons diagnosed with substance use disorders globally[2]. In 2019 alone, substance use disorders were linked to about 18 million years of healthy life lost. Also, about 180000 deaths were directly linked to substance use disorders, while another half million deaths were attributed to illicit drug use[3].

Substance use is generally defined as a patterned use of any substance (including alcohol and/or psychoactive drugs) in quantities (or through methods) that are harmful to the user or others[4]. Substance use is often associated with varying degrees of intoxication, which is associated with alteration of judgment, attention, and perception. The use of alcohol, illicit drugs, and illegal use of prescription medications has been associated with negative impact on the individual's health and productivity, as well as a high socioeconomic burden on the family and society[5,6]. Globally, there is a rapidly rising prevalence of substance use and substance use disorders, with an associated increase in the morbidity and mortality. Also, in Africa, the use of illicit substances such as cannabis (the most widely used substance in Africa, with a prevalence of between 5.2% and 13.5% in West and Central Africa), amphetamine-type stimulants, and benzodiazepines is increasing rapidly[7]. Again, in the last decade, Africa has begun to be recognized as a consumer and a destination for illicit drugs, compared to being previously regarded as mainly a transit zone for these drugs (serving as a link between Latin America and Europe)[8,9]. This reversal of the illicit drug trend is believed to be a contributing factor to the rapid development of substance use epidemic, particularly in the urban centers of Africa.

There is a consensus that substance use (particularly among adolescents and young adults) in Africa is emerging as a public health crises; however, there appears to be a paucity of scientific literature and data on the epidemiology, risk assessment, and contributing factors to substance use and the development of substance use disorders across Africa. Here, we reviewed the extant literature for information on the prevalence, trends, and influencers of substance use and the development of substance use disorders. This is with a view of understanding the determinants of substance use and the factors that influence the development of substance use disorders in the region, and how this information can be channeled towards developing a comprehensive interventions and treatment program.

History of substance use and substance use disorders

Substance use for medicinal, religious, and recreational purposes dates back centuries. The earliest mentions of the use of alcoholic or fermented beverages in Chinese writing dates far back as the 7th

millennia B.C.E[10], although there is also evidence from Sumerian writing (2100 B.C.E) of the use of opium from the poppy plant[11]. While the earliest use had been linked mainly to medicinal and religious purposes[10-12], there are also documentations of their use for recreational purposes[12]. However, since ancient times, humans have recognized the health problems that may be associated with excess alcohol consumption[12-14].

In 2019, the United Nations Office on Drugs and Crime reported an estimated 35 million people having a substance use disorder necessitating treatment[15]. Surveys and results of prospective studies examining patterns of drug use among the general population has revealed substance use peaks between 18 years and 25 years of age[15,16] with drug use among young people exceeding that of older people[15,17].

History of substance use in Africa: From transit nations to major illicit drug destinations

The African continent has a long history of drug cultivation, production, trade and consumption; and there are also indigenous plants and herbs with psychoactive effects such as cannabis resin (known as hashish in North Africa), Catha edulis (known as Kath in East Africa), and cannabis (known as dagga in Southern Africa) that have also been used traditionally for centuries[18-21]. In the last few years, rapidly growing large-scale trade and recreational use of opiates, synthetic psychoactive stimulants, and prescription drugs are emerging threats in the African continent[21].

The relationship between North Africa and cannabis has existed for centuries, predating the arrival of the Spanish and French in the 19th century. Also, during the colonial era, cannabis was cultivated in small quantities across the northern Rif mountains in Morocco, and throughout the northern parts of Tunisia and Algeria[22]. While production was mainly to meet local demands (with some smuggling and exportation to Europe), the era following independence of the different countries in the region saw regulations and laws being enacted and enforced to control the production, sale, and use of cannabis. However, across the four countries (Morocco, Algeria, Tunisia and Libya) that make up the Maghreb (an area also known as northwest Africa), the drug trade has not only continued to grow, it is also evolving. In the last few decades, a region known mainly for the production of cannabis destined for other markets (particularly the European market) has increasingly become an important route for the trafficking of cocaine and different psychotropic pills. Since the beginning of the 21st century, trafficking routes for cocaine, cannabis resin, and psychotropic pills that existed between South America, Africa, and Europe shifted to transect the Maghreb region[22]. This change has been partly attributed to an increase in the demand for drugs in the region, and the perturbations of other transit zones such as the Sahel region, which has become unstable. Most important is the geographic location of the region, being a link between Africa, Middle East and Europe. While drug transit routes through North Africa is increasing, of more importance is the increasing rate of consumption of these drugs in the region. The use of psychotropic drugs, which are very addictive, is nearing epidemic proportions in the region; also, other substances being consumed include cannabis, cocaine and opioids[22].

Before West Africa began to be considered a transit zone for drugs, it was also a producer of cannabis products (although not on the scale of the North African countries), which were shipped to Europe and the United States. Although, at the same time, marijuana was being imported into Nigeria from South Africa and a region now known as the Democratic Republic of Congo[23]. The smuggling of heroin through West Africa was first documented in 1952[23]; however, West Africa's rise as a major drug smuggling hub began sometime in the 1960s, coinciding with a period of increased demand for illegal drugs, including marijuana which was grown and exported from Nigeria in large quantities to Europe. Despite attempts by governments in these countries to stem the tide of the marijuana export, marijuana trade continued illegally for several years until the demand for newer psychoactive substances such as cocaine and heroin overtook the demand for marijuana[24]. By the 990th year of the 2nd millennium and the 90th year of the 20th century, West Africa had become a major transit and repackaging center for substances such as cocaine and heroin through a transnational trade route that originated from South America and Asia, to Europe. While drug trafficking through Africa was not new, an intense clamp-down on the South-North American trade routes by the United States anti-narcotics strategies and the increase in demand for drugs across Europe saw to the rapid expansion of the West African trade routes in the early 21st century[25,26]. The geography of the West African states (made up of large areas of uninhabited islands and archipelagoes found in countries like Guinea Bissau) eased transit and made detection difficult[27]. Also, the vulnerable political environment with the presence of civil wars/insurgencies created fertile grounds for the development of criminal networks in the West African sub region [27].

Previously, when compared to West Africa, the drug trafficking routes through the Eastern belt of Africa were less robust; however, in the last few decades of this century, the trend is an increase in the trafficking of and the variety of trafficked drugs through the East African states of Kenya, Uganda, and Tanzania. Specifically, the trafficking of heroin and cocaine through these countries has grown considerably. Trafficking routes begin in Afghanistan where heroin is produced, through Pakistan and then East Africa enroute over Europe. The cocaine transnational trafficking routes began to go through East Africa in a bid to bypass the West African routes that were increasingly being watched by anti-drug trafficking authorities[28]. Also observed was that the increased consumption of these substances coincided with an increase in trafficking and affordability of the drugs.

In South Africa, a country in the southern region of Africa, the trafficking of drugs has increased. There are reports that since the period prior to and following the transition to democracy, there has been an escalation of drug trafficking. Trafficking in these parts has increased as a result of the easing of the strict control of land, air and sea borders, and an increase in international trade that occurred following the reintegration of South Africa into the committee of nations following the end of apartheid. Also, the effective policing of traditional smuggling routes prompting the search for other shipping routes also accounts for the increased trafficking of drugs through South Africa[29]. The increased trafficking is also worsening the substance use problems as a proportion of the drugs trafficked end up on the local market. There have also been reports that drugs such as methaqualone are also produced in clandestine laboratories in the region[30]. Overall, the level of affluence in the region makes it an attractive 'emerging market' for illicit drugs[30-32]. South Africa also has a history of drug use that dates as far back as the 15thcentury. Cannabis, which is known as dagga in South Africa, has been consumed traditionally for centuries. The cannabis plant was brought to southern Africa by Saheli merchants from eastern Africa and some members of the bantu tribe of central and southern Africa where it has been cultivated since the 15th century. Around the 16th and 18th century, the consumption of cannabis increased significantly[33]. Although initially popular only among the African population, over time, its use extended to the white population of South Africa[30].

Overall, while the current substance use epidemic in the African continent could be linked to the global trend in substance use, the transformation of African nations from mainly transit points in the international drug network to consumer countries would seem inevitable[34]. Also, the rapid socioeconomic changes that have occurred across the different countries that make up the African continent could have facilitated this shift in what can be assumed to be the "normal trend".

EPIDEMIOLOGY OF SUBSTANCE USE ACROSS THE AFRICAN CONTINENT

Across Africa, reports spanning the last two decades show that substance use especially among adolescents and young adults is increasing at alarming rates[19,35-41]. The World Health Organization and the United Nations Office on Drugs and Crime reported, an exponential increase in the per capita consumption of alcohol as well as the cultivation, trade, and consumption of cannabis in most of the countries in Africa, with suggestions that this could inevitably have adverse socioeconomic and public health implications[42-44]. At the time, about 10 countries in Africa were listed among the 22 countries with the highest increases in the use of alcohol and other psychoactive substances including cannabis, tobacco, cocaine, and heroin[45]. In 2013, the United Nations Office on Drugs and Crime World Drug Report estimated that across the African continent, more than 28 million people had a current history of substance use. Cannabis was also reported to be the most commonly used drug on the continent, with the prevalence estimated to be 7.5%, which was almost twice the global average. The use of opioids was also reportedly on the rise[46].

While it has been recognized that Africa is beginning to battle a drug use epidemic, with an estimated 37000 people in Africa dying annually from substance use-associated complications[47-49]; available data for Africa are still either weak or nonexistent. To date, in many African countries, there is still a paucity of national data regarding the epidemiology and patterns of substance use across populations, with available data largely limited to small prospective population studies and retrospective hospital-based studies.

In West Africa, the paucity of data regarding the prevalence of drug use undermines our ability to adequately understand the full extent of the substance use problem, and how it is creating a public health problem that further threatens the already fragile health system that currently exists. It also creates a false sense of safety, because it fosters the erroneous belief that substance use is under control. However, in the last few years, this trend is becoming more difficult to ignore, because there is now increasing evidence from the increase in crime/criminal behaviors and an increasing need for medical attention that arises from the development of substance use disorders or complications of risky behaviors that are consequences of drug use. In the last decade, in West African countries like Ghana, incident reports from health professionals, lawyers, and law enforcement officers are beginning to show dramatic increases in the domestic consumption of illicit drugs. However, these reports do not adequately portray the scale of substance use problem; because there is a dearth of national figures that can accurately quantify the prevalence of drug use in Ghana or most other West African countries. All of these result in a huge dependence on small-scale cross-sectional studies (Table 1). A 2008 population-based study conducted among school-going adolescents, reported that the prevalence of any substance use in the preceding 1 mo was 3.6%[50]. The results of an earlier study that interviewed a sample of 894 high school students with a mean age of 17.4 years, reported that the lifetime alcohol use in these cohort was 25.1%; with cigarette use and lifetime marijuana use being 7.5% and 2.6%, respectively. Also, current alcohol use was reported to be 46.2%; current cigarette and marijuana use was 44.6% and 58.3%, respectively[51]. The result of a 2014 cross-sectional survey of a sample of 227 street children and youths revealed that the current prevalence of alcohol and marijuana use was 12% and 16.2%, respectively. Sex differences in substance use was also reported with more females using alcohol, marijuana, and

Table 1 Epidemiology of substance use across the African continent

Region	Study type	Study group	Result	Ref.
Ghana	Population-based study	School-going adolescents	3.6% prevalence of substance use in the preceding 1 mo	[50]
Ghana	Cross-sectional study	894 high school students with a mean age of 17.4 yr	Lifetime alcohol use was 25.1%; with cigarette use and lifetime marijuana use being 7.5% and 2.6% respectively. Current alcohol use was 46.2%; current cigarette and marijuana use was 44.6%; and 58.3%, respectively	[51]
Ghana	Cross-sectional survey	227 street children and youths	Current prevalence of alcohol and marijuana use was 12% and 16.2%, respectively	[52]
Nigeria	Cross-sectional study Northwestern Nigeria	280 secondary school students	56% of them had a history of substance use (kolanut, cigarettes, and marijuana)	[53]
Nigeria	Cross-sectional study Southwestern Nigeria	249 secondary school students	Prevalence of alcohol and substance use was 21.7% and 26.3%, respectively, tramadol being the substance of choice	[54]
Nigeria	National drug survey	Population-based	Approximately 14.3 million people (accounting for 14.4% of the population aged between 15-64 yr) had a history of current and continuing substance drug use, with close to 3 million having at least a form of drug use disorder	[55]
Ethiopia	Demographic and health survey	Population-based	4% of youths and 6.3% of individuals in age groups of 25-29 yr smoked cigarettes, while 53% of men and 45% of women consumed alcohol	[59]
Ethiopia	Analysis of data extracted from the 2016 Ethiopia Demographic and Health Survey	12688 male cohorts	62.5% (7931 males) had a current history of substance use (alcohol, Kath, or tobacco). Inhabitants of the Amhara, Tigray and Oromia regions had a current substance use prevalence of 18.5%, 14.2% and 12.8%, respectively	[60]
Ethiopia	Cross-sectional study Northeastern Ethiopia	730 university students in	Lifetime prevalence of alcohol consumption, Kath chewing, and cigarette smoking was 33.1%, 13% and 7.9%, respectively, and current prevalence was 27.9%, 10.4% and 6.4%	[61]
Ethiopia	Cross-sectional study	794 university students	73.7% had a history of substance use with the lifetime prevalence of illicit drugs being 23.3%	[63]
Egypt	Hospital-based study (single-center experience)	First episode drug-induced psychosis patients	Substance abuse rates are as high as 10%-20% the global average with cannabis and tramadol being the most abused substance	[65]
Tunisia	Cross-sectional study	298 persons with a history of drug use	Cannabis was the most widely consumed illicit drug, followed by benzodiazepines, buprenorphine, cocaine, and ecstasy	[68]
Tunisia	Mediterranean school survey project	Secondary school students	Tobacco, alcohol, and cannabis were the substances most frequently used	[66, 67]
Tunisia	Epidemiologic/toxicological investigation Northern Tunisia	11170 suspected drug users	A preponderance of males (97.4%), with a median age of 29 ± 7.91 yr. 91.3 % were single	[69]
South Africa	School-based survey	Secondary school students	13% of the students (aged 19 yr and below) had an history of cannabis use, although current use was 9%. 12% had a current use of heroin, 11% used inhalants and 6% consumed mandrax	[73]
South Africa	National household survey	Population-based	Past 3 mo prevalence for cannabis among 15-19-years-old was 3%	[74]

smoking cigarettes compared to males[52]. In Nigeria, reports from small-scale studies have demonstrated a high prevalence of substance use among adolescents and young adults. A 2009 study that examined the prevalence of substance use among 280 students at a senior secondary school in a town in Northwest Nigeria, revealed that about 56% of them had a history of substance use, with the most common being kolanut, cigarettes, and marijuana[53]. Idowu *et al*[54] also examined the prevalence of substance use among 249 students (mean age = 16.3 ± 2 standard deviations) of secondary schools in a metropolis in south western Nigeria and reported that the prevalence of alcohol and substance use was 21.7% and 26.3%, respectively, with tramadol being the substance of choice[54]. The magnitude of the effect was best conveyed by the results of the 2018 National Drug Use Survey which revealed that approximately 14.3 million people (accounting for 14.4% of the population aged between 15 years and 64 years) had a history of current and continuing substance drug use, with close to 3 million having at least a form of drug use disorder[48,55]. A difference was also observed in the prevalence of drug use between the Northern and Southern geopolitical zones, with a higher prevalence in the regions in the south (13.8%-22.4% of the population) compared to those in the northern geopolitical zone (10%-14.9% of the population). In Nigeria, cannabis was the most commonly used drug, which was followed by opioids (non-prescription or in cough syrup)[48,56]. The survey also highlighted

a rise in the current use of psychoactive substances (including cannabis), the non-medical use of prescription drugs such tramadol, codeine, morphine or cough syrups that contain codeine or dextromethorphan[55]. Also observed was an overall high incidence of drug use (excluding alcohol) among males compared to females (10.8 million males *vs* 3.4 million females), although the sex difference in the non-medical use of prescription opioids, cough syrups, and sedatives was not as significant (6% among men compared to 3.3 among women). The survey also reported a higher incidence of drug use among young adults (24-39) compared to those aged 24 and below[55].

In East Africa, there is also a dearth of national statistical data on the prevalence of substance use in a number of the countries, with researchers and policy makers needing to rely on information from studies involving subsets of the populations. In Ethiopia, alcohol, Kath and tobacco are the most popular substances that are consumed[57,58]. A 2012 Ethiopian demographic and health survey reported that 4% of youths and 6.3% of individuals in age groups of 25-29 years smoked cigarettes, whereas 53% of men and 45% of women consumed alcohol[59]. Also, the results of a study by Girma *et al*[60] that analyzed data extracted from the 2016 Ethiopia Demographic and Health Survey revealed that of the 12688 male cohorts of the Ethiopian Demographic and Health Survey, at least 62.5% (7931 males) had a current history of substance use (alcohol, Kath, or tobacco) as at the time of the survey. Inhabitants of the Amhara, Tigray, and Oromia regions have a current substance use prevalence of 18.5%, 14.2%, and 12.8%, respectively. Alcohol (53.1%) is reportedly the most commonly consumed substance, followed closely by Kath, which has a prevalence of 25.9%[60]. Reports of small cross-sectional studies have also corroborated the high prevalence of alcohol, Kath, and cigarette smoking among Ethiopian youths[61]. Adere *et al*[61] examined a cohort of 730 university students in Northeastern Ethiopia and reported that the lifetime prevalence of alcohol consumption, Kath chewing, and cigarette smoking was 33.1%, 13%, and 7.9%, respectively, whereas the current prevalence of these substances is 27.9%, 10.4%, and 6.4%, respectively[61]. The prevalence observed in this study was similar to that observed in an earlier study carried out among the students at a University in a town in North Ethiopia[62]. While earlier studies among university students did not report evidence to suggest the use of illicit drugs, the results of a 2021 cross-sectional study among 794 students of Addis Ababa University, showed that 73.7% of the study participants had a history of substance use with the use of illicit drugs having a lifetime prevalence of 23.3%[63]. However, similar to other studies, alcohol, Kath, and cigarettes were still the most commonly abused substances[63].

In North Africa, data and information on substance use, production, trafficking, and consumption are also limited. This has been attributed to a lack of capacity for data collection and analysis[64]. In Egypt, there are reports that substance abuse rates are as high as 10%-20% the global average, with cannabis and tramadol being the most abused substances[65]. In Tunisia, an increase in the trafficking and consumption of psychoactive substances have been observed since the political uprising that occurred in 2011[66]. There have also been reports of increased availability of drugs of abuse, particularly to school students[66]. These increases have been confirmed by a few epidemiological studies[66-68]. Moslah *et al*[68] carried out a study to examine the pattern of substance use among 298 persons with a history of drug use between 2010 and 2015. The results showed that among these cohort of young adults, cannabis was the most widely consumed illicit drug, followed by benzodiazepines, buprenorphine, cocaine, and ecstasy[68]. Reports from the Mediterranean School Survey Project on Alcohol and Other Drugs (II) carried out in Tunisia in 2017 revealed that tobacco, alcohol, and cannabis were the substances most frequently used by secondary school students[67], whereas psychotropic drugs such as ecstasy, cocaine, and buprenorphine were less frequently consumed. More importantly, it was observed that the frequency of use of these substances has increased significantly since the first survey published in 2014[66]. Chaouali *et al*[69] carried out an epidemiologic/toxicological investigation to evaluate patterns of drug abuse in 11170 suspected drug users. Urine samples collected between January 2016 and December 2018 were also analyzed. Results revealed a preponderance of males (97.4%) compared to females, with a median age of 29 ± 7.91 years. Also observed was that a large percentage of these drug users were single (91.3%). Examination of the urine samples revealed that about 48.4% tested positive for illicit drugs, with cannabis being the most widely consumed drug (95%), others were benzodiazepines, buprenorphine, cocaine, and opiates (0.13%). There was also a history of poly drug use[69].

In Southern Africa (although there are limited national data in most countries in the region), a rise in substance use has been reported[70]. In some of these countries including Zimbabwe, there is anecdotal evidence suggesting an increase in substance use among adolescents and young adults, with prevalence of substance use reportedly ranging from 6.1% to 13.8%[70]. Alcohol, cannabis, heroin, glue, and cough mixtures are among the most commonly consumed products in Zimbabwe. Cannabis, which is commonly known as mbanje, is grown locally (also smuggled into Zimbabwe from Malawi and Mozambique), and remains the most popular illicit drug among young Zimbabweans. Drugs are also trafficked through Zimbabwe to other countries in the region, including South Africa. In South Africa, an increase in substance use has been reported, which has been linked to the increased availability of illicit drugs including cannabis, cocaine, heroin, amphetamines, and ecstasy; either from diversion during trafficking or increased cultivation and local production[29,30,71,72]. Other factors that have contributed to the increase in substance use include an increase in migration and easing of border controls following the commencement of democracy, which have facilitated the development of youths'

movements that indirectly or directly promote substance use[30]. Results from surveys have revealed a gradual increase in cannabis consumption among adolescents and young adults in South Africa.

A 2002 school-based survey reported that 13% of the students (aged 19 years and below) had an history of cannabis use, although current use was 9%. About 12% had a current use of heroin, 11% used inhalants, and 6% consumed Mandrax[73]. The results of another study (a 2005 National household survey) showed that the prevalence in the past 3 mo for cannabis among 15-19-years-old was 3%[74]. In another study examining the prevalence and patterns of use of illicit substances among persons presenting at drug treatment centers in South Africa, it was revealed that cannabis (16.9%), methamphetamine (12.8%), cocaine (9.6%), and prescription drugs (2.6%) were the substances commonly used among patients. Also, there was evidence of poly drug use, with cannabis and mandrax having a prevalence of 3.4%, whereas heroin and opiates had a prevalence of 9.2%[75].

Prior to 1994 and the first democratic elections, alcohol, cannabis, and methaqualone were the primary substances of misuse in South Africa. With South Africa's transition to democracy and subsequent reopening of borders, there has been an influx of and a growing burden of harm associated with illicit drug use. Alcohol, however, remains the most commonly misused substance, with 14% of the population having a lifetime diagnosis of alcohol abuse and/or dependence (Herman *et al*[76], 2009). Although the overall levels of alcohol consumption do not exceed those in the developed world, the pattern of consumption differs markedly, with hazardous and binge drinking being common.

New and emerging psychoactive substances in Africa

Use of novel psychoactive substances is an emerging trend in substance use that is fast becoming a public health challenge globally[77,78]. Novel or new psychoactive substances have been defined by the United Nations Office on Drugs and Crime[79] as substances of abuse (existing either in its pure form or as a preparation) that are not controlled by either the 1961 or 1971 conventions on narcotic drugs and psychotropic substances, respectively, but pose significant threats to public health globally due to spikes in intoxications and fatalities associated with their use[79,80]. The term 'novel' or 'new' that is used in relation to these substances depicts their recent emergence in the global market. Substances that currently fall within the novel psychoactive substance category include (but are not limited to) synthetic cathinone and cannabinoids, synthetic opioids, image and performance-enhancing substances, tryptamine derivatives, piperazines, phencyclidine-like dissociatives, gamma amino-butyric acid (A)/beta receptor agonists, novel hallucinogens, benzodiazepines and psychotropic plants/herbs[77,81,82].

In the last few years or more, there has been a growing demand and supply chain for these new psychoactive substances[77,78,81]. In the last 10-12 years, the number of novel psychoactive substances has increased considerably. In 2009, only about 166 of them had been detected; however, by 2019, the number had risen to about 950, with more than 70% of these substances available in Europe[80,83]. While in the developed economies, a lot is being done to ensure continued documentation of novel psychoactive substances as they emerge, it would seem that Africa is only beginning to awaken to the emerging public health threat that these substances pose to her teeming population of adolescents and young adults[82]. While the lifetime prevalence of novel psychoactive substance use in countries such as the United States have been examined[80], there is a paucity of data on the prevalence of novel psychoactive substance use in Africa. Although across the continent, there is increasing awareness of the dangers of novel psychoactive substance use.

In 2017, attention was called to an increase in the use of designer drugs in Nigeria. Some of these substances which have street names such as "black mamba", Colorado", "Lamba", "happy boy", and" Scooby snax" are believed to contain synthetic cannabinoids. Their use is associated with a rise in the incidence of hallucinations, convulsions, psychiatric disorders, kidney failure and fatalities[84]. News outlets, including the British Broadcasting Corporation News and Premium Times, also reported that the use of and addiction to non-conventional psychoactive substances such as tramadol and codeine cough syrups among Nigerian youths was reaching epidemic proportions[85,86]. In Nigeria, available novel psychoactive substances also include mixtures with street names such as "gutter water", a cocktail of cannabis, tramadol, codeine and ethanol), and "monkey tail", a cocktail of locally made gin and cannabis (seeds, leaves, stems, and roots). Some people have also been in a state of euphoria from drinking the mixture of specific carbonated drinks and menthol flavored candies[82]. The sniffing of dry human fecal matter, dry cassava leaves and seeds, Datura metal seeds, Moringa leaf, burnt tires, sewer gas, and nail polish have also been reported[82,87]. Different parts of some lizards, including the whitish part of their dung, are also smoked in a bid to achieve a "high"[82,87]. The inhalation of urine, sewage, petrol, and glue are also common practice among drug users in Africa. It is believed that the hallucinogens present in hydrocarbons from petrol, and gases produced from fermentation of sewage have the ability to cause a "euphoric high" similar to (but longer lasting) when compared to that derived from the ingestion of cocaine[88].

In southern Africa, particularly South Africa, there have been reports of the use of "Nyaope" also known as "Whoonga", which is a cocktail of low-grade heroin (black tar heroin), marijuana, antiretroviral drugs (Efavirenz), and other undisclosed substances[88]. In East African countries such as Uganda and Kenya, the habit of using novel psychoactive substances such as the sniffing of aviation gas/jet fuel, toluene and glue is reaching epidemic proportions among persons aged between 16-25

years[89-91]. Other substances that are abused in this region include "kuber" and" shisha", also known as hookahs ,which are variants of smokeless tobacco. There have been reports that compared to cigarettes, the smoking of the shisha or hookah pipe exposes the user to higher volumes of smoke containing high levels of benzene, tar, and other carcinogens and increased risk of lung cancer[92-95].

In Northern Africa, the smoking of hashish and the chewing of Kath has become very rampant. Although there is little data from the region regarding the prevalence and patterns of use of novel psychoactive substances; reports from studies carried out in Egypt have suggested that the estimated prevalence of novel psychoactive substance use among adolescents in the country are largely underestimated[96]. However, tabloid reports have called attention to an increasing demand and use of novel psychoactive substances including "voodoo" and "strox" among adolescents and young adult in Egypt [97,98]. "Voodoo" is gaining popularity rapidly, and it is usually packaged and sold as an herbal incense. "Voodoo" is a heterogeneous mixture of several psychoactive substances, including synthetic cannabinoids, tramadol, amphetamine, methadone, benzodiazepines, penitrem A (a neurotoxin) and morphine derivatives. The concentrations of the chemical constituents and adulterants of voodoo also vary substantially among the different clandestine laboratories that produce it[96,99]. Another novel psychoactive substance that is gaining popularity in Egypt is "Strox"[100]. "Strox" or "Egyptian Spice" has been reported to account for approximately 4.3% of the over 10400 patients requiring medical support for drug-related complications[101]. Also, addiction to "strox" was responsible for 22% of calls to the addiction center hotline[101]. "Strox" is a potent synthetic narcotic that is mixed with tobacco and smoked; it is compounded in clandestine laboratories by adding veterinary grade chemicals to aromatic herbs such as marjoram. There have also been reports of the addition of pesticides to increase the potency, although this increases the toxicity[97].

