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Aims & Scope

Osong Public Health and Research Perspectives (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health.
PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

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Editorial

It is time to hold discussions with policymakers

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Over the past 4 years, numerous discussions have centered on preparing for future infectious disease pandemics. As we enter 2025, it is time to identify key issues for prioritized discussion and to develop persuasive policy recommendations.

First, real-time mortality monitoring is a critical issue for preparing for future infectious disease pandemics. During the fight against coronavirus disease 2019 (COVID-19), we emphasized that all-cause mortality is a crucial indicator. The fact that excess mortality exceeded the number of deaths directly attributed to COVID-19 suggests that the Republic of Korea's healthcare system was not managed with sufficient efficiency or effectiveness, necessitating a comprehensive performance evaluation and the development of appropriate tools. This issue features papers addressing these concerns this month. Although the government, academia, and the medical sector initially united to combat COVID-19, the prolonged crisis has recently taken a dramatic turn. The current abnormal conditions in the Republic of Korea are placing enormous strain on the healthcare system. At this critical juncture, we must carefully consider how to absorb, adapt to, and transform these challenges to rebuild a resilient and sustainable healthcare system. Some predict that a full recovery could take more than a decade. The expansion of medical school admissions in the Republic of Korea, aimed at reducing regional disparities in doctor distribution, has triggered disruptions in medical education and residency training, causing delays in surgeries and treatments at major hospitals. Regardless of the validity of claims that this situation has contributed to excess mortality, the importance of establishing a real-time mortality monitoring system has once again come to the forefront. This initiative involves designating sentinel hospitals for mortality tracking and implementing real-time confirmation of causes of death through systems such as the Republic of Korea's National Healthcare-Associated Infections Surveillance System, the Injury Statistics for Deep Dive Survey for Patient Discharge, the National Emergency Department Information System, and the hospital standardized mortality ratio assessments conducted by the Health Insurance Review and Assessment Service. A more in-depth investigation into the causes of death and a comprehensive performance evaluation of the healthcare system are essential.

Furthermore, there is an urgent need for a continuously operational alert system to monitor public health crises in real time. A precise analysis of mortality causes, followed by the evidence-based redistribution of healthcare resources, financial restructuring, and improvements in healthcare delivery at both the national and local levels—in both the public and private sectors—is required. Ultimately, such measures aim to reduce regional excess mortality and transform the

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healthcare system into an efficient, effective, and people-centered model. These efforts align with broader societal goals, such as economic development, social solidarity, and overall well-being, thereby necessitating urgent research and development [1].

Second, key attributes for building resilience for the post-COVID-19 period must be reinforced. The resilience of the Republic of Korea's healthcare system and society must be emphasized in the face of catastrophic events like COVID-19. A resilient society should maintain redundancy, or surplus capacity, to effectively address crises. However, the Republic of Korea's fee-for-service healthcare system is under constant cost-cutting pressure. This pressure has resulted in inadequate investment in critical services such as intensive care and emergency medicine, leading to an erosion of surplus capacity and an inability to accommodate excess demand during crises. Moreover, crisis-response skills and adaptive capacity should be developed through continuous education and training; yet investments in these areas have been insufficient. During COVID-19, public health professionals were tasked with a wide range of roles, often having to learn and adapt independently. This situation underscores the need for further research and development in capacity-building efforts [2].

Third, addressing the challenges of low birth rates and population aging is an important issue. The dual challenges of low birth rates and population aging—which threaten the sustainability of rural and regional areas—are becoming increasingly serious. The Republic of Korea is aging faster than any other country in the world and has already entered a super-aged society. The burden of medical expenses for older adults is rising rapidly, with senior healthcare costs reaching 37.6 trillion Korean won (KRW) in 2020 (an increase of 1.8 trillion KRW from the previous year), accounting for 43.4% of total medical expenditures [3]. During the COVID-19 pandemic, the Republic of Korea was one of the few Organisation for Economic Co-operation and Development (OECD) countries in which healthcare expenditure as a percentage of gross domestic product (GDP) increased, surpassing the OECD average and reaching 9.9% in 2023. It is expected to exceed 10% in 2024. In response, reforms across all social sectors—including pensions, education, employment, and industry—are being implemented to address the impact of low birth rates and an aging population. In the healthcare sector, key areas include aging-related medical care, regenerative medicine, elder care, self-care, and healthcare financing. Big data in health and social care and artificial intelligence can be leveraged to develop innovative solutions in these fields. Strengthening community-based participatory research—particularly cohort studies—is an urgent priority. Additionally, enhanced governance for research and better coordination of government-led research initiatives are needed.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
Jong-Koo Lee has been the editor-in-chief of *Osong Public Health and Research Perspectives* since October 2021.

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Review Article

The global prevalence of autism spectrum disorder in children: a systematic review and meta-analysis

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ABSTRACT

Objectives: The objective of this review was to analyze quantitative data on autism spectrum disorder (ASD) and to increase the accuracy of estimates of the prevalence of ASD.
Methods: This review, which was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, included studies conducted from January 2008 to June 2024 on children aged 3 to 18 years that used standardized measurement tools and reported cut-off scores for ASD. The prevalence of ASD was the primary outcome analyzed in this review. The PubMed, Clinical Key, Scopus, Embase, CINAHL, and Web of Science databases were reviewed for relevant studies. The review protocol was registered with PROSPERO and followed the Cochrane collaboration guidelines.
Results: A total of 66 studies reported on the prevalence of ASD, screening 21,313,061 children worldwide. Among these, 25 studies were conducted in Europe, 22 in Asia, and 13 in America. Additionally, 3 studies each were reported from Africa and Australia. According to a meta-analysis, 0.77% of children globally are diagnosed with ASD, with boys comprising 1.14% of this group. Notably, Australia showed the highest prevalence rate, with an effect size of 2.18, highlighting it as a critical area for public health focus.
Conclusion: ASD represents a significant global health burden. Early detection, increased awareness among parents, and prompt intervention are crucial for mitigating developmental problems in children later in life. It is essential for health policymakers to acknowledge the prevalence and growing trends of ASD in order to implement effective interventions.

Keywords: Autism spectrum disorder; Child; Mental disorders; Neurodevelopmental disorders; Prevalence

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Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by difficulties in social relationships and repetitive or restricted behaviors [1]. The spectrum encompasses various disorders, including autistic disorder, Rett disorder, Asperger syndrome, and pervasive developmental disorder [2]. Its prevalence is increasing worldwide, presenting significant challenges for affected individuals and their families [3]. The World Health Organization estimates that autism affects 0.76% of children globally, with higher incidence rates in developed countries [4]. Autism can be diagnosed as early as 18 to 24 months, as its symptoms often become distinguishable from typical development and other developmental delays during this period. Changes in diagnostic criteria have contributed to an increase in reported cases, along with heightened public awareness and understanding of ASD [5]. Environmental assessments and genetic testing play critical roles in identifying risk factors and enhancing predictions of ASD [6,7]. Together, these elements are driving the increased prevalence of ASD in developed countries [7].

Over the past 50 years, ASD has transformed from a narrowly defined, rare childhood condition into a widely recognized, researched, and advocated lifelong disorder. It is now understood to be common and highly heterogeneous. While the core features—social communication deficits and repetitive or unusual sensory-motor behaviors—remain largely unchanged [8], autism is now viewed as a spectrum that ranges from mild to severe. Many individuals with ASD require lifelong support, although this is not the case for everyone. ASD remains one of the top neurodevelopmental disorders among children. The first case of ASD was reported in 1943, and since then, the number of cases has increased worldwide. According to epidemiological data, the prevalence of ASD in the United States of America (USA) is reported to be 18.5 per 1,000 children under 8 years of age. The majority of countries have reported an increase in the number of ASD cases over the past decades [9]. Although South Asia accounts for over 20% of the global population, the prevalence of ASD is underreported there [10].

The Centers for Disease Control and Prevention reports that 1 in 54 children in the USA was diagnosed with ASD from 2014 to 2016 [11]. In Italy, the prevalence among 7- to 9-year-olds is 1.15% [12]. During the 1960s and 1970s, ASD rates ranged from 0.5 to 0.7 cases per 10,000 people. More recently, the Autism and Developmental Disabilities Monitoring Network found prevalence rates of 67 to 230 cases per 10,000, reflecting a 243% increase in the USA [13]. The revised Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision (DSM-5-TR) (2022) criteria require a higher threshold of clinical symptoms compared to the DSM, 4th Edition, Text Revision (DSM-IV-TR) criteria, enhancing the accuracy of ASD diagnoses among children [14,15]. Variations in diagnostic criteria and parental awareness may influence these prevalence rates. Early detection, standardized diagnostic criteria, counseling, awareness of ASD, and a safe environment can improve the reporting of ASD [16].

The updated DSM-5, improves diagnostic accuracy, particularly for cases that were previously undiagnosed [17]. In the USA, the estimated cost of autism, at 268.3 billion US dollars (USD), exceeds that of stroke and hypertension. The annual costs vary from 1.4 to 2.4 million USD. If current trends persist, these costs are projected to increase to between 11.5 trillion and 15 trillion USD by 2029 [18].

Thus, early diagnosis and intervention are crucial to reduce the financial burdens of this condition. An updated estimate assists health professionals in formulating public health strategies. Accurately estimating the prevalence of autism is crucial for assessing the economic burden and allocating adequate resources and services for individuals with autism and their families. Additionally, determining

HIGHLIGHTS

- This systematic review and meta-analysis investigated autism spectrum disorder (ASD), a chronic neurodevelopmental disorder that is increasing dramatically worldwide, posing significant challenges for healthcare workers, patients, and their families.
- Many countries, particularly low and middle-income nations, lack sufficient data on ASD. The global prevalence of ASD has been reported at 0.77%, with rates being higher among males at 1.14 per 100 children.
- High-income countries had an ASD prevalence of 0.86%. Notably, Sweden and Australia exhibited significantly higher rates, at 3.6% and 4.2%, respectively.
- Low and middle-income countries exhibited a lower prevalence of 0.30%, suggesting potential underdiagnoses or differences in healthcare access and awareness as possible explanations.
- The identification of mental disorders in children is often neglected and overlooked, potentially increasing the risk of mental health burdens and long-term psychiatric disorders in the future. Therefore, it is crucial to develop policies that address the psychological needs of both children and adults.

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prevalence helps identify vulnerable groups and associated geographical and environmental risk factors [19]. While previous meta-analyses have focused on ASD prevalence in the general population and reported cumulative results [13], our study specifically targets children and includes subgroup analyses based on sex and the income levels of countries. This review aims to provide a comprehensive pooled estimate of global ASD prevalence among children.

Materials and Methods

Eligibility Criteria

This systematic review and meta-analysis aimed to determine the pooled global prevalence of ASD in children. The review protocol was registered with PROSPERO (CRD42023445469), adhered to Cochrane collaboration guidelines [20], and was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]. The review included studies on children aged 3 to 18 years that utilized standardized measurement tools and provided cut-off scores for ASD. It considered original studies published in the English language from January 1, 2008, to June 31, 2024, that reported on the prevalence of ASD in children. Publications in non-English languages were excluded due to their limited impact and small sample sizes. Additionally, the results from these studies could not be validated by official authorities. Qualitative studies, case reports, and studies lacking prevalence data were also excluded. The primary outcome analyzed in this systematic review and meta-analysis was the prevalence of ASD.

Information Sources

A systematic review and meta-analysis were conducted by searching PubMed, ClinicalKey, Scopus, Embase, CINAHL, and Web of Science for studies published from January 1, 2008, to June 31, 2024.

Search Strategy

The search included terms such as "autism spectrum disorder," "prevalence," "autism," "autism spectrum disorders," "child development disorder," "deprived child," "pervasive developmental disorders," "children," "infant," "toddler," "school age," "adolescence," "cross-sectional study," "observational study," and "cohort study." Two authors (K.H. and A.I.) independently conducted searches on PubMed, ClinicalKey, Scopus, Embase, CINAHL, and Web of Science.

A comprehensive search strategy was developed using keywords and Medical Subject Heading (MeSH) terms related to population, intervention, comparator, and outcomes in Medline, and this strategy was adapted for use in other databases. The identified articles were imported into Rayyan software, where duplicates were eliminated using the "check for duplicates" tool [22]. The citations and references of relevant articles that met the inclusion criteria were manually searched to identify additional studies. All remaining original full-text articles were then screened according to the inclusion criteria.

Selection Process

A data extraction sheet was developed to gather information from the included studies. Two reviewers (K.H. and A.I.) independently extracted the data, which was subsequently reviewed by a third reviewer (A.S.). The extraction form captured several details, including the authors, publication year, country, study design, sample size, participant characteristics, tools used, and key findings as reported by the authors.

Data Collection Process

Two independent authors (K.H. and A.I.) conducted the data extraction procedure, while a third reviewer verified the accuracy of the retrieved data. The figures and tables that summarize and report the extracted data are available in Table S1.

Study Risk of Bias Assessment

The methodological quality and risk of bias in the articles were evaluated using a modified Newcastle-Ottawa scale (NOS). This scale ranges from 1 to 5, where 1 is the lowest and 5 is the highest possible score. A higher score indicates better study quality, which typically suggests a lower risk of bias. The scale is particularly suited for assessing the quality of non-experimental studies, including observational, cohort, and retrospective studies. The quality assessment encompasses 5 criteria: sample representativeness, sample size, response rate, measurement tools and cut-off scores, and statistical details. Each criterion contributes 1 point to the total score, with studies achieving a score above 3 considered to be at low risk.

Effect Measures

The pooled data from individual studies were manually entered and coded in Microsoft Excel (Microsoft Corp.) before being transferred to Stata software ver. 17 (Stata Corp LP). We assessed heterogeneity among the studies using the I^2 test, categorizing values as high (>75%), medium (50%–75%), and low (<50%) [23]. Due to the observed heterogeneity, a random effects model was employed. The effect size (ES) was calculated, along with 95% confidence intervals (CIs), using the Metaprop and Metan commands. We conducted

subgroup analysis based on geographical differences in the prevalence of ASD.

Synthesis Methods

Various subgroup analyses were initially planned for the retrieved data. However, the data demonstrated insufficient information and subtle differences between children and adults. As a result, we were unable to conduct a meta-analysis among the adult population. Consequently, this systematic review and meta-analysis included descriptive studies, and the pooled data were presented in dichotomous form.

Results

Study Selection

The search yielded 26,849 studies from online databases and an additional 4 from printed sources. After eliminating 4,514 duplicates, 21,987 articles were excluded for failing to meet the review criteria. We assessed 348 full-text articles, of which 88 and 194 were further excluded due to various issues, including difference in primary outcome, other illness, missing sample sizes and measurement tools, unspecified cut-off scores, inclusion of participants with other illnesses, and differences in primary outcomes. Ultimately, 66 articles were included in the meta-analysis. A flow diagram of the study selection process is depicted in Figure 1.

Study Characteristics

This systematic review and meta-analysis encompassed a total of 21.31 million children screened for ASD. A global compilation of 66 studies reported on the prevalence of ASD among children. Of these, 25 studies were conducted in Europe [12,24–47], 22 in Asia [48–68], and 13 in America [69–81]. Additionally, 3 studies each were reported from

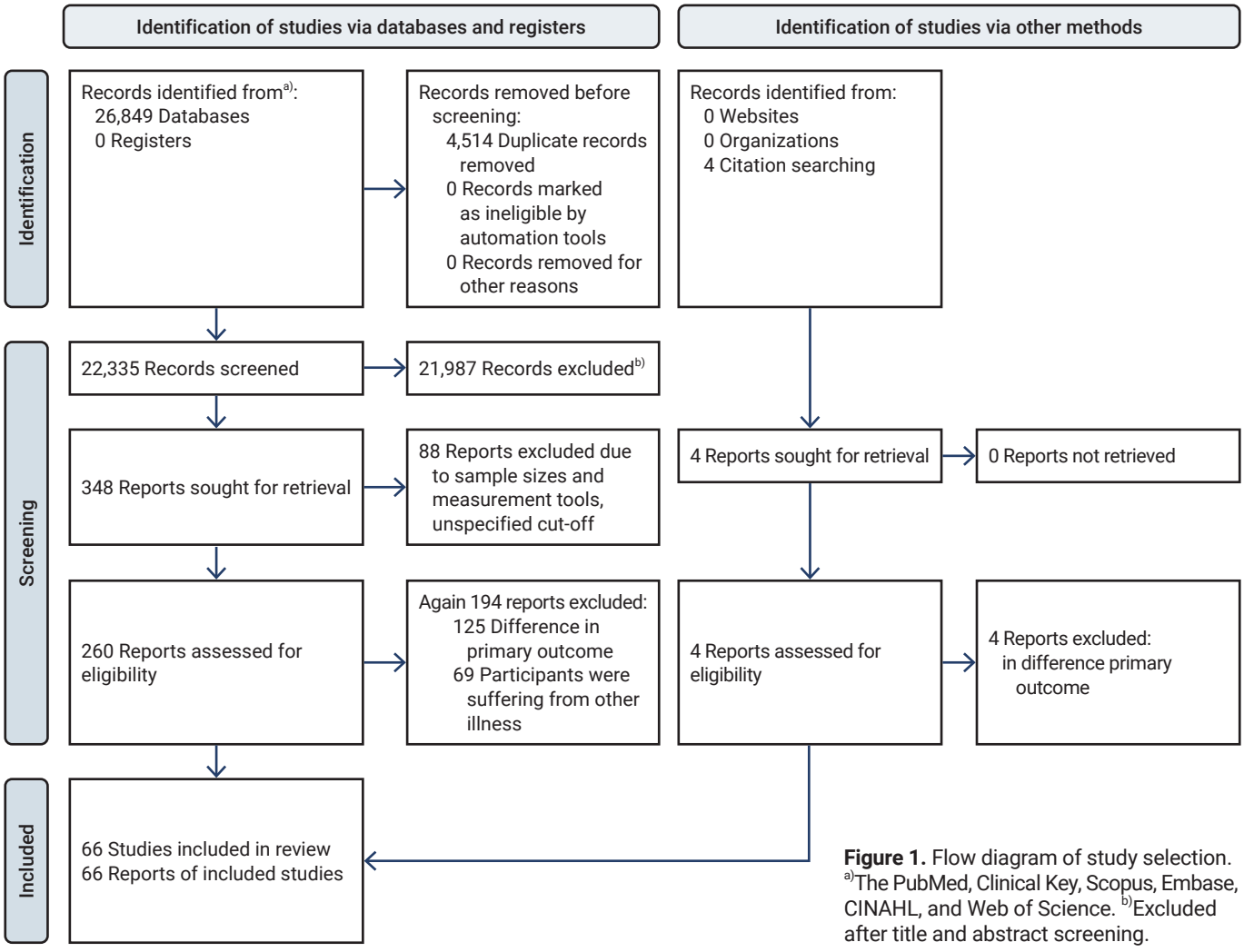

Figure 1. Flow diagram of study selection. [a]The PubMed, Clinical Key, Scopus, Embase, CINAHL, and Web of Science. [b]Excluded after title and abstract screening.