The search for novel psychoactive substances is fueled by the need to create drugs that are able to evade the chemical processes used for detection and the legal processes that criminalizes the use and possession of conventional drugs of abuse. Also, the need for compounds that deliver fast and sustained psychoactive effects when compared to the conventional drugs also drive the search for novel psychoactive compounds[102]. However, the variability of the chemical constituents and/or adulterants of the different compounds present a conundrum for the health professional who has to decipher and manage the divergent symptoms and signs that complicate the use of these substances. Hence. there is an increasing need for continuous surveillance so that new or emerging psychoactive substances can be discovered before they wreak havoc on our communities.

African plants and herbs with psychostimulant potential: Are they being abused?

Several plants and parts of plants have been shown to have central nervous system effects[103-109]. Also, current literature reveals that novel psychoactive substances can be derived from either synthetic compounds or from bioactive principles of natural compounds. These bioactive principles which are mainly alkaloids are present in a wide variety of plants including Ayahuasca, Catha edulis and nicotiana tabacum; and have been reported to possess hallucinogenic and/or stimulant effects[110]. Plants with psychoactive properties are found all over the globe and have been used for centuries by humans, for religious, therapeutic and recreational purpose[111,112]. Studies have shown that the bioactive principles of these plants enable the profound alteration of the human perception allowing for divination, ancestral contact, and spiritual enlightenment[111-113].

Africa has a high floral diversity and a rich tradition of indigenous medicinal plant and herb use [111]. Africa is also rich in flora of medicinal plants that possess central nervous system effects[107]. Although there is a paucity of ethnobotanical surveys on African plants with psychoactive effects, evidence from African traditional healers and diviners who use plants such as the 'Ubulawu', a preparation containing *Sileneundulata* and *Synaptolepis* are pointers that there are plants indigenous to Africa that contain compound which have mood altering effects[113]. A few plant species that are indigenous to Africa, such as the Cola species (Cola nitida, and Cola acuminata), Catha edulis (Kath), Datura species (Datura stramonium), Pausinystalia yohimbe (Burantashi Pausinytalia yohimbe) and Tabernanthe iboga have reported psychoactive properties[111,114], and have been used recreationally (Table 2) for centuries in the countries in which they are cultivated. However, in recent times, the use of and dependence on some of these plants by adolescents and young adults (either alone or combined with established illicit drugs) is reaching epidemic proportions. In this section, we reviewed the abuse potential of some psychoactive plants that are indigenous to the African continent.

Kath (Catha edulis Forsk) is a flowering plant native to countries in East Africa and the Horn of Africa. Fresh young leaves and twigs from Kath are chewed daily by large populations of people for its psycho-stimulatory properties. The chewing of Kath dates back centuries, being a practice that is rooted in tradition, social custom and the culture of the indigenous populations[115]. It has been reported that more than 20 million people worldwide chew Khat[116,117]. Although traditionally a custom associated with older middle Eastern and Eastern African men, Khat's use is now expanding to include women and younger persons. In the Eastern region of Ethiopia, approximately 30% of adolescent girls and 70% of adolescent boys chew Khat. The active principle contained in Khat is cathinone (an alkaloid), which is a stimulant that causes excitement, appetite loss and euphoria[117]. In countries such as Somalia, Ethiopia, Djibouti, and Kenya, the dependence on Kath is warranting its consideration as a substance of abuse. In Somalia a law prohibiting the use, cultivation, importation and trade of Kath was enacted and

Table 2 African plants and herbs with psychostimulant potential

Region	Herbal preparation	Plant	Bioactive compound	Central nervous system activity	Toxicity	Ref.
East Africa	Khat chewing, drink made from dried leaves or smoking dried leaves	Catha Edulis	Phenylalkylamines and the cathedulins (Cathinone)	Improves performance, stay alert and to increase work capacity, excitement, appetite loss and euphoria	Memory impairment, sleeping disorders, liver toxicity, cardiovascular disease, psychosis and poor academic performance	[115, 117, 124-126]
West Africa	Different parts of the plant are smoked or used to make concoctions	Datura specie including stramonium and Datura metal	Atropine, scopolamine, and hyoscamine	Anticholinergic and hallucinogenic activity	Hyperthermia, tachycardia, delirium, pronounced amnesia, severe mydriasis, bizarre behaviors and painful photophobia	[135, 136, 141, 145-148]
West Africa	Root bark concoctions	Tabernanthe iboga	Ibogaine	Stimulatory, hallucinogenic, and sedative effects	Development of ataxia, tremor, cardiac toxicity, and death	[149-151]
South Africa	Ubulawu drink	Silene undulata and Synaptolepis	Triterpenoid saponins	Mood altering effects including stimulating vivid or lucid dreams	Confusion	[113]
South Africa	Chewed, smoked, snorted or swallowed	Sceletium tortuosum	Mesembrenone, mesembrenol, mesembrine and tortuosamine	Increased libido, decreased stress, euphoria and appetite suppression	Anxiety, headache, hypertension, irritability, insomnia and nausea	[154, 155]

enforced by comprehensive national program[118]. At about the same period (approximately two decades ago), Kath was also considered by the World Health Organization and classified as a drug of abuse, although its abuse potential was not thought to constitute a serious problem compared with that of alcohol or tobacco[119]. Across a region extending across Africa and the Middle East, predominantly among the Ethiopians, Somalians and Yemenis, approximately 5 to 20 million people use Kath[116,120], with the consumers engaged in the practice for the best part of a day resulting in a loss of manpower and national income[121,122]. In 2005, a survey by the World Health Organization revealed a prevalence of 20% Kath abuse in Kenya, exceeding the prevalence observed in most of the other countries in the region[123]. However, more recent studies are demonstrating that in spite of attempts by the respective countries to criminalize the use of Kath, Kath chewing is fast becoming a common practice among young adults in countries like Kenya, Ethiopia, Somalia, Djibouti[124-126]. In Ethiopia, a study carried out among academic staff of a university revealed that the lifetime prevalence of Kath chewing was 41%[126], while another study carried out among college students reported a prevalence of 42%[124]. In Kenya, a recent household survey revealed that the prevalence of current Kath chewing in the region was 36.8%[125], which would suggest a significant rise from the 20% prevalence reported by the World Health Organization[123]. While Kath chewing was not previously known outside the regions within which it was cultivated, the effects of migration and trade have propelled it to a widely used psychostimulant globally[115,127]. Kath chewing has been associated with adverse health effects that is creating public health challenges in countries across Asia, Europe, Australia, and the United States of America[128-130]. When chewed concurrently with tobacco, there have been reports of cardiovascular stress response[129]. It has also been associated with the alteration of physical, mental, social and cognitive aspects of human functioning[131]. Chewing Kath chronically has been reported to cause memory impairment, sleeping disorders, liver toxicity, cardiovascular disease, psychosis and poor academic performance[126,132]. While attempts are being made by countries to criminalize the importation and trade of Kath, smugglers continue to find new avenues and trade routes. For example, in 2016, the National Drug Law Enforcement Agency of Nigeria reported seizures of Kath load, which was possibly destined for the Nigerian market or enroute countries[133]. However, in 2020, the United States customs reported seizure of Kath load from Nigeria destined for the United States suggesting that Nigeria is fast becoming a Kath transit hub[134].

In Nigeria, complicating the substance abuse epidemic is the emerging trend of experimenting with plant extracts or brews from a group of flowering plants belonging to the Datura specie, of the nightshade family Solanaceae[135,136]. Although members of the Datura specie which are broadly known as thorn apple, devil's apple, devil's trumpet or angel's trumpet have their origin in central Americas and in the south-west region of the United States if America[137,138], they have become naturalized all over the world, being widespread in Asia, Europe, and Africa[139]. The datura specie is made up of herbs and shrubs with erect or branched stems, with alternate simple basal leaves and opposite leaves on terminal branches[139]. The fruit has a spiny capsule and reniform seeds[139,140]. All parts of the Datura stramonium and Datura metal plant has been shown to contain tropane alkaloids such as atropine, scopolamine, and hyoscyamine which have significant anticholinergic and hallucinogenic activity[141]. The high tropane alkaloid content of these plants increases their medicinal value and also opens them up to potential abuse. In Nigeria, Datura stramonium (thorn apple, devil's

snare, devil's trumpet or jimsonweed) and Datura metal (Indian thorn apple) are naturalized. Similar to a number of countries across the world (United States of America and Canada) where there has been reports of datura-induced poisoning among adolescents who abuse the plant for its hallucinogenic effects[142-144], adolescents and young adults in Nigeria are also experimenting with the plant and getting poisoned[136]. Datura metal grows wildly (although at times it is cultivated) across the different regions of Nigeria where it is called 'Myaramuo' by the Igbos of south eastern Nigeria, 'Zakami' by Hausas of northern Nigeria and 'Apikan' by the Yorubas of southwestern Nigeria[145,146]. Datura stramonium also grows as a weed and is also cultivated across the different states of Nigeria. It is known as 'Gegemu' by the Yorubas and 'Zakami' by the Hausas[136]. Both plants have been reported to have hallucinogenic and euphoric effects when the different parts of the plant are either smoked or used to make concoctions[147]. Datura stramonium poisoning is associated with hyperthermia, tachycardia, delirium, pronounced amnesia, severe mydriasis, bizarre behaviors and painful photophobia[136,148]. These features can appear as early as 30 min to 1 h following consumption of the extract or smoking of the weed and have been reported to last several hours to days or at times even as long as 2 wk[148].

Another plant with psychoactive properties is the Western African shrub Tabernanthe iboga from whose root bark ibogaine, a hallucinogenic alkaloid is extracted. Traditionally, the concoctions from the roots have been used for their stimulatory, hallucinogenic, and sedative effects[149]. Ibogaine has been reported to exhibit stimulant effects at low doses and result in the development of hallucinations at high doses. Its use has also been associated with the development of ataxia, tremor, cardiac toxicity, and death[149-151]. There have also been reports that ibogaine has anti-addictive properties, although its use is limited by its deleterious effects[152,153].

In southern Africa, the use of extracts, dried-powdered herb, tincture, tea bags and seeds of the plant sceletium tortuosum also known as Kanna is also gaining traction. These different compositions of the plant can be chewed, smoked, snorted or swallowed resulting in increased libido, decreased stress, euphoria and appetite suppression. There are reports attributing the antidepressant and mood-elevating effects of the plant to the serotoninergic activity of its alkaloids including mesembrenone, mesembrenol, mesembrine, and tortuosamine. Indiscriminate use has been associated with the development of anxiety, headache, hypertension, irritability, insomnia and nausea[154,155]. A serotonin syndrome has also been observed especially when consumed alongside selective serotonin reuptake inhibitors or monoamine oxidase inhibitors. Although the use of a number of these plants and herbs may not be illegal in the countries in which they are consumed, increasing reports of poisoning arising from the use or these psychoactive plants solely or in combination with other compounds is drawing attention to the need to enact public health laws that can criminalize their use.

Synthetic cannabinoid in herbal products

Synthetic cannabinoids are compounds which are structurally similar to natural cannabinoids [tetrahydrocannabinol and cannabidiol (CBD)] allowing them to exert their effect through binding to cannabinoid receptors (CBD1 and CBD2)[156,157]. Synthetic cannabinoids can be agonists at the CB_1 receptors or antagonists at other cannabinoid receptors. Although many of the synthetic cannabinoids are used in pharmacology in structure - activity relationships and receptor binding studies, others have medicinal uses including in the treatment of anorexia, as antiemetics in cancer chemotherapy and in pain management. In the last two decades, commercial preparations containing synthetic cannabinoids have become popular for their use as designer drugs marketed as herbal incense or herbal blends under the names 'Spice', 'synthetic marijuana', and 'K2'[158-160]. The cannabinoid compound is sprayed onto inert plant material and smoked or ingested in liquid form[160,161]. Although often considered legal and safe alternatives to cannabis, there is evidence indicating that synthetic cannabinoids use is associated with significant health risks when compared to marijuana; there have also been reports that their distinct pharmacological effects and metabolic activity could also be a contributing factor to the increased toxicity observed following their use[157,162,163].

To date, the abuse of herbal preparations that have been spiked with synthetic cannabinoids continues to increase. This is evidenced by an increasing list of commercial preparations marketed in the United States and Europe under the names fairly legal, Pandora's box, Angry birds, exodus, bonzai, annihilation, weekend blend, fire, strong spice, green Buddha, smoke, and Scooby snacks[102,164]. In the last few years, Africa is also beginning to experience a surge in demand for and use of synthetic cannabinoids. In Mauritius, since the year 2015, there has been a reported increase the number of arrests involving synthetic cannabinoids[165]. In different countries in the continent they are marketed under various street names including, Wiz in South Africa[166]. In Nigeria it is marketed as Black Mamba, Colorado, Lamba, Happy Boy or Scooby Snax[167].

Across Africa, available evidence points to a growing use of novel psychoactive compounds which mainly contain synthetic cannabinoids. Synthetic cannabinoids have effects that are similar to that experienced with natural cannabis, although they are more potent and have been associated with more severe physical and psychological adverse effects necessitating hospitalizations[168,169].

PREVALENCE OF SUBSTANCE USE DISORDERS AND AVAILABILITY OF EVIDENCE-BASED TREATMENT CENTRES IN AFRICA

Substance use disorders are defined as the persistent use of alcohol or other psychoactive substances despite significant harm and untoward health consequences[170]. They are characterized by an array of social, emotional and behavioral problems. Across Africa, there is also a dearth of scientific data on the prevalence of substance use disorders or drug dependence[48,55,56,171]. In Nigeria, reports from the 2018 National Drug Survey revealed that one in every five persons who used drug in the past year also had a drug-related disorder[48,55,56]. In South Africa, results obtained from a nationally representative sample of 4351 persons aged 18 years and above revealed a lifetime prevalence of substance use disorders of 13%, with alcohol use disorder being the most prevalent type of substance use disorders[72,171-173]. In Egypt, reports obtained from the National Addiction Research Study revealed the prevalence of drug dependence in the different regions ranged from 3.2%-9.3%[174].

Left untreated, substance use disorders contribute significantly to the global burden of disease, including increasing morbidity and mortality and societal cost implications such as increased healthcare costs, lost productivity and costs related to social welfare and criminal justice[4,5]. Access to evidence-based treatment has been linked with a reduction in the risk for ill health[171]. Accordingly, towards reducing the burden of substance use globally, availability and access to evidence-based treatment facility were included in the United Nations' Sustainable Development Goals for 2030[175]. However, despite reports of increasing prevalence of drug dependence and substance use disorders, reports from surveys carried out in a number of countries in Africa suggest that the availability of treatment centers are limited[171,176]. Factors contributing to this treatment gap include treatment infrastructure constraints, poor funding, and the high cost of private-for-profit treatment centers[171,176].

How can Africa's burgeoning substance use and substance use disorder problem be addressed

It has become evident that there is a burgeoning illicit drug use problem across the African continent[47-49,177]. There had been predictions that by the year 2050, increased life expectancy and a rapidly growing population would result in approximately 130% increase in the burden of mental and substance use disorders to about 45 million years lived with disability in Africa[178]. While different factors, including increased access to illicit drugs and high level of youth unemployment have been adduced to explain the emerging drug use pandemic; its significant contribution to economic instability, crime, criminality and insecurity across Africa and worldwide means that governments and policy makers need to prioritize the need to develop ways to mitigate these problems. The dearth of comprehensive data and the uniqueness of the manifestation of illicit drug use to individual countries within the African region are factors that impede progress towards addressing this looming pandemic.

Understanding the different determinants of drug use within the different populations of Africans and how these impact the prevention and treatment of substance abuse disorders in the individual countries would be an important step towards addressing this emerging pandemic. Currently available data suggests that influencers of drug use (particularly in adolescents) which include family, social networks and peer pressure are common to most of the countries[179-184]. Other determinants of drug use also include childhood trauma and adverse life experiences such as sexual, emotional or physical abuse. Across age groups, demographic factors such as being male, lower level of education and attendance of private schools have also been reported by researchers from the different regions of Africa [185-187].

In addition to understanding the influencers and determinants of drug use, there is also a need for up-to-date national and regional data that can adequately determine the prevalence and incidence of drug use across all demographics. The availability of a detailed and comprehensive national data would provide a background against which policy successes or failures can be measured, it would also alert governments and international partners on the need for increased funding or more treatment facilities.

The deleterious health effects of drug use disorders means that the provision of effective prevention, treatment and care facilities for substance use disorders is a necessary investment in the health of the society as a whole. Research has shown that the availability of evidence based prevention programs and policies have the ability to significantly reduce substance use and related harmful effects[188]. Behavioral and medication-assisted treatment using a chronic-illness-management approach has also been shown to aid recovery and prevent relapse. There have been suggestions that easy access to support services assist previous substance users to achieve and maintain wellness long-term[188].

Addressing the ease of access to drugs and other illicit substances within communities and regions need to be taken more seriously. There is a need to gather information on the different types of novel psychoactive substances that are available within communities and also create awareness as to the adverse health effects associated with consuming these compounds.

Limitations and recommendations

One of the major limitations encountered in this review was the dearth of recent, community based and age specific scientific data on the prevalence and extent of the substance abuse problems in most of the countries in Africa. There was also a deficit of data on the details and impact of the country-specific

intervention protocols. This led to reliance mainly on third party data from international; partners and a few independent researchers. The battle to win this emerging substance–use pandemic in Africa can only be successful if there is increased emphasis in documenting the extent of the problem and country specific interventions; particularly at the community levels with emphasis on how different age groups are impacted by substance abuse.

CONCLUSION

In Africa, substance use and substance use disorders drain struggling economies and health care systems. While the continent might have some general idea of what it is up against, understanding the details of the problem and availability of the willpower/wherewithal to subdue it remains a challenge. It is becoming obvious that there is no substitute for well-designed, accurate and comprehensive population-focused efforts at obtaining data that relates to substance use and substance use disorders, since such data will form the foundations for designing effective intervention strategies. Also, in Africa, interventional strategies should place emphasis on prevention, through identification of and mitigation of risk factors, as this approach is likely to consume less resources in the long run.

FOOTNOTES

Author contributions: All authors contributed to the writing of this article.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Nigeria

ORCID number: Olakunle James Onaolapo 0000-0003-2142-6046; Anthony Tope Olofinnade 0000-0002-9492-9958; Foluso Olamide Ojo 0000-0002-5560-9740; Adejoke Yetunde Onaolapo 0000-0001-7126-7050.

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

REFERENCES

1 **Prom-Wormley EC**, Ebejer J, Dick DM, Bowers MS. The genetic epidemiology of substance use disorder: A review. *Drug Alcohol Depend* 2017; **180**: 241-259 [PMID: 28938182 DOI: 10.1016/j.drugalcdep.2017.06.040]
2 **United Nations Office on Drugs and Crime**. World Drug Report 2021. [cited 15 January 2022]. Available from: https://www.unodc.org/unodc/data-and-analysis/wdr2021.html
3 **World Health Organization**. Global health estimates: Leading causes of death. [cited 15 January 2022]. Available from: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death
4 **Leikin JB**. Substance-related disorders in adults. *Dis Mon* 2007; **53**: 313-335 [PMID: 17645897 DOI: 10.1016/j.disamonth.2007.04.001]
5 **GBD 2016 Alcohol and Drug Use Collaborators**. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry* 2018; **5**: 987-1012 [PMID: 30392731 DOI: 10.1016/S2215-0366(18)30337-7]
6 **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]
7 **World Health Organization**. Regional Office For Africa 2021. [cited 15 January 2022]. Available from: https://www.afro.who.int/
8 **Wyler LS**, Cook N. Illegal Drug Trade in Africa: Trends and U.S. Policy. Washington: Congressional Research Service, 2009
9 **Csete J**, Sánchez C. Telling the story of drugs in West Africa: The newest front in a losing war? Global Drug Policy Observatory, Swansea University, 2013
10 **McGovern PE**, Zhang J, Tang J, Zhang Z, Hall GR, Moreau RA, Nuñez A, Butrym ED, Richards MP, Wang CS, Cheng

G, Zhao Z, Wang C. Fermented beverages of pre- and proto-historic China. *Proc Natl Acad Sci U S A* 2004; **101**: 17593-17598 [PMID: 15590771 DOI: 10.1073/pnas.0407921102]
11 **Norn S**, Kruse PR, Kruse E. [History of opium poppy and morphine]. *Dan Medicinhist Arbog* 2005; **33**: 171-184 [PMID: 17152761]
12 **Crocq MA**. Historical and cultural aspects of man's relationship with addictive drugs. *Dialogues Clin Neurosci* 2007; **9**: 355-361 [PMID: 18286796 DOI: 10.31887/DCNS.2007.9.4/macrocq]
13 **O'Brien JM**. Alexander and Dionysus: the invisible enemy: a biography. New York: Routledge, 1992
14 **Berrios G**, Porter R. A History of Clinical Psychiatry The Origin and History of Mental Disorders. London: The Athlone Press, 1995: 656
15 **United Nations**. World Drug Report 2019. [cited 15 January 2022]. Available from: https://www.unodc.org/unodc/en/data-and-analysis/wdr2021.html
16 **Merikangas KR**, McClair VL. Epidemiology of substance use disorders. *Hum Genet* 2012; **131**: 779-789 [PMID: 22543841 DOI: 10.1007/s00439-012-1168-0]
17 **United Nations Office on Drugs and Crime**. World Drug Report 2018. [cited 15 January 2022]. Available from: https://www.unodc.org/wdr2018/
18 **Hill BG**. Chat (Catha edulis forsk). *J Ethiop Stud* 1965; **3**: 13-23
19 **Acuda W**, Othieno CJ, Obondo A, Crome IB. The epidemiology of addiction in Sub-Saharan Africa: a synthesis of reports, reviews, and original articles. *Am J Addict* 2011; **20**: 87-99 [PMID: 21314750 DOI: 10.1111/j.1521-0391.2010.00111.x]
20 **Ambler C**. The drug empire: control of drugs in Africa, a global perspective. In: Klantschnig G, Carrier N, Ambler C. Drugs in Africa: histories and ethnographies of use, trade and control. New York: Palgrave Macmillan, 2014: 25-47
21 **Eligh J**. The evolution of illicit drug markets and drug policy in Africa. Jun 30, 2019. [cited 15 January 2022]. Available from: https://enactafrica.org/research/continental-reports/the-evolution-of-illicit-drug-markets-and-drug-policy-in-africa
22 **Herbert M**, Gallien M. A rising tide Trends in production, trafficking and consumption of drugs in North Africa. Switzerland: Global Initiative Against Transnational Organized Crime, 2020
23 **Ellis S**. West Africa's International Drug Trade. *Afr Aff* 2009; **108**: 171-196 [DOI: 10.1093/afraf/adp017]
24 **Akyeampong E**. Diaspora and Drug Trafficking in West Africa: A Case Study of Ghana. *Afr Aff* 2005; **104**: 429-447 [DOI: 10.1093/afraf/adi015]
25 **United Nations**. World Drug report 2011. [cited 15 January 2022]. Available from: https://www.unodc.org/unodc/en/data-and-analysis/WDR-2011.html
26 **United Nations Office on Drugs and Crime**. Regional Programme West Africa 2010-2014. [cited 15 January 2022]. Available from: https://www.unodc.org/documents/evaluation/indepth-evaluations/2015/RP_West_Africa_Final_In-Depth_Evaluation_Report_Dec_2015.pdf
27 **Aning K**, Pokoo J. Understanding the nature and threats of drug trafficking to national and regional security in West Africa. *Stability: Int J Secur Dev* 2014; **3**: p.Art. 8 [DOI: 10.5334/sta.df]
28 **Aucoin C**. Analysing drug trafficking in East Africa A media-monitoring approach. Jul 2, 2018. [cited 15 January 2022]. Available from: https://enactafrica.org/research/research-papers/analysing-drug-trafficking-in-east-africa-a-media-monitoring-approach
29 **Pasche S**, Myers B. Substance misuse trends in South Africa. *Hum Psychopharmacol* 2012; **27**: 338-341 [PMID: 22585594 DOI: 10.1002/hup.2228]
30 **United Nations Office on Drugs and Crime**. South Africa country profile on drugs and crime. [cited 15 January 2022]. Available from: https://www.unodc.org/pdf/southafrica/country_profile_southafrica_1.pdf
31 **Kibble S**. Drugs and development in South Africa: How Europe could help. London: Catholic Institute for International Relations, 1998
32 **Parry C**. The illegal narcotics trade in Southern Africa: A programme for action. *South African Institute of International Affairs* 1997; **5**: 38-70 [DOI: 10.1080/10220469709545209]
33 **Obervatoire Geopolitique des Drogues**. The Geopolitical Drug Dispatch. Boston: Northeastern University Press, 1996: 235
34 **Affinnih YH**. A review of literature on drug use in Sub-Saharan Africa countries and its economic and social implications. *Subst Use Misuse* 1999; **34**: 443-454 [PMID: 10082066 DOI: 10.3109/10826089909035655]
35 **Anochie IC**, Nkanginieme KEO. Social correlates of drug use among secondary school students in Port Harcourt, Southern Nigeria. *Sahel Med J* 2000; **3**: 87-92
36 **Ayuba LS**, Audu DM. Alcohol and illicit drug abuse among children and adolescents in Jos Nigeria. *Highland Med Res J* 2005; **1**: 18-22 [DOI: 10.4314/hmrj.v1i3.33809]
37 **Lamptey J**. Socio-demographic Characteristics of Substance Abusers Admitted to a Private Specialist Clinic. *Ghana Med J* 2005; **39**: 2-7 [PMID: 17299533 DOI: 10.4314/gmj.v39i1.35973]
38 **Bronwyn M**, Charles DHP. Access to substance abuse treatment services for black South Africans: Findings from audits of specialist treatment. *African J Psychiatry* 2005; **8** [DOI: 10.4314/ajpsy.v8i1.30179]
39 **Betencourt OA**, Herrera MM. Alcohol and drug problems and sexual and physical abuse at three urban high schools in Mthatha. *SAFP* 2006; **48**: 17-17c [DOI: 10.1080/20786204.2006.10873369]
40 **Okwaraji FE**. Substance abuse among secondary school adolescents in Enugu. *J Med College* 2006
41 **Ngesu LM**, Ndiku J, Masese A. Drug dependence and abuse in Kenyan secondary schools: Strategies for intervention. *Educ Res Rev* 2008; **3**: 304-308 [DOI: 10.5897/ERR.9000107]
42 **World Health Organization**. Global Status Report on Alcohol 2004. [cited 15 January 2022]. Available from: https://www.who.int/publications/i/item/global-status-report-on-alcohol-2004
43 **Morojele NK**, Brook JS. Substance use and multiple victimisation among adolescents in South Africa. *Addict Behav* 2006; **31**: 1163-1176 [PMID: 16253426 DOI: 10.1016/j.addbeh.2005.09.009]
44 **United Nations Office on Drugs and Crime**. Cannabis in Africa. [cited 15 January 2022]. Available from:

https://www.unodc.org/documents/data-and-analysis/Can_Afr_EN_09_11_07.pdf
45 **Olawole-Isaac A**, Ogundipe O, Amoo EO, Adeloye D. Substance use among adolescents in sub-Saharan Africa: a systematic review and meta-analysis. *S Afr J Child Health* 2018; **12**: 79 [DOI: 10.7196/SAJCH.2018.v12i2b.1524]
46 **United Nations Office on Drugs and Crime**. World Drug Report 2013. [cited 15 January 2022]. Available from: https://www.unodc.org/unodc/en/scientists/world-drug-report-2013.html
47 **United Nations Office on Drugs and Crime**. World Drug Report 2016. [cited 15 January 2022]. Available from: https://www.unodc.org/wdr2016/
48 **United Nations Office on Drugs and Crime**. Drug use in Nigeria. [cited 15 January 2022]. Available from: https://www.unodc.org/documents/data-and-analysis/statistics/Drugs/Drug_Use_Survey_Nigeria_2019_BOOK.pdf
49 **United Nations Office on Drugs and Crime**. World Drug Report 2019. [cited 15 January 2022]. Available from: https://wdr.unodc.org/wdr2019/
50 **Owusu A**. Ghana Country report on the global school-based health survey (GSHS). Atlanta: Center for Disease Control and Prevention, 2008
51 **Adu-Mireku S**. The Prevalence of Alcohol, Cigarette, and Marijuana Use Among Ghanaian Senior Secondary Students in an Urban Setting. *J Ethn Subst Abuse* 2003; **2**: 53-65 [DOI: 10.1300/J233v02n01_05]
52 **Oppong Asante K**, Meyer-Weitz A, Petersen I. Substance use and risky sexual behaviours among street connected children and youth in Accra, Ghana. *Subst Abuse Treat Prev Policy* 2014; **9**: 45 [PMID: 25428774 DOI: 10.1186/1747-597X-9-45]
53 **Idris SH**, Sambo MN. Psycho-active substance use among in-school adolescents in Zaria, north western Nigeria: what are the triggers? *Niger J Med* 2009; **18**: 291-294 [PMID: 20120648 DOI: 10.4314/njm.v18i3.51191]
54 **Idowu A**, Aremu AO, Olumide A, Ogunlaja AO. Substance abuse among students in selected secondary schools of an urban community of Oyo-state, South West Nigeria: implication for policy action. *Afr Health Sci* 2018; **18**: 776-785 [PMID: 30603011 DOI: 10.4314/ahs.v18i3.36]
55 **United Nations Office on Drugs and Crime**. Drug use in Nigeria Executive summary. [cited 15 January 2022]. Available from: https://www.unodc.org/documents/data-and-analysis/statistics/Drugs/Drug_Use_Survey_Nigeria_2019_Exsum.pdf
56 **Jatau AI**, Sha'aban A, Gulma KA, Shitu Z, Khalid GM, Isa A, Wada AS, Mustapha M. The Burden of Drug Abuse in Nigeria: A Scoping Review of Epidemiological Studies and Drug Laws. *Public Health Rev* 2021; **42**: 1603960 [PMID: 33796340 DOI: 10.3389/phrs.2021.1603960]
57 **Teferra S**. Substance use among university students in Ethiopia: A systematic review and meta-analysis. *Ethiop J Health Dev* 2018; **32**: 265-277
58 **Abajobir AA**, Kassa GM. A meta-analytic review of gender disparity in the magnitude of substance use among young people in Ethiopia. *Ethiop Med J* 2019; **57**: 295-307
59 Central Statistical Agency [Ethiopia] and ICF International. Ethiopia demographic and health survey. Addis Ababa and Calverton: Central Statistical Agency and ICF International, 2011: 2012
60 **Girma E**, Mulatu T, Ketema B. Polysubstance use behavior among the male population in Ethiopia: Findings from the 2016 Ethiopia Demographic and Health Survey. *Ethiop J Health Dev* 2020; **34**
61 **Adere A**, Yimer NB, Kumsa H, Liben ML. Determinants of psychoactive substances use among Woldia University students in Northeastern Ethiopia. *BMC Res Notes* 2017; **10**: 441 [PMID: 28870246 DOI: 10.1186/s13104-017-2763-x]
62 **Gebreslassie M**, Feleke A, Melese T. Psychoactive substances use and associated factors among Axum University students, Axum Town, North Ethiopia. *BMC Public Health* 2013; **13**: 693 [PMID: 23895376 DOI: 10.1186/1471-2458-13-693]
63 **Shegute T**, Wasihun Y. Prevalence of Substance Use in University Students, Ethiopia. *Subst Abuse* 2021; **15**: 11782218211003558 [PMID: 33854324 DOI: 10.1177/11782218211003558]
64 **Badri N**. Drug Policy in Tunisia: Towards an Evidence based Human Rights and Public Health Approach. Tunisia: Centre for Applied Policy Research, 2017
65 **Taha M**, Taalab YM, Abo-Elez WF, Eldakroory SA. Cannabis and Tramadol are Prevalent among the First Episode Drug-Induced Psychosis in the Egyptian Population: Single Center Experience. *Reports* 2019; **2**: 16 [DOI: 10.3390/reports2020016]
66 **Aounallah-skhiri H**, Zalila H, Zid T, Boukassoula H, Ben Salah N. Drug situation and policy in Tunisia. [cited 15 January 2022]. Available from: https://rm.coe.int/drug-situation-and-policy-by-pr-hajer-aounallah-skhiri-medecin-epidemi/168075f2a4
67 Résultats de l'enquête nationale MedSPAD II (Mediterranean School Survey Project on Alcohol and Other Drugs). [cited 15 January 2022]. Available from: https://rm.coe.int/2017-ppg-med-41-medspad-tunisia-report-fra/16808cbf44
68 **Moslah B**, Araoud M, Nouioui MA, Najjar S, Amira D, Ben Salah N, Hedhili A. Fast screening tests for the simultaneous detection of 11 drugs of abuse in urine specimens. A forensic epidemiology study of 28,298 cases in Tunisia. *Forensic Sci Int* 2018; **283**: 35-40 [PMID: 29248810 DOI: 10.1016/j.forsciint.2017.12.004]
69 **Chaouali N**, Moslah B, Salem KB, Amira D, Hedhili A, Salah NB. Illicit substances identified in the urine of 11.170 suspected drug users in North Tunisia. *Pan Afr Med J* 2021; **38**: 20 [PMID: 34567345 DOI: 10.11604/pamj.2021.38.20.26781]
70 **Matutu V**, Mususa D. Drug and Alcohol Abuse Among Young People in Zimbabwe: A Crisis of Morality or Public Health Problem. *SSRN Electron J* 2019 [DOI: 10.2139/ssrn.3489954]
71 **Atkins A**. The illegal drugs trade and development in South Africa: some observations. London: Catholic Institute for International Relations, 1997
72 **Manu E**, Douglas M, Ayanore MA. Socio-ecological influences of adolescence marijuana use initiation: Qualitative evidence from two illicit marijuana-growing communities in South Africa. *S Afr J Psychiatr* 2020; **26**: 1477 [PMID: 32934841 DOI: 10.4102/sajpsychiatry.v26i0.1477]
73 **Reddy SP**, Panday S, Swart D, Jinabhai CC, Amosun SL, James S, Monyeki KD, Stevens G, Morejele N, Kambaran NS,

Omardien RG, Van den Borne HW. Umthenthe Uhlaba Usamila - The 1st South African Youth Risk Behaviour Survey 2002. Cape Town: South African Medical Research Council, 2003

74 **Shisana O**, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S, Pillay V. South African National HIV prevalence, HIV incidence, Behaviour and Communication Survey. Cape Town: HSRC Press, 2005

75 **Peltzer K**, Ramlagan S, Johnson BD, Phaswana-Mafuya N. Illicit drug use and treatment in South Africa: a review. *Subst Use Misuse* 2010; **45**: 2221-2243 [PMID: 21039113 DOI: 10.3109/10826084.2010.481594]

76 **Herman AA**, Stein DJ, Seedat S, Heeringa SG, Moomal H, Williams DR. The South African Stress and Health (SASH) study: 12-month and lifetime prevalence of common mental disorders. *S Afr Med J* 2009; **99**: 339-344 [PMID: 19588796]

77 **Elliott S**, Evans J. A 3-year review of new psychoactive substances in casework. *Forensic Sci Int* 2014; **243**: 55-60 [PMID: 24810679 DOI: 10.1016/j.forsciint.2014.04.017]

78 **Peacock A**, Bruno R, Gisev N, Degenhardt L, Hall W, Sedefov R, White J, Thomas KV, Farrell M, Griffiths P. New psychoactive substances: challenges for drug surveillance, control, and public health responses. *Lancet* 2019; **394**: 1668-1684 [PMID: 31668410 DOI: 10.1016/S0140-6736(19)32231-7]

79 **UNODC**. UNODC Early Warning Advisory on New Psychoactive substances. [cited 15 January 2022]. Available from: https://www.unodc.org/LSS/Home/NPS

80 **Neicun J**, Yang JC, Shih H, Nadella P, van Kessel R, Negri A, Czabanowska K, Brayne C, Roman-Urrestarazu A. Lifetime prevalence of novel psychoactive substances use among adults in the USA: Sociodemographic, mental health and illicit drug use correlates. Evidence from a population-based survey 2007-2014. *PLoS One* 2021; **16**: e0251006 [PMID: 33125395 DOI: 10.1371/journal.pone.0241056]

81 **Vicknasingam B**, Narayanan S, Singh D, Corazza O. Global strategy for New Psychoactive Substances: an update. *Curr Opin Psychiatry* 2020; **33**: 295-300 [PMID: 32398543 DOI: 10.1097/YCO.0000000000000612]

82 **Dumbili EW**, Ebuenyi ID, Ugoeze KC. New psychoactive substances in Nigeria: A call for more research in Africa. *Emerging Trends Drugs, Addictions, Health* 2021; **1**: 100008 [DOI: 10.1016/j.etdah.2021.100008]

83 **European Monitoring Centre for Drugs and Drug Addiction**. European Drug Report 2020: Trends and Developments. [cited 15 January 2022]. Available from: https://www.emcdda.europa.eu/publications/edr/trends-developments/2020_en

84 **Akande S**. A new deadly form of marijuana is slowly wreaking havoc in Nigeria's cities. Jul 24, 2017. [cited 15 January 2022]. Available from: https://www.pulse.ng/gist/synthetic-marijuana-black-mamba-a-new-deadly-form-of-marijuana-is-slowly-wreaking/r4dmxpn#:~:text=A%20new%20deadly%20form%20of%20marijuana%20is%20slowly,that%20can%20lead%20to%20death.%20%7C%20Pulse%20Nigeria

85 **Premium Times**. Katsina NDLEA seizes trailer loaded with codeine cough syrups. Mar 20, 2018. [cited 15 January 2022]. Available from: https://www.premiumtimesng.com/regional/nwest/262409-katsina-ndlea-seizes-trailer-loaded-with-codeine-cough-syrups.html

86 Nigeria's Deadly Codeine Cough Syrup Epidemic. 2021. London: BBC News

87 **Danjuma A**, Taiwo A, Omoniyi S, Balarabe S, Kolo S, Sarah S, Nassa Y. Nonconventional use of substances among youth in Nigeria: viewpoints of students in a Nigerian Tertiary Institution. *J Nurs Care* 2015 [DOI: 10.4172/2167-1168.1000311]

88 **Ong'olo JM**. An Overview of Drug Use in Africa - a Continental Perspective. [cited 15 January 2022]. Available from: https://www.issup.net/files/2020-09/Overview%20of%20Drug%20Use%20in%20Africa%20-%20JMO-AU_15.9.20.pdf

89 Nairobi Glue Pusher Preys on Addicted Kids to Help Her Own. Rear Window [Film]; 2012. Boston: The World from PRX

90 Inside the dark world of sniffing fuel. January 23, 2018. [cited 15 January 2022]. Available from: https://www.monitor.co.ug/uganda/news/insight/inside-the-dark-world-of-sniffing-fuel-1737140

91 **Dutta NS**, Roy SD. Are Kenyan kids turning into Zombies? Read to know more about the horrifying documentary 'Zombies of Nairobi'. [cited 15 January 2022]. Available from: https://www.northeasternchronicle.in/news/are-kenyan-kids-turning-into-zombies-read-to-know-more-about-the-horrifying-documentary-zombies-of-nairobi/

92 **Blank MD**, Cobb CO, Kilgalen B, Austin J, Weaver MF, Shihadeh A, Eissenberg T. Acute effects of waterpipe tobacco smoking: a double-blind, placebo-control study. *Drug Alcohol Depend* 2011; **116**: 102-109 [PMID: 21277706 DOI: 10.1016/j.drugalcdep.2010.11.026]

93 **Shihadeh A**, Salman R, Jaroudi E, Saliba N, Sepetdjian E, Blank MD, Cobb CO, Eissenberg T. Does switching to a tobacco-free waterpipe product reduce toxicant intake? *Food Chem Toxicol* 2012; **50**: 1494-1498 [PMID: 22406330 DOI: 10.1016/j.fct.2012.02.041]

94 **Qasim H**, Alarabi AB, Alzoubi KH, Karim ZA, Alshbool FZ, Khasawneh FT. The effects of hookah/waterpipe smoking on general health and the cardiovascular system. *Environ Health Prev Med* 2019; **24**: 58 [PMID: 31521105 DOI: 10.1186/s12199-019-0811-y]

95 **Kahuthia-Gathu R**, Okwarah P, Gakunju R, Thungu J. Trends and emerging drugs in Kenya: A case study in Mombasa and Nairobi County. *J Appl Biosci* 2013; **67**: 5308 [DOI: 10.4314/jab.v67i0.95055]

96 **Hussien R**, El-Setouhy M, Shinawi ME, El-Hariri HM, Hirshon JM. Acute Toxic Effects of the New Psychoactive Substance "Voodoo" among Patients presented to the Poison Control Center of Ain Shams University Hospitals (PCC-ASUH), Egypt, during 2017. *Subst Abuse Treat Prev Policy* 2021; **16**: 71 [PMID: 34544462 DOI: 10.1186/s13011-021-00408-4]

97 **Abdelaty A**. Egypt says cheap new drug 'Strox' threatens its youth Healthcare Pharma. Nov 20, 2018. [cited 15 January 2022]. Available from: https://www.arabnews.com/node/1408131/middle-east

98 Voodoo and Strox: the synthetic drugs wreaking havoc in Cairo. The France 24 Observers. 23 Jul 2018. Available from: https://observers.france24.com/en/voodoo-strox-synthetic-drugs-wreaking-havoc-cairo

99 **Hussien R**, Ahmed S, Awad H, El-Setouhy M, El-Shinawi M, Hirshon JM. Identification of 'Voodoo': an emerging substance of abuse in Egypt. *Int J Environ Anal Chem* 2022; **102**: 104-116 [PMID: 35002018 DOI: 10.1080/03067319.2020.1715384]

100 **El-Masry M**, Abdelkader SI. Clinical profile of designer drug "Strox" intoxicated cases presented to Poison control center

Ain Shams University, Egypt from first of January 2017 to end of January 2018. *Ain Shams J Forensic Med Clin Toxicol* 2021; **36**: 98-105 [DOI: 10.21608/ajfm.2021.138857]

101 **Hashim AMM**, Hassan AM, Amin GE, Allam MF. Prevalence of Strox Smoking Among University Students in Cairo, Egypt. *Open Public Health J* 2020; **13**: 425-429 [DOI: 10.2174/1874944502013010425]

102 **Hassan Z**, Bosch OG, Singh D, Narayanan S, Kasinather BV, Seifritz E, Kornhuber J, Quednow BB, Müller CP. Novel Psychoactive Substances-Recent Progress on Neuropharmacological Mechanisms of Action for Selected Drugs. *Front Psychiatry* 2017; **8**: 152 [PMID: 28868040 DOI: 10.3389/fpsyt.2017.00152]

103 **Olofinnade AT**, Alawode A, Onaolapo AY, Onaolapo OJ. Lepidium meyenii Supplemented Diet Modulates Neurobehavioral and Biochemical Parameters in Mice Fed High-Fat High-Sugar Diet. *Endocr Metab Immune Disord Drug Targets* 2021; **21**: 1333-1343 [PMID: 32955007 DOI: 10.2174/1871530320666200821155005]

104 **Olofinnade AT**, Onaolapo AY, Stefanucci A, Mollica A, Olowe OA, Onaolapo OJ. Cucumeropsis mannii reverses high-fat diet induced metabolic derangement and oxidative stress. *Front Biosci (Elite Ed)* 2021; **13**: 54-76 [PMID: 33048776 DOI: 10.2741/872]

105 **Olofinnade AT**, Onaolapo AY, Onaolapo OJ, Olowe OA, Mollica A, Zengin G, Stefanucci A. Corylus avellana L. modulates neurobehaviour and brain chemistry following high-fat diet. *Front Biosci (Landmark Ed)* 2021; **26**: 537-551 [PMID: 33049682 DOI: 10.2741/4906]

106 **Olofinnade AT**, Onaolapo AY, Onaolapo OJ, Olowe OA. Hazelnut Modulates Neurobehaviour and Ameliorates Ageing-induced Oxidative Stress, and Caspase-3-Mediated Apoptosis in Mice. *Curr Aging Sci* 2021; **14**: 154-162 [PMID: 33371863 DOI: 10.2174/1874609813666201228112349]

107 **Onaolapo AY**, Onaolapo OJ. African Plants with Antidiabetic Potentials: Beyond Glycaemic Control to Central Nervous System Benefits. *Curr Diabetes Rev* 2020; **16**: 419-437 [PMID: 31702529 DOI: 10.2174/1573399815666191106104941]

108 **Onaolapo AY**, Abdusalam SZ, Onaolapo OJ. Silymarin attenuates aspartame-induced variation in mouse behaviour, cerebrocortical morphology and oxidative stress markers. *Pathophysiology* 2017; **24**: 51-62 [PMID: 28254270 DOI: 10.1016/j.pathophys.2017.01.002]

109 **Onaolapo OJ**, Odeniyi AO, Onaolapo AY. Parkinson's Disease: Is there a Role for Dietary and Herbal Supplements? *CNS Neurol Disord Drug Targets* 2021; **20**: 343-365 [PMID: 33602107 DOI: 10.2174/1871527320666210218082954]

110 **Lo Faro AF**, Di Trana A, La Maida N, Tagliabracci A, Giorgetti R, Busardò FP. Biomedical analysis of New Psychoactive Substances (NPS) of natural origin. *J Pharm Biomed Anal* 2020; **179**: 112945 [PMID: 31704129 DOI: 10.1016/j.jpba.2019.112945]

111 **Stafford GI**, Jäger AK, Staden JV. African Psychoactive Plants. In: African Natural Plant Products: New Discoveries and Challenges in Chemistry and Quality. Washington: American Chemical Society, 2010: 323-346

112 **Umit Sayin H**. Psychoactive Plants Used during Religious Rituals. In: Victor RP. Neuropathology of Drug Addictions and Substance Misuse. London: Academic Press, 2016: 17-28

113 **Sobiecki JF**. Psychoactive ubulawu spiritual medicines and healing dynamics in the initiation process of Southern Bantu diviners. *J Psychoactive Drugs* 2012; **44**: 216-223 [PMID: 23061321 DOI: 10.1080/02791072.2012.703101]

114 **Oestreich-Janzen S**. Caffeine: Characterization and Properties. In: Caballero B, Finglas PM, Toldrá F. Encyclopedia of Food and Health. London: Academic Press, 2016: 556-572

115 **Patel NB**. "Natural Amphetamine" Khat: A Cultural Tradition or a Drug of Abuse? *Int Rev Neurobiol* 2015; **120**: 235-255 [PMID: 26070760 DOI: 10.1016/bs.irn.2015.02.006]

116 **Corkery J**, Schifano F, Oyefeso A, Ghodse AH, Tonia T, Naidoo V, Button J. 'Bundle of fun' or 'bunch of problems'? *Drugs Educ Prev Policy* 2011; **18**: 408-425 [DOI: 10.3109/09687637.2010.504200]

117 **Malasevskaia I**, Al-Awadhi AA, Mohammed L. Tea in the Morning and Khat Afternoon: Health Threats Due to Khat Chewing. *Cureus* 2020; **12**: e12363 [PMID: 33527046 DOI: 10.7759/cureus.12363]

118 **Elmi AS**, Ahmed YH, Samatar MS. Experience in the control of khat-chewing in Somalia. *Bull Narc* 1987; **39**: 51-57 [PMID: 2896525]

119 **Al-Juhaishi T**, Al-Kindi S, Gehani A. Khat: A widely used drug of abuse in the Horn of Africa and the Arabian Peninsula: Review of literature. *Qatar Med J* 2012; **2012**: 1-6 [PMID: 25003033 DOI: 10.5339/qmj.2012.2.5]

120 **Mateen FJ**, Cascino GD. Khat chewing: a smokeless gun? *Mayo Clin Proc* 2010; **85**: 971-973 [PMID: 21037041 DOI: 10.4065/mcp.2010.0658]

121 **Chapman MH**, Kajihara M, Borges G, O'Beirne J, Patch D, Dhillon AP, Crozier A, Morgan MY. Severe, acute liver injury and khat leaves. *N Engl J Med* 2010; **362**: 1642-1644 [PMID: 20427816 DOI: 10.1056/NEJMc0908038]

122 **Gudata ZG**, Cochrane L, Imana G. An assessment of khat consumption habit and its linkage to household economies and work culture: The case of Harar city. *PLoS One* 2019; **14**: e0224606 [PMID: 31689323 DOI: 10.1371/journal.pone.0224606]

123 **World Health Organization**. Expert Committee on Drug Dependence. [cited 15 January 2022]. Available from: https://www.who.int/groups/who-expert-committee-on-drug-dependence

124 **Teni FS**, Surur AS, Hailemariam A, Aye A, Mitiku G, Gurmu AE, Tessema B. Prevalence, Reasons, and Perceived Effects of Khat Chewing Among Students of a College in Gondar Town, Northwestern Ethiopia: A Cross-Sectional Study. *Ann Med Health Sci Res* 2015; **5**: 454-460 [PMID: 27057386 DOI: 10.4103/2141-9248.177992]

125 **Ongeri L**, Kirui F, Muniu E, Manduku V, Kirumbi L, Atwoli L, Agure S, Wanzala P, Kaduka L, Karimi M, Mutisya R, Echoka E, Mutai J, Mathu D, Mbakaya C. Khat use and psychotic symptoms in a rural Khat growing population in Kenya: a household survey. *BMC Psychiatry* 2019; **19**: 137 [PMID: 31064338 DOI: 10.1186/s12888-019-2118-3]

126 **Yeshaw Y**, Zerihun MF. Khat chewing prevalence and correlates among university staff in Ethiopia: a cross-sectional study. *BMC Res Notes* 2019; **12**: 673 [PMID: 31639065 DOI: 10.1186/s13104-019-4706-1]

127 **Nencini P**, Grassi MC, Botan AA, Asseyr AF, Paroli E. Khat chewing spread to the Somali community in Rome. *Drug Alcohol Depend* 1989; **23**: 255-258 [PMID: 2568922 DOI: 10.1016/0376-8716(89)90089-6]

128 **Al-Samarraie M**, Khiabani HZ, Opdal MS. [Khat--a new drug of abuse in Norway]. *Tidsskr Nor Laegeforen* 2007; **127**: 574-576 [PMID: 17332809]

129 **al'Absi M**, Nakajima M, Dokam A, Sameai A, Alsoofi M, Saem Khalil N, Al Habori M. Concurrent tobacco and khat use is associated with blunted cardiovascular stress response and enhanced negative mood: a cross-sectional investigation. *Hum Psychopharmacol* 2014; **29**: 307-315 [PMID: 24706595 DOI: 10.1002/hup.2403]

130 **El-Menyar A**, Mekkodathil A, Al-Thani H, Al-Motarreb A. Khat use: history and heart failure. *Oman Med J* 2015; **30**: 77-82 [PMID: 25960830 DOI: 10.5001/omj.2015.18]

131 **Gebrie A**, Alebel A, Zegeye A, Tesfaye B. Prevalence and predictors of khat chewing among Ethiopian university students: A systematic review and meta-analysis. *PLoS One* 2018; **13**: e0195718 [PMID: 29649253 DOI: 10.1371/journal.pone.0195718]

132 **Vento S**, Dzudzor B, Cainelli F, Tachi K. Khat-related liver disease in sub-Saharan Africa: neglected, yet important - Authors' reply. *Lancet Glob Health* 2019; **7**: e311 [PMID: 30784631 DOI: 10.1016/S2214-109X(18)30521-7]

133 **Sahara Reporters**. NDLEA Reveals Circulation Of New Illicit Drug In Nigeria, As Agency Nabs 4,838 Traffickers In First Half Of 2016. [cited 15 January 2022]. Available from: https://saharareporters.com/2016/10/06/ndlea-reveals-circulation-new-illicit-drug-nigeria-agency-nabs-4838-traffickers-first

134 **Loudoun NOW**. Dulles CBP Seizes Khat Load from Nigeria. Apr 2, 2020. [cited 15 January 2022]. Available from: https://www.loudounnow.com/2020/04/02/dulles-cbp-seizes-khat-load-from-nigeria/

135 **Soni P**, Siddiqui AA, Dwivedi J, Soni V. Pharmacological properties of Datura stramonium L. as a potential medicinal tree: an overview. *Asian Pac J Trop Biomed* 2012; **2**: 1002-1008 [PMID: 23593583 DOI: 10.1016/S2221-1691(13)60014-3]

136 **Adegoke SA**, Alo LA. Datura stramonium poisoning in children. *Niger J Clin Pract* 2013; **16**: 116-118 [PMID: 23377485 DOI: 10.4103/1119-3077.106783]

137 **Symon DE**, Haegi L Datura (Solanaceae) is a new world genus. In: Hawkes JG, Lester RN, Nee M, Estrada N. Solanaceae III: taxonomy, chemistry, evolution. London: Royal Botanic Gardens Kew, 1991: 197-210

138 **Luna-Cavazos M**, Bye R, Jiao M. The origin of Datura metel (Solanaceae): genetic and phylogenetic evidence. *Genet Resour Crop Evol* 2009; **56**: 263-275 [DOI: 10.1007/s10722-008-9363-5]

139 **Kerchner A**, Farkas Á. Worldwide poisoning potential of Brugmansia and Datura. *Forensic Toxicol* 2020; **38**: 30-41 [DOI: 10.1007/s11419-019-00500-2]

140 **Castroviejo S**, Aedo C, Laínz M, Muñoz Garmendia F, Nieto Feliner G, Paiva J, Benedí C. Flora iberica. Vol. 11. Gentianaceae-Boraginaceae. Madrid: Real Jardín Botánico, CSIC, 2012: 216-222

141 **Gupta PK**. Drugs of use, dependence, and abuse. In: Illustrated Toxicology. London: Academic Press, 2018: 331-356

142 **Marc B**, Martis A, Moreau C, Arlie G, Kintz P, Leclerc J. Intoxications aiguës à Datura stramonium aux urgences [Acute Datura stramonium poisoning in an emergency department]. *Presse Med* 2007; **36**: 1399-1403 [PMID: 17560071 DOI: 10.1016/j.lpm.2007.04.017]

143 **Wiebe TH**, Sigurdson ES, Katz LY. Angel's Trumpet (Datura stramonium) poisoning and delirium in adolescents in Winnipeg, Manitoba: Summer 2006. *Paediatr Child Health* 2008; **13**: 193-196 [PMID: 19252697 DOI: 10.1093/pch/13.3.193]