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Africa [68,82,83] and Australia [84–86]. Among these studies, 25 articles specifically reported the prevalence of ASD among boys (Table 1) [12,24,27–29,37,44,46,49–53,56–58,60,61,63,67,70,84,86–88].

Further, 47 studies were reported from high-income countries [12,24–47,56,62,65,66,69–80,84–87,89,90], 16 studies from middle-income countries [48–55,57–59,61,63,64,67,88], and 3 studies from low-income countries (Table 1) [68,82,83].

The sample sizes in the included trials ranged from 374 [59] to 6,900,000 [35], with participant ages varying from 1 to 18 years. The primary outcome of these studies was the prevalence of autism. Various instruments were employed to measure this prevalence, including the modified checklist for autism in toddlers (CHAT), social communication questionnaire (SCQ), Indian scale for assessment of autism (ISAA), DSM-IV, International Classification of Disease (ICD-9), autism diagnostic observation schedule (ADOS), DSM-5, strengths and difficulties questionnaire (SDQ), Qatar School survey (QSS), and autism diagnostic interview-revised (Table 2) [12,24–53,55–79,81–90].

Results of Individual Studies

Prevalence of ASD in different geographical regions

The use of more sophisticated diagnostic criteria may increase the prevalence rates. Many countries do not maintain statistical data on ASD; therefore, cases may only be recognized when a child visits the hospital for other health issues. Symptoms can range from mild to severe, and many children improve and lead normal lives. The meta-analysis found that 0.77% of children worldwide were diagnosed with ASD (ES, 0.77; 95% CI, 0.52–0.86; $p=0.001$; $I^2=97.5\%$). Among the continents, Australia had the highest prevalence of ASD in children (ES, 2.18; 95% CI, 0.08–4.28; $p=0.001$; $I^2=99.3\%$), followed by Africa (ES, 1.51; 95% CI, 0.28–2.74; $p=0.001$; $I^2=98.2\%$) [68,82,83], America (ES, 1.10; 95% CI, 0.79–1.41; $p=0.00$; $I^2=98.9\%$) [69–81], Europe (ES, 0.71; 95% CI, 0.54–0.88; $p=0.001$; $I^2=97.5\%$) [12,24–47], and Asia (ES, 0.28; 95% CI, 0.19–0.38; $p=0.001$; $I^2=99.7\%$) (Figure 2) [48–68].

Prevalence of ASD in boys

A meta-analysis was conducted of 25 studies that reported the prevalence of ASD in boys. Most primary studies indicated that the prevalence in boys was 2 to 3 times higher than that in girls. This meta-analysis found that 1.14% of children worldwide were diagnosed with ASD (ES, 1.14; 95% CI, 0.61–1.67; $p=0.00$; $I^2=99.9\%$) (Figure 3) [12,24,27–29,37,44,46,49–53,56–68,70,84,86–88].

The prevalence of ASD among children in low middle- and high-income countries

According to the World Bank, countries are classified as high-income, middle-income, or low-income. Based on 47 studies with relevant data reported that 0.86% of ASD cases were from high-income countries (ES, 0.86; 95% CI, 0.66–1.06; $p=0.00$; $I^2=99.9\%$) [12,24–47,56,62,65,66,69–80,84–87,89,90]. Among these, 2 studies reported notably higher prevalence rates: 3.6% in Sweden [44] and 4.2% in Australia [84] (Figure 4).

Similarly, 16 studies reported a prevalence of ASD in middle-income countries (ES, 0.30; 95% CI, 0.17–0.43; $p=0.00$; $I^2=99.4\%$) [48–55,57–59,61,63,64,67,88]. Three studies reported prevalence of ASD from low-income countries (ES, 1.5; 95% CI, 0.28–2.74; $p=0.00$; $I^2=99.4\%$) (Figure 5) [68,82,83].

Developed countries have focused more on health infrastructure and services. In contrast, low- and middle-income countries face challenges such as inadequate knowledge of diagnostic tools, poor healthcare infrastructure, and a lack of trained medical professionals. Additionally, these countries experience a scarcity of research studies. Cultural values and traditional practices also contribute to disparities in access to healthcare facilities [91].

Heterogeneity of included studies

The Galbraith plot is a graphical representation that illustrates study-specific ESs and their precisions, as well as the overall ES, and detects potential outliers. The plot features 2 horizontal lines: the green line, which represents the reference line indicating no effect, and the red line, which is the regression line. The slope of the red line reflects the overall ES and the standardized log risk ratio for each study. Circles below the green line indicate an increased risk. However, no studies were reported below the reference line (green line) in this analysis. The present meta-analysis revealed that most circles were found within the shaded region, except for 3 studies, suggesting that these studies appeared within the 95% CI. The Galbraith plot concluded that 3 out of the 66 studies fell outside the shaded region, indicating considerable heterogeneity after employing a random effect model among the ESs in the present meta-analysis. Heterogeneity and publication bias are reported in Figures 6 and 7.

Discussion

This updated systematic review and meta-analysis estimated the global prevalence of ASD over the past decade. The adoption of standardized diagnostic criteria and assessment tools has led to an increase in reported ASD cases worldwide. Additionally, improved screening and community surveillance have improved detection at the peripheral level [92,93].

Table 1. Characteristics of the included studies

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Asia								
Akhter et al. [50]	2018	Bangladesh	Cross-sectional	T, 5,286; M, 3,436; F, 1,850	1.5–3	Information was gathered from household data on the rural population of Bangladesh.	CHAT	The study found that 0.075% of children were diagnosed with ASD in rural areas of Bangladesh.
Heys et al. [48]	2018	Nepal	Cross-sectional	4,098	9–13	The parents of children under 18 years of age residing in rural areas, with a known history of developmental delay, were considered.	Autism quotient-10	The study revealed that 14 students scored more than 6 out of 10, indicating that the tool used in the study could be adopted in Nepal. The study also showed that the sensitivity and specificity of the scale yielded consistent results.
Raina et al [49]	2017	India	Cross-sectional	T, 28,070; M, 14,019; F, 14,051	1–10	Children with poor cognitive development were included from tribal, rural, and urban areas.	ISAA	ASD was reported to be 2 times higher in rural areas and 3.2 times more prevalent in boys. A total of 0.15% of children were reported to have ASD.
Rudra et al. [51]	2017	India	Cross-sectional	T, 5,947; M, 3,344; F, 2,603	3–8	The data were obtained from teachers and parents of students attending special disability schools in Kolkata.	SCDC, SCQ, ADOS	In eastern India, 0.23% of children were reported to have ASD, with teachers rating children higher than parents did.
Chaaya et al. [52]	2016	Lebanon	Cross-sectional	T, 998; M, 537; F, 462	1.3–4	Data were collected from syndicate nurseries in Lebanon.	M-CHAT	Approximately 1.53% of children were diagnosed with autism. Further studies are recommended with a larger sample size.
Huang et al. [53]	2014	China	Cross-sectional	T, 8,000; M, 537; F, 7,463	1.5–3	The cases were identified based on the DSM-IV criteria checklist for children from urban and rural areas.	CHAT mixed	The prevalence of ASD was higher in boys compared to girls. Compared to western countries, ASD incidence was lower. Social stigma and lack of awareness were major contributing factors.
Raz et al. [89]	2015	Israel	Survey study	T, 2,431,649; M, 1,247,552; F, 118,097	8	ASD cases were identified through computerized records from hospitals and official Israeli websites.	DSM	The study revealed that 0.37% of children experienced autism. The findings highlight areas for government facilities to improve.
Poovathinal et al. [63]	2016	India	Community-based survey	T, 18,480; M, 9,132; F, 9,348	1–3	Structured questionnaires were used to gather data from primary health workers in both rural and urban areas.	DSM	ASD was reported in 23.3 per 10,000 children aged 6 to 10 years and 16 to 20 years, with the majority of cases previously undiagnosed.
Raina et al. [55]	2015	India	Cross-sectional	T, 11,000; M, 9,132; F, 5,757	1–10	The data collection was conducted in 2 stages: the first stage involved assessing children using an indigenous autism scale, and the second stage involved evaluating autism symptoms.	ISAA	The results showed that 0.9% of children were reported to have ASD. Socioeconomic status was a significant factor influencing ASD prevalence.

(Continued to the next page)