144 **Trancă SD**, Szabo R, Cociș M. Acute poisoning due to ingestion of Datura stramonium - a case report. *Rom J Anaesth Intensive Care* 2017; **24**: 65-68 [PMID: 28913501 DOI: 10.21454/rjaic.7518.241.szb]

145 **Babalola SA**. Datura Metel L: Analgesic or Hallucinogen? *MEJSR* 2014 [DOI: 10.5829/idosi.mejsr.2014.21.06.21554]

146 **Imo C**, Arowora KA, Ezeonu CS, Yakubu OE, Nwokwu CD, Azubuike NC, Sallah YG. Effects of ethanolic extracts of leaf, seed and fruit of Datura metel L. on kidney function of male albino rats. *J Tradit Complement Med* 2018; **9**: 271-277 [PMID: 31453122 DOI: 10.1016/j.jtcme.2017.09.001]

147 **Al-Snafi AE**. Medical importance of Datura fastuosa (syn: Datura metel) and Datura stramonium - A review. *IOSR J Pharmacy* 2017; **7**: 43-58 [DOI: 10.9790/3013-0702014358]

148 **Kuete V**. Physical, Hematological, and Histopathological Signs of Toxicity Induced by African Medicinal Plants. In: Kuete V. Toxicological Survey of African Medicinal Plants. New York: Elsevier, 2014: 635-657

149 **Ujváry I**. Psychoactive natural products: overview of recent developments. *Ann Ist Super Sanita* 2014; **50**: 12-27 [PMID: 24695249 DOI: 10.4415/ANN_14_01_04]

150 **Schifano F**, Orsolini L, Duccio Papanti G, Corkery JM. Novel psychoactive substances of interest for psychiatry. *World Psychiatry* 2015; **14**: 15-26 [PMID: 25655145 DOI: 10.1002/wps.20174]

151 **Zanda MT**, Fattore L. Novel Psychoactive Substances: A New Behavioral and Mental Health Threat. In: Watson RR, Zibadi S. Addictive Substances and Neurological Disease. New York: Academic Press, 2017: 341-353

152 **152 Glick SD**, Maisonneuve IM. Development of novel medications for drug addiction. The legacy of an African shrub. *Ann N Y Acad Sci* 2000; **909**: 88-103 [PMID: 10911925 DOI: 10.1111/j.1749-6632.2000.tb06677.x]

153 **Iyer RN**, Favela D, Zhang G, Olson DE. The iboga enigma: the chemistry and neuropharmacology of iboga alkaloids and related analogs. *Nat Prod Rep* 2021; **38**: 307-329 [PMID: 32794540 DOI: 10.1039/d0np00033g]

154 **Gericke N**, Viljoen AM. Sceletium--a review update. *J Ethnopharmacol* 2008; **119**: 653-663 [PMID: 18761074 DOI: 10.1016/j.jep.2008.07.043]

155 **Manganyi MC**, Bezuidenhout CC, Regnier T, Ateba CN. A Chewable Cure "Kanna": Biological and Pharmaceutical Properties of *Sceletium tortuosum*. *Molecules* 2021; **26** [PMID: 33924742 DOI: 10.3390/molecules26092557]

156 **De Luca MA**, Castelli MP, Loi B, Porcu A, Martorelli M, Miliano C, Kellett K, Davidson C, Stair JL, Schifano F, Di Chiara G. Native CB1 receptor affinity, intrinsic activity and accumbens shell dopamine stimulant properties of third generation SPICE/K2 cannabinoids: BB-22, 5F-PB-22, 5F-AKB-48 and STS-135. *Neuropharmacology* 2016; **105**: 630-638 [PMID: 26686391 DOI: 10.1016/j.neuropharm.2015.11.017]

157 **Sholler DJ**, Huestis MA, Amendolara B, Vandrey R, Cooper ZD. Therapeutic potential and safety considerations for the clinical use of synthetic cannabinoids. *Pharmacol Biochem Behav* 2020; **199**: 173059 [PMID: 33086126 DOI: 10.1016/j.pbb.2020.173059]

158 **Dresen S**, Ferreirós N, Pütz M, Westphal F, Zimmermann R, Auwärter V. Monitoring of herbal mixtures potentially containing synthetic cannabinoids as psychoactive compounds. *J Mass Spectrom* 2010; **45**: 1186-1194 [PMID: 20857386 DOI: 10.1002/jms.1811]

159 **Banister SD**, Stuart J, Kevin RC, Edington A, Longworth M, Wilkinson SM, Beinat C, Buchanan AS, Hibbs DE, Glass M, Connor M, McGregor IS, Kassiou M. Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS Chem Neurosci* 2015; **6**: 1445-1458 [PMID: 25921407 DOI: 10.1021/acschemneuro.5b00107]

160 Synthetic Marijuana Linked To Seizures, Psychosis And Death. Feb 7, 2017. [cited 15 January 2022]. Available from: https://www.cedargroup.org/cannabis/synthetic-marijuana-linked-to-seizures-psychosis-and-death/

161 **Diao X**, Huestis MA. Approaches, Challenges, and Advances in Metabolism of New Synthetic Cannabinoids and Identification of Optimal Urinary Marker Metabolites. *Clin Pharmacol Ther* 2017; **101**: 239-253 [PMID: 27727455 DOI: 10.1002/cpt.534]

162 **Tai S**, Fantegrossi WE. Pharmacological and Toxicological Effects of Synthetic Cannabinoids and Their Metabolites. *Curr Top Behav Neurosci* 2017; **32**: 249-262 [PMID: 28012093 DOI: 10.1007/7854_2016_60]

163 **Weinstein AM**, Rosca P, Fattore L, London ED. Synthetic Cathinone and Cannabinoid Designer Drugs Pose a Major Risk for Public Health. *Front Psychiatry* 2017; **8**: 156 [PMID: 28878698 DOI: 10.3389/fpsyt.2017.00156]

164 **Scourfield A**, Flick C, Ross J, Wood DM, Thurtle N, Stellmach D, Dargan PI. Synthetic cannabinoid availability on darknet drug markets-changes during 2016-2017. *Toxicol Commun* 2019; 7-15 [DOI: 10.1080/24734306.2018.1563739]

165 **Chelin R**. Drug trafficking synthetic drugs in the rise despite Mauritius best efforts. [cited 15 January 2022]. Available from: https://enactafrica.org/enact-observer/synthetic-drugs-on-the-rise-despite-mauritiuss-best-efforts

166 **Chelin R**. New Wiz drug targets South African youths. [cited 17 January 2022]. Available from: https://enactafrica.org/enact-observer/new-wiz-drug-targets-south-africas-youth

167 **Akande S**. A new deadly form of marijuana is slowly wreaking havoc in Nigeria's cities. Jul 24, 2017. [cited 17 January 2022]. Available from: https://www.pulse.ng/gist/synthetic-marijuana-black-mamba-a-new-deadly-form-of-marijuana-is-slowly-wreaking/r4dmxpn

168 **Cooper ZD**. Adverse Effects of Synthetic Cannabinoids: Management of Acute Toxicity and Withdrawal. *Curr Psychiatry Rep* 2016; **18**: 52 [PMID: 27074934 DOI: 10.1007/s11920-016-0694-1]

169 **Cohen K**, Weinstein AM. Synthetic and Non-synthetic Cannabinoid Drugs and Their Adverse Effects-A Review From Public Health Prospective. *Front Public Health* 2018; **6**: 162 [PMID: 29930934 DOI: 10.3389/fpubh.2018.00162]

170 Diagnostic and statistical manual of mental disorders (5th ed). Arlington: American Psychiatric Association, 2013

171 **Myers B**, Koch JR, Johnson K, Harker N. Factors associated with patient-reported experiences and outcomes of substance use disorder treatment in Cape Town, South Africa. *Addict Sci Clin Pract* 2022; **17**: 8 [PMID: 35109915 DOI: 10.1186/s13722-022-00289-3]

172 **Corazza O**, Roman-Urrestarazu A. Handbook of Novel Psychoactive substances: What Clinicians Should Know About NPS. New York: Routledge, 2019

173 **Harker Burnhams N**, Bharat C, Williams DR, Stein DJ, Myers B. Transitions between lifetime alcohol use, regular use and remission: Results from the 2004 South African Stress and Health Survey. *S Afr Med J* 2018; **109**: 40-46 [PMID: 30606303 DOI: 10.7196/SAMJ.2018.v109i1.13061]

174 **Rabie M**, Shaker NM, Gaber E, El-Habiby M, Ismail D, El-Gaafary M, Lotfy A, Sabry N, Khafagy W, Muscat R. Prevalence updates of substance use among Egyptian adolescents. *Middle East Curr Psychiatry* 2020; **27** [DOI: 10.1186/s43045-019-0013-8]

175 **United Nations**. Transforming our world: the 2030 agenda for sustainable development. Resolution of the United Nations General Assembly. [cited 17 January 2022]. Available from: https://sdgs.un.org/2030agenda

176 **Onifade PO**, Somoye EB, Ogunwobi OO, Ogunwale A, Akinhanmi AO, Adamson TA. A descriptive survey of types, spread and characteristics of substance abuse treatment centers in Nigeria. *Subst Abuse Treat Prev Policy* 2011; **6**: 25 [PMID: 21923946 DOI: 10.1186/1747-597X-6-25]

177 **Myers BJ**, Louw J, Pasche SC. Inequitable access to substance abuse treatment services in Cape Town, South Africa. *Subst Abuse Treat Prev Policy* 2010; **5**: 28 [PMID: 21073759 DOI: 10.1186/1747-597X-5-28]

178 **Charlson FJ**, Diminic S, Lund C, Degenhardt L, Whiteford HA. Mental and substance use disorders in Sub-Saharan Africa: predictions of epidemiological changes and mental health workforce requirements for the next 40 years. *PLoS One* 2014; **9**: e110208 [PMID: 25310010 DOI: 10.1371/journal.pone.0110208]

179 **Deressa W**, Azazh A. Substance use and its predictors among undergraduate medical students of Addis Ababa University in Ethiopia. *BMC Public Health* 2011; **11**: 660 [PMID: 21859483 DOI: 10.1186/1471-2458-11-660]

180 **Birhanu AM**, Bisetegn TA, Woldeyohannes SM. High prevalence of substance use and associated factors among high school adolescents in Woreta Town, Northwest Ethiopia: multi-domain factor analysis. *BMC Public Health* 2014; **14**: 1186 [PMID: 25410657 DOI: 10.1186/1471-2458-14-1186]

181 **Ogunsola OO**, Fatusi AO. Risk and protective factors for adolescent substance use: a comparative study of secondary school students in rural and urban areas of Osun State, Nigeria. *Int J Adolesc Med Health* 2016; **29** [PMID: 26824975 DOI: 10.1515/ijamh-2015-0096]

182 **Jere DL**, Norr KF, Bell CC, Corte C, Dancy BL, Kaponda CP, Levy JA. Substance Use and Risky Sexual Behaviors Among Young Men Working at a Rural Roadside Market in Malawi. *J Assoc Nurses AIDS Care* 2017; **28**: 250-265 [PMID: 26264258 DOI: 10.1016/j.jana.2015.07.003]

183 **Jumbe S**, Kamninga TM, Mwalwimba I, Kalu UG. Determinants of adolescent substance use in Africa: a systematic review and meta-analysis protocol. *Syst Rev* 2021; **10**: 125 [PMID: 33906677 DOI: 10.1186/s13643-021-01680-y]

184 **Seid L**, Gintamo B, Mekuria ZN, Hassen HS, Gizaw Z. Substance use and associated factors among preparatory school students in Kolfe-Keranyo sub-city of Addis Ababa, Ethiopia. *Environ Health Prev Med* 2021; **26**: 110 [PMID: 34798804 DOI: 10.1186/s12199-021-01032-1]

185 **Oshodi OY**, Aina OF, Onajole AT. Substance use among secondary school students in an urban setting in Nigeria: prevalence and associated factors. *Afr J Psychiatry (Johannesbg)* 2010; **13**: 52-57 [PMID: 20428599 DOI: 10.4314/ajpsy.v13i1.53430]

186 **Kiburi SK**, Molebatsi K, Obondo A, Kuria MW. Adverse childhood experiences among patients with substance use

disorders at a referral psychiatric hospital in Kenya. *BMC Psychiatry* 2018; **18**: 197 [PMID: 29914409 DOI: 10.1186/s12888-018-1780-1]

187 **Muchiri BW**, Dos Santos MML. Family management risk and protective factors for adolescent substance use in South Africa. *Subst Abuse Treat Prev Policy* 2018; **13**: 24 [PMID: 29914541 DOI: 10.1186/s13011-018-0163-4]

188 **Substance Abuse and Mental Health Services Administration**; Office of the Surgeon General. Facing Addiction in America: The Surgeon General's Report on Alcohol, Drugs, and Health [Internet]. Washington: US Department of Health and Human Services, 2016

World Journal of Psychiatry

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

World J Psychiatry 2022 October 19; 12(10): 1287-1297

DOI: 10.5498/wjp.v12.i10.1287

ISSN 2220-3206 (online)

MINIREVIEWS

Artificial intelligence-assisted psychosis risk screening in adolescents: Practices and challenges

Xiao-Jie Cao, Xin-Qiao Liu

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, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cianci P, Italy; Mijwil MM, Iraq

Received: July 11, 2022
Peer-review started: July 11, 2022
First decision: August 1, 2022
Revised: August 9, 2022
Accepted: September 22, 2022
Article in press: September 22, 2022
Published online: October 19, 2022

Xiao-Jie Cao, Graduate School of Education, Peking University, Beijing 100871, China

Xin-Qiao Liu, School of Education, Tianjin University, Tianjin 300350, China

Corresponding author: Xin-Qiao Liu, PhD, Associate Professor, School of Education, Tianjin University, No. 135 Yaguan Road, Jinnan District, Tianjin 300350, China.
xinqiaoliu@pku.edu.cn

Abstract

Artificial intelligence-based technologies are gradually being applied to psychiatric research and practice. This paper reviews the primary literature concerning artificial intelligence-assisted psychosis risk screening in adolescents. In terms of the practice of psychosis risk screening, the application of two artificial intelligence-assisted screening methods, chatbot and large-scale social media data analysis, is summarized in detail. Regarding the challenges of psychiatric risk screening, ethical issues constitute the first challenge of psychiatric risk screening through artificial intelligence, which must comply with the four biomedical ethical principles of respect for autonomy, nonmaleficence, beneficence and impartiality such that the development of artificial intelligence can meet the moral and ethical requirements of human beings. By reviewing the pertinent literature concerning current artificial intelligence-assisted adolescent psychosis risk screens, we propose that assuming they meet ethical requirements, there are three directions worth considering in the future development of artificial intelligence-assisted psychosis risk screening in adolescents as follows: nonperceptual real-time artificial intelligence-assisted screening, further reducing the cost of artificial intelligence-assisted screening, and improving the ease of use of artificial intelligence-assisted screening techniques and tools.

Key Words: Psychosis risk; Adolescents; Artificial intelligence; Big data; Social media; Medical ethics; Chatbot; Machine learning

Core Tip: Artificial intelligence-assisted psychosis risk screening must be emphasized and applied in adolescents. This review summarizes the application of two artificial intelligence-assisted screening methods (chatbot and large-scale social media data analysis), and proposes that the first challenge in applying artificial intelligence to psychosis risk screening concerns ethical issues. The methods must follow four biomedical ethics principles, *i.e.*, respect for autonomy, nonmaleficence, beneficence, and justice. Three directions should be considered in the future: nonperceptual real-time artificial intelligence-assisted screening, further reducing the cost of artificial intelligence-assisted screening, and improving the ease of use of artificial intelligence-assisted screening techniques and tools.

Citation: Cao XJ, Liu XQ. Artificial intelligence-assisted psychosis risk screening in adolescents: Practices and challenges. *World J Psychiatry* 2022; 12(10): 1287-1297
URL: https://www.wjgnet.com/2220-3206/full/v12/i10/1287.htm
DOI: https://dx.doi.org/10.5498/wjp.v12.i10.1287

INTRODUCTION

In recent years, the prevalence of psychosis among adolescents has been increasing. According to the data released by the World Health Organization, approximately one in five children and adolescents worldwide suffers from a mental disorder, and half of these individuals show symptoms before the age of 14[1]. The risk of psychosis shows not only a trend of a younger age but also many disease categories and high heterogeneity[2-5], and its potentially high prevalence warrants attention. Two studies in Europe and North America revealed that adolescents with prodromal symptoms of psychosis who actively sought help still experienced a risk of eventual psychosis at rates of 19% and 35%, respectively [6,7]. In fact, due to the lack of independence, fear of being discriminated against by people around them, and a dearth of adequate attention from parents and schools, some adolescents even do not actively seek medical treatment and thus often miss their best treatment window. Since 2020, the rapid spread and persistence of the coronavirus disease 2019 pandemic worldwide has caused further major and hidden risks to population health, including psychosis. A study revealed that the deadly hazard of coronavirus disease 2019 and the resulting national lockdown policies in Italy caused intense psychosocial stress in individuals, which can be a trigger for first-episode psychosis[8]. In particular, children and adolescents are the most vulnerable groups[9]. Compared with other groups, children and adolescents are more vulnerable to the negative effects of the pandemic[10,11], *e.g.*, anxiety, depression, and posttraumatic symptoms, which increase the psychosis risk and may cause long-term negative consequences[12,13]. Additionally, adolescents are at a greater risk of first-episode psychosis than adult-onset psychosis, which is often associated with more severe symptoms and worse outcomes[14,15]. People who suffer from severe mental disorders die 10 years to 20 years earlier than the average person [1] and are more vulnerable to long-term disadvantages in terms of career advancement in the labor market, social status, mental health, and life beliefs[2,16]. Undoubtedly, this reality is not conducive to the stable economic and social development of any country worldwide.

Influencing factors

The prior literature has concluded that psychosis risk is the result of an interaction between various internal and external factors[12,17], which can be divided into three main categories. First, national and social factors, such as those associated with schizophrenia, are unequally distributed across cultures and countries[18], and a cultural atmosphere that stigmatizes psychosis can create barriers to the timely detection of the illness[19]. The second category comprises family factors, including the two aspects of congenital inheritance and acquired growth environment. Adolescents who grow up in families with psychotic parents, domestic violence, or abuse are at a greater risk of psychosis[20]; adolescents suffering from psychosis have higher rates of broken homes, substance abuse, chronic disease[21], and lack of social capital[22]. Third, individual factors include demographic characteristics and addictive behaviors; for example, males account for a larger proportion of children and adolescents with first-episode psychosis[21], while marijuana use is also a risk factor for psychosis[23,24]. Indeed, a combination of risk factors, including genetics, birth season, birth complications, infection and immune system factors, autoimmune diseases, ethnicity, marijuana use, and urban residence, increase an individual's risk of developing schizophrenia[18].

Main benefits of artificial intelligence-assisted adolescent psychosis risk screening

Despite this severe reality, shortages of medical resources and professional psychiatrists and uneven medical care are still common. Many nonpsychiatric specialists in hospitals and psychological service personnel on campus or in the community are unable to accurately and efficiently identify psychotic patients, and even if they diagnose the condition, they still cannot perform effective follow-up and

treatment[25-28]. A consensus holds that one of the best strategies to promote early intervention against psychosis is to improve the early identification of individuals at risk for psychosis through screening[29-31]. However, screening for psychosis mainly relies on scales, complicating the accurate identification of adolescents with a psychosis risk in a timely manner.

Over the past few years, artificial intelligence has shown explosive development inseparable from the emergence of new algorithms and the speed of high-performance parallel computing, coupled with the development of large-capacity storage space and video, text, sound, and other technologies to promote its rapid growth. Recent advancements in artificial intelligence have promoted improvement in the methods and technological innovations used in the treatment of human mental diseases, and artificial intelligence-based technologies are gradually being applied to psychiatric research and practice[19,32-35]. The main benefits of artificial intelligence-assisted adolescent psychosis risk screening are as follows: (1) Compared with traditional screening, the introduction of artificial intelligence can improve the speed and timeliness of identifying those who are already sick or who have a potential risk of a disease[36], which helps with early intervention and treatment[37,38] and timely correction of patients' risky behaviors, all of which can prevent the occurrence and further aggravation of symptoms; (2) Using advanced technology and objective data, artificial intelligence further enhances the accuracy and objectivity of screening methods. Appropriate screening tools that have been developed for all conditions in adolescent psychosis risk are relatively inadequate[39,40], while the clinical significance of adolescent self-assessment results is limited[41]; and (3) Artificial intelligence mitigates the scarcity of medical resources[42] and increases the coverage of screenings. Additionally, artificial intelligence can process massive amounts of data and use these data to improve generalization[43,44] while playing a pivotal role in identifying and detecting heterogeneity in schizophrenia and other mental illnesses[5] and can help doctors make the right decisions for subsequent diagnostic treatment[45].

Existing challenges

Ethical issues constitute one of the greatest challenges encountered in the application of AI to psychosis risk screening in adolescents in terms of both technical development and concrete practice[46,37] in the following four aspects: (1) Whether the autonomy of adolescents to participate in screening is duly respected and protected[47]; if the screening is conducted without their full approval, they should be responsible for the possible negative consequences; (2) The personal information and privacy of adolescents are leaked and exposed to unauthorized surveillance and security risks; the use and management of data collected based on artificial intelligence technology deserves attention[48,49]; (3) There is no unified understanding of the ethical assessment and acceptance of technology among different stakeholders[37]; and (4) The benefits of AI technology development do not reach all adolescents fairly and equitably.

Contribution

Clearly, there is a strong necessity and feasibility to focus on and apply artificial intelligence-assisted psychiatric risk screening in adolescents. However, there is a paucity of research concerning artificial intelligence-assisted psychiatric screening and a dearth of narrative literature reviews focusing on this important population characteristic of adolescents. Therefore, this paper reviews the main literature concerning artificial intelligence-assisted adolescent psychiatric risk screening to clarify the current state of development and recent explorations of this important topic in terms of practice and challenges with the aim to contribute to a more effective use of artificial intelligence methods for adolescent psychiatric risk screening in the future on a global scale.

PRACTICES

Traditional psychosis risk screening methods are mostly based on various self-assessment questionnaires with obvious limitations as follows: (1) Performance is not comparable among different screening tools; (2) The measurement criteria (such as content, number of items, and thresholds) widely vary; and (3) Dynamic and longitudinal tracking data are lacking[40]. In addition, scale-based self-assessment relies on individual self-perceptions, recollections, and subjective evaluations, and in some situations, individuals may exaggerate or mask some of their symptoms, weakening the accuracy of the results. For example, a general recall bias is evident among patients with depression, and symptoms can fluctuate over time or even throughout the day, which complicates capturing dynamic changes in symptoms with high accuracy[50].

The emergence of artificial intelligence can address and largely overcome the above limitations. The main machine learning algorithms currently used for psychosis screening are traditional ones, *e.g.*, decision tree, naive Bayes, random forest, support vector machine, K-nearest neighbor, and shallow neural networks. Of these, relevant studies have shown that the support vector machine method is the most commonly used[51,52]. With the advancement of deep learning algorithms, algorithms, such as convolutional neural networks, autoencoders, and deep belief networks, have begun to be used in psychosis risk screening research and are viewed as an important development trend of the future[3,53,

54]. By summarizing the pertinent literature, the artificial intelligence tools most often applied to psychosis risk screening are chatbot and large-scale social media data analysis.

Chatbot

Chatbot is a computer program that allows human–computer interactions in the form of textual dialog based on the technology of natural language processing[55]. The world's first chatbot, ELIZA, was developed in the 1960s[56] and responds according to special rules by recognizing keywords in user-entered texts[57]. Due to substantial advancements in artificial intelligence, chatbots have developed from being driven by static databases and learning new responses and contexts based on real-time interactions with humans to the fusion of real-time learning and evolutionary algorithms. Currently, chatbots have powerful capabilities of simulating the structures of natural language communication and creating a realistic environment in which users can achieve human–computer interaction. Chatbots in the healthcare field include Tess, HealthBuddy, Florence, Buoy Health, and Your.Md. In addition to natural language processing, the machine learning methods adopted by chatbots also include natural language understanding, artificial neural networks, and recurrent neural networks[58].

The prior literature has shown that psychosis is usually strongly correlated with human manifestations, such as facial expressions, voice, textual tone, and gestures. According to these human manifestations, chatbots with cognitive ability can ascertain the needs of users in real time to provide emotional responses and predictions and assessments of their mental health conditions[46,59]. Based on existing experience, one study improved upon the feature extraction of previous studies by using deep learning and fusion regression methods to construct an artificial intelligence system that automatically predicted depression levels based on vocal and visual expressions, which showed better predictive performance than other existing methods using the same dataset. Artificial intelligence is currently used in some chatbots. This study used deep learning methods to extract key visual features from facial expression frames, spectral low-level descriptors and mel-frequency cepstral coefficient features from short audio segments, and time movements in feature space through feature dynamic history histograms (FDHHs). Finally, regression techniques were used to fuse these FDHHs and audio features to predict the Baker Depression Scale II scores. The artificial intelligence developed in that study was a general framework that can be used to automatically predict depression scale scores from facial and vocal representations. It has FDHH dynamic functionality, leveraging the ideas of motion history histograms on deep learning images and handcrafted feature spaces, and enables feature fusion of different descriptors of face images[34].

The chatbot Woebot is used as an example. Woebot can be used on mobile communication devices in the form of short daily conversations and mood tracking to help users acquire anxiety reduction skills by identifying cognitive distortions to monitor anxiety and depression episodes while using fully automated conversational agents to address poor adherence to some extent. In a previous randomized controlled trial using Woebot, 70 college students who reported symptoms of depression and anxiety were randomly assigned to an intervention group that chatted with Woebot in an instant messaging application and a control group that received the National Institute of Mental Health e-book on depression in college students. The results revealed that the anxiety levels decreased in both groups, and the students who interacted with Woebot had significantly lower levels of depression compared to those reading the e-book. Future validation of the findings is needed with more participants, longer doses, and longer-term follow-up data[60].

In summary, the advantage of chatbots is that they can bring hope to psychosis risk screening for those who were previously inaccessible to screenings or who are economically constrained[61], build trusting relationships with potential patients, increase self-disclosure, and reduce the shame that patients or their families often feel when talking to doctors about mental illness. Nevertheless, these chatbots still have some shortcomings as follows: (1) They can be promoted by financial sponsors, causing conflicts of commercial interests; (2) In contrast to humans, they do not truly have subtle emotional awareness or empathic responses; and (3) They have issues with privacy, ethical risks, and other negative problems.

Large-scale social media data analysis

Currently, large numbers of users express their emotions and communicate daily through social media, such as Facebook and Twitter. Based on informative data such as textual information, emojis, user log information, and pictures, psychosis can be identified and predicted by combining natural language processing, sentiment analysis, and machine learning[49,62,63].