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Chien et al. [57]	2011	Taiwan	Survey study	T, 372,642; M, 185,420; F, 187,222	17	Data obtained from the national database were used to examine the prevalence and incidence of ASD.	DSM mixed	The prevalence of ASD increased from 1.79 to 28.72 per 10,000 between 1996 and 2005, with annual incidence rising from 0.91 to 4.41 per 10,000. The prevalence was higher among boys aged 0 to 5 years.
Kim et al. [58]	2011	China, Korea	Longitudinal study	T, 22,660; M, 11,679; F, 10,981	7–12	Cases identified from disability schools were considered for further evaluation of ASD.	ASSQ, ADOS, ADI-R	The study found that two-thirds of the cases were undiagnosed and untreated. The authors emphasized the importance of timely screening for better detection, assessment, and treatment of ASD.
Perera et al. [59]	2009	Sri Lanka	Cross-sectional	T, 374	1.5–2	Children were identified from registers maintained by Primary Health Centers, and all eligible children were further screened for ASD.	M-CHAT	About 7.4% of children showed red flags for ASD. High prevalence was detected through community-based screening, but there is a need to develop culturally sensitive screening tools.
Sun et al. [60]	2015	China	Survey study	T, 714; M, 371; F, 343	1.5–2	Cases were identified through the official records of the Beijing China Disabled Persons' Federation, a state-run special rehabilitation center, and ASD-approved hospitals.	CAST, ADOS, ADI-R	The majority of children (119 per 10,000) were undiagnosed with ASD, underscoring the need for further screening using appropriate diagnostic methods. Similar rates were reported in developed nations.
Al-Farsi et al. [87]	2011	Oman	Cross-sectional	T, 798,913; M, 412,675; F, 386,238	1–14	Children were screened for autism using standardized scales, including DSM-IV-TR criteria, and all participants came from rural and urban communities in Oman.	CARS	The overall prevalence of ASD was 1.4%, with more than 75% of cases reported in boys from low-income families. Poor diagnosis and unrecognized cases contributed to the low numbers reported in Oman.
Li et al. [64]	2011	China	Survey study	616,940	0–17	Cases were also identified by systematically evaluating family histories of ASD from the China National Sample Survey on Disability.	DSM-5	The study revealed that untrained or inadequately trained professionals and poor knowledge of ASD among healthcare workers led to poor diagnosis, increasing the number of undiagnosed cases. These findings can help in planning interventions.
Al-Mamri et al. [65]	2019	Oman	Retrospective study	T, 837,655	0–14	Data were retrieved from the 3 main autism diagnostic centers in Oman: Sultan Qaboos University Hospital, Royal Hospital, and Al-Massarah Hospital. Identified cases were referred to these diagnostic centers.	DSM-5	Between 2012 and 2018, 20.35 per 10,000 children were diagnosed with ASD, with boys 3.4 times more likely to be affected than girls. Compared to the prevalence in 2011, the ASD rate was 15 times higher, indicating improvements in screening and diagnostic criteria.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Alshaban et al. [66]	2019	Qatar	Survey study	T, 9,074; M, 3,716; F, 5,358	5–12	The data collection involved 2 phases: in the first phase, children were identified through screening, and in the second phase, those who met the initial criteria underwent further evaluation.	QSS-SCQ	A total of 844 ASD cases were identified, with most children having language issues, including word articulation (75.1%) and phrase speech (91.4%). Pre- and perinatal risk factors contributing to neurodevelopment were also identified.
Zhou et al. [67]	2020	China	Survey study	T, 125,806; M, 66,687; F, 59,119	6–12	Cases were selected from the Public Security Bureau Household Registration System, with data collected from both regular and special disability schools in China.	DSM-IV TR	The overall prevalence of ASD was 0.29%, with most cases reported in boys. Many of the children attended regular schools and led normal lives. Of the children with ASD, 90.4% had more than 1 neuropsychiatric comorbidity.
Sun et al. [88]	2019	China	Survey study	T, 7,167; M, 3,282; F, 3,885	6–10	Children were selected based on median economic levels, with all information sourced from the National Statistics in Mainland China.	DS M-I V TR	The study found that 77 cases of ASD were reported among 72,697 children, accounting for 97 out of every 10,000 children with ASD. Similar findings were reported in western China.
Jin et al. [61]	2018	China	Survey study	T, 72,697	3–12	Cases were also identified from special education schools. Data were collected in 2 stages: first, parents and teachers were invited to screen children using the SCQ (Social Communication Questionnaire).	SCQ	The study revealed that 8.3 per 10,000 children were likely to be diagnosed with ASD. Most diagnosed children had an IQ below 40, and many ASD cases were previously undiagnosed.
Al-Zahrani [62]	2013	USA	Cross-sectional	T, 22,950	7–12	The sample was recruited by screening and assessing children from regular schools. Parents and teachers were invited to screen children using the ASSQ, and those scoring above 10 were considered positive.	DSM, ASSQ	The overall prevalence of autism was 0.035% among a sample population of 22,950 students, with ASD more frequently reported in males (0.031%) than females (0.004%). Counseling and education for parents and teachers were found to aid in appropriate management.
America								
van Balkom et al. [40]	2009	Island	Survey study	T, 13,109	0–9	Cases were identified through the screening of official records, using data from previous studies and children's psychiatry hospitals in Aruba.	DSM-IV	The study revealed that 1.9 out of every 1,000 children had autistic disorders, and 5.3 per 1,000 were diagnosed with ASD. Samples were identified from the Centers for Educational and Counseling Support.
Nicholas et al. [69]	2009	USA	Survey study/ Cohort study	T, 8,156	4	Children with autism were identified through records and community-based screenings. The data were categorized by region and compared with other relevant information.	DS M-I V TR	The study revealed that 8.0 in 1,000 children were diagnosed with ASD. Previous data indicated that 7.6 in 1,000 children were diagnosed in 2000, and 7.0 in 1,000 children in 2002, within the same geographical region.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Kogan et al. [70]	2018	USA	Survey study	T, 43,283	3–17	The data were collected from the United States Centers for Disease Control and Prevention and the ADDM Network. Further evaluations were conducted to ensure the accuracy of ASD diagnoses.	DSM-IV-TR	The majority of children received symptomatic treatment, with 27% undergoing treatment specifically for ASD and 64% receiving behavioral therapy. However, the prevalence of ASD, reported as 1 in 40 children, varied based on income and social background.
Baio et al. [71]	2018	USA	Survey study	T, 325,483	8	Samples were identified through the ADDM Network, and families or parents residing near ADDM sites were included. Data collection was conducted at 11 selected sites.	DSM-IV-TR	The overall prevalence of ASD ranged from 13.1 to 29.3 per 1,000 children. The study also found that boys were diagnosed with ASD more often than girls, particularly among non-Hispanic White children.
Christensen et al. [79]	2016	USA	Survey study	T, 346,978	8	Data were obtained from official records maintained by US authorities. Additionally, detailed screening was performed for those who scored above the normal range.	DSM-IV-TR	The prevalence of ASD was higher among 8-year-old boys than girls of the same age. Non-Hispanic White children had a higher prevalence of ASD than non-Hispanic Black children, with an overall estimated prevalence of 14.6 per 1,000.
Durkin et al. [73]	2017	USA	Cross-sectional	T, 1,308,641; M, 668,575; F, 640,066	8	Cases were identified from special disability schools, followed by further screening in the second stage to confirm the accuracy of the autism diagnoses.	DSM-IV-TR	The study identified a significant association between ASD and racial demographics. Diagnosis rates varied along a socioeconomic status gradient between 2002 and 2010.
Fombonne et al. [74]	2016	Mexico	Survey study	T, 4,195	8	ASD cases were identified in medical and educational institutions, including special disability schools, and evaluated by qualified professionals.	LASI	The study revealed that 0.87% of children (80.6% male) were diagnosed with ASD. One-fourth of the children had intellectual disabilities, and 69% exhibited behavioral issues.
Nicholas et al. [75]	2008	USA	Survey study	T, 47,726	8	Cases were identified through hospital records, and further evaluations were conducted to assess the severity of ASD from 2000 to 2015. Each case was linked to 1 of the specified ASD diagnosis codes.	DSM-IV-TR	In South Carolina, ASD affected 1 in 162 children aged 8. The study projected that the number of cases may increase over time.
Diallo et al. [76]	2018	USA	Survey study	T, 1,447,660	1–17	Samples were recruited from Spanish-speaking schools in the metropolitan district of Quito.	ICD-10, ICD-9	The prevalence of ASD increased by approximately 1.2% from 2014 to 2015. This finding supports the need for medical services to adapt to the evolving requirements of patients and families.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Dekkers et al. [77]	2015	Ecuador	Survey study	T, 51,453	5–15	Cases were identified from a specialized hospital in Maracaibo County, with participants screened using standard autism diagnostic criteria.	DSM-III	The study reported an overall ASD prevalence of 0.11%, with 0.21% suspected cases. However, this low prevalence suggests that many children with ASD are not included in regular education.
Montiel-Nava and Pena [78]	2008	Venezuela	Cross-sectional	T, 254,905	3–9	Data collection occurred in 2 phases: the first phase involved gathering clinical information in a community setting, and the second phase referred cases for systematic ASD examinations.	ADOS	The study revealed that 1.7 per 1,000 children were diagnosed with ASD, highlighting the need for health and education authorities to reassess services provided to children.
Christensen et al. [72]	2019	USA	Survey study	T, 363,749	8	The study included children residing in specific areas during 2020. Cases from special disability schools were also considered.	DSM-IV-TR, ICD-9	The prevalence was 18.5 per 1,000 among 8-year-old children, with ASD being 4.3 times more common in boys. Prevalence rates were similar for non-Hispanic White, non-Hispanic Black, and Asian/Pacific Islander children but lower for Hispanic children.
Shaw et al. [81]	2023	USA	Survey study	T, 72,277	4	Cases were identified through community medical and educational services. Children with neurodevelopmental delays were referred to higher centers for further screening.	DSM-IV-TR, ICD-9	The study found that ASD prevalence was higher in boys and 1.8 times higher in Hispanic children, 1.6 times in non-Hispanic Black children, and 1.4 times in Asian children. The majority of children had intellectual and memory difficulties.
Maenner et al. [90]	2020	USA	Survey study	T, 275,419	8	Children with autism were identified through records and community-based screenings. The data were categorized by region and compared with other relevant information.	DSM-IV	The study revealed that 27.6% of 8-year-old children were diagnosed with ASD, with prevalence 3.8 times higher in males. ASD was most commonly seen in non-Hispanic White children (24.3%) and non-Hispanic American Indian children (26.5%). It was also prevalent among children from low socioeconomic backgrounds.
Africa								
Lagunju et al. [68]	2014	Nigeria	Cohort study	T, 2,320	3.9	The samples were recruited from the pediatric neurology and child psychiatry clinic of University College Hospital and screened for autistic disorder.	DSM-IV	The study revealed that the majority of cases were identified during the study period, with 2.3% (2,320) new ASD cases diagnosed in children. Most of these children had neurodevelopmental comorbidities.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Zeglam and Maound [82]	2012	Libya	Cross-sectional	T, 38,508	0–16	Cases were identified between 2005 and 2009 and screened for language and behavioral difficulties at the Neurodevelopment Clinic of Al-Khadra Hospital in Tripoli.	DSM-IV	The study found that ASD prevalence was 4 times higher in boys than in girls. The cases were commonly reported in children between the ages of 2 and 5 years, with the majority diagnosed 6–28 months after the onset of symptoms.
Hewitt et al. [83]	2016	Somalia	Cross-sectional	T, 12,329; M, 6,163; F, 6,166	7–9	Samples were recruited through household screenings. Following this, clinical examinations were conducted, and positive cases were referred for further evaluation.	DSM-IV	The study emphasized the importance of screening positive for both ASD and other neurodevelopmental conditions. It recommended conducting neurodevelopmental assessments alongside ASD screenings.
Europe								
Kocovska et al. [24]	2012	Faroe Islands	Longitudinal study	T, 7,128; M, 3,590; F, 3,538	15–24	Cases were identified through mass screening conducted from 2002 to 2009 in the Faroe Islands.	ASSQ, ADOS	The study revealed that cases of ASD increased from 0.56% in 2002 to 0.94% in 2009, with a comparatively limited range.
Nygren et al. [25]	2012	Sweden	Survey study	T, 5,007	2	Samples were recruited from 2-year-old children, and suspected cases were referred for detailed screening. These children underwent further evaluation at higher centers.	M-CHAT	The findings indicated that 0.8% of children were diagnosed with ASD. Mass screening using a standardized scale improved the accuracy of ASD diagnoses in children.
Morales-Hidalgo et al. [26]	2018	Spain	Survey study	T, 2,765	4–11	The study included participants under 11 years of age, with ASD screening performed by school teachers and parents using a standardized autism scale.	ADOS, ADI-R	The study showed that 1.5% of children were diagnosed with ASD at age 4, while 1% were diagnosed between the ages of 6 and 11 years. Boys were diagnosed with ASD at a 4:1 ratio compared to girls.
Fernell and Gillberg [27]	2010	Sweden	Cohort	T, 24,084; M, 12,342; F, 11,742	6	Cases were identified through clinical assessments and follow-up care, which included screening for cognitive and functional development in children.	ADOS	About 6.2 out of every 1,000 children were diagnosed with ASD, and one-third of these children led normal lives without cognitive or language problems.
Skonieczna-Zydecka et al. [28]	2017	Poland	Survey study	T, 707,975; M, 344,506; F, 3,63,469	0–16	Data were collected from government registries, including Provincial Disability Services Commissions.	ADOS, Q-CHA	The results revealed that ASD prevalence was 4 times higher in boys, with 35 out of every 10,000 children diagnosed.
Idring et al. [29]	2015	Sweden	Cohort	T, 735,096; M, 376,617; F, 3,58,479	0–27	Samples were identified using official records maintained in Sweden.	ICD-10	The study reviewed the increasing prevalence of ASD due to screening and awareness programs.
Davidovitch et al. [56]	2013	Israel	Cross-sectional study	T, 423,524; M, 218,076; F, 205,448	1–12	Data from Israeli health organizations were used to estimate the occurrence of ASD in children under 12 years old.	DSM	The results showed that approximately 0.48% of children are prone to ASD, with many cases reported in 8-year-old children. Differences in incidence rates were noted between Israel and the US.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Saemundsen et al. [30]	2013	Iceland	Cohort	T, 22,229; M, 11,424; F, 10,805	1–15	Cases were identified from hospital records, and suspected cases underwent further evaluation for medical conditions and chromosomal abnormalities after clinical diagnosis.	ADOS, ADI-R	The prevalence of all ASD types was 120.1 per 10,000, with 172.4 per 10,000 for boys and 64.8 per 10,000 for girls. Early diagnosis and intervention improved reporting of ASD cases.
Posserud et al. [31]	2010	Norway	Survey study	T, 6,609	7–9	Children scoring above the 95th percentile were further screened, and parents or teachers were asked to complete the ASSQ for additional diagnosis.	ASSQ, DAWBA, DISCO	The prevalence of ASD increased from 0.72% to 0.87%. The study emphasized the need to assess cases and implement social awareness programs.
Isaksen et al. [32]	2012	Norway	Survey study	T:31,015	12	Samples were identified from special disability schools, with additional information gathered from healthcare records maintained by local health centers.	ADOS ADI-R	The prevalence of ASD increased 10-fold. Recent findings significantly influence policymakers to establish improved diagnostic and management criteria for ASD.
Mattila et al. [33]	2011	Finland	Survey study	T, 4,422	8	Cases were identified by systematically assessing children's activities in schools, using standardized ASD diagnostic criteria administered by trained personnel.	ASSQ, ADOS, ADI-R, FSIQ	The prevalence of ASDs was 8.4 per 1,000, and autism alone was 4.1 per 1,000. Most children with ASD had low IQs, cognitive dysfunctions, or other chromosomal and high-functioning disorders.
van Bakel et al. [34]	2015	France	Survey study	T, 307,751	7	Cases were identified through official records maintained by the French authorities. The average age of the children was 7 years, and the study was conducted between 1997 and 2003.	ICD-10	Approximately 36.5 per 10,000 children were diagnosed with ASD, the majority of whom were male (4:1 ratio). Nearly 47.3% of these children had intellectual disabilities.
Narzisi et al. [12]	2018	Italy	Survey study	T, 10,138; M, 5,231; F, 4,907	7–9	Autism cases were identified by medical practitioners and verified by the ASDEU team. In the next stage, teachers and children completed the ASD diagnostic form.	DSM-5, SCQ	The majority of ASD cases went undiagnosed until mass screenings were conducted. About 1% of new cases were identified during these screenings.
Bachmann et al. [35]	2018	Germany	Survey study	T, 6,900,000	0–24	Samples were identified from health records maintained by the outpatient department of the nationwide health insurance fund.	ICD-10	The study revealed that the prevalence of ASD was unclear. Developed countries showed higher prevalence rates due to poor diagnosis or inadequate ASD screening.
Baron-Cohen et al. [36]	2009	UK	Survey study	T, 11,700	5–9	Cases were obtained from the Special Educational Needs register, and children were invited for detailed examinations with the help of their parents.	CAST, ADOS ADI-R	The study found that 11 children were diagnosed with ASD after screening. An estimated 157 per 10,000 children were diagnosed, highlighting the need for planning and implementing new policies.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Hansen et al. [37]	2015	Denmark	Survey study	T, 677,915	0–20	Cases were identified in official health authority records in Denmark. Children were continuously screened from birth until their ASD diagnosis.	ICD-8, ICD-10	The study reported that 33% of children diagnosed with ASD could be attributed to new diagnostic criteria, which improved ASD screening and intervention.
Parner et al. [38]	2008	Denmark	Cohort study	T, 407,458	0–11	Cases were retrieved from the Danish Medical Birth Registry and the Danish National Psychiatric Register, with all participants screened using a standardized ASD scale.	ICD-10	The majority of ASD cases were reported in young children. The study emphasized that ASD can be diagnosed in younger children over time. Accurate screening with appropriate tools could reduce the incidence of ASD.
Thomaidis et al. [39]	2020	Greece	Population-based cohort study	T, 182,879; M, 93,897; F, 88,982	10–11	Samples were identified from the Centers for Educational and Counseling Support, which were directly linked to special educational support schools.	ICD-1	The study found that 1.15% of children had ASD, with a higher prevalence in males (4:1 ratio). By age 4, 3.8% of children had been diagnosed, and 42.7% were diagnosed before age 6, with a mean age of diagnosis at 6.1 years.
Suren et al. [41]	2012	Norway	Survey study	T, 731,318	0–11	Autism cases were identified from the Norwegian Patient Register, an official document maintained by the Norwegian healthcare authority.	DSM-IV	The study reported that 0.7% of children had ASD, with a higher prevalence in males (4.3:1 ratio). ASD significantly impacted neurodevelopmental milestones, especially in 11-year-old children.
Fuentes et al. [42]	2021	Spain	Survey study	T, 14,734	7–9	Cases of autism were identified through a community survey involving a two-stage screening process: the first stage consisted of the community survey, and the second stage involved screening by teachers and parents.	ADOS, ADI-R, SCQ	The study showed that 0.59% of children were diagnosed with ASD, which was lower than in previous studies. Due to its cross-sectional nature, further longitudinal studies are recommended to better understand ASD prevalence.
Boilson et al. [43]	2016	Ireland	Survey study	T, 5,589	6–11	Samples were identified using standardized autism screening formats to diagnose children across Europe.	SCQ	Screening for ASD was implemented using the EAIS protocol, which employed the Social Communication Questionnaire as a first-level screening tool in Irish national schools.
Linnsand et al. [44]	2021	Sweden	Survey study	T, 902; M, 454; F, 548	2–5	Cases were identified among individuals who had immigrated from various places, with the screening process involving history-taking and the collection of significant information.	DSM-5	The prevalence of autism was 3.66% among children aged 2 to 5 years, with higher rates reported among the immigrant population. Collaboration with healthcare personnel could help reduce incidences.
Taylor et al. [45]	2013	UK	Survey study	T, 256,278; M, 132,143; F, 124,135	2–8	Cases were identified through media and healthcare records officially maintained by hospitals.	DSM-IV	The rate of autism gradually increased to 3.8 per 1,000 boys and 0.8 per 1,000 girls, with a fivefold increase over time.

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Table 1. Continued

Study	Published year	Country	Research design	Sample size	Age (y)	Inclusion	Tool/criteria	Findings
Williams et al. [46]	2008	UK	Cohort study	T, 14,062; M, 7,111; F, 6,951	11	Cases were identified from the Pupil Level Annual Schools Census, with suspected cases diagnosed by healthcare personnel using standardized scales.	DSM-IV	Autism is often associated with other chromosomal disorders. Most children with ASD were reported to have neurodevelopmental disorders, including learning and cognitive impairments.
Scattoni et al. [47]	2023	Italy	Survey study	T, 35,823	7–9	Samples were identified in 2 phases: in the first phase, data were obtained from local Ministry of Education disability registries; in the second phase, direct screening was conducted in schools. Scores above 15 were considered positive.	SCQ-L	The study revealed that 13.4% of children were diagnosed with ASD. Most diagnoses occurred at ages 7 to 9, with boys being diagnosed 4.4 times more often than girls. These findings guide health policymakers in implementing appropriate interventions.
Australia								
May et al. [84]	2020	Australia	Cohort study	T, 3,381; M, 1,690; F, 1,691	12–13	Samples were identified through parents and teachers. Two cohorts were included: “Kinder” and “Birth.” Data were compared between these 2 groups, with and without cohort overlap.	SDQ	The study revealed that 4.36% of children aged 12–13 years were reported to have ASD. The Kinder cohort exhibited higher social problems and a lower quality of life compared to the Birth cohort, as reported by teachers and parents.
Bowden et al. [85]	2020	Australia	Cohort study	T, 1,551,342	0–24	The study identified samples from health records to systematically assess and compare normal children with those diagnosed with autism.	DSM-IV	The study findings contribute to the development of screening and diagnostic criteria for autism. They also support the formulation of treatment and rehabilitation policies.
Randall et al. [86]	2016	Australia	Longitudinal study	T, 8,366; M, 4,216; F, 4,150	6–7	Children were recruited from kindergarten, and their behaviors, including verbal and nonverbal communication, were observed over a 2-year period.	DSM-5 crit	The study revealed that children with ASD experienced a lower quality of life and disturbed emotional bonds with their parents and siblings. Approximately 6%–9% of children with mild symptoms were able to behave normally.

T, total; M, male; F, female; CHAT, modified checklist for autism in toddlers; ASD, autism spectrum disorder; ISAA, Indian scale for assessment of autism; SCDC, social and communication disorders checklist; M-CHAT, modified CHAT; ADOS, autism diagnostic observation schedule; SCQ, social communication questionnaire; ASSQ, autism spectrum screening questionnaire; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; ADI-R, autism diagnostic interview-revised; CAST, childhood autism spectrum test; CARS, childhood autism rating scale; QSS, Qatar School survey; ADDM, autism and developmental disabilities monitoring; LASI, longitudinal ageing study in India; Q-CHA, quantitative checklist for autism; ICD, International Classification of Diseases; DAWBA, development and well-being assessment; DISCO, diagnostic interview for social and communication disorders; FSIQ, full-scale IQ; ASDEU, ASD in the European Union; SCQ-L, SCQ-life version; SDQ, strengths and difficulties questionnaire.

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Table 2. Quality appraisal of the included studies using the modified Newcastle-Ottawa scale

Study	Published year	Country	Research design	More than 70% representativeness	Sample size of more than 250	More than 70% response rate	Appropriate tool with cut-off scores	Detailed results not requiring further calculations	Total score	Study quality
Akhter et al. [50]	2018	Bangladesh	Cross-sectional	*	*	*	-	*	4/5	Low risk
Heys et al. [48]	2018	Nepal	Cross-sectional	-	*	*	-	*	3/5	Low risk
Raina et al [49]	2017	India	Cross-sectional	-	*	*	*	*	4/5	Low risk
Rudra et al. [51]	2017	India	Cross-sectional	*	*	-	*	*	4/5	Low risk
Chaaya et al. [52]	2016	Lebanon	Cross-sectional	-	*	*	-	*	3/5	Low risk
Huang et al. [53]	2014	China	Cross-sectional	*	*	*	*	*	5/5	Low risk
Raz et al. [89]	2015	Israel	Survey study	*	*	*	*	*	5/5	Low risk
Poovathinal et al. [63]	2016	India	Community survey	*	*	*	-	*	4/5	Low risk
Raina et al. [55]	2015	India	Cross-sectional	*	*	*	-	*	4/5	Low risk
Davidovitch et al. [56]	2013	Israel	Cross-sectional study	*	*	*	*	*	5/5	Low risk
Chien et al. [57]	2011	Taiwan	Survey study	*	*	*	*	*	5/5	Low risk
Kim et al. [58]	2011	China Korea	Longitudinal study	*	*	*	*	*	5/5	Low risk
Perera et al. [59]	2009	Sri Lanka	Cross-sectional	*	*	*	*	-	4/5	Low risk
Sun et al. [60]	2015	China	Survey study	*	*	*	*	-	4/5	Low risk
Al-Farsi et al. [87]	2011	Oman	Cross-sectional	*	*	*	*	*	5/5	Low risk
Li et al. [64]	2011	China	Survey study	*	*	*	*	*	5/5	Low risk
Al-Mamri et al. [65]	2019	Oman	Retrospective study	*	*	*	*	*	5/5	Low risk
Alshaban et al. [66]	2019	Qatar	Survey study	*	*	*	*	*	5/5	Low risk
Zhou et al. [67]	2020	China	Survey study	*	*	*	*	*	5/5	Low risk
Sun et al. [88]	2019	China	Survey study	*	*	*	*	*	5/5	Low risk
Jin et al. [61]	2018	China	Survey study	*	*	*	*	*	5/5	Low risk
Al-Zahrani [62]	2013	USA	Cross-sectional	*	*	*	*	*	5/5	Low risk
Nicholas et al. [69]	2009	USA	Cohort study	*	*	*	*	*	5/5	Low risk
Kogan et al. [70]	2018	USA	Survey study	*	*	*	*	*	5/5	Low risk
Baio et al. [71]	2018	USA	Survey study	*	*	*	*	*	5/5	Low risk
Christensen et al. [79]	2016	USA	Survey study	*	*	*	*	*	5/5	Low risk
Durkin et al. [73]	2017	USA	Cross-sectional	*	*	*	*	*	5/5	Low risk
Fombonne et al. [74]	2016	Mexico	Survey study	*	*	*	*	-	4/5	Low risk
Nicholas et al. [75]	2008	USA	Survey study	-	*	*	*	*	4/5	Low risk
Diallo et al. [76]	2018	USA	Survey study	*	*	*	*	-	4/5	Low risk
Dekkers et al. [77]	2015	Ecuador	Survey study	*	*	*	*	*	5/5	Low risk
Montiel-Nava and Pena [78]	2008	Venezuela	Cross-sectional	*	*	*	*	*	5/5	Low risk
Christensen et al. [72]	2019	USA	Survey study	*	*	*	*	*	5/5	Low risk
Shaw et al. [81]	2023	USA	Survey study	*	*	*	*	*	5/5	Low risk

(Continued to the next page)

Table 2. Continued

Study	Published year	Country	Research design	More than 70% representativeness	Sample size of more than 250	More than 70% response rate	Appropriate tool with cut-off scores	Detailed results not requiring further calculations	Total score	Study quality
Maenner et al. [90]	2020	USA	Survey study	*	*	*	*	*	5/5	Low risk
Lagunju et al. [68]	2014	Nigeria	Cohort study	*	*	*	*	*	5/5	Low risk
Zeglam and Maound [82]	2012	Libya	Cross-sectional	*	*	*	*	-	4/5	Low risk
Hewitt et al. [83]	2016	Somalia	Cross-sectional	*	*	*	*	*	5/5	Low risk
Kocovska et al. [24]	2012	Faroe Islands	Longitudinal study	*	*	*	*	*	5/5	Low risk
Nygren et al. [25]	2012	Sweden	Survey study	*	*	*	*	*	5/5	Low risk
Morales-Hidalgo et al. [26]	2018	Spain	Survey study	*	*	*	*	*	455	Low risk
Fernell and Gillberg [27]	2010	Sweden	Cohort	*	*	*	*	-	4/5	Low risk
Skonieczna- Zydecka et al. [28]	2017	Poland	Survey study	*	*	*	*	*	5/5	Low risk
Idring et al. [29]	2015	Sweden	Cohort	*	*	*	*	*	5/5	Low risk
Saemundsen et al. [30]	2013	Iceland	Cohort	*	*	*	*	*	5/5	Low risk
Posserud et al. [31]	2010	Norway	Survey study	*	*	*	*	*	5/5	Low risk
Isaksen et al. [32]	2012	Norway	Survey study	*	*	*	*	*	5/5	Low risk
Mattila et al. [33]	2011	Finland	Survey study	*	*	*	*	*	5/5	Low risk
van Bakel et al. [34]	2015	France	Survey study	*	*	*	*	*	5/5	Low risk
Narzisi et al. [12]	2018	Italy	Survey study	*	*	*	*	*	5/5	Low risk
Bachmann et al. [35]	2018	Germany	Survey study	*	*	*	*	-	4/5	Low risk
Baron-Cohen et al. [36]	2009	UK	Survey study	*	*	*	*	-	4/5	Low risk
Hansen et al. [37]	2015	Denmark	Survey study	-	*	*	*	*	4/5	Low risk
Parner et al. [38]	2008	Denmark	Cohort study	-	*	*	*	*	4/5	Low risk
Thomaidis et al. [39]	2020	Greece	Cohort study	*	*	*	*	-	4/5	Low risk
van Balkom et al. [40]	2009	Island	Survey study	-	*	*	*	*	4/5	Low risk
Suren et al. [41]	2012	Norway	Survey study	*	*	*	*	-	4/5	Low risk
Fuentes et al. [42]	2021	Spain	Survey study	*	*	*	*	-	4/5	Low risk
Boilson et al. [43]	2016	Ireland	Survey study	*	*	*	*	*	5/5	Low risk
Linnsand et al. [44]	2021	Sweden	Survey study	-	*	*	*	*	5/5	Low risk
Taylor et al. [45]	2013	UK	Survey study	*	*	*	*	*	4/5	Low risk
Williams et al. [46]	2008	UK	Cohort study	*	*	*	*	*	5/5	Low risk
Scattoni et al. [47]	2023	Italy	Survey study	*	*	*	*	*	5/5	Low risk
May et al. [84]	2020	Australia	Cohort study	*	*	*	*	*	5/5	Low risk
Bowden et al. [85]	2020	Australia	Cohort study	*	*	*	*	*	5/5	Low risk
Randall et al. [86]	2016	Australia	Longitudinal study	*	*	*	*	*	5/5	Low risk

*, Scores over 3 are considered low-risk; -, zero score.

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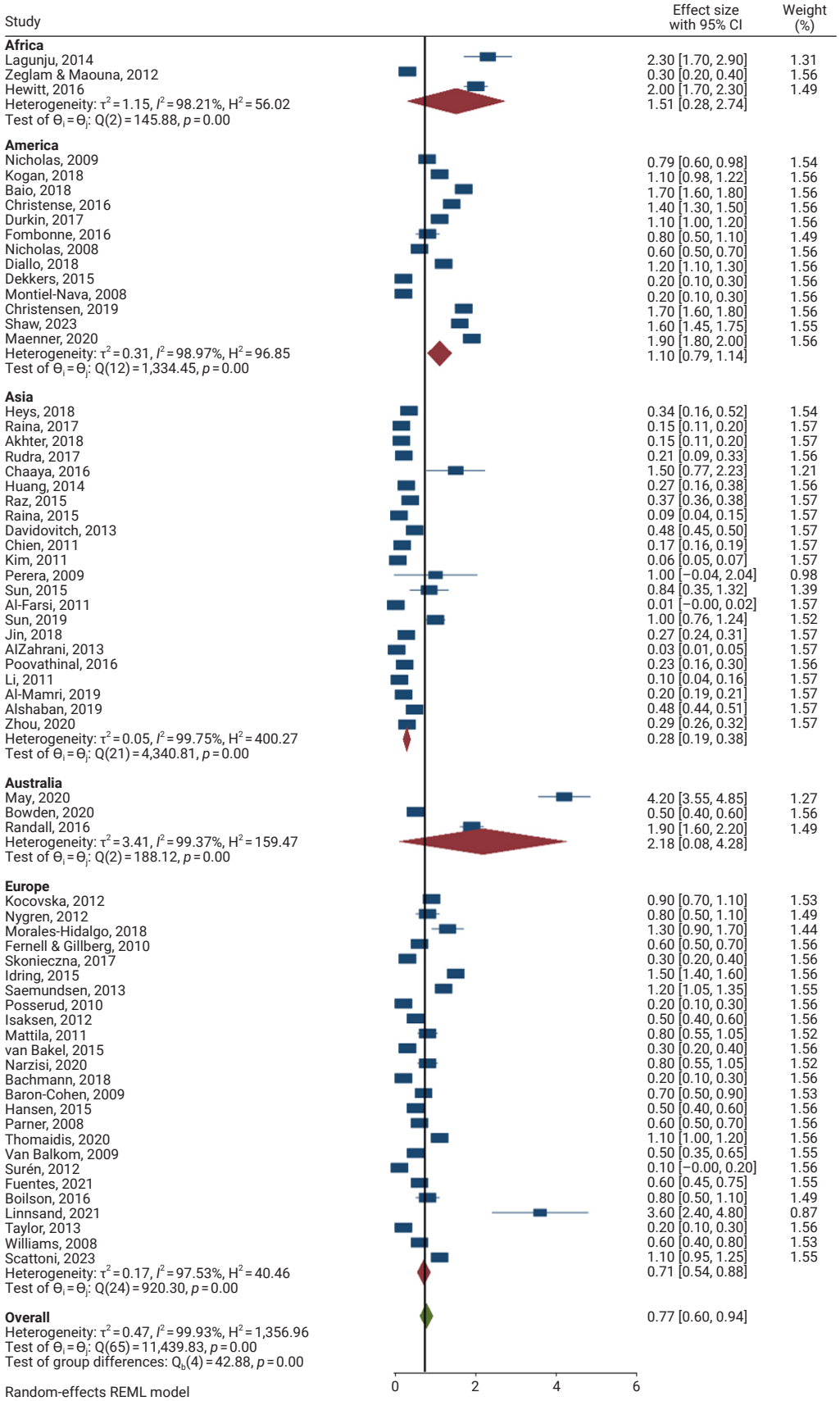

Figure 2. Global prevalence of autism spectrum disorder by continent. CI, confidence interval.

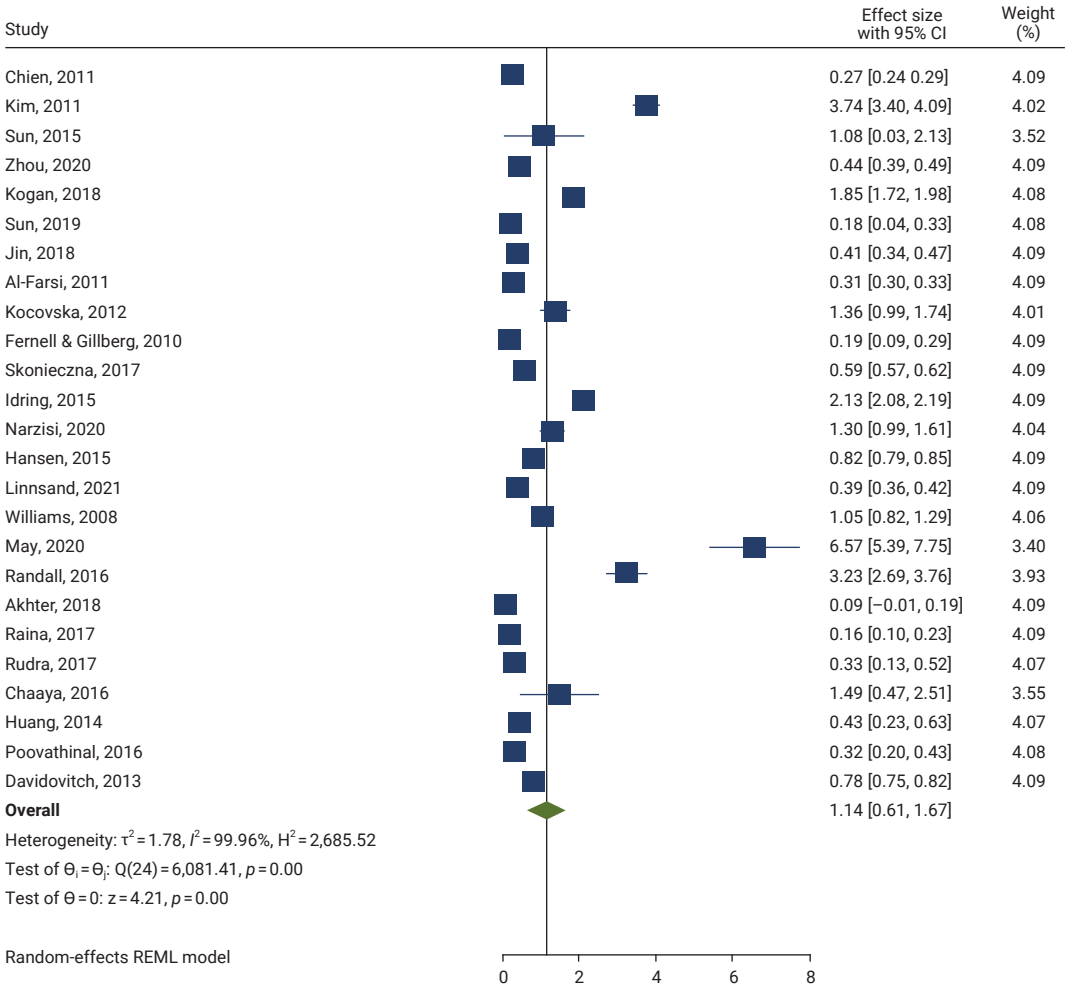

Figure 3. Prevalence of autism spectrum disorder among boys. CI, confidence interval.

Although previous studies have explored the diagnosis and occurrence of ASD [94], there is still a lack of evidence concerning its identification and management. A meta-analysis indicates that perinatal and postnatal factors could increase the risk of ASD, although the specific risk factors are inconsistent. Genetic factors play a significant role, as the presence of siblings with autism increases the incidence [94]. Environmental factors, including exposure to various drugs and chemicals, may also contribute to the risk of ASD [95–97].

The findings of this systematic review and meta-analysis provide significant insights into the global prevalence of ASD among children, with a substantial sample size exceeding 21 million. The meta-analysis incorporated data from 66 studies spanning various continents, revealing geographical disparities in ASD prevalence rates. Notably, Australia showed the highest prevalence rate, with an ES of 2.18, marking it as a critical area for public health focus [98]. In contrast, the lowest prevalence was recorded in Asia, with an ES of 0.34, which may reflect differences in diagnostic practices or reporting mechanisms [99].

The data also highlighted that the prevalence of ASD is notably higher in boys, with an ES of 1.14, suggesting a male-to-female ratio ranging from 2:1 to 3:1 across various studies [36,100]. This finding aligns with previous research indicating a disparity between the sexes in ASD diagnoses, warranting further investigation into the biological and environmental factors that may contribute to this difference.

The analysis further categorized studies by income level, revealing that high-income countries reported an ASD prevalence of 0.86% (ES, 0.86), with Sweden and Australia showing particularly elevated rates (3.6% and 4.2%, respectively). This suggests that higher-income countries may have better resources and screening practices, leading to more accurate diagnoses. In contrast, middle-income countries reported a lower prevalence of 0.30%, indicating potential underdiagnoses or differences in healthcare

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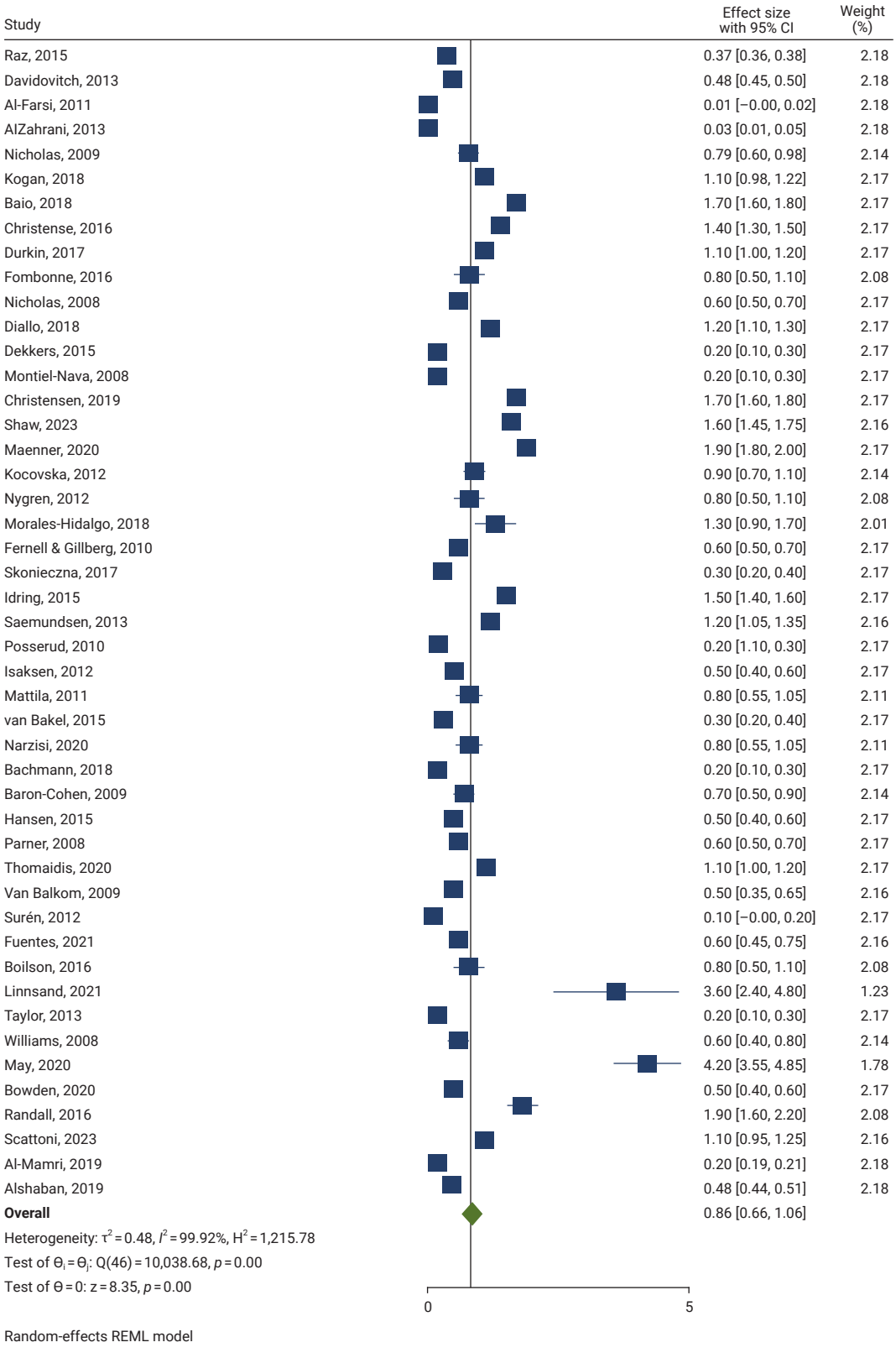

Figure 4. Prevalence of autism spectrum disorder in high-income countries. CI, confidence interval.