As the use of social media platforms becomes increasingly common in people's lives, screening for psychosis risk based on collected social media data will become easier. For instance, one study systematically analyzed artificial intelligence depression detectors and concluded that artificial intelligence systems that identify users at a high risk for depression from their social media data have made remarkable progress[37]. Given that depression is common in the adolescent population[26,64] and is underdiagnosed and undertreated, which underscores the need to expand the current screening methods, some investigators used the text of posts of consenting individuals on Facebook to predict depression as documented in electronic medical records and demonstrated correlative accuracy in identifying people with depression[65,66]. Therefore, the use of machine learning technology to screen

depression patients by acquiring the social media data for consenting individuals may become an effective and scalable supplement to existing screening methods[67]. Based on the language behaviors of Facebook user posts, Islam *et al*[68] achieved a classification accuracy of 99.0% with a depression prediction model using the decision tree method. Another study applied a logistic regression and highly randomized trees as modeling algorithms to approximately 20 million words of social media posts by 999 consenting volunteers and found that applying the method to Facebook posts significantly improved the predictive accuracy of demographic variables (age, sex, and ethnicity) in 18 of 21 disease categories, and it was particularly effective at predicting mental health conditions (anxiety, psychosis, and depression)[69]. In one study, big data were collected from China's Sina Weibo to understand differences in language style, emoji use, and the number of followers between depressive patients and nondepressed patients by using a deep neural network for feature extraction and dimensionality reduction. By constructing input data suitable for the classifier and applying the deep integrated support vector machine algorithm to classify the input data, the study achieved a more stable and accurate identification of depression in college students[70]. The development of Internet-of-Things technology has realized the exchange of information between hardware such that various wearable devices can carry a large amount of health information. Applying the Internet of Things to the field of psychosis through machine learning, the objective behavioral characteristics collected through mobile phones and wearable devices can effectively predict depressive symptoms[71,72]. Data related to daily activity, sleep, social communication, *etc.* have been collected through smartphone sensors to predict individuals' depression situations[73,74]. Advanced artificial intelligence methods, including natural language analysis and chatbots, were used by the Horyzons website to analyze the sentiment and language of newsfeed posts and other relevant factors (*e.g.*, user preferences and history), which enabled personalized treatment recommendations to be made for adolescents with early symptoms of psychosis [75]. Orabi *et al*[76] extracted unstructured text data posted on Twitter by 327 depression patients, 246 posttraumatic stress disorder patients, and 572 healthy individuals, and based on these data, users with depression tendencies were detected using the convolutional neural network method. Convolutional neural networks represent the most popular deep learning method in the field of natural language processing, boasting an accuracy as high as 87.9%, and have achieved remarkable progress in the field of image recognition[76]. In the future, more technologies, such as multimodal perception, understanding, and natural dialog and interaction (a multimodal auxiliary screening mechanism established through artificial intelligence perception technology), are needed to achieve more comprehensive and accurate screening of psychosis risk among adolescents.

CHALLENGES

The technology of artificial intelligence-assisted psychosis risk screening in adolescents will become more mature and a major development trend in the future. However, it can only do so by overcoming the existing challenges in the application of artificial intelligence-assisted psychosis screening in the adolescent population, which have rarely been addressed to date. Especially when applying artificial intelligence to psychosis risk screening, the primary challenge is ethical issues. The four principles of biomedical ethics, *i.e.*, respect for autonomy, nonmaleficence, beneficence, and justice[77], must always be firmly followed. On this basis, a new principle aiming to realize other principles through understandability and accountability[78] such that the development of artificial intelligence can truly meet the moral and ethical requirements of mankind has been proposed. Table 1 presents the four widely accepted ethical principles, their connotations, and the corresponding issues that adolescents may face.

Respect for autonomy

Respect for autonomy requires respect for the patient's personal dignity and autonomy, such as ensuring informed consent and informed choice, ensuring that humans have complete and effective autonomy, and requiring that the operation of any artificial intelligence be supervised by humans. Adolescents are still minors, and this age group is in the typical age when psychosis develops. Discussions have addressed whether adolescents have autonomy and how they should be "empowered". For example, in the United Kingdom, adolescents under the age of 16 can be competent to give consent if they demonstrate sufficient maturity and intelligence (as judged through Gillick competence). For minors deemed incompetent (and adults who are incompetent due to mental illness), questions arise regarding whether guardian advocates or those with parental responsibility should be empowered to provide proxy consent for psychosis risk screening[80]. Therefore, assuming that a given artificial intelligence-assisted psychosis risk screening method is safe and trustworthy, improving the awareness and attitudes of teenagers and their parents toward the psychosis risk and the importance of early screening is vital as their willingness to use artificial intelligence for screening can be increased only with their full approval[79]. Moreover, how to improve adolescents' autonomous participation in psychosis risk screening by ensuring effective informed consent and meaningful disclosure of results still requires further discussion.

Table 1 Connotations of ethical principles and issues faced by adolescents

Ethical principles	Connotations	Issues faced by adolescents
Respect for autonomy	Ensuring informed consent and informed choice, ensuring that humans have complete and effective autonomy, and requiring that the operation of any artificial intelligence be supervised by humans	Safety and trustworthiness of screening methods; full approval from adolescents and parents; willingness to use artificial intelligence for screening[79]
Nonmaleficence	Privacy, security and "capability warnings"[78]; artificial intelligence technology must be able to strongly resist malicious use, including avoiding harm to the natural environment and all living things	Privacy leakage and data abuse; difficulties in oversight and accountability; adverse effects and stigma with irreversible damage
Beneficence	Must be beneficial for not only the patients but also the medical cause, medical sciences and even the well-being of the entire human race	Screening scales need to be refined; no consensus (such as ethical evaluation acceptance of the technology) among different stakeholders[37]
Justice	Everyone in society has equal rights to reasonably enjoy health resources and participate in the distribution; prosperity is promoted; and unity is maintained	Development of artificial intelligence cannot benefit all groups of young people[12,14,21,22,80]; intergenerational transmission maintains inequality[46,78]

Nonmaleficence

Nonmaleficence requires privacy, security, and "capability warning"[78]. To protect the integrity of the human body, mind, and dignity, artificial intelligence technology must be able to strongly resist malicious use, including avoiding harm to the natural environment and all living things. Smart data collection technologies are becoming increasingly powerful, posing a greater threat to user privacy and security. The protection of adolescents' personal information and privacy is very important, but some privacy leakage and data abuse problems remain, which have been extremely harmful. With the rapid development of artificial intelligence, the existing ethical and regulatory norms have fallen behind. Their failure to keep pace with the latest environmental and artificial intelligence technologies creates difficulties in oversight and accountability. Especially in the presence of potential commercial interests or vested interests, *e.g.*, some social platforms may be abused by enterprises/people with criminal minds or illegal attempts, the usage of artificial intelligence in biomedical fields must be monitored and regulated from an ethical and moral standpoint. Furthermore, an artificial intelligence-assisted screening result may have adverse effects on some adolescents with a psychosis risk and introduce stigma when they are labeled with psychosis, which may, in turn, cause irreversible damage to their mental health, interpersonal relationships, and even long-term personal development. Thus, in addition to psychosis, many social factors related to its diagnosis cause extra damage to adolescents.

Beneficence

Beneficence requires that something be beneficial for not only the patients but also the medical cause, medical sciences and even the well-being of the entire human race. Although many studies have confirmed the positive role of artificial intelligence in psychosis risk screening, people still use scales for screening in practice. On the one hand, time is required to ensure that any technology is foolproof, and on the other hand, different stakeholders (adolescents and their parents, doctors, research and development personnel, *etc.*) have not yet reached a consensus, and the ethical evaluation and acceptance of the technology are still open questions[37], *e.g.*, whether medical professionals are willing to replace traditional screening with artificial intelligence-driven products and technologies. Therefore, whether this technology is truly beneficial for the health and well-being of society as a whole and humanity is worth discussing.

Justice

Justice requires everyone in society to have equal rights to reasonably enjoy health resources, resources to be fairly distributed, everyone to have the right to participate in the distribution and use of these resources and the benefits of artificial intelligence to be distributed fairly and equitably while avoiding any discrimination or stigma, promoting prosperity, and maintaining unity. The development of artificial intelligence cannot benefit all groups of young people. Previous studies revealed that adolescents born in the lower classes of society and those from disadvantaged families are more likely to suffer from psychosis[21,22]. In fact, vulnerable groups have a greater need to exploit the advantages of artificial intelligence technology for psychosis risk screening[12,14,80]. In reality, a "digital divide" and a "knowledge gap" still exist between urban and rural youths, the accessibility of digital technologies and services is unevenly distributed, and some youths still do not have the opportunity to access advanced technologies[81,82]. Furthermore, this unevenness is exacerbated by intergenerationally maintained inequality[46,78].

In addition to ethical issues, artificial intelligence-assisted psychosis risk screening in adolescents faces several other issues, including: (1) Small sample sizes: the use of machine learning to establish prediction models with high accuracy and strong generalization ability requires large samples[83], but

many studies have mentioned the problem of too few samples, resulting in overfitting, which may lead to model errors and low accuracy[21,84,85]; (2) The prediction model must be optimized: for the same problem and the same sample set, the prediction accuracies of prediction models based on different algorithms vary, and the applicable scope and characteristics of each algorithm are different[86,87]; (3) Compliance: the level of the technical knowledge of patients is a key factor affecting their compliance [88], which also directly affects the accuracy of conclusions; and (4) Research bias: most research samples are active users of social media or patients who are informed in advance, while broader groups of real-world patients are not included; thus, the representativeness of the samples and generalizability of the findings may be limited.

LIMITATIONS

This study has two limitations. First, this paper is a narrative review and provides an outlook. This paper discusses the current status and challenges of using artificial intelligence-assisted methods for screening adolescents for psychiatric disorders, but we do not use an explicit approach, such as a systematic review. Therefore, the study is primarily intended to evoke research interest in the field but cannot be directly applied to clinical care. Second, this paper only summarizes the relevant literature in English and does not consider the literature published in languages other than English.

CONCLUSION

While focusing on the psychosis risk faced by adolescents worldwide, this paper reviews the influencing factors of adolescent psychosis risk, which can be divided into the following three main categories: national and social factors, family factors, and individual factors. This paper summarizes the benefits of artificial intelligence-assisted psychosis risk screening in adolescents, which are mainly manifested in improving the speed and timeliness of screening for those who are already sick and those with a potential risk of disease, promptly correcting the risky behavior of patients to prevent the occurrence and further aggravation of symptoms, and improving the accuracy and objectivity of screenings and the screening coverage. The application of chatbots and large-scale social media data analysis in psychosis risk screening is discussed in detail. The advantage of chatbots in psychosis risk screening is that they can provide services to those with psychosis who have limited resources or accessibility problems, although privacy concerns and other ethical issues may exist. The accuracy of large-scale social media data analysis is gradually improving, and more technologies based on multimodal perception, understanding, and natural dialog and interactions are still needed to help comprehensively and accurately screen for psychosis risk in adolescents.

After surveying the current literature concerning artificial intelligence-assisted adolescent psychosis risk screening, we found that although artificial intelligence has been gradually applied to early psychosis risk screening, it has rarely been applied in studies that directly use adolescents as subjects. In view of the prevalence and harm of psychosis among adolescents worldwide, the timely screening of adolescent psychosis risks with artificial intelligence technology has considerable prospects for development. Furthermore, scientific progress must follow relevant ethical principles, not ignore vulnerable groups of adolescents, and ensure that artificial intelligence-assisted psychosis risk screening is conducted in an ethically acceptable manner, thereby minimizing potential adverse effects.

Based on the current status of psychiatric artificial intelligence research and practice, we propose that ethical issues constitute the main challenge of artificial intelligence-assisted psychosis risk screening in adolescents. The four biomedical ethics principles (respect for autonomy, nonmaleficence, beneficence, and justice) should be strictly obeyed. In addition to ethical issues, artificial intelligence-assisted psychosis risk screening in adolescents faces problems, such as small sample sizes, unoptimized prediction models, compliance, and research bias.

We propose that assuming compliance with ethical requirements, three main directions can be considered for artificial intelligence-assisted psychosis risk screening in adolescents in the future. First, we should develop nonperceptual real-time artificial intelligence screening with the help of technological advancements, such as 5G technology and the Internet of Things, to allow both the collection of individual emotional and health data and the prediction of individuals' mental health status in real time. Second, we should further reduce the cost of artificial intelligence-assisted screening. Psychosis is an important part of human health, and both poor and rich people should enjoy the benefits of technological progress. The long-term goal of artificial intelligence-assisted psychosis risk screening is that users should not pay high prices for the screening. Third, we should improve the ease of use of artificial intelligence-assisted screening techniques and tools such that regardless of an individual's level of knowledge, he or she can easily use artificial intelligence tools to screen for a psychosis risk.

FOOTNOTES

Author contributions: Liu XQ designed the study; Cao XJ and Liu XQ wrote the manuscript and managed the literature analyses; all authors approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: China

ORCID number: Xiao-Jie Cao 0000-0002-7252-831X; Xin-Qiao Liu 0000-0001-6620-4119.

S-Editor: Gao CC
L-Editor: A
P-Editor: Gao CC

REFERENCES

1 **World Health Organization**. Mental health. Geneva, Switzerland: WHO, 2019. [cited 27 April 2022]. In: World Health Organization [Internet]. Available from: https://www.who.int/health-topics/mental-health#tab=tab_1
2 **Marquand AF**, Wolfers T, Mennes M, Buitelaar J, Beckmann CF. Beyond Lumping and Splitting: A Review of Computational Approaches for Stratifying Psychiatric Disorders. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2016; **1**: 433-447 [PMID: 27642641 DOI: 10.1016/j.bpsc.2016.04.002]
3 **Liu GD**, Li YC, Zhang W, Zhang L. A Brief review of artificial intelligence applications and algorithms for psychiatric disorders. *Engineering* 2020; **6**: 462-467 [DOI: 10.1016/j.eng.2019.06.008]
4 **Drysdale AT**, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, Fetcho RN, Zebley B, Oathes DJ, Etkin A, Schatzberg AF, Sudheimer K, Keller J, Mayberg HS, Gunning FM, Alexopoulos GS, Fox MD, Pascual-Leone A, Voss HU, Casey BJ, Dubin MJ, Liston C. Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med* 2017; **23**: 28-38 [PMID: 27918562 DOI: 10.1038/nm.4246]
5 **Schnack HG**. Improving individual predictions: Machine learning approaches for detecting and attacking heterogeneity in schizophrenia (and other psychiatric diseases). *Schizophr Res* 2019; **214**: 34-42 [PMID: 29074332 DOI: 10.1016/j.schres.2017.10.023]
6 **Cannon TD**, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, Seidman LJ, Perkins D, Tsuang M, McGlashan T, Heinssen R. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry* 2008; **65**: 28-37 [PMID: 18180426 DOI: 10.1001/archgenpsychiatry.2007.3]
7 **Ruhrmann S**, Schultze-Lutter F, Salokangas RK, Heinimaa M, Linszen D, Dingemans P, Birchwood M, Patterson P, Juckel G, Heinz A, Morrison A, Lewis S, von Reventlow HG, Klosterkötter J. Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry* 2010; **67**: 241-251 [PMID: 20194824 DOI: 10.1001/archgenpsychiatry.2009.206]
8 **D Agostino A**, D'Angelo S, Giordano B, Cigognini AC, Chirico ML, Redaelli C, Gambini O. Brief Psychotic Disorder During the National Lockdown in Italy: An Emerging Clinical Phenomenon of the COVID-19 Pandemic. *Schizophr Bull* 2021; **47**: 15-22 [PMID: 32761196 DOI: 10.1093/schbul/sbaa112]
9 **Blakemore SJ**. Adolescence and mental health. *Lancet* 2019; **393**: 2030-2031 [PMID: 31106741 DOI: 10.1016/S0140-6736(19)31013-X]
10 **Lee J**. Mental health effects of school closures during COVID-19. *Lancet Child Adolesc Health* 2020; **4**: 421 [PMID: 32302537 DOI: 10.1016/S2352-4642(20)30109-7]
11 **Kaufman KR**, Petkova E, Bhui KS, Schulze TG. A global needs assessment in times of a global crisis: world psychiatry response to the COVID-19 pandemic. *BJPsych Open* 2020; **6**: e48 [PMID: 32250235 DOI: 10.1192/bjo.2020.25]
12 **Marques de Miranda D**, da Silva Athanasio B, Sena Oliveira AC, Simoes-E-Silva AC. How is COVID-19 pandemic impacting mental health of children and adolescents? *Int J Disaster Risk Reduct* 2020; **51**: 101845 [PMID: 32929399 DOI: 10.1016/j.ijdrr.2020.101845]
13 **Liu X**, Cao X, Gao W. Does Low Self-Esteem Predict Anxiety Among Chinese College Students? *Psychol Res Behav Manag* 2022; **15**: 1481-1487 [PMID: 35719193 DOI: 10.2147/PRBM.S361807]
14 **Pyle M**, Broome MR, Joyce E, MacLennan G, Norrie J, Freeman D, Fowler D, Haddad PM, Shiers D, Hollis C, Smith J, Liew A, Byrne RE, French P, Peters S, Hudson J, Davies L, Emsley R, Yung A, Birchwood M, Longden E, Morrison AP. Study protocol for a randomised controlled trial of CBT *vs* antipsychotics *vs* both in 14-18-year-olds: Managing Adolescent first episode Psychosis: a feasibility study (MAPS). *Trials* 2019; **20**: 395 [PMID: 31272477 DOI: 10.1186/s13063-019-3506-1]
15 **Liu X**, Gao X, Ping S. Post-1990s college students academic sustainability: the role of negative emotions, achievement goals, and self-efficacy on academic performance. *Sustainability* 2019; **11**: 775 [DOI: 10.3390/su11030775]
16 **Tsang HW**, Leung AY, Chung RC, Bell M, Cheung WM. Review on vocational predictors: a systematic review of

predictors of vocational outcomes among individuals with schizophrenia: an update since 1998. *Aust N Z J Psychiatry* 2010; **44**: 495-504 [PMID: 20482409]

17 **Liu XQ**, Guo YX, Zhang WJ, Gao WJ. Influencing factors, prediction and prevention of depression in college students: A literature review. *World J Psychiatry* 2022; **12**: 860-873 [PMID: 36051603 DOI: 10.5498/wjp.v12.i7.860]

18 **Messias EL**, Chen CY, Eaton WW. Epidemiology of schizophrenia: review of findings and myths. *Psychiatr Clin North Am* 2007; **30**: 323-338 [PMID: 17720026 DOI: 10.1016/j.psc.2007.04.007]

19 **Inkster B**, Sarda S, Subramanian V. An Empathy-Driven, Conversational Artificial Intelligence Agent (Wysa) for Digital Mental Well-Being: Real-World Data Evaluation Mixed-Methods Study. *JMIR Mhealth Uhealth* 2018; **6**: e12106 [PMID: 30470676 DOI: 10.2196/12106]

20 **Levinson DF**. The genetics of depression: a review. *Biol Psychiatry* 2006; **60**: 84-92 [PMID: 16300747 DOI: 10.1016/j.biopsych.2005.08.024]

21 **Castro-Fornieles J**, Parellada M, Gonzalez-Pinto A, Moreno D, Graell M, Baeza I, Otero S, Soutullo CA, Crespo-Facorro B, Ruiz-Sancho A, Desco M, Rojas-Corrales O, Patiño A, Carrasco-Marin E, Arango C; CAFEPS group. The child and adolescent first-episode psychosis study (CAFEPS): design and baseline results. *Schizophr Res* 2007; **91**: 226-237 [PMID: 17267179 DOI: 10.1016/j.schres.2006.12.004]

22 **Yoo JH**, Jeong EJ. Psychosocial effects of SNS use: a longitudinal study focused on the moderation effect of social capital. *Comput Hum Behav* 2017; **69**: 108-119 [DOI: 10.1016/j.chb.2016.12.011]

23 **Barnes TR**, Mutsatsa SH, Hutton SB, Watt HC, Joyce EM. Comorbid substance use and age at onset of schizophrenia. *Br J Psychiatry* 2006; **188**: 237-242 [PMID: 16507965 DOI: 10.1192/bjp.bp.104.007237]

24 **Degenhardt L**, Hall W. Is cannabis use a contributory cause of psychosis? *Can J Psychiatry* 2006; **51**: 556-565 [PMID: 17007222 DOI: 10.1177/070674370605100903]

25 **Bedi G**, Carrillo F, Cecchi GA, Slezak DF, Sigman M, Mota NB, Ribeiro S, Javitt DC, Copelli M, Corcoran CM. Automated analysis of free speech predicts psychosis onset in high-risk youths. *NPJ Schizophr* 2015; **1**: 15030 [PMID: 27336038 DOI: 10.1038/npjschz.2015.30]

26 **Gao W**, Luo Y, Cao X, Liu X. Gender differences in the relationship between self-esteem and depression among college students: a cross-lagged study from China. *J Res Pers* 2022; **97**: 104202 [DOI: 10.1016/j.jrp.2022.104202]

27 **Bathina KC**, Ten Thij M, Lorenzo-Luaces L, Rutter LA, Bollen J. Individuals with depression express more distorted thinking on social media. *Nat Hum Behav* 2021; **5**: 458-466 [PMID: 33574604 DOI: 10.1038/s41562-021-01050-7]

28 **Liu X**, Ping S, Gao W. Changes in Undergraduate Students' Psychological Well-Being as They Experience University Life. *Int J Environ Res Public Health* 2019; **16** [PMID: 31405114 DOI: 10.3390/ijerph16162864]

29 **Koutsouleris N**, Meisenzahl EM, Davatzikos C, Bottlender R, Frodl T, Scheuerecker J, Schmitt G, Zetzsche T, Decker P, Reiser M, Möller HJ, Gaser C. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Arch Gen Psychiatry* 2009; **66**: 700-712 [PMID: 19581561 DOI: 10.1001/archgenpsychiatry.2009.62]

30 **de Jong Y**, Mulder CL, Boon AE, Deen M, van 't Hof M, van der Gaag M. Screening for psychosis risk among adolescents in Child and Adolescent Mental Health Services: a description of the first step with the 16-item version of the Prodromal Questionnaire (PQ-16). *Early Interv Psychiatry* 2018; **12**: 669-676 [PMID: 27860294 DOI: 10.1111/eip.12362]

31 **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]

32 **Vieira S**, Pinaya WH, Mechelli A. Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications. *Neurosci Biobehav Rev* 2017; **74**: 58-75 [PMID: 28087243 DOI: 10.1016/j.neubiorev.2017.01.002]

33 **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]

34 **Nguyen TH**, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, Dang QT, Nguyen DP, Nguyen HP, To SD, Nguyen vV, Nguyen MD, Campbell J, Schultsz C, Parry C, Torok ME, White N, Nguyen TC, Stepniewska K, Farrar JJ. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med* 2007; **357**: 2431-2440 [PMID: 18077808 DOI: 10.1109/tcds.2017.2721552]

35 **Durstewitz D**, Koppe G, Meyer-Lindenberg A. Deep neural networks in psychiatry. *Mol Psychiatry* 2019; **24**: 1583-1598 [PMID: 30770893 DOI: 10.1038/s41380-019-0365-9]

36 **Lane NM**, Hunter SA, Lawrie SM. The benefit of foresight? *Neuroimage Clin* 2020; **26**: 102228 [PMID: 32173346 DOI: 10.1016/j.nicl.2020.102228]

37 **Laacke S**, Mueller R, Schomerus G, Salloch S. Artificial Intelligence, Social Media and Depression. A New Concept of Health-Related Digital Autonomy. *Am J Bioeth* 2021; **21**: 4-20 [PMID: 33393864 DOI: 10.1080/15265161.2020.1863515]

38 **Souza Filho EM**, Veiga Rey HC, Frajtag RM, Arrowsmith Cook DM, Dalbonio de Carvalho LN, Pinho Ribeiro AL, Amaral J. Can machine learning be useful as a screening tool for depression in primary care? *J Psychiatr Res* 2021; **132**: 1-6 [PMID: 33035759 DOI: 10.1016/j.jpsychires.2020.09.025]

39 **Michel C**, Schultze-Lutter F, Schimmelmann BG. Screening instruments in child and adolescent psychiatry: general and methodological considerations. *Eur Child Adolesc Psychiatry* 2014; **23**: 725-727 [PMID: 25164263 DOI: 10.1007/s00787-014-0608-x]

40 **Kline E**, Schiffman J. Psychosis risk screening: a systematic review. *Schizophr Res* 2014; **158**: 11-18 [PMID: 25034762 DOI: 10.1016/j.schres.2014.06.036]

41 **Brandizzi M**, Schultze-Lutter F, Masillo A, Lanna A, Curto M, Lindau JF, Solfanelli A, Listanti G, Patanè M, Kotzalidis G, Gebhardt E, Meyer N, Di Pietro D, Leccisi D, Girardi P, Fiori Nastro P. Self-reported attenuated psychotic-like experiences in help-seeking adolescents and their association with age, functioning and psychopathology. *Schizophr Res* 2014; **160**: 110-117 [PMID: 25458860 DOI: 10.1016/j.schres.2014.10.005]

42 **Chen JH**, Asch SM. Machine Learning and Prediction in Medicine - Beyond the Peak of Inflated Expectations. *N Engl J Med* 2017; **376**: 2507-2509 [PMID: 28657867 DOI: 10.1056/NEJMp1702071]

43 **Yamashita A**, Sakai Y, Yamada T, Yahata N, Kunimatsu A, Okada N, Itahashi T, Hashimoto R, Mizuta H, Ichikawa N,

Takamura M, Okada G, Yamagata H, Harada K, Matsuo K, Tanaka SC, Kawato M, Kasai K, Kato N, Takahashi H, Okamoto Y, Yamashita O, Imamizu H. Generalizable brain network markers of major depressive disorder across multiple imaging sites. *PLoS Biol* 2020; **18**: e3000966 [PMID: 33284797 DOI: 10.1371/journal.pbio.3000966]

44 **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]

45 **Mijwil MM**, Aggarwal K. A diagnostic testing for people with appendicitis using machine learning techniques. *Multimed Tools Appl* 2022; **81**: 7011-7023 [PMID: 35095329 DOI: 10.1007/s11042-022-11939-8]

46 **Fiske A**, Henningsen P, Buyx A. Your Robot Therapist Will See You Now: Ethical Implications of Embodied Artificial Intelligence in Psychiatry, Psychology, and Psychotherapy. *J Med Internet Res* 2019; **21**: e13216 [PMID: 31094356 DOI: 10.2196/13216]

47 **Lee EE**, Torous J, De Choudhury M, Depp CA, Graham SA, Kim HC, Paulus MP, Krystal JH, Jeste DV. Artificial Intelligence for Mental Health Care: Clinical Applications, Barriers, Facilitators, and Artificial Wisdom. *Biol Psychiatry Cogn Neurosci Neuroimaging* 2021; **6**: 856-864 [PMID: 33571718 DOI: 10.1016/j.bpsc.2021.02.001]

48 **Torous J**, Keshavan M, Gutheil T. Promise and perils of digital psychiatry. *Asian J Psychiatr* 2014; **10**: 120-122 [PMID: 25042968 DOI: 10.1016/j.ajp.2014.06.006]

49 **Yin Z**, Sulieman LM, Malin BA. A systematic literature review of machine learning in online personal health data. *J Am Med Inform Assoc* 2019; **26**: 561-576 [PMID: 30908576 DOI: 10.1093/jamia/ocz009]

50 **Wirz-Justice A**. Diurnal variation of depressive symptoms. *Dialogues Clin Neurosci* 2008; **10**: 337-343 [PMID: 18979947 DOI: 10.31887/dcns.2008.10.3/awjustice]

51 **Aladağ AE**, Muderrisoglu S, Akbas NB, Zahmacioglu O, Bingol HO. Detecting Suicidal Ideation on Forums: Proof-of-Concept Study. *J Med Internet Res* 2018; **20**: e215 [PMID: 29929945 DOI: 10.2196/jmir.9840]

52 **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]

53 **Stead WW**. Clinical Implications and Challenges of Artificial Intelligence and Deep Learning. *JAMA* 2018; **320**: 1107-1108 [PMID: 30178025 DOI: 10.1001/jama.2018.11029]