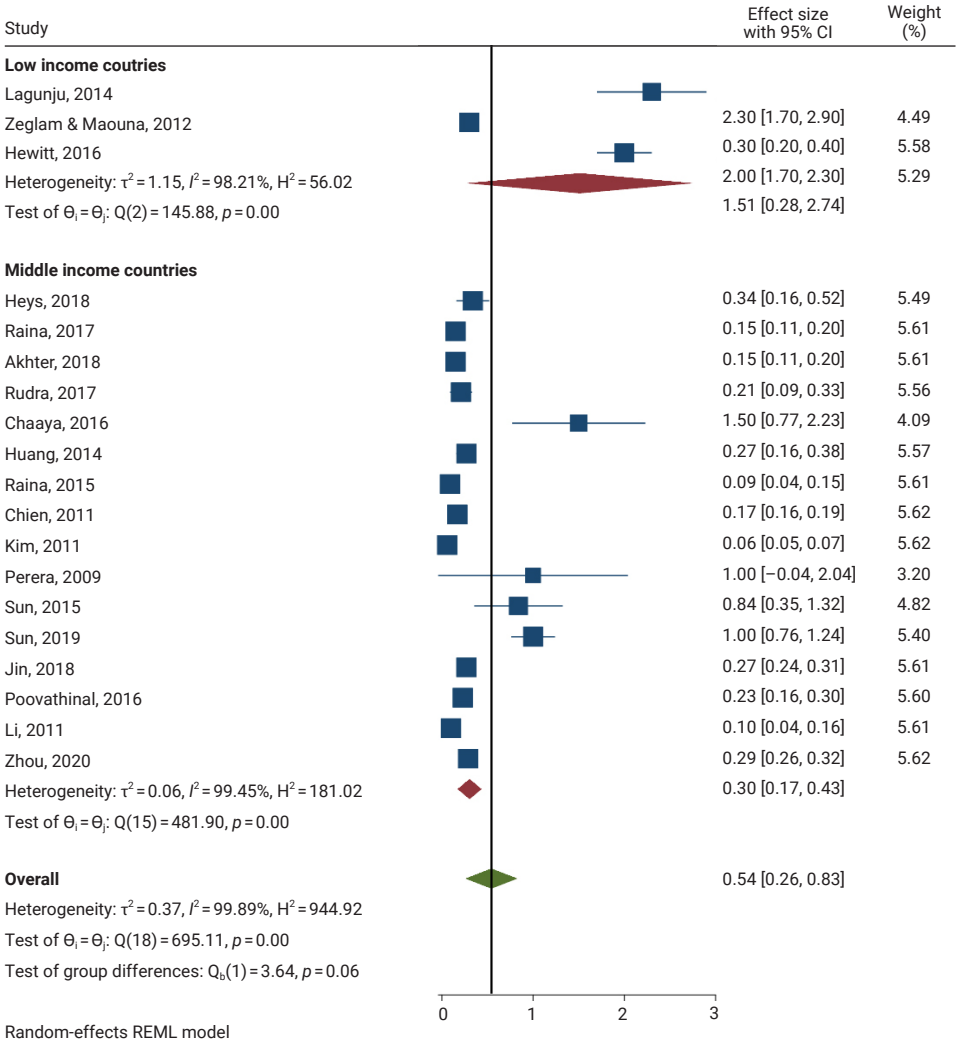

Figure 5. Prevalence of autism in middle- and low-income countries. CI, confidence interval.

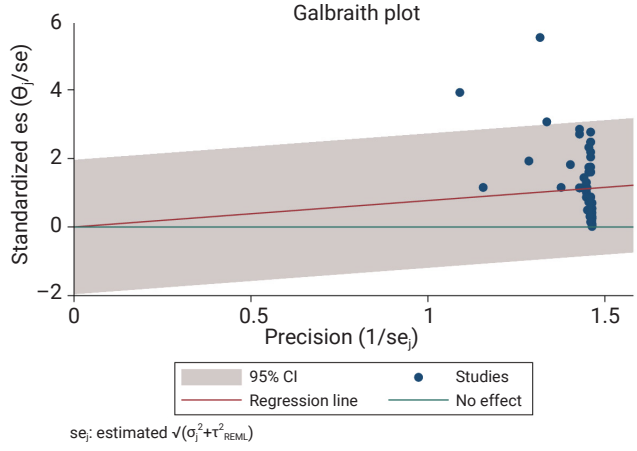

Figure 6. Heterogeneity of the included studies. CI, confidence interval.

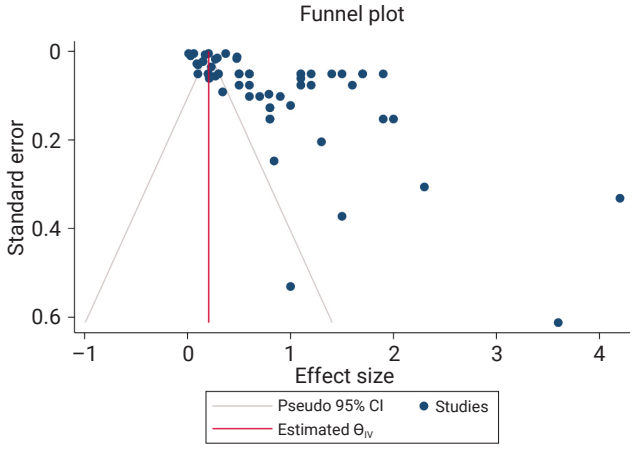

Figure 7. Publication bias. CI, confidence interval.

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access and awareness [13,101].

The reported prevalence of anxiety in low-income countries is alarmingly high [102], highlighting concerns about the availability of mental health resources in these areas. This variation in prevalence across different income levels underscores the importance of designing interventions that are tailored to specific socioeconomic contexts.

The significant heterogeneity observed in the included studies, with I^2 values frequently exceeding 97%, underscores the difficulties in comparing findings across diverse populations and methodologies. This variability could be attributed to differences in diagnostic criteria, cultural perceptions of ASD, and the structures of health systems. Many countries do not have comprehensive statistical data on ASD and often only identify cases during healthcare visits for unrelated issues.

Culture, race, and ethnicity play a significant role in the neuropsychological development of children and affect early diagnosis and treatment. Healthcare professionals must consider the cultural backgrounds and customs of families, which in turn helps them understand perceptions of healthcare services. Due to social stigma, parents may hesitate to disclose their child's symptoms. Therefore, understanding cultural perceptions is a crucial component in diagnosing ASD [103–105].

The prevalence of ASD has increasingly garnered global attention. However, assessing its occurrence poses challenges due to the absence of national data in many regions. Some nations have begun to officially recognize ASD as a disability, providing valuable data that aids in calculating and categorizing its prevalence across different ages, genders, and geographical locations. In contrast, many countries still fail to report local and national ASD data. Previous research has indicated that phenotypic characteristics, environmental factors, and gender differences contribute to a higher incidence of ASD in boys than in girls [106,107]. Nevertheless, further experimental studies are necessary to accurately determine the risk factors associated with different genders and geographical regions.

According to the Australian National Disability Insurance Agency, the annual cost of ASD is projected to increase by 100 billion USD by 2032. The prevalence of ASD in Australia is similar to that in Japan, where early diagnosis and timely interventions contribute to higher reported numbers. Additionally, several studies indicate that changes in diagnostic criteria and increased awareness of ASDs have resulted in more people receiving diagnoses. However, some clinicians have been confusing the diagnosis of ASD with attention deficit hyperactivity disorder and dyslexia. Moreover, government policies, particularly the National Disability Insurance Scheme, play a crucial role in encouraging more reporting of ASD cases in Australia. The current study revealed that the prevalence of ASD in Australia is higher among boys, but the reason for this disparity remains unclear [108–112].

Overall, the findings of this meta-analysis not only contribute to the existing literature on ASD prevalence but also underscore the need for increased global awareness, improved diagnostic practices, and targeted public health initiatives, especially in underrepresented regions and low-resource settings. As our global understanding of ASD continues to evolve, further research is crucial to navigate the complexities of diagnosis, support, and treatment for affected children and their families.

Conclusion

The recent increase in ASD prevalence is concerning, particularly in developing countries where accurate estimates are essential for devising effective public health strategies. Early diagnosis and intervention can significantly enhance outcomes for children with ASD. However, it remains uncertain whether this rise indicates true trends or merely reflects changes in diagnostic criteria. Future research should utilize consistent methodologies, as many existing studies are not accessible due to language barriers. Moreover, the absence of prevalence data in some countries highlights the urgent need for further research to improve ASD management globally.

Supplementary Material

Table S1. Search strategy. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0286.

Notes

Ethics Approval

This is a review study registered with PROSPERO (CRD42023445469), and available online.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: KH, AI; Data curation: AS, LT, VRV; Formal analysis: PM, VK; Investigation: KH, AS, IC; Methodology: KH, KK, PM; Project

administration: AS, LT; Resources: AI, KK; Software: PM, VK; Supervision: AS; Validation: PM, LT; Visualization: AS, KK; Writing–original draft: KH, AI; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Review Article

The prevalence of tobacco, alcohol, stimulant, khat, and cannabis use among school-going students in African and Arab countries: a systematic review and meta-analysis

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ABSTRACT

Objectives: The objectives of this review and meta-analysis were twofold: first, to determine the prevalence of substance use among school-going children in Arab and African countries; and second, to highlight the considerable influence of variables such as the nation's region and the timeframe of the study on the prevalence of substance use.

Methods: Research was sourced from Science Direct, Scopus, Web of Science, Google Scholar, and PubMed. Thirty-seven articles were incorporated in accordance with the PRISMA guidelines. This review included studies published from 2013 to 2023. The statistical meta-analysis was performed using Comprehensive Meta-Analysis ver. 3 software. Across 37 studies, the total number of study participants was 73,508.

Results: The meta-analysis revealed that tobacco was the most commonly used substance, with a prevalence of 16% (95% confidence interval [CI], 12.7%–20.02%). This was closely followed by alcohol, which had a prevalence of 15% (95% CI, 10.5%–22.8%), stimulants at 11.4% (95% CI, 7.4%–17%), khat at 10% (95% CI, 5.7%–15%), and cannabis at 8% (95% CI, 3.3%–18.4%). Notably, alcohol was the only substance that showed an increasing trend in prevalence from before to after 2019, rising from 13.3% (95% CI, 6.2%–26.1%) to 17% (95% CI, 10.2%–27%) ($p < 0.001$). Additionally, the prevalence of substance use varied significantly between Arab and African countries ($p < 0.001$).

Conclusion: Although the prevalence of substance use among school-going populations has significantly decreased over time, with the exception of alcohol, it is imperative that both African and Arab countries implement comprehensive measures and stringent laws to address the production and marketing of substances.

Keywords: Africa; Arabs; Meta-analysis; Prevalence; Students; Substance-related disorders

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Introduction

Today, the world is home to 1.9 billion adolescents, the highest number in history, accounting

for 24% of the global population [1]. In the Middle East and North Africa region, predominantly composed of low- and middle-income countries, adolescents aged 10 to 19 constitute 17% of the population, with nearly half of the region's inhabitants under 30. Despite significant potential benefits, efforts to improve adolescent health in this region are advancing slowly [2]. While the incidence of communicable diseases has significantly decreased in recent decades, this progress has been overshadowed by the emergence of non-communicable diseases, mental health issues, unintentional injuries, self-harm, and the health consequences of ongoing regional conflicts. Moreover, preventable risk factors such as high body mass index and tobacco use continue to be widespread [3].

Substance use has emerged as a significant public health issue among adolescents, defined by the regular consumption of substances such as alcohol or psychoactive drugs in harmful quantities or through dangerous methods [4]. Early initiation and polysubstance use are strong predictors of future problems related to substance use. Despite this, adolescents frequently do not seek help for these issues, underscoring the importance of early interventions to prevent long-term consequences [4].

Globally, substance use results in significant health impacts, accounting for 494,000 deaths and 30.9 million disability-adjusted life years as reported in the World Drug Report 2021 [5]. In addition to health consequences, substance use presents moral, social, and economic challenges. No country is immune to these issues. However, certain regions, such as North Africa and the Eastern Mediterranean—key transit areas for illicit drugs—are especially vulnerable. This vulnerability is exacerbated by rapid social changes and ongoing conflicts. The rising trends of substance use among youth (ages 15–24) and women, with increasing dependence on substances like cannabis, sedatives, opiates, and stimulants, reflect this vulnerability [6].

Understanding the terminology related to substance use is essential: harmful use involves consumption that directly damages health, hazardous use refers to consumption that increases the risk of harm, and intoxication is a disruption of mental and physical functions due to acute effects. Substance abuse is characterized as a pattern of use that leads to significant impairment or distress [7]. Several factors contribute to substance use, such as genetic predisposition, family dynamics, environmental influences, and psychological well-being [8].

In Africa, cannabis is the most commonly used illicit substance, with prevalence rates ranging from 5.2% to 13.5% in West and Central Africa. Amphetamine-type stimulants rank as the second most prevalent, while benzodiazepines and inhalants are also used in some countries. For instance, in Sierra Leone, 3.7% of youth engage in injecting drug use [9]. In the Middle East and North Africa region, where 50% of the population is under 24 and 1 in 5 individuals is aged between 10 and 24, these young people have the potential to drive change if provided with opportunities for education and skill development [10]. However, substance use among students poses significant risks, including academic decline and increased vulnerability to sexually transmitted infections, such as human immunodeficiency virus, during intoxication [11].

Despite numerous studies, comprehensive assessments of substance use prevalence among school-going students in Africa and Arab countries remain limited. This systematic review and meta-analysis aimed to address this gap by offering a broad perspective on substance use among school-going populations in both Africa and Arab countries. Additionally, it examined how regional conditions influence substance use trends over time, providing insights to inform effective prevention and intervention strategies.

HIGHLIGHTS

- This research provides insights into the prevalence of commonly used substances in African and Arabic nations, including alcohol, tobacco, cannabis, khat, and stimulants.
- This study focused on the primary psychoactive substances within a specific age group in both Arabic and African countries. It is hoped that the data will guide policymakers and healthcare professionals in tailoring preventive actions for this particular population.
- This research examined how the location of a country and the time frame of the study influence the prevalence of substance use among the school-going population in 2 highly populated regions (African countries and Arab countries) by showing the decrease and increase rates over the years, with comparisons between countries.

Materials and Methods

Protocol and Registration

This systematic review and meta-analysis was prepared and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Material 1) [12]. The protocol was registered on PROSPERO (CRD4202345643).

Search Strategy

In order to conduct this meta-analysis, the chosen studies were required to meet the following criteria: they were published between January 1, 2013, and June 1, 2023. A comprehensive search was conducted across several databases, including Web of Science, Scopus, Google Scholar, Science Direct, and PubMed. These databases are commonly utilized for indexing publications related to health and substance use. The study was conducted from August to October 2023. Given the rapid evolution of knowledge in health and behavioral sciences, our systematic review aims to synthesize the most recent evidence from the past decade concerning substance use, thereby providing valuable insights for practitioners, policymakers, and researchers. The research algorithm used involved various permutations of keywords, which were categorized as follows: (1) topic (e.g., substance use, substance consumption, prevalence of substance use); (2) population (e.g., students, school-going children, adolescents); (3) outcome (e.g., prevalence of psychoactive substance use, prevalence of substance consumption).

Table S1 provides a detailed explanation of the algorithmic strategy used in this research. This document specifies the dates, platforms/interfaces, and databases utilized, lists the terms incorporated, describes the conjunctions employed to form the search string, and presents the resulting number of findings.

Inclusion and Exclusion Criteria

This review included publications in English that provided accessible abstracts and focused on research conducted in African countries or the Arab countries. The studies specifically targeted school-going children, aiming to measure the prevalence of psychoactive substance use. Inclusion criteria were limited to research published between January 1, 2013, and June 1, 2023, that specifically examined school-going populations. Studies were excluded if they failed to provide data on the prevalence of substance use among students, were qualitative without quantifying substance use, or were literature reviews or book chapters.

Study Selection

The selection process involved multiple steps to ensure a thorough and unbiased review. Initially, 2 postgraduate students independently examined studies by reviewing their titles, abstracts, and keywords. They removed duplicates and those that did not meet the inclusion criteria. Subsequently, they carefully assessed the full texts of the remaining articles to determine their eligibility based on the established criteria. In cases of disagreement, the 2 primary assessors (E.C.M. and M.G.) resolved issues through structured discussion. If consensus could not be reached, a senior professor was consulted to provide a final judgment. This process ensured that any potential bias or inconsistencies in evaluation were resolved through an impartial third party.

Review Question

This evaluation followed the guidelines set forth in the PRISMA framework [12]. The primary objective of this study was to explore 2 main questions: "Which studies have investigated the prevalence of substance use among students in the Arab region and Africa?" and "What was the reported prevalence of substance use according to the category of substances used in each study?" Additionally, the study aimed to compare and emphasize the potential impact of variables such as the geographical location of the country and the time period of the study on the prevalence of psychoactive substance use among students.

Data Screening and Selection

Data collection was conducted using a structured form to gather the following details: citation information, authorship years, geographical location, prevalence of substances, categories of substances used, and methods for analyzing the prevalence of substance use in studies. To ensure the accuracy and reliability of the data, 2 independent postgraduate students cross-checked the extracted data to verify consistency with the original studies. Any discrepancies in data extraction were resolved through consensus between the 2 assessors, and the final data were verified by a senior professor. This multi-step verification process was implemented to maintain the quality and accuracy of the data used in the analysis.