54 **Zou J**, Huss M, Abid A, Mohammadi P, Torkamani A, Telenti A. A primer on deep learning in genomics. *Nat Genet* 2019; **51**: 12-18 [PMID: 30478442 DOI: 10.1038/s41588-018-0295-5]

55 **Khanna A**, Pandey B, Vashishta K, Kalia K, Pradeepkumar B, Das T. A study of today's A.I. through chatbots and rediscovery of machine intelligence. *Int J u- e-Serv Sci Technol* 2015; **8**: 277-284 [DOI: 10.14257/ijunesst.2015.8.7.28]

56 **Weizenbaum J**. ELIZA—a computer program for the study of natural language communication between man and machine. *Commun ACM* 1966; **9**: 36-45 [DOI: 10.1145/365153.365168]

57 **Bassett C**. The computational therapeutic: exploring Weizenbaum's ELIZA as a history of the present. *AI Soc* 2019; **34**: 803-812 [DOI: 10.1007/s00146-018-0825-9]

58 **Adamopoulou E**, Moussiades L. Chatbots: history, technology, and applications. *Mach Learn Appl* 2020; **2**: 100006 [DOI: 10.1016/j.mlwa.2020.100006]

59 **Tapus A**, Peca A, Aly A, Pop CA, Jisa L, Pintea S, Rusu AS, David DO. Children with autism social engagement in interaction with Nao, an imitative robot. *Interact Stud* 2012; **13**: 315-347 [DOI: 10.1075/is.13.3.01tap]

60 **Fitzpatrick KK**, Darcy A, Vierhile M. Delivering Cognitive Behavior Therapy to Young Adults With Symptoms of Depression and Anxiety Using a Fully Automated Conversational Agent (Woebot): A Randomized Controlled Trial. *JMIR Ment Health* 2017; **4**: e19 [PMID: 28588005 DOI: 10.2196/mental.7785]

61 **Sachan D**. Self-help robots drive blues away. *Lancet Psychiatry* 2018; **5**: 547 [PMID: 29941139 DOI: 10.1016/S2215-0366(18)30230-X]

62 **Hussain J**, Satti FA, Afzal M, Khan WA, Bilal HSM, Ansaar MZ, Ahmad HF, Hur T, Bang J, Kim J-I, Park GH, Seung H, Lee S. Exploring the dominant features of social media for depression detection. *J Inf Sci* 2020; **46**: 739-759 [DOI: 10.1177/0165551519860469]

63 **Zhang B**, Zaman A, Silenzio V, Kautz H, Hoque E. The Relationships of Deteriorating Depression and Anxiety With Longitudinal Behavioral Changes in Google and YouTube Use During COVID-19: Observational Study. *JMIR Ment Health* 2020; **7**: e24012 [PMID: 33180743 DOI: 10.2196/24012]

64 **Gao W**, Ping S, Liu X. Gender differences in depression, anxiety, and stress among college students: A longitudinal study from China. *J Affect Disord* 2020; **263**: 292-300 [PMID: 31818792 DOI: 10.1016/j.jad.2019.11.121]

65 **Reece AG**, Reagan AJ, Lix KLM, Dodds PS, Danforth CM, Langer EJ. Forecasting the onset and course of mental illness with Twitter data. *Sci Rep* 2017; **7**: 13006 [PMID: 29021528 DOI: 10.1038/s41598-017-12961-9]

66 **De Choudhury M**, Gamon M, Counts S, Horvitz E. Predicting depression via social media. Proceedings of the Seventh International AAAI Conference on Weblogs and Social Media. Association for the Advancement of Artificial Intelligence, Weblogs and Social Media, 2013: 128-137

67 **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]

68 **Islam MR**, Kabir MA, Ahmed A, Kamal ARM, Wang H, Ulhaq A. Depression detection from social network data using machine learning techniques. *Health Inf Sci Syst* 2018; **6**: 8 [PMID: 30186594 DOI: 10.1007/s13755-018-0046-0]

69 **Merchant RM**, Asch DA, Crutchley P, Ungar LH, Guntuku SC, Eichstaedt JC, Hill S, Padrez K, Smith RJ, Schwartz HA. Evaluating the predictability of medical conditions from social media posts. *PLoS One* 2019; **14**: e0215476 [PMID: 31206534 DOI: 10.1371/journal.pone.0215476]

70 **Strimpakos AS**, Syrigos KN, Saif MW. Pharmacogenetics in pancreatic cancer. Highlights from the 45th ASCO annual meeting. Orlando, FL, USA. May 29-June 2, 2009. *JOP* 2009; **10**: 357-360 [PMID: 19581734 DOI: 10.1109/access.2020.2987523]

71 **Colombo D**, Palacios AG, Alvarez JF, Patané A, Semonella M, Cipresso P, Kwiatkowska M, Riva G, Botella C. Current state and future directions of technology-based ecological momentary assessments and interventions for major depressive disorder: protocol for a systematic review. *Syst Rev* 2018; **7**: 233 [PMID: 30545415 DOI: 10.1186/s13643-018-0899-y]

72 **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]

73 **Sarda A**, Munuswamy S, Sarda S, Subramanian V. Using Passive Smartphone Sensing for Improved Risk Stratification of Patients With Depression and Diabetes: Cross-Sectional Observational Study. *JMIR Mhealth Uhealth* 2019; **7**: e11041 [PMID: 30694197 DOI: 10.2196/11041]

74 **Chikersal P**, Doryab A, Tumminia M, Villalba DK, Dutcher JM, Liu X, Cohen S, Creswell KG, Mankoff J, Creswell JD, Goel M, Dey AK. Detecting depression and predicting its onset using longitudinal symptoms captured by passive sensing. *ACM Trans Comput-Hum Interact* 2021; **28**: 1-41 [DOI: 10.1145/3422821]

75 **D'Alfonso S**, Santesteban-Echarri O, Rice S, Wadley G, Lederman R, Miles C, Gleeson J, Alvarez-Jimenez M. Artificial Intelligence-Assisted Online Social Therapy for Youth Mental Health. *Front Psychol* 2017; **8**: 796 [PMID: 28626431 DOI: 10.3389/fpsyg.2017.00796]

76 **Orabi AH**, Buddhitha P, Orabi MH, Inkpen D. Deep learning for depression detection of twitter users. In: Loveys K, Niederhoffer K, Prud'Hommeaux E, Resnik R, Resnik P. From Keyboard to Clinic. Proceedings of the Fifth Workshop on Computational Linguistics and Clinical Psychology: From Keyboard to Clinic; 2018 Jun 5; New Orleans, Louisiana. Association for Computational Linguistics, 2018: 88-97

77 **Beauchamp TL**, Childress JF. Principles of biomedical ethics. Oxford: Oxford University Press, 2001: 1-23

78 **Floridi L**, Cowls J, Beltrametti M, Chatila R, Chazerand P, Dignum V, Luetge C, Madelin R, Pagallo U, Rossi F, Schafer B, Valcke P, Vayena E. AI4People-An Ethical Framework for a Good AI Society: Opportunities, Risks, Principles, and Recommendations. *Minds Mach (Dordr)* 2018; **28**: 689-707 [PMID: 30930541 DOI: 10.1007/s11023-018-9482-5]

79 **Floyd DL**, Prentice-Dunn S, Rogers RW. A meta-analysis of research on protection motivation theory. *J Appl Soc Psychol* 2000; **30**: 407-429 [DOI: 10.1111/j.1559-1816.2000.tb02323.x]

80 **Corsico P**. The risks of risk. Regulating the use of machine learning for psychosis prediction. *Int J Law Psychiatry* 2019; **66**: 101479 [PMID: 31706401 DOI: 10.1016/j.ijlp.2019.101479]

81 **Livingstone S**, Helsper E. Gradations in digital inclusion: children, young people and the digital divide. *New Media Soc* 2007; **9**: 671-696 [DOI: 10.1177/1461444807080335]

82 **Van Dijk J**, Hacker K. The digital divide as a complex and dynamic phenomenon. *Inf Soc* 2003; **19**: 315-326 [DOI: 10.1080/01972240309487]

83 **Gao S**, Calhoun VD, Sui J. Machine learning in major depression: From classification to treatment outcome prediction. *CNS Neurosci Ther* 2018; **24**: 1037-1052 [PMID: 30136381 DOI: 10.1111/cns.13048]

84 **Gold JM**, Waltz JA, Frank MJ. Effort cost computation in schizophrenia: a commentary on the recent literature. *Biol Psychiatry* 2015; **78**: 747-753 [PMID: 26049208 DOI: 10.1016/j.biopsych.2015.05.005]

85 **Aggarwal K**, Mijwil MM, Al-Mistarehi AH, Alomari S, Gök M, Alaabdin AMZ, Abdulrhman SH. Has the Future Started? *IJCSM* 2022; **3**: 115-123 [DOI: 10.52866/ijcsm.2022.01.01.013]

86 **Hasanzadeh F**, Mohebbi M, Rostami R. Prediction of rTMS treatment response in major depressive disorder using machine learning techniques and nonlinear features of EEG signal. *J Affect Disord* 2019; **256**: 132-142 [PMID: 31176185 DOI: 10.1016/j.jad.2019.05.070]

87 **Karhade AV**, Ogink PT, Thio QCBS, Cha TD, Gormley WB, Hershman SH, Smith TR, Mao J, Schoenfeld AJ, Bono CM, Schwab JH. Development of machine learning algorithms for prediction of prolonged opioid prescription after surgery for lumbar disc herniation. *Spine J* 2019; **19**: 1764-1771 [PMID: 31185292 DOI: 10.1016/j.spinee.2019.06.002]

88 **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**: 393-409 [PMID: 35433319 DOI: 10.5498/wjp.v12.i3.393]

World Journal of Psychiatry

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

World J Psychiatry 2022 October 19; 12(10): 1298-1312

DOI: 10.5498/wjp.v12.i10.1298

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Overlap of orthorexia, eating attitude and psychological distress in some Italian and Spanish university students

Paola Aiello, Elisabetta Toti, Débora Villaño, Anna Raguzzini, Ilaria Peluso

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, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Ekine-Afolabi B, United Kingdom; Wierzbicka A, Poland

Received: March 19, 2022
Peer-review started: March 19, 2022
First decision: May 30, 2022
Revised: June 15, 2022
Accepted: September 2, 2022
Article in press: September 2, 2022
Published online: October 19, 2022

Paola Aiello, Department of Physiology and Pharmacology "V. Erspamer", Sapienza University, Rome 00185, Italy

Elisabetta Toti, Anna Raguzzini, Ilaria Peluso, Research Centre for Food and Nutrition, Council for Agricultural Research and Economics, Rome 00178, Italy

Débora Villaño, Food Science and Technology Department, UCAM, Murcia 30107, Spain

Corresponding author: Ilaria Peluso, PhD, Research Scientist, Research Centre for Food and Nutrition, Council for Agricultural Research and Economics, Via Ardeatina 546, Rome 00178, Italy. ilaria.peluso@crea.gov.it

Abstract

BACKGROUND

Orthorexia nervosa (ON) is the persistent concern of maintaining the self-imposed diet to improve one's health. Many factors have been associated to ON in university students.

AIM

To assess the prevalence of ON in Italian and Spanish university students in relation to eating attitude and psychological distress, and the possible overlaps between ON (evaluated with different scored questionnaires from the originally proposed ORTO-15), distress and risk of eating disorders.

METHODS

This study was carried out on 160 students recruited at La Sapienza University of Rome and at the Catholic University of Murcia. Questionnaires were administered to evaluate ON (ORTO-15 and sub-scores), body concerns (Multidimensional Body-Self Relations Questionnaire, MBSRQ, and Body Uneasiness test, BUT), psychological distress (Kessler Psychological Distress Scale, K10), physical activity (International Physical Activity Questionnaire, IPAQ), eating attitude (Eating Attitudes Test, EAT-26) and malnutrition (Starvation Symptom Inventory, SSI). Sex differences, within the same country, and differences between Italian and Spanish students, within the same sex, were evaluated.

RESULTS

The ORTO-15 positive subjects, assessed with the originally proposed cut-off, were above 70% in both Italian and Spanish students, with a higher prevalence in

the Spanish sample (Italian females 76.3%, Italian males 70.7%; Spanish females 97.0%, Spanish males 96.3%). According to ORTO-7, about 30% of Italian and 48% of Spanish students were positive to ON with no significant sex differences. When excluding students underweight (UW), overweight (OW) or obese (OB), as well as those potentially at risk of eating disorders or presenting mild, moderate and severe distress, in the resultant normal weight (NW)-K10^{neg}-EAT-26^{neg} subgroup, we did not find many correlations observed in the whole sample, including those between ORTO scores and BUT, SSI, Total MBSRQ and some of its components. Moreover, ORTO-7 resulted in the only ON score unrelated with Body Mass Index, MBSRQ components and IPAQ-assessed intense activity, in the NW-K10^{neg}-EAT-26^{neg} subgroup. After this sort of "exclusion diagnosis", the prevalence of ON of these students on the overall sample resulted in 16.9%, 12.2%, 15.2% and 25.9% for Italian females, Italian males, Spanish females and Spanish males, respectively.

CONCLUSION

In some university students ON could be a symptom of other conditions related to body image concerns and distress, as well as to high physical activity and appearance, fitness, health or illness orientation (from MBSRQ). However, ORTO-7 became independent from these confounding variables, after the exclusion of UW, OW, OB and students positive to EAT-26 and K10, suggesting the possibility of identifying orthorexic subjects with this specific questionnaire.

Key Words: Diet; Exercise; Food avoidance; Other Specified Feeding and Eating Disorder; Lifestyle

Core Tip: This study explores the overlap of orthorexia nervosa with eating attitude and psychological distress in Italian and Spanish university students. After excluding, among normal weight students, those with high score on the Kessler Distress Scale and Eating Attitudes Test, we did not find correlations among orthorexia and Starvation Symptoms Inventory, Body Uneasiness Test, and Multidimensional Body Self-Relations Questionnaire (MBSRQ), observed in the whole sample. After this kind of "exclusion diagnosis", sub-scores of MBSRQ indicating body concerns correlated with ORTO-12 and ORTO-9, whereas ORTO-7 resulted the only score unrelated with all outcomes, including fitness and health orientations (MBSRQ), and intense physical activity.

Citation: Aiello P, Toti E, Villaño D, Raguzzini A, Peluso I. Overlap of orthorexia, eating attitude and psychological distress in some Italian and Spanish university students. *World J Psychiatry* 2022; 12(10): 1298-1312

URL: https://www.wjgnet.com/2220-3206/full/v12/i10/1298.htm

DOI: https://dx.doi.org/10.5498/wjp.v12.i10.1298

INTRODUCTION

The term orthorexia nervosa (ON) is referred to the psychological obsession with a healthy, organic and pure diet, and it is often based on stereotyped or erroneous nutritional beliefs, which can lead to dietary restrictions with resulting nutritional deficiencies[1-4]. Although ON shares several aspects in common with Anorexia Nervosa (AN)[5] and other eating disorders (EDs)[6], and around 70% of health professionals[7,8] believe that ON should be a distinct, clinically recognized ED, it is not included in the ICD-11 (International Statistical Classification of Diseases and Related Health Problems)[9,10]. In the Diagnostic and Statistical Manual of Mental Disorders, the terminology "eating disorders" has been changed to "Feeding and Eating Disorders", including eight categories: AN, bulimia nervosa, binge ED, pica, rumination, Avoidant or Restrictive Food Intake Disorder (ARFID), Other Specified Feeding and Eating Disorder (OSFED), and unspecified feeding and EDs[11]. Among these, ON has yet to be recognized as a separate ED, but has been included in OSFED, whereas ARFID refers to a persistent avoidance of food for various reasons (depressed temperament, phobias, sensory repulsion of the appearance, smell, texture of food), not necessarily associated with the search for a healthy diet that characterizes the subject with ON.

Although individuals with ON have an obsessive focus on healthy eating and may eliminate entire food groups, fearing they are unhealthy, they can later develop a typical ED[7,11]. Despite the awareness of clinicians on this condition[7,8,12], it is assumed that the estimate of subjects affected by ON is very complex, given the lack of explicit diagnostic criteria[13-16]. In particular, it has been

recently pointed out that the conflicting data on the prevalence of ON depend on differences in the tools used and in the cut-off points[17]. Moreover, authors concluded that the use of the ORTO-15 questionnaire to diagnose ON is questionable due to a high percentage of false-positive results[17], and different cut-offs or sub-scores have been proposed[18-24]. Abdullah *et al*[18] have suggested that a cut-off point of 35 is preferable than a cut-off at 40, and have reported that ON tendency is affected by sex and body mass index (BMI), and not affected by educational level. No differences were found in the prevalence of ON among students attending health-scientific, economic-humanistic, sport sciences and dietetics and nutrition university courses[25,26]. However, the reported prevalence of ON in university students was variable and affected by EDs, dieting and a high level of physical activity (PA)[25-30].

Among the criticisms relative to ORTO-15, Roncero *et al*[31] highlighted the risk of including those who are on-diet among the individuals with ON, and the redundancy between the ORTO-15 and the Eating Attitudes Test (EAT-26). Accordingly, an overlap between ORTO-15 and EAT-26 has been reported in university students[32,33], but individuals with ON had lower psychological distress than those with ED risk[33]. Furthermore, it has been reported that overweight (OW) preoccupation and appearance orientation (AO), assessed with the Multidimensional Body-Self Relations Questionnaire-Appearance Scale (MBSRQ-AS), were significant predictors of ON[34].

The aim of this observational study was to evaluate the prevalence of ON in Italian and Spanish university students in relation to eating attitude and psychological distress, and the possible overlaps between ON (evaluated with different scored questionnaires), distress and risk of EDs. Moreover, a decision tree for the exclusion diagnosis of ON in healthy university students has been proposed.

MATERIALS AND METHODS

Study design, recruitment, and data collection

This study was carried out on a sub-group of participants from a previous study[35]. Undergraduate and doctoral students aged between 18 years and 35 years were recruited at La Sapienza University of Rome and at the Catholic University of Murcia. All the volunteers included in the study signed the informed consent, accompanied by an informative note, and the recruiter assigned them an alphanumeric code to guarantee privacy during the data management (all details about recruitment and protocol are available online at https://www.clinicaltrials.gov/ct2/show/NCT04099420). Body mass and stature were measured with the OMRON BF511 electronic scale and the SECA 217 portable stadiometer, respectively. BMI was calculated with the following formula: BMI = weight (kg)/height squared (m^2). Moreover, several standardized questionnaires were administered.

ON

The ORTO-15 test is a questionnaire made up of 15 multiple-choice items based on a Likert scale (always, often, sometimes, never)[36]. The items concern three areas: the cognitive-rational area (items 1, 5, 6, 11, 12, 14), the clinical area (items 3, 7-9, 15), mainly related to anxiety-inducing and obsessive psychiatric disorders, and the emotional area (items 2, 4, 10, 13)[36]. A score of 1 was given to responses that were more indicative of ON, whereas a score of 4 was attributed to those that indicated a normal eating behavior. Therefore, lower scores correspond to a more pathological behavior, and total score ranges from 15 to 60, with the cut-off point equal to 40[36]. This value has been questioned as it was considered too high; consequently, a lower cut-off (35) was also chosen[18,19].

Additional versions of the ORTO test have been developed based on the selection of ORTO-15 items that more specifically could be indicative of the presence of symptoms of ON. ORTO-12 is a shorter version of 12 items, obtained by excluding items 5, 6 and 8 from the original ORTO-15, since they contribute less to the definition of ON, but a specific cut-off point was not determined[20]. ORTO-11 excludes items 5, 8, 14 and 15 of the ORTO-15. Final score ranges from 11 to 44, and a cut-off point < 25 has been considered the most appropriate to suggest a tendency to ON[21]. The ORTO-9 is a version of ORTO test which excludes items 1, 2 and 8, with a cut-off < 26.7. This test was found to be ineffective in predicting ON[22]. The ORTO-7 is based on items (1, 3, 4, 7, 9, 11 and 13) that mostly highlight the presence of ON with a cut-off ≤ 19[23,24].

Body image concerns

Two questionnaires were used to evaluate body image concerns, the MBSRQ[37,38] and the Body Uneasiness Test (BUT).

We evaluated the total MBSRQ and the MBSRQ Factor Subscales (FSs): AO, fitness orientation (FO), health orientation (HOr) and illness orientation (IO). In addition to these FSs, we evaluated the MBSRQ subscales: body areas satisfaction scale (BASS) and OW preoccupation (OP). Each of the MBSRQ scales has its corresponding items that can be answered by a primary number from 1 (strongly disagree) to 5 (strongly agree). The score of contraindicative items (6, 15-17, 23, 25, 28, 32-34, 36-38, 40, 42, 43, 45, 47-49) is reversed (*i.e.*, 1 = 5, 2 = 4, 4 = 2, 5 = 1). MBSRQ subscale scores are the means of the constituent items. The MBSRQ-AS is the shorter (34-item version) form of MBSRQ that assesses only the appearance-related components of the body image construct[37].

On the other hand, BUT includes two parts, BUT A (34 statements) and BUT B (37 body parts). Items are rated on a 6 points Likert-type scale (range 0-5, from "never" to "always") and high rates indicate greater body uneasiness[39]. In addition to the total score, we evaluated BUT A weight phobia (WP, fear of being or becoming fat) and body image concerns (BIC, worries related to physical appearance) components.

Eating attitudes and malnutrition

Eating Attitudes Test (EAT-26) and Starvation Symptom Inventory (SSI) were administered to participants. The former is a standardized measure of symptoms and concerns characteristic of EDs, whereas the latter can reveal the presence of malnutrition.

EAT-26 is made up of 26 items and represent a screening tool to assess "ED risk"[40]. Although it does not provide a diagnosis of ED, the EAT-26 items include the subscales: "dieting" scale (items 1, 6, 7, 10, 11, 12, 14, 16, 17, 22, 23, 24, 26) and "bulimia and food preoccupation" scale (items 3, 4, 9, 18, 21, 25). Four behavioral questions are included to determine the presence of extreme weight-control behaviors. These items assess self-reported binge eating, self-induced vomiting, use of laxatives and treatment for ED over the preceding 6 mo. Participants were required to judge whether the item applied "always", "very often", "often", "sometimes", "rarely" or "never". Each extreme response in the "anorexic" direction is scored as a worth of 3 points, while the adjacent alternatives are weighted as 2 points and 1 point, respectively. A score ≥ 20 on the EAT-26 does not necessarily mean that respondent has an ED. However, it indicates a high level of concern about dieting, body weight or problematic eating behaviors.

SSI is a 16-item questionnaire and participants were asked to estimate the number of days out of the preceding 28, in which they had experienced symptoms of starvation (hunger, poor concentration, heightened satiety, dizziness, reduction in rate of weight loss) on a 7-point Likert scale: never (0), 1-5 d (1), 6-12 d (2), 13-15 (3), 16-22 (4), 23-27 (5), and always (6)[41]. The highest score indicates increased frequency of starvation symptoms over the last 28 d.

Psychological distress and PA

The Kessler Psychological Distress Scale (K10)[42] and the International Physical Activity Questionnaire (IPAQ)[43] were used to evaluate distress and PA level, respectively.

K10 is a 10-item questionnaire about emotional states, each with a five-level response scale. The measure can be used as a brief screen to identify levels of distress[42]. Each item is scored from 1 (none of the time) to 5 (all of the time). Scores from the 10 items were then summed, yielding a minimum score of 10 and a maximum score of 50. According to the total score, the likelihood of having a mental disorder (psychological distress) is established[42]; in particular, 10-19 likely to be well, 20-24 likely to have a mild disorder, 25-29 likely to have a moderate disorder, and 30-50 likely to have a severe disorder.

The IPAQ (short form)[43] includes items assessing the frequency and duration of PA in three ranges of intensity: intense PA (8.0 metabolic equivalent of tasks: METs), moderate PA (4.0 METs), and walking fast (3.3 METs), moderate (3.0 METs) and slow (2.5 METs) pace[43]. Based on collected data about the frequency and duration of PA, energy expenditure (expressed as MET-min/wk) has been estimated. One MET is the rate of energy expenditure at rest, and it is approximately equal to 3.5 mL O2 kg-1 min-1 in adults. According to the Italian Society of Endocrinology, IPAQ allows to classify population in three PA levels: Low (the lowest level of PA, less than 700 METs-min/wk), Moderate (Total PA between 700 and 2519 METs-min/wk) and High (Total PA of at least 2520 METs- min/wk).

Statistical analysis

Categorical variables were expressed as percentages and significance assessed by the χ^2 test. Continuous variables showing a normal pattern (normality test Shapiro-Wilk passed) were expressed as means with SD, otherwise data were expressed as median (25%-75% range). Results were analyzed by analysis of variance (ANOVA, Shapiro-Wilk test passed), or by Kruskal-Wallis one-way analysis of variance on ranks (Shapiro-Wilk test failed). The significance of the differences between females and males within the same country, and those between the different countries within the same sex, were evaluated using the Student-Newman-Keuls method (Shapiro-Wilk test passed) or the Dunn's method (Shapiro-Wilk Test failed). Spearman correlation was performed between variables. The level of significance was set below 5% ($P < 0.05$).

RESULTS

Country and sex differences

Characteristics of students and differences between Italy and Spain (evaluated within the same sex), and sex differences (evaluated within the same country) are reported in Table 1. Only in Italy, females (IT-F) had a significant lower BMI than males (IT-M), whereas the different prevalence of underweight (UW),

Table 1 Students' characteristics

	IT-F, *n* = 59	IT-M, *n* = 41	SP-F, *n* = 33	SP-M, *n* = 27
Age (yr)	24 (23-28)	25 (23-28)	23 (21-28)	24 (24-26)
Height (m)	1.64 ± 0.06[a]	1.78 ± 0.08[a]	1.63 ± 0.06[a]	1.78 ± 0.07[a]
Weight (kg)	55.9 (53.0-61.0)[a]	77.0 (70.9-87.5)[a]	58.7 (52.4-66.5)[a]	76.3 (67.1-82.0)[a]
BMI (kg/m^2)	20.7 (19.4-22.4)[a]	24.5 (22.1-27.1)[a]	23.3 (20.2-24.5)	24.1 (21.8-25.5)
Underweight (%)	11.9	0.0	9.1	3.7
Overweight (%)	6.8	31.7	15.1	25.9
Obese (%)	5.1	9.7	3.0	3.7
IPAQ (MET-min/wk)	2232 (1080-4986)	4380 (2305-6277)	2100 (1202-4395)[a]	4970 (2575-6780)[a]
IPAQ walking	630 (315-1260)	700 (488-1323)	525 (244-1230)	600 (240-1470)
IPAQ moderate	720 (160-1680)	600 (240-1440)	600 (240-1440)	720 (120-1440)
IPAQ intense	480 (0-1920)[a]	2160 (400-3840)[a]	800 (0-1680)[a]	2400 (960-4320)[a]
PA low (%)	16.9	7.3	18.2	7.4
PA moderate (%)	40.7	19.5	36.4	14.8
PA high (%)	42.4	73.2	45.5	77.8
Smokers (%)				
Habitual	15.3	19.5	9.1	7.7
Occasional	16.9	19.5	15.2	15.4
Ex-smokers	8.5	9.8	9.1	3.8
K10	15.0 (13.0-19.0)	14.0 (12.0-17.0)	19.0 (15.0-27.5)	17.0 (14.0-20.0)
Mild (%)	11.9	0.0[b]	15.2	25.9[b]
Moderate (%)	6.9	9.8	18.2	3.7
Severe (%)	5.1	4.9	15.2	3.7

[a]$P < 0.05$ between females and males within country.
[b]$P < 0.05$ between Italians and Spaniards within sex.
Categorical variables are expressed as percentages. Continuous variables are expressed as means with standard deviation (Shapiro-Wilk Test passed), or as median (25%-75% range, Shapiro-Wilk Test failed). BMI: Body mass index; IPAQ: International Physical Activity Questionnaire; IT-F: Italian females; IT-M: Italian males; K10: Kessler Psychological Distress Scale; SP-F: Spanish females; SP-M: Spanish males; PA: Physical activity.