Appraisal of Study Quality and Risk of Bias

The methodological quality and risk of bias assessment were primarily conducted by C.E.M. and M.G., with additional input provided through discussions among all authors. This comprehensive evaluation adhered to the Joanna Briggs Institute (JBI) Meta-analysis of Statistics Assessment and Review Instrument (MAStARI) protocol [13]. The findings from these studies were categorized by their quality as high, moderate, or low. The Grading of Recommendations, Assessment, Development, and Evaluations (GRADE approach) was used to evaluate the overall quality of evidence for each reported outcome (Table S2) [11,14–48], and the Cochrane Collaboration assessment tool was employed to assess the risk of bias [49].

The risk of bias was categorized into 3 levels based on responses of "yes" or "no." A study was considered to have a low risk of bias if over 70% of the responses were "yes." A moderate risk was indicated if affirmative responses ranged

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from 50% to 70%, and a high risk was noted if less than 50% of the responses were affirmative (Table S3) [11,14–48]. To ensure reliability, 2 postgraduate students independently assessed each study for quality and bias. Any discrepancies in their evaluations were resolved through discussion to reach a consensus. If necessary, a senior professor reviewed the study to make the final decision. This rigorous, multi-step process ensured a comprehensive and balanced evaluation of the overall quality and potential biases in the included studies.

Data Analysis and Synthesis

The decision regarding the type of meta-analysis model (random effects, fixed effects, or mixed effects) depended significantly on the presence or absence of heterogeneity. Once this was determined, forest plots were generated to illustrate the prevalence of substance use, with a 99% confidence interval (CI) presented on a logarithmic scale. Heterogeneity was evaluated using the I^2 method [50,51], which quantifies the proportion of variability in outcomes across studies that can be attributed to heterogeneity rather than sampling error [52] The I^2 value indicates the degree of heterogeneity, with values between 50% and 75% signifying moderate heterogeneity and values exceeding 75% indicating high heterogeneity. Values below 50% suggest homogeneity among the study results, and forest plots were used to visualize this apparent heterogeneity. The risk of bias, specifically publication bias, between studies was assessed by examining the symmetry or asymmetry of the funnel plots. The meta-analysis was conducted using Comprehensive Meta-Analysis version 3 software, (Biostat Inc.). The goal of this analysis is to provide recommendations for prevention strategies to be implemented during efforts to reduce and prevent substance use among young school-going children.

Results

Search Results

The search identified 5,246 studies from Science Direct, 499 from PubMed, 171 from Web of Science, 65 from Scopus, and 1 from Google Scholar. These journals and databases were specifically chosen for their relevance to health and substance use research, particularly focusing on peer-reviewed publications that target school-going populations in African and Arab countries. After eliminating 970 duplicates and applying the inclusion and exclusion criteria, 80 studies were considered eligible for review. Subsequently, 43 of these studies were excluded after full-text assessments revealed issues such as inadequate sample sizes and the absence of reliability or validity evaluations. Ultimately, 37 studies met all criteria and were included in the final review (Figure 1).

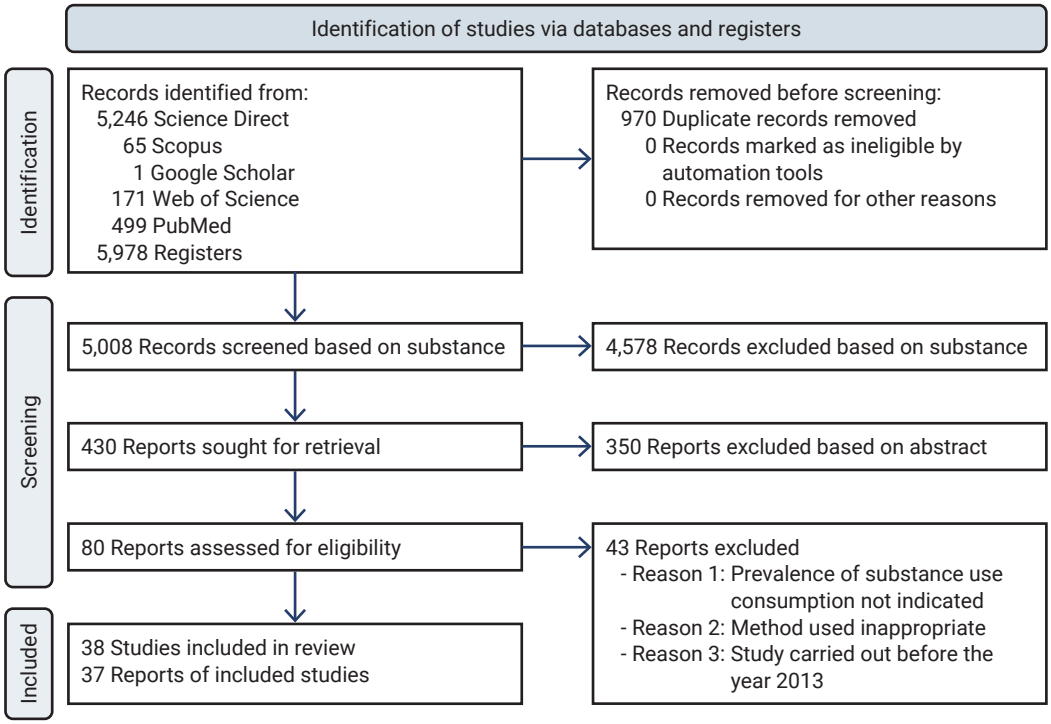

Figure 1. Flow diagram of the studies included in the systematic review and meta-analysis of substance use among school-going children in Africa and Arab countries.

Study Characteristics

Every study included in this systematic review and meta-analysis utilized a cross-sectional design. The sample sizes varied across the studies, ranging from 234 to 10,684 participants. In total, this systematic review and meta-analysis included 73,508 participants. The research was conducted between 2013 and 2023 and spanned various regions in African and Arab countries, with the mean (or median) age of participants ranging from 13 to 21 years (Table 1) [11,14–48,53].

The review included studies from 19 countries, with the majority conducted in Africa, especially in North Africa (n=13) [18–30], followed by Eastern African countries (n=7) [11,31–36] Western African countries (n=5) [37–40,53], Southern African countries (n=2) [41,42], and Central African countries (n=1) [43]. Additionally, studies from Arab countries were included (n=9) [14–17,44–48].

Risk of Bias in Studies and Appraisal of Study Quality

Among the 37 studies included in this review, 13 demonstrated

Table 1. Characteristics and outcomes of the included studies in the systematic review and meta-analysis

Study	Year	Country	Continent/ subregion	Study design	Main categories of substances analyzed	Sample size	Mean age (y)[a]	Predominant substances	Prevalence of predominant substances (%)
Hirpa et al. [31]	2023	Ethiopia	Eastern Africa	Cross-sectional	Alcohol, khat, tobacco, marijuana	3,347	16.5±1.4	Alcohol	41.8
Melkam et al. [32]	2023	Ethiopia	Eastern Africa	Cross-sectional	Alcohol, khat, tobacco	406	17.51±1.42	Alcohol	49
Bio-Sya et al. [53]	2022	Benin	Western Africa	Cross-sectional	Alcohol, stimulants, and tobacco	627	17±2	Alcohol	62.67
Mavura et al. [33]	2022	Tanzania	Eastern Africa	Cross-sectional	Alcohol, tobacco, cocaine, heroin, and marijuana	3,224	10–19	Alcohol	8.2
Mehanovic et al. [37]	2022	Nigeria	Western Africa	Cross-sectional	Tobacco, alcohol, and drug use	4,078	NA	Alcohol	34
Metuge et al. [43]	2022	Cameroon	Middle Africa	Cross-sectional	Tobacco, alcohol, tramadol, and cannabis	625	22.2±2.837	Tobacco	26.2
Mutiso et al. [34]	2022	Kenya	Eastern Africa	Cross-sectional	Alcohol, cannabis, tobacco, sedatives, Khat/amphetamine	9742	21.4±2.4	Alcohol	17.7
Olashore et al. [41]	2022	Botswana	Southern Africa	Cross-sectional	Alcohol, tobacco products, cannabis, inhalants, amphetamine	742	15.26±1.57	Alcohol	25.1
Baklouti et al. [18]	2021	Tunisia	Northern Africa	Cross-sectional	Tobacco, alcohol, and illicit drug use	1,210	14	Tobacco	13.9
Maalej et al. [19]	2021	Tunisia	Northern Africa	Cross-sectional	Cigarettes	234	16.59±0.908	Tobacco	38.3
Seid et al. [35]	2021	Ethiopia	Eastern Africa	Cross-sectional	Alcohol, tobacco, khat	383	18.1±1.077	Alcohol	16
Al-Gburi et al. [44]	2020	Iraq	Asia/Arab country	Cross-sectional	Alcohol	810	17.15±1.20	Alcohol	9.50
Amara et al. [20]	2020	Tunisia	Northern Africa	Cross-sectional	Tobacco, alcohol, illicit drugs	1,195	13–16	Tobacco	16.70
Hamdan-Mansour et al. [45]	2020	Jordan	Asia	Cross-sectional	Tobacco, stimulants	1,497	16–17	Tobacco	18.3
Mohamed et al. [21]	2020	Sudan	Northern Africa	Cross-sectional	Tobacco	1,229	15–19	Tobacco	31
Obadeji et al. [38]	2020	Nigeria	Western Africa	Cross-sectional	Alcohol, tobacco, tramadol, cannabis, codeine,sedatives	682	16	Alcohol	8.9

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Table 1. Continued

Study	Year	Country	Continent/ subregion	Study design	Main categories of substances analyzed	Sample size	Mean age (y)[a]	Predominant substances	Prevalence of predominant substances (%)
Hamdi et al. [22]	2016	Egypt	Northern Africa	Cross-sectional	Nicotine, benzodiazepines alcohol, and organic solvents	10.648	13–18	Nicotine	8.1
Ben Ayed et al. [23]	2020	Tunisia	Northern Africa	Cross-sectional	Tobacco	1,210	15.6±4.2	Tobacco	16.7
Ben El Jilali et al. [24]	2020	Morocco	Northern Africa	Cross-sectional	Alcohol	1,236	16.9±2.2	Alcohol	9
Charfi et al. [25]	2020	Tunisia	Northern Africa	Cross-sectional	Alcohol	315	NA	Alcohol	19.7
Othman et al. [26]	2019	Sudan	Northern Africa	Cross-sectional	Shisha tobacco	3,387	14–17	Tobacco	16.8
Badr et al. [46]	2018	Kuwait	Asia/Arab country	Cross-sectional	Smoking and drug use	1,310	14.5±0.03	Tobacco and drugs	26.6
Damiri et al. [47]	2018	Palestine	Asia	Cross-sectional	Tobacco, alcohol, and illicit drugs	831	15–16	Tobacco	40.6
El Kazdouh et al. [27]	2018	Morocco	Northern Africa	Cross-sectional	Tobacco, alcohol, and drug use	764	NA	Tobacco	16.2
Idowu et al. [39]	2018	Nigeria	Western Africa	Cross-sectional	Cigarette smoking, cocaine, tramadol, heroin, cannabis, alcohol	249	16.3±2	Tramadol	39
Riva et al. [42]	2018	Botswana	Southern Africa	Cross-sectional	Alcohol, illicit drugs, marijuana	1,936	NA	Alcohol	42.1
Al-Alawi AS et al. [28]	2018	Sudan	Northern Africa	Cross-sectional	Cigarettes, herbal cigarettes, shisha, and tombak	1,229	14.5	Cigarettes	13
Zammit et al. [29]	2021	Tunisia	Northern Africa	Cross-sectional	Illicit substances, tobacco	4,272	13.3±1.2	Tobacco	12.9
Babatunde et al. [40]	2018	Nigeria	Western Africa	Cross-sectional	Cigarettes	2,000	NA	Tobacco	13.6
Chivandire et al. [36]	2016	Zimbabwe	Eastern Africa	Cross-sectional	Alcohol, smoking, cigarettes, cannabis	311	16.8	Cannabis	8
Zarrouq et al. [30]	2016	Morocco	Northern Africa	Cross-sectional	Cannabis, alcohol, inhalants, psychotropics, cocaine, heroin, amphetamine	3,020	16±2	Tobacco	16.1
McKelvey et al. [48]	2015	Jordan	Asia	Cross-sectional	Tobacco	1,454	12.6	Cigarette	29.8
Birhanu et al. [11]	2014	Ethiopia	Eastern Africa	Cross-sectional	Alcohol, cigarettes, and khat	651	17.25±1.24	Alcohol	40.9
Crookes and Wolff [14]	2014	United Arab Emirates	Asia/Arabian Peninsula	Cross-sectional	Tobacco products	394	16.9	Tobacco	23.4
Alsanosy et al. [15]	2013	Kingdom of Saudi Arabia	Asia/Arabian Peninsula	Cross-sectional	Khat	3,923	15±2.01	Khat	20.5
Gaffar et al. [16]	2013	Kingdom of Saudi Arabia	Asia/Arabian Peninsula	Cross-sectional	Tobacco	3,923	12–21	Tobacco	10.7
Raffee et al. [17]	2021	Jordan	Asia	Cross-sectional	Stimulants	414	NA	Stimulants	16.9

NA, not available; SD, standard deviation.

[a]Data are presented as mean±SD or ranges.

a 100% risk of bias, which corresponds to a low risk of bias. The reporting of the substances analyzed, the measured prevalence for each type of substance, the methods used, and a well-described study protocol in the Materials and Methods section were free from bias. The prevalence of substance use, the reporting of the most commonly used substances, and the indication of the study year were reported without bias in 36 of the included studies. Only 1 study, conducted by Raffee et al. [17], had a 71.42% risk of bias concerning the prevalence of substance use and the most commonly used substance in the sample. Fifteen studies reported on the risk of bias associated with funded studies, highlighting that financial support often led to an expansion of the sample size. Table S3 discloses the affirmative (yes) response percentages for each study included in this review and provides detailed information concerning the responses related to the evaluation of bias risk.

The quality appraisal of studies included in this systematic review was conducted using the JBI characteristics. The appraisal revealed that all 37 studies assessed demonstrated strong methodological rigor. Specifically, the following criteria were evaluated: (1) Sample frame: All studies provided an appropriate sample frame addressing the target population; (2) Participant characteristics: Each study clearly described the characteristics of the participants; (3) Sample size: All studies reported adequate sample sizes for their respective analyses; (4) Study subjects and setting: Detailed descriptions of the study subjects and settings were provided in each article; (5) Data analysis: Sufficient coverage of the identified sample was evident in the data analysis conducted; (6) Study objectives: The objectives of the studies were clearly stated and aligned with the findings; (7) Statistical analysis: Each study employed appropriate statistical analyses to support their conclusions.

Given that all appraisal criteria were met, we assessed the overall quality of evidence as high according to the GRADE framework. This high-quality assessment indicates that the findings reported in this review are reliable and can be confidently applied in practice and policy (Table S4).

Results of Syntheses

Prevalence of substance use according to the category of substances

The meta-analysis showed that tobacco is the most commonly used substance among those examined. There was significant variability in outcomes across studies, indicating substantial heterogeneity in the results. Notably, the prevalence of alcohol consumption and stimulant use were also high, followed by the use of khat and cannabis. All statistics were calculated using a random-effects model (Figures 2–6).

Prevalence of substance use according to continent

The prevalence of tobacco use, the most commonly used substance, was estimated to be higher in the Arab countries at 18% compared to 14% in Africa (95% CI, 13.7%–23.2%; $p < 0.001$; 95% CI, 11.3%–18.6%; $p < 0.001$).

The estimated prevalence of alcohol consumption was higher in Africa at 16.7% than in the Arab countries at 7% (95% CI, 10.6%–25.2%; $p < 0.001$; 95% CI, 3.6%–13.2%; $p < 0.001$) respectively. However, the use of khat was significantly more prevalent in Arab countries, at 14%, than in Africa, where the prevalence rate was 9% (95% CI, 3.4%–44.1%; $p < 0.001$ and 95% CI, 4.3%–21.3%; $p < 0.001$, respectively).

The prevalence of stimulant use was estimated to be approximately 10% in Africa and 9% in the Arab countries % CI, 6.4%–15.9%; $p < 0.001$ and 95% CI, 5%–16.1%; $p < 0.001$, respectively). For cannabis use, the prevalence rates in the Arab countries and Africa were relatively similar (9%; 95% CI, 2.8%–25.2%; $p < 0.001$ and 6%; 95% CI, 2.6%–13.2%; $p < 0.001$, respectively).

Main substance categories explored and utilized

The studies included in this meta-analysis demonstrate that researchers have investigated a wide variety of psychoactive substances. A frequency analysis of substance use, performed using NVIVO ver. 12 software, shows that tobacco was the most commonly used substance, followed by alcohol, stimulants, khat, and cannabis (Table 1).

Influence of the study duration on the prevalence of psychoactive substances

The number of studies has significantly increased over the years, focusing on the 5 substances examined in this study: tobacco, alcohol, khat, cannabis, and stimulants. The overall prevalence of these substances varied between the 2 periods (before and after 2019).

The prevalence of alcohol use significantly increased in a comparison of the 2 periods before and after 2019, from 13.3% to 17%, respectively (95% CI, 6.2%–26.1%; $p < 0.001$ and 95% CI, 10.2%–27.0%, respectively; $p < 0.001$).

The prevalence of cannabis use significantly decreased after 2019, from 10.9% to 6% r (95% CI, 3.3%–30.8%; $p < 0.001$ and 95% CI, 1.9%–17.8%, respectively; $p < 0.001$).