OW and obese (OB) students, as well as of volunteers who practice Low, Moderate or High PA, did not reach significance in both countries (Table 1). However, Spanish males (SP-M) on average practiced more PA than females (SP-F), and sex differences were found in IPAQ intense (MET-min/wk from intense activities) in both countries (Table 1). No differences were found in smoking habits, whereas a high percentage of SP-M reported mild psychological distress (assessed by K10) than IT-M (Table 1). SP-M were also those with higher total MBSRQ, MBSRQ-AO, -FO, -HOr, -AS and -BASS, whereas no differences were found in MBSRQ-IO and -OP (Table 2). On the contrary, IT-F had higher BUT-A - BIC and - WP than IT-M, but lower compared to SP-F (Table 2). Differences in total BUT and in its components (BUT-A and BUT-B) did not reach statistical significance (Table 2).

Concerning ORTO-15, lower values (indicating high ON) were observed in Spanish students compared to Italians, when using the first proposed cut-off point of 40[36], and with ORTO-12, -11 and -9 (Table 3). By using the lower cut-off point of 35 for ORTO-15 or the ORTO-11, -9, and -7, IT-F resulted with less tracts of ON than SP-F (Table 3). Both SP-F and SP-M had higher EAT-26 total score than Italian counterparts, despite dieting and bulimia components did not reach statistical significance (Table 3). Similar results came from SSI, suggesting more starvation symptoms in Spaniards compared to Italians (Table 3).

Overlaps and correlations among outcomes

Figure 1A illustrates the prevalence of ON in the whole sample (n = 160), by using different cut-off points and scores for ORTO questionnaire, among students who presented ED risk (EAT-26) or mild, moderate, and severe psychological distress (K10). In addition to the overlaps among these conditions

Table 2 Body image concerns

	IT-F, *n* = 59	IT-M, *n* = 41	SP-F, *n* = 33	SP-M, *n* = 27
MBSRQ	227.0 ± 21.7	231.6 ± 27.6[b]	227.9 ± 24.3[a]	249.3 ± 27.5[a,b]
MBSRQ-AO	3.3 ± 0.9	3.2 ± 0.5[b]	3.5 ± 0.5	3.5 ± 0.5[b]
MBSRQ-FO	3.4 (3.0-3.9)	3.5 (3.2-4.2)	3.5 (3.0-4.0)[a]	4.2 (3.6-4.4)[a]
MBSRQ-HOr	3.4 ± 0.5	3.4 ± 0.6	3.2 ± 0.6[a]	3.6 ± 0.6[a]
MBSRQ-IO	3.3 ± 0.6	3.3 ± 0.5	3.4 ± 0.5	3.6 ± 0.6
MBSRQ-AS	3.1 ± 0.3	3.1 ± 0.4[b]	3.1 ± 0.4[a]	3.4 ± 0.4[a,b]
MBSRQ-BASS	3.2 ± 0.7	3.4 ± 0.6	3.1 ± 0.8[a]	3.5 ± 0.7[a]
MBSRQ-OP	2.0 (1.8-2.8)	2.5 (1.8-3.0)	2.5 (2.1-3.0)	2.5 (2.0-3.3)
BUT	33.0 (19.0-61.0)	16.0 (6.0-39.0)	60.0 (30.5-82.0)	35.0 (21.0-74.0)
BUT-A	16.0 (9.0-36.0)	10.0 (2.0-20.0)	33.0 (12.5-51.0)	18.0 (13.0-42.0)
BUT-A - WP	0.9 (0.4-1.6)[b]	0.5 (0.1-1.0)	1.8 (0.8-2.6)[b]	1.1 (0.6-1.8)
BUT-A - BIC	0.7 (0.2-1.3)[a]	0.2 (0.0-0.9)[a]	0.9 (0.5-1.6)	0.6 (0.2-1.6)
BUT-B	15.0 (7.0-31.0)	11.0 (3.5-21.0)	25.5 (14.0-42.5)	21.0 (8.0-36.0)

[a]$P < 0.05$ between females and males within country.
[b]$P < 0.05$ between Italians and Spaniards within sex.
Categorical variables are expressed as percentages. Continuous variables are expressed as means with standard deviation (Shapiro-Wilk Test passed), or as median (25%-75% range, Shapiro-Wilk Test failed). AO: Appearance orientation; AS: Appearance scales; BASS: Body areas satisfaction scale; BIC: Body image concerns; BUT: Body Uneasiness Test; FO: Fitness orientation; HOr: Health orientation; IO: Illness orientation; IT-F: Italian females; IT-M: Italian males; MBSRQ: Multidimensional Body-Self Relations Questionnaire; OP: Overweight preoccupation; SP-F: Spanish females; SP-M: Spanish males; WP: Weight phobia.

and ON, psychological distress was observed both in students presenting ED risk or in those resulting negative to the EAT-26 test, without sex differences (Figure 1B). On the other hand, in Figure 2 is presented the prevalence of ON among different BMI classes and lifestyle factors, such as PA level and smoking habits.

From the aforementioned results, and in order to reduce the potential confounder as being on caloric restriction[31], Spearman correlations were evaluated in both the total sample (n = 160, 92 F and 68 M) and a subgroup of students (n = 66, 38 F and 28 M) with normal weight (NW), excluding those who suffered from mild, moderate and severe distress, or potentially at ED risk (NW-K10^{neg}-EAT-26^{neg}).

As regards the NW-K10^{neg}-EAT-26^{neg} group, all subjects resulted with ON when ORTO-15 (40 cut-off point) was applied, whereas a prevalence of 37.9% was observed applying ORTO-15 (35 cut-off point), 18.2% considering ORTO-11, 22.7% with ORTO-9, and 40.0% with ORTO-7. Concerning lifestyle, the percentage of non-smokers (60.6%) was higher ($P < 0.05$) compared to those of ex-smokers (7.6%) and smokers (13.6%) among students with ON, assessed with ORTO-15 (40 cut-off). Similar results were reported when ORTO-15 (35 cut-off point) was used, with a prevalence of ON in non-smokers and smokers corresponding to 60.0% and 16.0%, respectively, as well as for results of ORTO-11 (prevalence of ON: non-smokers 66.7% and smokers 16.7%), ORTO-9 (prevalence of ON: non-smokers 66.7% and smokers 13.3%) and ORTO-7 (prevalence of ON: non-smokers 74.1% and smokers 7.4%). Among the students with ON, the percentage of those practicing high PA was higher ($P < 0.05$) compared to low PA for ORTO-15 (cut-off 40: high PA 54.4% and low PA 15.2%; cut-off 35: high PA 68.0% and low PA 8.0%), ORTO-11 (high PA 75.0% and low PA 0%), ORTO-9 (high PA 80.0% and low PA 0.0%) and ORTO-7 (high PA 59.3% and low PA 11.1%).

Considering the whole sample, among the different ORTO scores a relationship between ORTO-9 and BMI was found, and Table 4 depicts the Spearman correlations between ORTO scores and those from the other questionnaires. All ORTO scores were inversely correlated to SSI (Table 4), which indicates that high ON corresponds to more starvation symptoms since ORTO has reverse scores. Similarly, all ORTO scores were correlated to EAT-26 and its components (Table 4). On the contrary, the relationships between each ORTO score and BUT components were different (Table 4). Weight phobia (BUT A-WP) was correlated with ORTO-12, ORTO-9 and ORTO-7. The latter resulted the only one not related to MBRSQ-AS, MBSRQ and its health component (MBSRQ-HOr), as well as to the MBSRQ-OP (Table 4). Moreover, the correlation coefficients between ORTO scores and MBSRQ-AO and -FO were lower for ORTO-7 compared to the other scores (Table 4). On the other hand, ORTO-7 resulted in the only one that was related to the MBSRQ-BASS, and ORTO-9 was the only score related to IPAQ and to its intense activities and walking components (Table 4).

Table 3 Orthorexia, eating attitude and malnutrition

	IT-F, *n* = 59	IT-M, *n* = 41	SP-F, *n* = 33	SP-M, *n* = 27
ORTO-15	36.8 ± 3.4[a]	36.4 ± 34.2[a]	34.2 ± 3.6[a]	33.8 ± 3.4[a]
Cut-off 40 (%)	76.3[a]	70.7[a]	97.0[a]	96.3[a]
Cut-off 35 (%)	23.7[a]	36.5	48.5[a]	55.5
ORTO-12	30.7 ± 3.0[a]	30.4 ± 3.4[a]	27.5 ± 2.9[a]	27.2 ± 2.7[a]
ORTO-11	27.8 ± 2.8[a]	27.6 ± 3.4[a]	25.2 ± 2.9[a]	25.4 ± 3.0[a]
Cut-off 25 (%)	11.9[a]	19.5[a]	36.4[a]	25.9[a]
ORTO-9	30.4 ± 3.4[a]	30.0 ± 3.7[a]	27.8 ± 3.2[a]	27.1 ± 3.2[a]
Cut-off 26.7 (%)	13.6[a]	19.5[a]	30.3[a]	40.7[a]
ORTO-7	20.0 (18.0-22.0)[a]	19.0 (18.0-21.0)	19.0 (15.5-19.5)[a]	19.0 (16.0-19.0)
Cut-off 19 (%)	32.2	29.3	48.5	48.1
EAT-26	6.0 (3.0-10.0)[a]	5.0 (3.0-8.5)[a]	11.0 (5.0-17.5)[a]	13.0 (7.0-17.0)[a]
Cut-off 20 (%)	8.5	4.9	21.2	11.1
Dieting	2.0 (0.0-5.0)	2.0 (0.04.5)	4.0 (0.5-9.5)	6.0 (3.0-9.0)
Bulimia	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-5.5)	3.0 (3.0-5.0)
SSI	14.0 (8.0-22.0)[a]	10.0 (4.5-16.0)[a]	24.0 (20.0-43.0)[a]	18.0 (12.0-30.0)[a]

[a]$P < 0.05$ between Italians and Spaniards within sex. Not significant between females and males within country.
Categorical variables are expressed as percentages. Continuous variables are expressed as means with standard deviation (Shapiro-Wilk Test passed), or as median (25%-75% range, Shapiro-Wilk Test failed). EAT-26: Eating Attitudes Test; IT-F: Italian females; IT-M: Italian males; ORTO: Scores for orthorexia nervosa (ON, reverse scores, lower values indicate high ON); SP-F: Spanish females; SP-M: Spanish males; SSI: Starvation Symptom Inventory.

In the NW-K10^{neg}-EAT-26^{neg} subgroup, we did not find many correlations as observed in the whole sample, including those between ORTO scores and BUT, SSI, total MBSRQ and some of its components (Table 4). Although no relationship was found among ORTO score and SSI in the NW-K10^{neg}-EAT-26^{neg} subgroup, SSI was correlated with MBSRQ-OP (0.291, $P < 0.05$). The latter, as well as MBSRQ-AO and -AS, was correlated with ORTO-12 and ORTO-9 (Table 4), but also with BMI (0.260, $P < 0.05$).

On the other hand, in the NW-K10^{neg}-EAT-26^{neg} subgroup, MET-min/wk from intense activities correlated with ORTO-15, -12, -11 and -9 (Table 4), as well as with BMI (0.442, $P < 0.001$), MBSRQ-FO (0.629, $P < 0.001$), -HOr (0.387, $P < 0.01$), that were highly related (coefficient of correlation MBSRQ-FO *vs* MBSRQ-HOr: 0.629, $P < 0.001$) and, to a lesser extent, IPAQ-intense activity was related to MBSRQ-OP (0.253, $P < 0.05$). MBSRQ-IO correlated with both MBSRQ-HOr (0.447, $P < 0.001$) and -AO (0.256, $P < 0.05$), that was related to MBSRQ-FO (0.329, $P < 0.01$). Interestingly, ORTO-7 resulted in the only score unrelated neither with BMI nor with the other evaluated outcomes in the NW-K10^{neg}-EAT-26^{neg} subgroup (Table 4). The prevalence of ON from ORTO-7 in students included in the NW-K10^{neg}-EAT-26^{neg} subgroup on the overall sample resulted to be 16.9%, 12.2%, 15.2% and 25.9% for IT-F, IT-M, SP-F and SP-M, respectively.

DISCUSSION

In light of the reported overlaps of ON with other conditions and of the criticism highlighted from literature about ORTO-15[17-34], we have evaluated the prevalence of ON among 160 Italian and Spanish university students, from the 194 recruited in a previous study[35], who agreed to fill the standardized questionnaires: EAT-26, K10, BUT, MBSRQ, and IPAQ. The sample had, on average, a medium adherence to the Mediterranean diet and a low risk of excessive alcohol consumption[35]. Concerning country differences, the prevalence of mild distress was higher in SP-M compared to IT-M (Table 1), whereas IT-F had lower BUT-A -WP than SP-F (Table 2). SP-M had higher total MBSRQ, MBSRQ-AO, -FO, -HOr, -BASS and -AS, whereas no differences were found in MBSRQ-IO and -OP (Table 2).

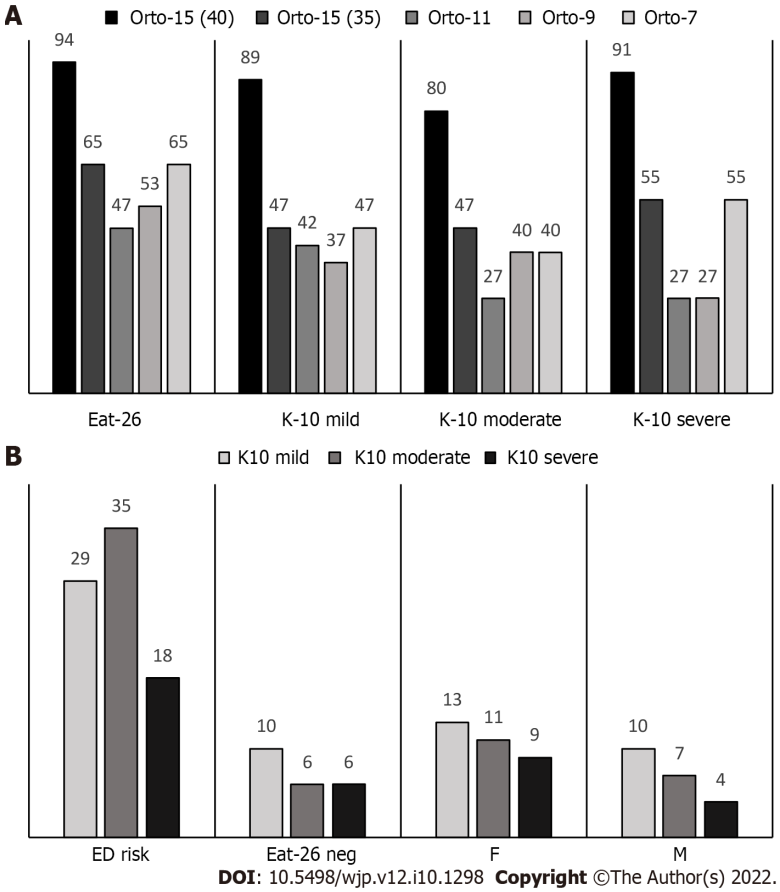
Higher SSI, EAT-26 and ON, by using ORTO-15 (40 cut-off), -12, -11 and -9, were observed in Spanish students compared to Italians, regardless of sex (Table 3). Accordingly, no significant difference between female and male students in ORTO-15 has been reported in university students[25,44,45].

Table 4 Spearman correlations

	ORTO-15	ORTO-12	ORTO-11	ORTO-9	ORTO-7
BMI (n = 160)	NS	NS	NS	-0.184[a]	NS
BMI NW-K10^{neg}-EAT-26^{neg} (n = 66)	-0.315[a]	-0.304[a]	-0.284[a]	-0.432[c]	NS
SSI (n = 160)	-0.169[a]	-0.264[c]	-0.223[b]	-0.244[b]	-0.228[b]
EAT-26 (n = 160)	-0.363[c]	-0.414[c]	-0.349[c]	-0.432[c]	-0.357[c]
Dieting (n = 160)	-0.429[c]	-0.444[c]	-0.387[c]	-0.516[c]	-0.307[c]
Bulimia (n = 160)	-0.188[a]	-0.263[c]	-0.180[a]	-0.304[c]	-0.223[b]
BUT (n = 160)	NS	NS	NS	NS	-0.160[a]
BUT A – WP (n = 160)	NS	-0.187[a]	NS	-0.181[a]	-0.166[a]
BUT B (n = 160)	NS	NS	NS	NS	-0.165[a]
MBSRQ (n = 160)	-0.354[c]	-0.279[c]	-0.341[c]	-0.414[c]	NS
MBSRQ-AO (n = 160)	-0.333[c]	-0.296[c]	-0.326[c]	-0.359[c]	-0.177[a]
MBSRQ-AO NW-K10^{neg}-EAT-26^{neg} (n = 66)	NS	-0.285[a]	NS	-0.289[a]	NS
MBSRQ-FO (n = 160)	-0.361[c]	-0.310[c]	-0.358[c]	-0.414[c]	-0.180[a]
MBSRQ-FO NW-K10^{neg}-EAT-26^{neg} (n = 66)	-0.304[a]	-0.371[a]	-0.373[a]	-0.450[c]	NS
MBSRQ-HOr (n = 160)	-0.341[c]	-0.248[b]	-0.333[c]	-0.402[c]	NS
MBSRQ-HOr NW-K10^{neg}-EAT-26 ^{neg} (n = 66)	-0.358[b]	-0.408[c]	-0.433[c]	-0.491[c]	NS
MBSRQ-IO (n = 160)	-0.162[a]	NS	-0.181[a]	NS	NS
MBSRQ-BASS (n = 160)	NS	NS	NS	NS	-0.169[a]
MBSRQ-OP (n = 160)	-0.177[a]	-0.216[b]	-0.165[a]	-0.302[c]	NS
MBSRQ-OP NW-K10^{neg}-EAT-26^{neg} (n = 66)	NS	-0.366[b]	NS	-0.357[b]	NS
MBRSQ-AS (n = 160)	-0.195[a]	-0.155[a]	-0.161[a]	-0.265[c]	NS
MBSRQ-AS NW-K10^{neg}-EAT-26^{neg} (n = 66)	NS	-0.244[a]	NS	-0.306[a]	NS
IPAQ (n = 160)	NS	NS	NS	-0.183[a]	NS
Walking (n = 160)	NS	NS	NS	-0.162[a]	NS
Intense activity (n = 160)	NS	NS	NS	-0.178[a]	NS
Intense activity NW-K10^{neg}-EAT-26^{neg} (n = 66)	-0.404[c]	-0.330[b]	-0.273[a]	-0.461[c]	NS

[a]P < 0.05.
[b]P < 0.01.
[c]P < 0.001.
AO: Appearance orientation; AS: Appearance scales; BASS: Body areas satisfaction scale; BMI: Body mass index; BUT: Body Uneasiness Test; EAT-26: Eating Attitudes Test; FO: Fitness orientation; HOr: Health orientation; IO: Illness orientation; IPAQ: International Physical Activity Questionnaire; MBSRQ: Multidimensional Body-Self Relations Questionnaire; NS: Not significant; NW- K10^{neg}-EAT-26^{neg}: Normal weight students excluded those with K10 or EAT-26 positive test; OP: Overweight preoccupation; ORTO: Scores for orthorexia nervosa; SSI: Starvation Symptom Inventory; WP: Weight phobia.

Among NW Polish university students, ORTO-15 correlated with MBSRQ-OP, -AO, -FO, -HOr and -BASS in females, whereas in male students, body image concerns were not associated with ON[38]. The Spearman correlations (Table 4) confirmed the previously reported relationship between ON, depending on ORTO score applied to the whole sample, and MBSRQ-OP, -AO[34], and EAT-26[32,33], and we have observed overlaps between ORTO scores, EAT-26 and K10 (Figure 1). Although the prevalence of UW, OW and OB students did not reach significance in the whole sample, IT-F had a lower BMI (Table 1) and higher BUT-A – BIC (Table 2) than IT-M.

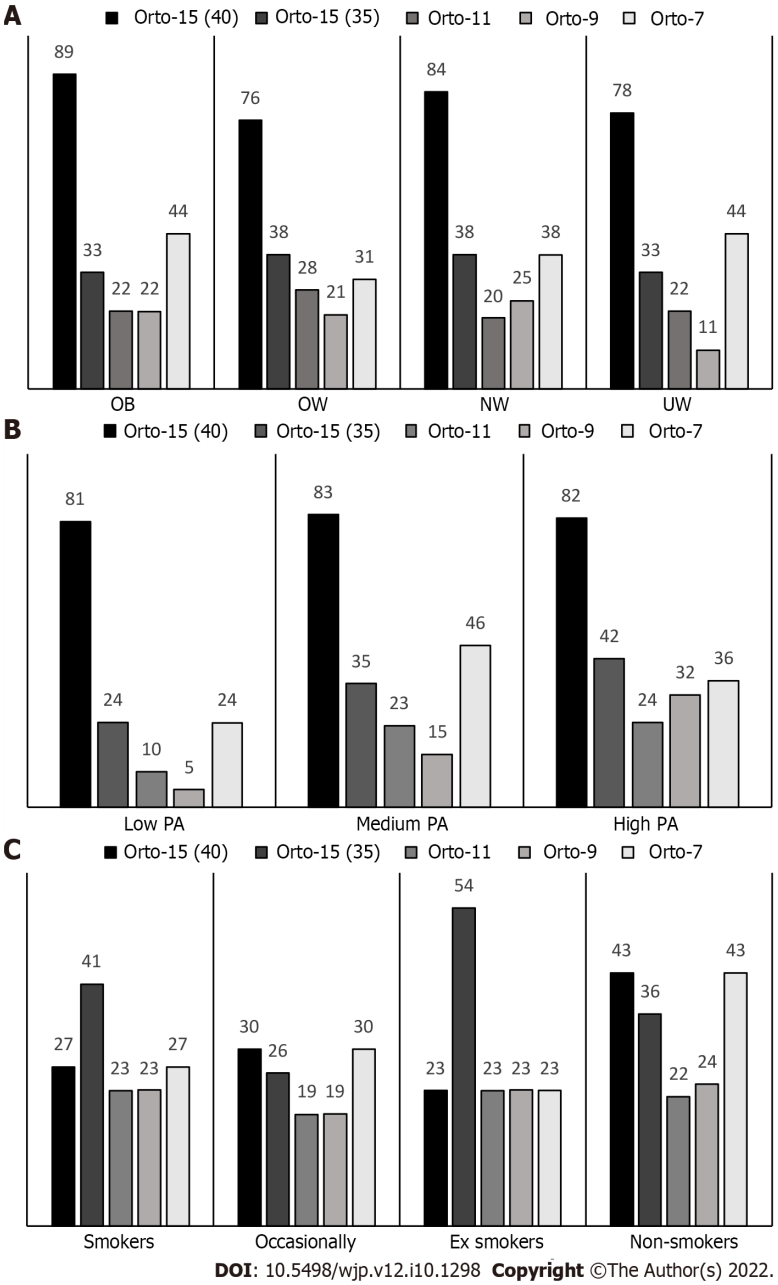


DOI: 10.5498/wjp.v12.i10.1298

Figure 1 Prevalence of orthorexia nervosa. A and B: Prevalence of orthorexia nervosa among students who presented an eating disorder (ED) risk [Eating Attitudes Test (EAT)-26] or psychological distress [Kessler Psychological Distress Scale (K10)] (A) and overlap of EAT-26 and K10 (B), in the whole sample. ORTO: Scores for orthorexia nervosa; K10: Kessler Psychological Distress Scale; EAT-26: Eating Attitudes Test; F: Italian and Spanish females; M: Italian and Spanish males; ED: Eating disorder.

In order to reduce the potential confounder as being on a diet[31], we have evaluated a subgroup of NW students, excluding volunteers who presented distress or ED risk (NW-K10^{neg}-EAT-26^{neg}). All students in the NW-K10^{neg}-EAT-26^{neg} group had ON, when ORTO-15 with the 40 cut-off was applied, whereas the percentage of ON varied with ORTO-15 (35 cut-off), -11, -9 and -7. Concerning lifestyle, the percentage of non-smokers was higher compared to those of smokers among students with ON in the NW-K10^{neg}-EAT-26^{neg} group. In this context, it has been proposed to distinguish between ON and healthy orthorexia (HO), a non-pathological tendency to follow a healthy diet[46]. HO can be the successful result of dissemination campaigns aimed to increase nutrition knowledge from WHO and National recommendations, but the proposed etiology of ON includes high level of education, pseudoscientific nutritional news on social media and psychological factors[12]. From a study carried out in nutrition and dietetics, university students emerged that Instagram use might be considered as an ON-risk factor[47]. Besides, K10 median of the scores of students enrolled in health-related study courses was higher than those of non-health-related degree courses[48]. Furthermore, it has been suggested that obsessive healthy eating fixations may increase the risk for ED in athletes and that more education and awareness are warranted to minimize the risk for ON and ED in student-athletes[30]. High level of PA in association with ON, assessed with ORTO-15 using cut-off scores of 35, was more often seen in men from sports science and less often in women from business course[27]. With a cut-off of 40, ORTO-15 resulted lower among students who performed more than ten h/wk of exercise, regardless of the engagement in university sport teams, including athletes competing in aesthetic and weight dependent sports[28]. In our sample, sex differences were found in MET-min/wk from intense activities in both countries (Table 1). In the NW-K10^{neg}-EAT-26^{neg} group, among the students with ON, the percentage of those practicing high PA was higher compared to those having low PA, whereas we did not find correlations observed in the whole sample, including those between ORTO scores and BUT, SSI, and total MBSRQ.