The prevalence of tobacco use significantly decreased after 2019, from 20.8% to 13.2% (95% CI, 14.9%–28.3%; $p < 0.001$ and 95% CI, 9.7%–17.7%; $p < 0.001$, respectively). Similarly, the prevalence of khat use also showed a significant decline, from 25.1% before 2019 to 8% afterwards (95% CI, 8.7%–54.0%; $p < 0.001$ and 95% CI, 4%–15.3%; $p < 0.001$, respectively). Additionally, the prevalence of stimulant use decreased notably, from 17.4% to 3% during the same periods (95%

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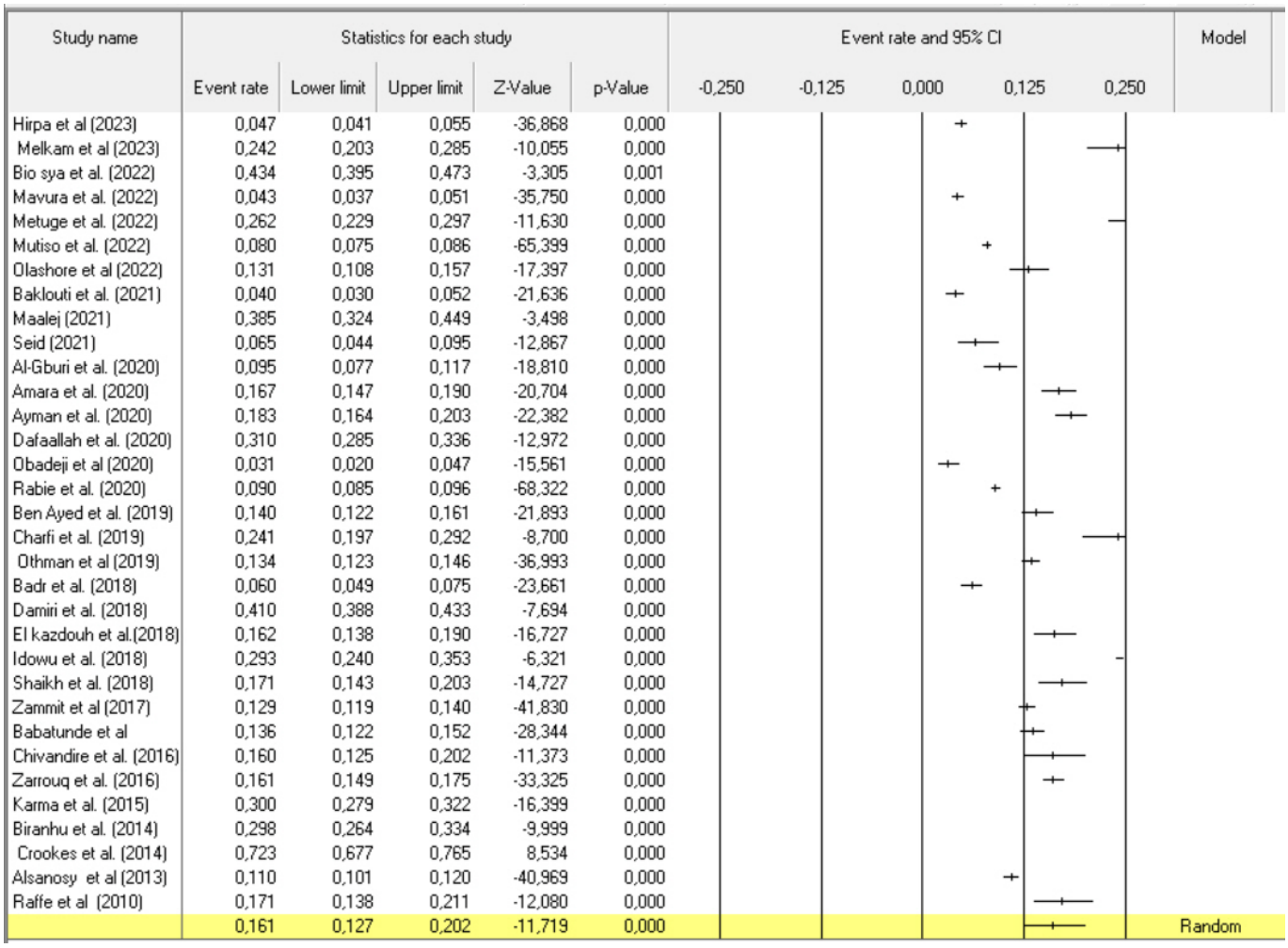

Figure 2. Prevalence of tobacco use among school-children in African and Arab countries 2013–2023 (%). CI, confidence interval.

CI, 8.2%–33.1%; $p < 0.001$ and 95% CI, 5.5%–15.4%; $p < 0.001$, respectively). An asymmetric funnel plot suggested the presence of reporting bias and/or heterogeneity between studies.

Discussion

This review provides a comprehensive overview of the prevalence of substance use among school-going youth in African and Arab countries, based on 37 studies published between 2013 and 2023. Earlier reviews often focused on specific countries [54] or specific substances [55]. In contrast, our study offers a broader regional perspective, including both Africa and the Arab countries. Key findings indicate substance use prevalence rates of 16% for tobacco, 15% for alcohol, 11.4% for stimulants, 10% for cannabis, and 10% for khat. These results add to the growing body of literature on youth substance use, underscoring regional differences and trends that warrant further investigation.

The prevalence of alcohol use was significantly higher in African countries (16.7%) than in the Arab region (7%). This discrepancy reflects cultural and regulatory differences between these regions, where alcohol consumption may be more restricted by religious and social norms in Arabic countries. Additionally, we observed a significant increase in alcohol use post-2019 (17% compared to 13.3% before 2019, $p < 0.001$), a trend consistent with the Global Status Report on Alcohol and Health 2018, which documented rising alcohol consumption globally [56]. This increase may be attributed to evolving social norms, economic growth, and Western influences in parts of Africa. The social cognitive theory supports the role of social context in shaping these substance use patterns [57]. Regional variations within African countries further support the role of cultural and social factors in substance use. For instance, in Morocco, alcohol use was reported by 12.4% of boys and 7.2% of girls

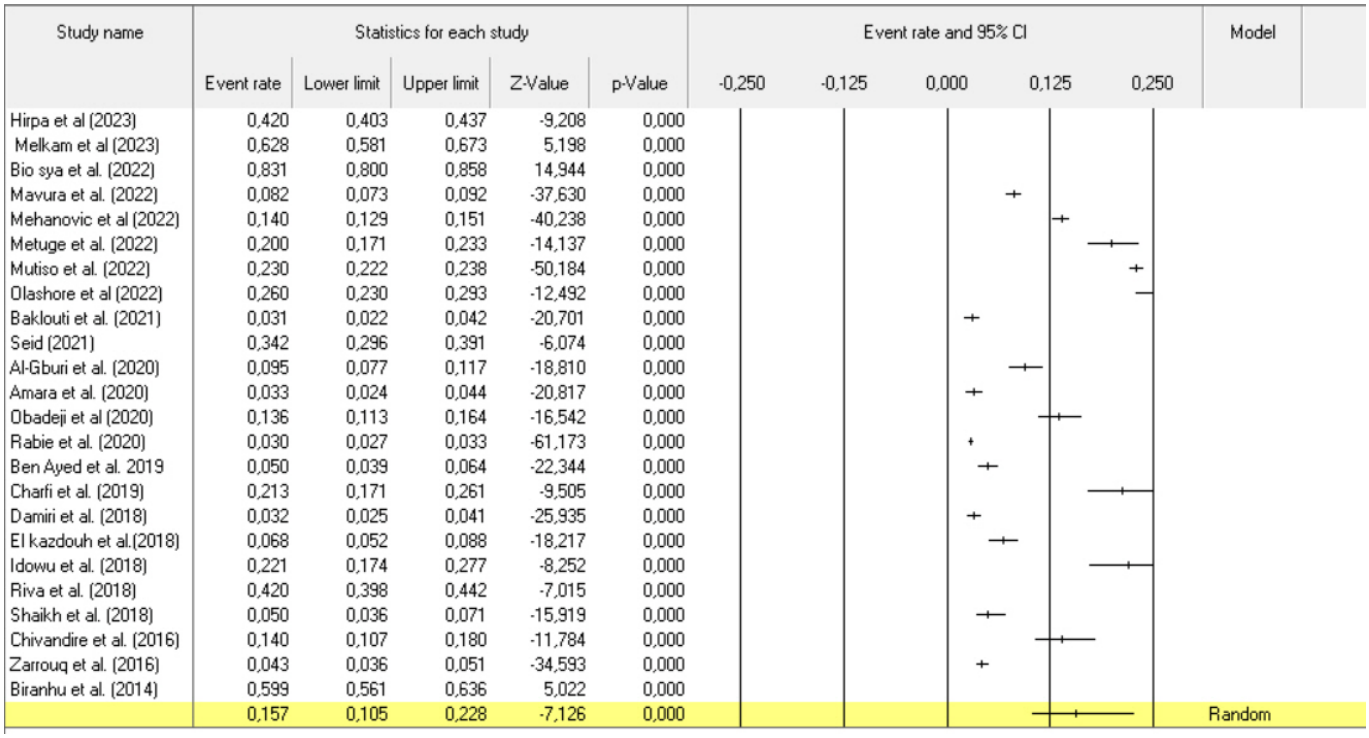

Figure 3. Prevalence of alcohol use among school-children in African and Arab countries 2013–2023 (%). CI, confidence interval.

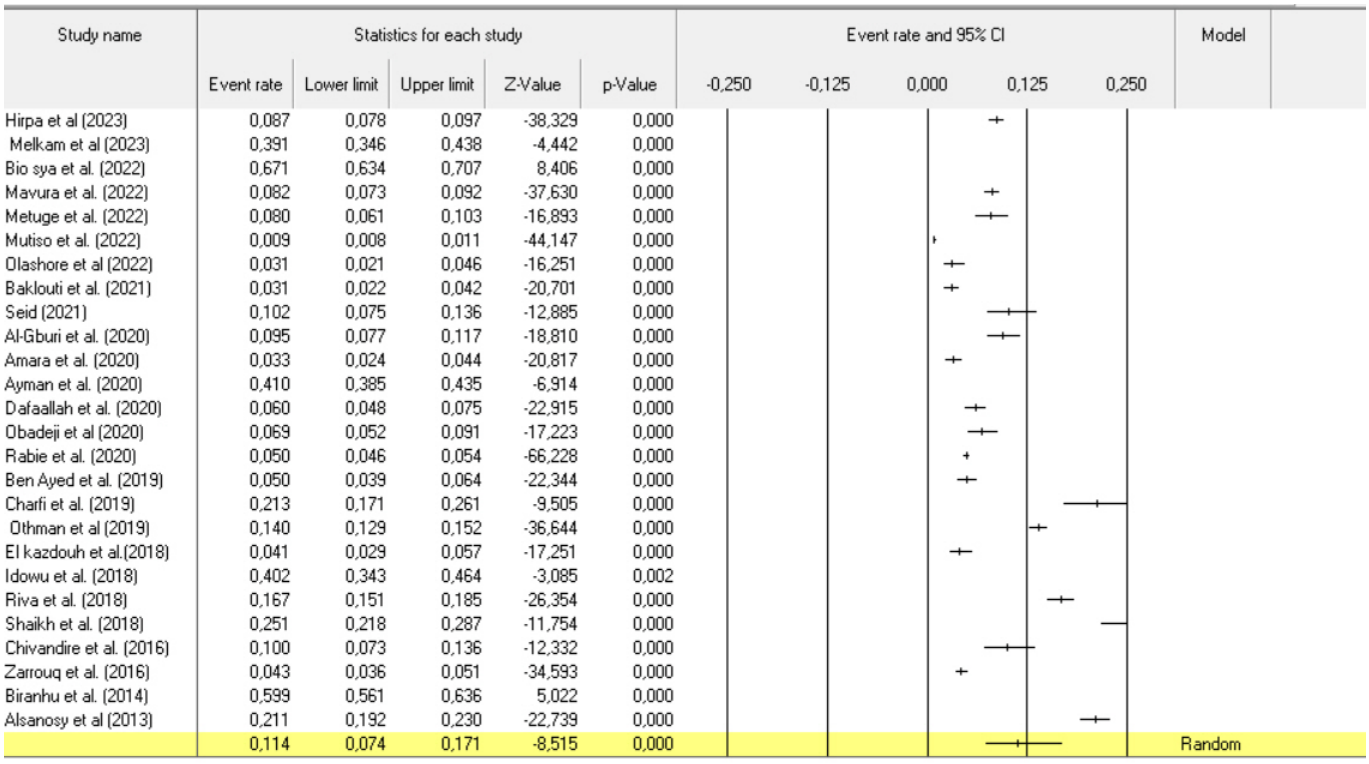

Figure 4. Prevalence of stimulant use among school-children in African and Arab countries 2013–2023 (%). CI, confidence interval.

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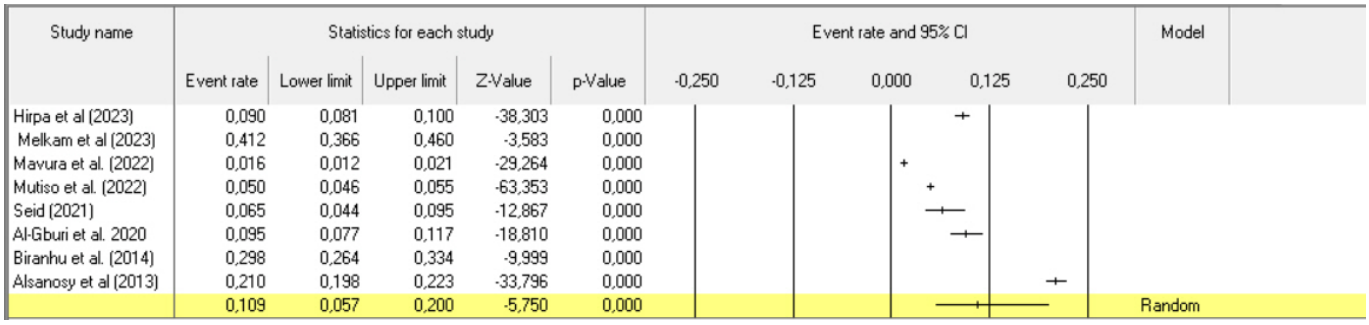

Figure 5. Prevalence of khat use among school-children in African and Arab countries 2013–2023 (%). CI, confidence interval.

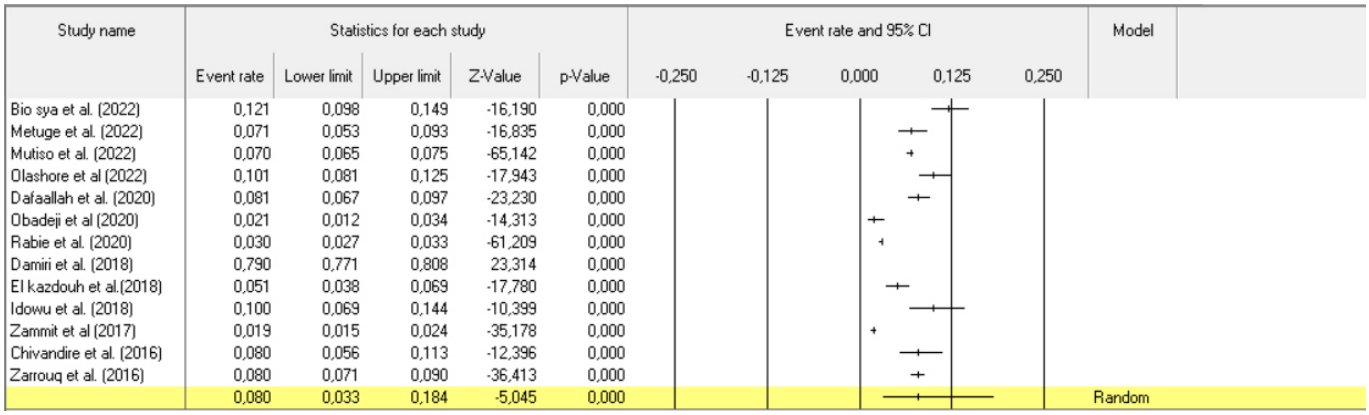

Figure 6. Prevalence of cannabis use among school-children in African and Arab countries 2013–2023 (%). CI, confidence interval.

aged 15 to 17 [58], while in Tunisia, 8.0% of students reported having consumed alcohol at least once in their lifetime [59]. In contrast, Egypt exhibited a much lower prevalence of 2.9%. The variability in alcohol use across these countries underscores the importance of localized public health strategies that consider cultural, religious, and legal contexts [60]. A broader analysis of Sub-Saharan Africa estimated the prevalence of alcohol use at 11.3% [61]. However, our study observed a higher prevalence of 16.7% (95% CI, 10.6%–25.2%) for alcohol use in African countries, highlighting a notable increase compared to previous estimates. This suggests an upward shift in alcohol consumption trends in the region, which may reflect changing social, economic, and cultural dynamics impacting substance use.

Our study observed higher smoking rates among youth in Arab countries (18%) compared to those in Africa (14%). However, there was a significant decline in smoking prevalence over time, decreasing from 20.8% before 2019 to 13.2% after 2019 ($p < 0.001$). This reduction may be attributed to effective tobacco control measures, especially in countries like Tunisia, where enhanced legislation and collaboration with the World Health Organization have bolstered anti-tobacco initiatives. This trend is consistent with global patterns, where increased awareness of the health risks associated with smoking and stricter regulations have led to lower smoking rates [62]. This observation is consistent with the health belief model, which suggests that increased perception of risk can motivate behavioral change [63].