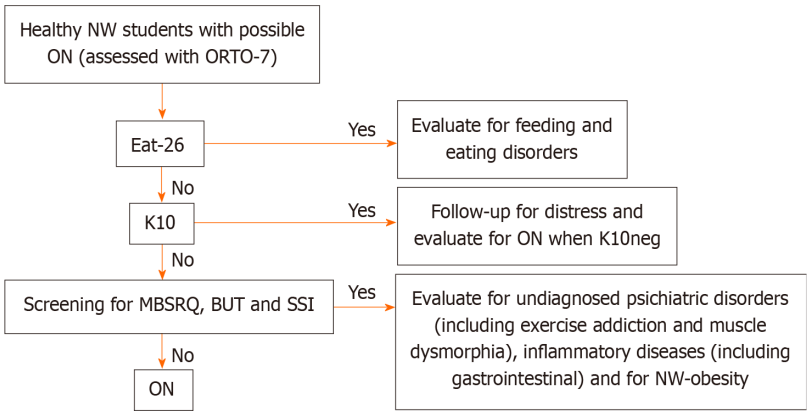
The present study has both strengths and limitations, taking into account the suggestion of a pilot study[49] that reported high levels of disparity among psychometric scores, including ORTO-15, EAT-26 and MBSRQ, recommending the use of multiple psychometric instruments for ON diagnosis. Furthermore, the evaluation of dietary intakes of 10 individuals (assessed using 24-h recall) failed to meet the guidelines for several nutrients[49]. As a point of strength, we have used different stan-



DOI: 10.5498/wjp.v12.i10.1298

Figure 2 Prevalence of orthorexia nervosa among different body mass index classes and lifestyle factors. A: Body mass index; B: Physical activity; C: Lifestyle factors. ORTO: Scores for orthorexia nervosa; OB: Obese; OW: Overweight; NW: Normal weight; UW: Underweight; PA: Physical activity.

dardized questionnaires in order to exclude students presenting overlaps. As a limitation, we did not evaluate the nutritional status. However, the relationships between SSI and all ORTO scores observed in the whole sample, but not in the NW-K10^{neg}-EAT-26^{neg} subgroup, suggest that students with more starvation symptoms were excluded from the applied exclusion criteria. In fact, the greatest strength is that ORTO-7 resulted in the only score unrelated neither with BMI nor with the other evaluated outcomes in the NW-K10^{neg}-EAT-26^{neg} subgroup (Table 4). The prevalence of ON from ORTO-7 after the "exclusion diagnosis" in the NW-K10^{neg}-EAT-26^{neg} subgroup on the overall sample ranged between 12.2% and 25.9%, values lower than those reported in the whole sample. However, it was higher than some observed with other sub-scores of ORTO test (Table 4). This finding suggests that, among the limitations, we did not include the OCD in the "exclusion diagnosis"[50]. However, Łucka *et al*[29] using ORTO-15 (score of 35 was considered as cut-off point), EAT-26 and Maudsley Obsessive Compulsive Inventory (MOCI), found that individuals with suspected ON (ORTO-15, score of 35) had higher BMI and EAT-26 score, whereas MOCI did not differ from ORTO-15 negative group. From that, authors suggested that ON meets the criteria of ED and not of OCD[29]. On the other hand, considering the relationship among other ORTO scores and body concerns, and high PA component of IPAQ, also questionnaires evaluating exercise addiction[51,52] and muscle dysmorphia[26] should be included in the "exclusion diagnosis".



DOI: 10.5498/wjp.v12.i10.1298

Figure 3 Decision tree for the exclusion diagnosis of orthorexia nervosa (ON) in healthy normal weight university students. ORTO-7: Score for orthorexia nervosa; K10: Kessler Psychological Distress Scale; EAT-26: Eating Attitudes Test; MBSRQ: Multidimensional Body-Self Relations Questionnaire; BUT: Body Uneasiness Test; SSI: Starvation Symptom Inventory; NW: Normal weight.

Among exclusion diagnosis (gastrointestinal disorders) there are functional dyspepsia[53], non-celiac gluten sensitivity (NCGS)[54,55] and irritable bowel syndrome (IBS)[55]. Both NCGS and IBS are more prevalent in young women compared to men[55], and up to 90% of patients with IBS exclude certain foods to improve their gastrointestinal symptoms[56]. Besides, negative effects of prescribing restrictive diets can be observed due to the association between ED and gastrointestinal symptoms[56]. In this context, the differential diagnosis and assessment of AN already began with the exclusion of diseases, including inflammatory bowel disease (Crohn's disease or ulcerative colitis), malignancies, thyrotoxicosis, diabetes, cerebral tumor, major depressive or schizophrenic illnesses[10].

Although the scientific community is divided into those who consider ON as a separate ED and those who do not[7], agreement exists on the needs of prevention (primary and secondary) and some diagnostic criteria, as reviewed by Atzeni *et al*[16], including: obsessive concern for healthy eating, fear anxiety and avoidance of certain foods components (additives, preservatives, fats or other elements considered unhealthy). Furthermore, there is broad consensus on the induction of malnutrition by ON and impacts on social and professional functioning. Other suggested criteria (not endorsed by all experts) included differences between ON and OCD or from schizophrenia, excessive time spent or rituals in preparing meals, excessive spending money for buying healthy foods; anxieties and fears concerning transgressions, and the exclusion of individuals who observe a religious practice or have medical problems[16]. Our work suggests including EDs and psychological distress among the medical problems for the exclusion diagnosis of ON in healthy NW individuals. Otherwise, we suggest considering ON as a symptom of other diseases or a disease-induced comorbidity.

CONCLUSION

Although a generalization to the whole population should not be made, considering the recent suggestions on the need for further investigation of the comorbidity between ON and OCD across different cultural groups[50], it emerged that ON could be an indicator/symptom of other problems related to body image perception, as well as high PA, psychological distress, appearance, fitness, health, or IO, in some university students. Accordingly, recent studies have found relationships between ON, vigorous-intensity PA and dieting[47,57]. In our study, the ORTO-7 was found to be independent from these confounders, after the exclusion of UW, OW, OB, and EAT-26 and K10 positive students, suggesting the possibility of defining subjects with ON. Therefore, considering the overlap conditions, we suggest a decision tree for differential/exclusion diagnosis of ON (Figure 3). In order to identify the real orthorexic subjects among healthy students with NW, firstly the presence of EDs should be assessed, followed by the evaluation of the distress level, and lastly the presence of body image concerns and malnutrition (Figure 3). Moreover, a high percentage of students (25.5% males and 40.1% females) with NW obesity (NWO) have been reported, and stress management behavior decreased the risk of NWO in females[58]. In this context, Villa *et al*[47] observed that ON was associated not only with heavy exercise but also with sedentary behavior. In students with NWO, low PA could be associated with dieting, inducing ON. In conclusion, due to the several confounders and overlap conditions, flowcharts, diagnostic algorithms and a decision tree for differential diagnosis and management of ON should be included, as well as guidelines and consensus statements of experts in the future.

ARTICLE HIGHLIGHTS

Research background

Many factors have been associated to orthorexia nervosa in university students.

Research motivation

To assess the prevalence of orthorexia nervosa in Italian and Spanish university students.

Research objectives

To assess the prevalence of orthorexia nervosa in relation to eating attitude and psychological distress.

Research methods

Questionnaires were administered to evaluate orthorexia nervosa, body concerns, psychological distress, physical activity, eating attitude and starvation symptoms.

Research results

When excluding students underweight (UW), overweight (OW) or obese (OB), as well as those potentially at risk of eating disorders or presenting distress, in the resultant normal weight (NW)-K10^{neg}-EAT-26^{neg} subgroup, we did not find many correlations observed in the whole sample, including those between ORTO scores and Body Uneasiness Test, Starvation Symptom Inventory, Total Multidimensional Body-Self Relations Questionnaire (MBSRQ) and some of its components. Moreover, ORTO-7 resulted the only ON score unrelated with Body Mass Index, MBSRQ components and IPAQ-assessed intense activity, in the NW-K10^{neg}-EAT-26^{neg} subgroup. After this sort of "exclusion diagnosis", ORTO-7 became independent from these confounding, after the exclusion of UW, OW, OB and students positive to EAT-26 and K10, suggesting the possibility of identifying orthorexic subjects with this specific questionnaire.

Research conclusions

In some university students ON could be a symptom of other conditions related to body image concerns and distress, as well as to high physical activity and appearance, fitness, health or illness orientation. ORTO-7 became independent from these confounding factors, after the exclusion of UW, OW, OB and students positive to EAT-26 and K10, suggesting the possibility of identifying orthorexic subjects with this specific questionnaire.

Research perspectives

Considering the overlap conditions, we suggest a decision tree for differential/exclusion diagnosis of ON.

FOOTNOTES

Author contributions: Peluso I and Villaño D contributed to the conceptualization; Aiello P, Toti E and Raguzzini A contributed to the investigation; Aiello P and Peluso I contributed to the original draft preparation; Toti E, Raguzzini A and Villaño D contributed to the review and editing; Peluso I contributed to the supervision.

Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee for Human Experimentation of the La Sapienza University of Rome (protocol code 1382/2019, approved on 16 July 2019) and by the Ethics Committee of the Catholic University of Murcia (UCAM) (protocol code CE071906, approved on 3 July 2019).

Informed consent statement: Informed consent was obtained from all subjects involved in the study. Volunteers did not sign consent to share single individual data, but only cumulative results.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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: Italy

ORCID number: Paola Aiello 0000-0001-6136-0294; Elisabetta Toti 0000-0003-3798-7745; Débora Villaño 0000-0002-8162-8857; Anna Raguzzini 0000-0003-4021-6829; Ilaria Peluso 0000-0002-6210-5241.

S-Editor: Gao CC
L-Editor: Filipodia
P-Editor: Zhang XD

REFERENCES

1 **Parra-Fernández ML**, Manzaneque-Cañadillas M, Onieva-Zafra MD, Fernández-Martínez E, Fernández-Muñoz JJ, Prado-Laguna MDC, Brytek-Matera A. Pathological Preoccupation with Healthy Eating (Orthorexia Nervosa) in a Spanish Sample with Vegetarian, Vegan, and Non-Vegetarian Dietary Patterns. *Nutrients* 2020; **12** [PMID: 33371252 DOI: 10.3390/nu12123907]
2 **Voglino G**, Parente E, Bert F, Lo Moro G, Corradi A, Lapiccirella M, Gualano MR, Siliquini R. Orthorexia Nervosa, a challenging evaluation: analysis of a sample of customers from organic food stores. *Psychol Health Med* 2021; **26**: 478-486 [PMID: 32449870 DOI: 10.1080/13548506.2020.1771386]
3 **Moroze RM**, Dunn TM, Craig Holland J, Yager J, Weintraub P. Microthinking about micronutrients: a case of transition from obsessions about healthy eating to near-fatal "orthorexia nervosa" and proposed diagnostic criteria. *Psychosomatics* 2015; **56**: 397-403 [PMID: 25016349 DOI: 10.1016/j.psym.2014.03.003]
4 **Dunn TM**, Bratman S. On orthorexia nervosa: A review of the literature and proposed diagnostic criteria. *Eat Behav* 2016; **21**: 11-17 [PMID: 26724459 DOI: 10.1016/j.eatbeh.2015.12.006]
5 **Dell'Osso L**, Carpita B, Muti D, Cremone IM, Massimetti G, Diadema E, Gesi C, Carmassi C. Prevalence and characteristics of orthorexia nervosa in a sample of university students in Italy. *Eat Weight Disord* 2018; **23**: 55-65 [PMID: 29134507 DOI: 10.1007/s40519-017-0460-3]
6 **Busatta D**, Cassioli E, Rossi E, Campanino C, Ricca V, Rotella F. Orthorexia among patients with eating disorders, student dietitians and general population: a pilot study. *Eat Weight Disord* 2022; **27**: 847-851 [PMID: 33852153 DOI: 10.1007/s40519-021-01184-7]
7 **Gramaglia C**, Gattoni E, Ferrante D, Abbate-Daga G, Baldissera E, Calugi S, Cascino G, Castellini G, Collantoni E, Favaro A, Marzola E, Monteleone AM, Monteleone P, Oriani MG, Renna C, Ricca V, Salvo P, Santonastaso P, Segura-Garcia C, Volpe U, Zeppegno P. What do Italian healthcare professionals think about orthorexia nervosa? *Eat Weight Disord* 2022; **27**: 2037-2049 [PMID: 35000187 DOI: 10.1007/s40519-021-01336-9]
8 **Reynolds R**, McMahon S. Views of health professionals on the clinical recognition of orthorexia nervosa: a pilot study. *Eat Weight Disord* 2020; **25**: 1117-1124 [PMID: 31079349 DOI: 10.1007/s40519-019-00701-z]
9 **Claudino AM**, Pike KM, Hay P, Keeley JW, Evans SC, Rebello TJ, Bryant-Waugh R, Dai Y, Zhao M, Matsumoto C, Herscovici CR, Mellor-Marsá B, Stona AC, Kogan CS, Andrews HF, Monteleone P, Pilon DJ, Thiels C, Sharan P, Al-Adawi S, Reed GM. The classification of feeding and eating disorders in the ICD-11: results of a field study comparing proposed ICD-11 guidelines with existing ICD-10 guidelines. *BMC Med* 2019; **17**: 93 [PMID: 31084617 DOI: 10.1186/s12916-019-1327-4]
10 **Treasure J**, Duarte TA, Schmidt U. Eating disorders. *Lancet* 2020; **395**: 899-911 [PMID: 32171414 DOI: 10.1016/S0140-6736(20)30059-3]
11 **Balasundaram P**, Santhanam P. Eating Disorders. 2022 Jun 27. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan- [PMID: 33620794]
12 **Douma ER**, Valente M, Syurina EV. Developmental pathway of orthorexia nervosa: Factors contributing to progression from healthy eating to excessive preoccupation with healthy eating. Experiences of Dutch health professionals. *Appetite* 2021; **158**: 105008 [PMID: 33069774 DOI: 10.1016/j.appet.2020.105008]
13 **Opitz MC**, Newman E, Alvarado Vázquez Mellado AS, Robertson MDA, Sharpe H. The psychometric properties of Orthorexia Nervosa assessment scales: A systematic review and reliability generalization. *Appetite* 2020; **155**: 104797 [PMID: 32652100 DOI: 10.1016/j.appet.2020.104797]
14 **Valente M**, Syurina EV, Donini LM. Shedding light upon various tools to assess orthorexia nervosa: a critical literature review with a systematic search. *Eat Weight Disord* 2019; **24**: 671-682 [PMID: 31228168 DOI: 10.1007/s40519-019-00735-3]
15 **Cena H**, Barthels F, Cuzzolaro M, Bratman S, Brytek-Matera A, Dunn T, Varga M, Missbach B, Donini LM. Definition and diagnostic criteria for orthorexia nervosa: a narrative review of the literature. *Eat Weight Disord* 2019; **24**: 209-246 [PMID: 30414078 DOI: 10.1007/s40519-018-0606-y]
16 **Atzeni E**, Converso D, Loera B. [Orthorexia Nervosa between growing attention to food quality and eating disorders: diagnostic criteria and evaluation tools]. *Riv Psichiatr* 2020; **55**: 201-212 [PMID: 32724232 DOI: 10.1708/3417.33996]
17 Niedzielski A, Kaźmierczak-Wojtaś N. Prevalence of Orthorexia Nervosa and Its Diagnostic Tools-A Literature Review. Int J Environ Res Public Health 2021; 18 [PMID: 34065506 DOI: 10.3390/ijerph18105488]
18 **Abdullah MA**, Al Hourani HM, Alkhatib B. Prevalence of orthorexia nervosa among nutrition students and nutritionists: Pilot study. *Clin Nutr ESPEN* 2020; **40**: 144-148 [PMID: 33183528 DOI: 10.1016/j.clnesp.2020.09.175]
19 **Plichta M**, Jezewska-Zychowicz M. Orthorexic Tendency and Eating Disorders Symptoms in Polish Students: Examining Differences in Eating Behaviors. *Nutrients* 2020; **12** [PMID: 31952161 DOI: 10.3390/nu12010218]

20 **Babeau C**, Le Chevanton T, Julien-Sweerts S, Brochenin A, Donini LM, Fouques D. Structural validation of the ORTO-12-FR questionnaire among a French sample as a first attempt to assess orthorexia nervosa in France. *Eat Weight Disord* 2020; **25**: 1771-1778 [PMID: 31863296 DOI: 10.1007/s40519-019-00835-0]

21 **Parra-Fernandez ML**, Rodríguez-Cano T, Perez-Haro MJ, Onieva-Zafra MD, Fernandez-Martinez E, Notario-Pacheco B. Structural validation of ORTO-11-ES for the diagnosis of orthorexia nervosa, Spanish version. *Eat Weight Disord* 2018; **23**: 745-752 [PMID: 30196527 DOI: 10.1007/s40519-018-0573-3]

22 **Missbach B**, Hinterbuchinger B, Dreiseitl V, Zellhofer S, Kurz C, König J. When Eating Right, Is Measured Wrong! *PLoS One* 2015; **10**: e0135772 [PMID: 26280449 DOI: 10.1371/journal.pone.0135772]

23 **Moller S**, Apputhurai P, Knowles SR. Confirmatory factor analyses of the ORTO 15-, 11- and 9-item scales and recommendations for suggested cut-off scores. *Eat Weight Disord* 2019; **24**: 21-28 [PMID: 29796780 DOI: 10.1007/s40519-018-0515-0]

24 **Moller S**, Apputhurai P, Knowles SR. Correction to: Confirmatory factor analyses of the ORTO 15-, 11- and 9-item scales and recommendations for suggested cut-off scores. *Eat Weight Disord* 2019; **24**: 981 [PMID: 31154632 DOI: 10.1007/s40519-019-00714-8]

25 **Guglielmetti M**, Ferraro OE, Gorrasi ISR, Carraro E, Bo S, Abbate-Daga G, Tagliabue A, Ferraris C. Lifestyle-Related Risk Factors of Orthorexia Can Differ among the Students of Distinct University Courses. *Nutrients* 2022; **14** [PMID: 35268086 DOI: 10.3390/nu14051111]

26 **Gorrasi ISR**, Bonetta S, Roppolo M, Abbate Daga G, Bo S, Tagliabue A, Ferraris C, Guglielmetti M, Arpesella M, Gaeta M, Gallé F, Di Onofrio V, Liguori F, Liguori G, Gilli G, Carraro E. Traits of orthorexia nervosa and muscle dysmorphia in Italian university students: a multicentre study. *Eat Weight Disord* 2020; **25**: 1413-1423 [PMID: 31529388 DOI: 10.1007/s40519-019-00779-5]

27 **Malmborg J**, Bremander A, Olsson MC, Bergman S. Health status, physical activity, and orthorexia nervosa: A comparison between exercise science students and business students. *Appetite* 2017; **109**: 137-143 [PMID: 27889495 DOI: 10.1016/j.appet.2016.11.028]

28 **Clifford T**, Blyth C. A pilot study comparing the prevalence of orthorexia nervosa in regular students and those in University sports teams. *Eat Weight Disord* 2019; **24**: 473-480 [PMID: 30264390 DOI: 10.1007/s40519-018-0584-0]

29 **Łucka I**, Janikowska-Hołoweńko D, Domarecki P, Plenikowska-Ślusarz T, Domarecka M. Orthorexia nervosa - a separate clinical entity, a part of eating disorder spectrum or another manifestation of obsessive-compulsive disorder? *Psychiatr Pol* 2019; **53**: 371-382 [PMID: 31317964 DOI: 10.12740/PP/OnlineFirst/85729]

30 **Uriegas NA**, Winkelmann ZK, Pritchett K, Torres-McGehee TM. Examining Eating Attitudes and Behaviors in Collegiate Athletes, the Association Between Orthorexia Nervosa and Eating Disorders. *Front Nutr* 2021; **8**: 763838 [PMID: 34859033 DOI: 10.3389/fnut.2021.763838]

31 **Roncero M**, Barrada JR, Perpiñá C. Measuring Orthorexia Nervosa: Psychometric Limitations of the ORTO-15. *Span J Psychol* 2017; **20**: E41 [PMID: 28929989 DOI: 10.1017/sjp.2017.36]

32 **Gramaglia C**, Gambaro E, Delicato C, Marchetti M, Sarchiapone M, Ferrante D, Roncero M, Perpiñá C, Brytek-Matera A, Wojtyna E, Zeppegno P. Orthorexia nervosa, eating patterns and personality traits: a cross-cultural comparison of Italian, Polish and Spanish university students. *BMC Psychiatry* 2019; **19**: 235 [PMID: 31362720 DOI: 10.1186/s12888-019-2208-2]

33 **Farchakh Y**, Hallit S, Soufia M. Association between orthorexia nervosa, eating attitudes and anxiety among medical students in Lebanese universities: results of a cross-sectional study. *Eat Weight Disord* 2019; **24**: 683-691 [PMID: 31183627 DOI: 10.1007/s40519-019-00724-6]

34 **Barnes MA**, Caltabiano ML. The interrelationship between orthorexia nervosa, perfectionism, body image and attachment style. *Eat Weight Disord* 2017; **22**: 177-184 [PMID: 27068175 DOI: 10.1007/s40519-016-0280-x]

35 **Aiello P**, Peluso I, Villaño Valencia D. Alcohol Consumption by Italian and Spanish University Students in Relation to Adherence to the Mediterranean Diet and to the Food Neophobia: A Pilot Study. *Healthcare (Basel)* 2022; **10** [PMID: 35207005 DOI: 10.3390/healthcare10020393]

36 **Donini LM**, Marsili D, Graziani MP, Imbriale M, Cannella C. Orthorexia nervosa: validation of a diagnosis questionnaire. *Eat Weight Disord* 2005; **10**: e28-e32 [PMID: 16682853 DOI: 10.1007/BF03327537]

37 **Roncero M**, Perpiñá C, Marco JH, Sánchez-Reales S. Confirmatory factor analysis and psychometric properties of the Spanish version of the Multidimensional Body-Self Relations Questionnaire-Appearance Scales. *Body Image* 2015; **14**: 47-53 [PMID: 25867527 DOI: 10.1016/j.bodyim.2015.03.005]

38 **Brytek-Matera A**, Donini LM, Krupa M, Poggiogalle E, Hay P. Orthorexia nervosa and self-attitudinal aspects of body image in female and male university students. *J Eat Disord* 2015; **3**: 2 [PMID: 25774296 DOI: 10.1186/s40337-015-0038-2]

39 **Cuzzolaro M**, Vetrone G, Marano G, Garfinkel PE. The Body Uneasiness Test (BUT): development and validation of a new body image assessment scale. *Eat Weight Disord* 2006; **11**: 1-13 [PMID: 16801740 DOI: 10.1007/BF03327738]

40 **Rivas T**, Bersabé R, Jiménez M, Berrocal C. The Eating Attitudes Test (EAT-26): reliability and validity in Spanish female samples. *Span J Psychol* 2010; **13**: 1044-1056 [PMID: 20977051 DOI: 10.1017/s1138741600002687]

41 **Calugi S**, Miniati M, Milanese C, Sartirana M, El Ghoch M, Dalle Grave R. The Starvation Symptom Inventory: Development and Psychometric Properties. *Nutrients* 2017; **9** [PMID: 28862653 DOI: 10.3390/nu9090967]

42 **Kessler RC**, Barker PR, Colpe LJ, Epstein JF, Gfroerer JC, Hiripi E, Howes MJ, Normand SL, Manderscheid RW, Walters EE, Zaslavsky AM. Screening for serious mental illness in the general population. *Arch Gen Psychiatry* 2003; **60**: 184-189 [PMID: 12578436 DOI: 10.1001/archpsyc.60.2.184]

43 **Società Italiana Endocrinologia**. Questionario sull'attività fisica quotidiana (IPAQ). [cited 10 October 2021]. In: Società Italiana Endocrinologia [Internet]. Available from: http://www.societaitalianadiendocrinologia.it/public/pdf/questionario_ipaq.pdf

44 **Brytek-Matera A**, Fonte ML, Poggiogalle E, Donini LM, Cena H. Orthorexia nervosa: relationship with obsessive-compulsive symptoms, disordered eating patterns and body uneasiness among Italian university students. *Eat Weight Disord* 2017; **22**: 609-617 [PMID: 28840493 DOI: 10.1007/s40519-017-0427-4]

45 **Oberle CD**, Samaghabadi RO, Hughes EM. Orthorexia nervosa: Assessment and correlates with gender, BMI, and personality. *Appetite* 2017; **108**: 303-310 [PMID: 27756637 DOI: 10.1016/j.appet.2016.10.021]

46 **Depa J**, Barrada JR, Roncero M. Are the Motives for Food Choices Different in Orthorexia Nervosa and Healthy Orthorexia? *Nutrients* 2019; **11** [PMID: 30934544 DOI: 10.3390/nu11030697]

47 **Villa M**, Opawsky N, Manriquez S, Ananías N, Vergara-Barra P, Leonario-Rodriguez M. Orthorexia nervosa risk and associated factors among Chilean nutrition students: a pilot study. *J Eat Disord* 2022; **10**: 6 [PMID: 35016711 DOI: 10.1186/s40337-022-00529-6]

48 **Pehlivan Ş**, Tokur Kesgi N M, Uymaz P. Psychological distress and mental health literacy in university students. *Perspect Psychiatr Care* 2021; **57**: 1433-1441 [PMID: 33330978 DOI: 10.1111/ppc.12709]

49 **Mitrofanova E**, Mulrooney H, Petróczi A. Assessing psychological and nutritional impact of suspected orthorexia nervosa: a cross-sectional pilot study. *J Hum Nutr Diet* 2021; **34**: 42-53 [PMID: 33216395 DOI: 10.1111/jhn.12797]

50 **Brytek-Matera A**, Pardini S, Modrzejewska J, Modrzejewska A, Szymańska P, Czepczor-Bernat K, Novara C. Orthorexia Nervosa and its association with obsessive-compulsive disorder symptoms: initial cross-cultural comparison between Polish and Italian university students. *Eat Weight Disord* 2022; **27**: 913-927 [PMID: 34076878 DOI: 10.1007/s40519-021-01228-y]

51 **Trott M**, Jackson SE, Firth J, Fisher A, Johnstone J, Mistry A, Stubbs B, Smith L. Exercise Addiction Prevalence and Correlates in the Absence of Eating Disorder Symptomology: A Systematic Review and Meta-analysis. *J Addict Med* 2020; **14**: e321-e329 [PMID: 32496431 DOI: 10.1097/ADM.0000000000000664]

52 **Oberle CD**, Watkins RS, Burkot AJ. Orthorexic eating behaviors related to exercise addiction and internal motivations in a sample of university students. *Eat Weight Disord* 2018; **23**: 67-74 [PMID: 29260414 DOI: 10.1007/s40519-017-0470-1]

53 **Mounsey A**, Barzin A, Rietz A. Functional Dyspepsia: Evaluation and Management. *Am Fam Physician* 2020; **101**: 84-88 [PMID: 31939638]

54 **Tanveer M**, Ahmed A. Non-Celiac Gluten Sensitivity: A Systematic Review. *J Coll Physicians Surg Pak* 2019; **29**: 51-57 [PMID: 30630570 DOI: 10.29271/jcpsp.2019.01.51]

55 **Ahmed H**, Hallam R, Webster G, Rej A, Croall ID, Coleman SH, Key T, Buckle R, Shaw CC, Goodwin J, Aziz I, Sanders DS. NCGS like IBS 'type' symptoms is a diagnosis of exclusion. *Nutr J* 2021; **20**: 79 [PMID: 34496849 DOI: 10.1186/s12937-021-00737-x]

56 **McGowan A**, Harer KN. Irritable Bowel Syndrome and Eating Disorders: A Burgeoning Concern in Gastrointestinal Clinics. *Gastroenterol Clin North Am* 2021; **50**: 595-610 [PMID: 34304790 DOI: 10.1016/j.gtc.2021.03.007]

57 **Brytek-Matera A**, Pardini S, Szubert J, Novara C. Orthorexia Nervosa and Disordered Eating Attitudes, Self-Esteem and Physical Activity among Young Adults. *Nutrients* 2022; **14** [PMID: 35334945 DOI: 10.3390/nu14061289]

58 **Maitiniyazi G**, Chen Y, Qiu YY, Xie ZX, He JY, Xia SF. Characteristics of Body Composition and Lifestyle in Chinese University Students with Normal-Weight Obesity: A Cross-Sectional Study. *Diabetes Metab Syndr Obes* 2021; **14**: 3427-3436 [PMID: 34349536 DOI: 10.2147/DMSO.S325115]

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