Our study also highlighted a notable decline in stimulant use, from 17.4% before 2019 to 3% after 2019 ($p < 0.001$). This significant reduction contrasts with global trends, where stimulant use has generally increased. The sharp decline observed in our sample may indicate the effectiveness of recent drug policies or targeted youth prevention programs, which could be explored further in future research. In Africa, the prevalence of cocaine use is estimated at 0.2% to 0.5%, and the number of amphetamine users ranges from 1.5 to 5.2 million individuals annually, suggesting a broader upward trend in stimulant use [64]. However, the lower prevalence observed in our study points to regional differences in substance availability and enforcement, as well as potential shifts in youth behavior, consistent with the theory of planned behavior, where behavior is shaped by societal norms and perceived control [65].

The prevalence of khat use in our study was 10%, which is lower than the rates reported in studies involving university students, where the prevalence was approximately 14.16% [59]. Khat use was notably high in countries such as Saudi Arabia (18.85%), Ethiopia (13.59%), and Yemen (13.04%) [66], where cultural practices and limited enforcement of prohibitions contribute to its continued use. The differences noted above may be explained by the fact that our meta-analysis included data from countries where khat use is illegal, including Saudi Arabia, Egypt, Morocco, Sudan, and Kuwait [67]. These findings underscore the complexity of addressing khat use, as legal restrictions alone are insufficient without strong enforcement and community engagement, particularly in areas where khat is culturally significant.

Regarding cannabis use, we observed a decline in prevalence in the African region, from 10% before 2019 to 6% after 2019. This finding aligns with previous research [68] and is consistent with decreased cannabis consumption trends in both African and Arab countries. This decline may be attributed to changes in the legal framework for cannabis cultivation in Lebanon and Morocco, the primary cultivators in North Africa. Additionally, a report [69] noted that while cannabis use among 15- to 16-year-olds often exceeds that of the general population aged 15 to 64, Africa is the exception, with similar prevalence rates of 7% in both age groups [68]. This finding is supported by the Public Health Model, which suggests that changes in the legal and social environment can influence health behaviors, including substance use. The model posits that modifying these external factors can lead to changes in individual behavior, including reductions in substance use [70].

The robustness of this review is underscored by the inclusion of a substantial number of studies ($n=37$) across 19 countries, and the focus on substances that constitute the most problematic used worldwide: alcohol, tobacco, khat, cannabis, and stimulants.

In this comprehensive systematic review and meta-analysis, which assessed substance use among school-going youth in African and Arabic countries, we observed significant prevalence rates for various substances: tobacco (16%), alcohol (15%), stimulants (11.4%), cannabis (10%), and khat (10%). Notably, alcohol use was higher in African countries (16.7%) than in Arab countries (7%), with a marked increase observed post-2019. Conversely, smoking prevalence was greater in Arab countries (18%) than in Africa (14%), though it has significantly declined over time. Similarly, stimulant use showed a substantial decrease from 17.4% before 2019 to 3% after 2019. The relatively lower prevalence of khat use (10%) compared to that among university students underscores regional variations and the influence of legal restrictions [71]. Cannabis use in Africa also decreased from 10% to 6% after 2019. These findings highlight the necessity for targeted educational interventions, policy development, and support programs that take into account regional and cultural factors.

Strengths and Limitations

A key limitation of this study is its reliance on self-reported data, which may introduce biases due to underreporting or overreporting, as well as social desirability biases that could influence the findings. To mitigate these issues, we included only studies that utilized validated instruments and met a minimum sample size threshold to enhance data reliability. Additionally, the cross-sectional nature of the studies prevents us from drawing causal conclusions, underscoring the need for future longitudinal research. To reduce publication bias, we conducted a comprehensive search across multiple databases, incorporating both grey literature and unpublished studies. Random-effects modeling was applied to address the significant heterogeneity among studies, as indicated by the I^2 statistic. Future research should focus on exploring regional differences and assessing the effectiveness of interventions targeting substance use among youth.

Study Implications

The clinical implications of this study are significant, particularly in guiding early interventions and prevention strategies for substance use among adolescents. By identifying the prevalence and patterns of substance use in school-going populations across Africa and Arab countries, this research highlights critical areas for targeted interventions. Clinically, the findings underscore the need for healthcare professionals, educators, and policymakers to focus on early screening and intervention programs in schools to mitigate the long-term health impacts of substance use, such as mental health disorders, addiction, and related physical health complications. Furthermore, the study emphasizes the importance of culturally adapted prevention programs that consider regional differences in substance use trends. These findings can inform clinicians about the necessity of integrating mental health services with substance use prevention programs to address co-occurring issues like anxiety, depression, and self-harm, which are often linked with adolescent substance use.

Conclusion

Substance use among school-going adolescents continues to be a major public health concern in Africa and the Arab countries. The varying prevalence rates of tobacco, alcohol,

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cannabis, khat, and stimulant use underscore the necessity for interventions that are specifically designed to meet the unique challenges and resources of each country. It is critical to address socio-environmental factors and to promote preventive strategies through educational and mentorship programs to reduce substance use. Early intervention, especially targeting gateway substances such as tobacco and alcohol, is vital for preventing the progression to more harmful drugs. Collaborative, multi-sectoral efforts are essential to address this escalating problem and safeguard adolescent health.

Supplementary Material

Supplementary Material 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist; **Table S1.** Search details and review forms; **Table S2.** Quality appraisal studies included in the systematic review and meta-analysis according to Joanna Briggs Institute characteristics; **Table S3.** Risk of bias; **Table S4.** The Joanna Briggs Institute criteria used for methodological quality assessment. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0204.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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None.

Availability of Data
The datasets used and/or analyzed during the current study are cited in this article.

Authors' Contributions
Conceptualization: CEM; Data curation: CEM, MG; Investigation: CEM; Project administration: MC, AH; Supervision: MC, AH; Validation: CEM, MG; Visualization: CEM, MG; Writing–original draft: CEM, MG; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Excess mortality in older adults and cumulative excess mortality across all ages during the COVID-19 pandemic in the 20 countries with the highest mortality rates worldwide

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ABSTRACT

Objectives: Mortality statistics during the coronavirus disease 2019 (COVID-19) pandemic are crucial for the allocation of medical care resources and public health decision-making. This study was initiated to investigate the excess mortality among older adults during the pandemic. Our research focuses on 2 primary areas. First, we analyzed the cumulative excess mortality across all age groups to assess the global impact and specifically examined the top 20 countries with the highest mortality rates during the pandemic. Second, we explored excess deaths among older adults by categorizing data from the years 2020 and 2021 into age groups: 65–74, 75–84, and above 85.

Methods: We analyzed data from the top 20 countries with the highest mortality rates globally, focusing on 3 components: all-cause mortality means, expected deaths mean, and excess deaths mean for both older men and women.

Results: Although excess mortality is higher among older men and women across all 3 age groups (65–74, 75–84, and >85), the highest mean excess mortality was observed in women over the age of 85.

Conclusion: The results indicate that the severe acute respiratory syndrome coronavirus 2 virus had a disproportionately intense impact on older women. We developed 2 types of statistical models using the data: a binomial distribution model and a correlation coefficient model, both considering the mean excess deaths in older men and women across these 3 age groups. Estimating the excess mortality among older adults will aid in the formulation of healthcare policies for this demographic.

Keywords: COVID-19; Elderly; Excess mortality; Pandemics; Public health

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has had a catastrophic impact on the global economy, human health, and all sociological aspects. The world was caught unprepared [1–3]. The pandemic has resulted in massive numbers of infections and deaths across various countries. Despite the implementation of lockdowns by most countries, the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus led to increasing infection and death rates. Every country has focused on tracking these 2 critical statistics: infection and death rates. To monitor the real-time status of COVID-19 and understand its spread and mortality, several web-based dashboards have been developed [4]. The World Health Organization (WHO) has also established a dashboard to project the numbers of infections and deaths. As of March 31, 2024, there have been approximately 774.9 million cumulative infection cases and 7.04 million cumulative death cases recorded. Researchers have been investigating the life years lost due to COVID-19. Most epidemiological studies have aimed to assess infection and mortality rates to better understand the disease processes associated with COVID-19 [5]. Various models have been created using COVID-19 mortality data to explore different factors related to mortality. Pourhomayoun and Shakibi [6] analyzed various machine learning algorithms, including decision trees, networks, random forest, artificial neural logistic regression, K-nearest neighbor, and support vector machine, to predict the mortality rate among COVID-19 patients. Aslam and Biswas [7] developed a method using machine learning techniques for real-time forecasting of COVID-19 death rates.

Along with the mortality during COVID-19, researchers sought to understand excess mortality. Excess mortality refers to the difference between the total number of deaths during an emergency and the number of deaths under normal conditions. It reflects increased mortality over what would be expected based on historical trends and may include both direct and indirect deaths. Analyzing excess mortality provides insight into the augmented global mortality rate and can indicate the severity of a global health crisis, aiding in the formulation of new policies [8,9]. Researchers aimed to explore the trends in excess mortality throughout this pandemic. Therefore, they examined excess mortality during various time frames, either in specific locations or globally. COVID-19 Excess Mortality Collaborators evaluated the excess deaths in 191 countries and territories, as well as several subnational locations, during the COVID-19 pandemic from 2020 to 2021. They reported approximately 18.2 million deaths, with an all-age rate of excess mortality of 120.3 deaths per 100,000 population during this period [9]. Msemburi et al. [10] estimated excess deaths using a consistent and comprehensive approach based on WHO estimates for 2020 and 2021. They calculated a global excess mortality of about 14.83 million during these years, which was 2.74 times higher than the reported deaths (5.42 million) during the COVID-19 period. Karlinsky and Kobak analyzed excess mortality across countries during the COVID-19 pandemic. They collected all-cause mortality (ACM) data (weekly, monthly, quarterly) from 103 countries using the world mortality database. They identified Peru, Ecuador, Bolivia, and Mexico as the countries most severely affected, with excess deaths exceeding 50% of the expected annual deaths. Bulgaria, Peru, North Macedonia, and Serbia reported more than 400 excess deaths per 0.1 million people. Conversely, countries like Australia and New Zealand experienced mortality rates lower than usual during the pandemic. They also noted that several countries, including Uzbekistan, Russia, and Nicaragua, underreported their COVID-19 mortality [8]. In addition to global analyses, researchers also estimated excess mortality in specific locations. Cevallos-Valdiviezo et al. [11] assessed excess mortality in Ecuador from March 17, 2020, to October 22, 2020. They found that all-cause excess mortality amounted to 36,922 during the analysis period. Similarly, Chen et al. [12] investigated excess mortality among Californians aged 18–65, considering their occupation and sector. The study recorded 11,628 more deaths than expected among working-age adults, equivalent to 46 excess deaths and a 22% relative excess per 0.1 million individuals. The highest per-capita and relative excess deaths occurred in the agriculture/food, logistics/transportation, manufacturing, and facilities sectors. In the agriculture/food sector, there were 75 excess deaths per 100,000 people (39% relative excess). The study also analyzed the highest per-capita and relative excess mortality across ethnic and racial

HIGHLIGHTS

- Excess mortality of aging adults was higher during COVID-19.
- The study calculated excess mortality in elderly (3 age groups: 65–74, 75–84, and >85) in 20 higher mortality countries.
- The study observed a higher excess mortality mean in the >85 age group female.
- It helps to formulate the health care strategy for aging adults.

groups, with Latino working-age Californians experiencing the highest relative excess mortality (37%). However, there is an urgent need to understand excess mortality among older adults. Modig et al. [13]. estimated excess mortality for individuals over the age of 70 in Sweden during the first wave of the COVID-19 pandemic (2020). They divided this age group into 3 categories: independently living, those supported with home care, and those residing in care homes. They observed the highest excess mortality among those in care homes, with rates in April, May, and June ranging from 75%–100%, 25%–50%, and 0%–25%, respectively, depending on age. Understanding excess mortality in older adults globally requires further analysis across different age groups.

In this study, we approached our research from 2 perspectives. First, we analyzed the cumulative excess mortality across all age groups globally and specifically in the top 20 countries affected during the COVID-19 pandemic. Second, we conducted a detailed evaluation of excess deaths among older adults. For this demographic, we categorized the 2020 and 2021 data into age groups: 65–74, 75–84, and over 85, using information from those 20 countries. We employed 2 statistical models in our analysis: the binomial distribution and the correlation coefficient model. The findings from our analysis of excess mortality will be instrumental in shaping healthcare policies for older adults.

Materials and Methods

Overview

We summarized the estimates of excess mortality, providing detailed descriptions of the data used and the methodology applied in this study. Initially, we retrieved the cumulative mortality data for 234 countries from the WHO's official COVID-19 dashboard (https://covid19.who.int/info). Subsequently, we ranked the country-wise mortality data and identified the top 20 countries. For these countries, we estimated the excess mortality in 2 specific categories: (1) overall estimated excess mortality and (2) excess mortality among older adults.

In this study, we conducted a detailed analysis of excess mortality among older adults. We categorized the data into age groups: 65–74, 75–84, and over 85. Additionally, we examined excess mortality in older adults from January 2020 to December 2021.

Literature Survey

We conducted an extensive literature review using databases such as PubMed, Web of Science, and Google Scholar. The search employed various keywords including "excess mortality," "pandemic," "COVID-19," "elderly adults," and "global mortality," either individually or in combination. Our search yielded a single paper focused on excess mortality in Sweden during the COVID-19 pandemic in 2020 [13]. This indicates a need for further research to understand excess deaths among older adults.

Dataset

We utilized data from the WHO, specifically the official COVID-19 dashboard, to assess cumulative mortality on a global scale. Subsequently, we identified the top 20 countries based on mortality data. In these countries, we focused on estimating excess mortality among older adults. Additionally, we employed the WHO dataset for older adults to analyze the estimated excess mortality.

For overall excess mortality, we used Our World in Data (https://ourworldindata.org/). In this study, we initially retrieved the cumulative mortality rates for 234 countries from the WHO's official COVID-19 dashboard. Subsequently, we ranked these countries based on their mortality data and identified the top 20. We then analyzed the cumulative excess mortality globally and for these top 20 countries across all age groups during the COVID-19 pandemic.

Procedure of Analysis

All-ages cumulative excess mortality analysis throughout the world and in the top 20 nations with the highest mortality rates during the pandemic period

We analyzed the cumulative excess mortality for all ages worldwide, utilizing data from Our World in Data.

In this study, we conducted a comprehensive analysis of cumulative excess mortality across all age groups, focusing on the top 20 countries with the highest mortality rates. For this analysis, we also utilized data from Our World in Data.

Analysis of excess mortality in older adults in the top 20 countries with the highest mortality rates during the pandemic period

We analyzed excess mortality in the top 20 countries with the highest mortality rates using WHO data [14]. The data for older adults were categorized into 3 age groups: 65–74, 75–84, and over 85. We included data from both men and women in our analysis, which covered the period from January 2020 to December 2021. Our methodology adhered to WHO's established methods for data analysis. We examined ACM, expected deaths, excess deaths, and negative excess deaths, providing extensive definitions for each term in Supplementary Material 1.

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Statistical Analysis

Statistical models were developed periodically. For the analysis of excess mortality among older adults, we employed models based on the binomial distribution and correlation coefficients. The correlation coefficient, usually represented by "r," quantifies the strength and direction of a linear relationship between 2 variables. This coefficient can vary between -1 and 1, with each value providing insights into the nature of the relationship between the variables. We provide a detailed description of the correlation coefficient model in Supplementary Material 1.

The range of values is as follows: r=1 indicates a perfect positive linear correlation, where 1 variable increases at a constant rate as the other does. r=–1 signifies a perfect negative linear correlation, characterized by 1 variable decreasing at a constant rate as the other increases. r=0 denotes no linear correlation, meaning there is no apparent linear relationship between the 2 variables, although they may still have a nonlinear relationship. The magnitude of the correlation is categorized as follows: a correlation coefficient (|r|) ranging from 0 to 0.3 indicates a weak correlation, suggesting little to no linear relationship between the 2 variables. A coefficient from 0.3 to 0.7 signifies a moderate correlation, where a noticeable linear relationship exists, though it is not perfect. A coefficient from 0.7 to 1 denotes a strong correlation, indicating a clear linear relationship, either positive or negative [15,16]. We utilized the open-source software package R to develop the statistical models for all data.

Justification of the Statistical Methods

When selecting specific models, such as the binomial distribution or logistic regression, for analyzing data across various age groups in studies related to COVID-19 or other health issues, it is crucial to base the choice on the nature of the data, the research objectives, and the way these models manage different types of relationships.

The binomial distribution is suitable when each outcome in a population is binary, categorized as either success or failure. It is used to model the probability of achieving a certain number of successes within a predetermined set of trials. This distribution is particularly appropriate for age-specific data when the main focus is on modeling counts or proportions associated with events such as infection, hospitalization, or death.

Logistic regression enhances a binomial model by analyzing the relationships between 1 or more predictor variables and a binary outcome, thereby increasing its flexibility. It models the log odds of the outcome as a function of various predictors, such as age, health status, and exposure levels.

We employ the binomial distribution when our primary interest lies in binary outcomes, aiming to model the probability of success within distinct age groups. Conversely, logistic regression is utilized when analyzing more complex relationships that involve multiple predictors, interactions, or nonlinear effects, such as assessing the impact of various demographic and health factors on age-specific outcomes.

This approach ensures that the selected model aligns with the nature of the data and the research questions, ultimately leading to more accurate and interpretable results.

Lastly, a flowchart was created to explain the overall methodology of the study (Figure 1).

Results

Estimation of Global All-Ages Cumulative Excess Mortality

We estimated the cumulative excess mortality rate for all ages per 1,000,000 people worldwide during COVID-19. The central estimate globally is 358.89, with an upper bound of 442.98 and a lower bound of 232.72. The confirmed global COVID-19 death rate stands at 88.10 per 100,000 people at this time (Figure 2A).

Using data from Our World in Data, a world map illustrates the cumulative excess mortality per 1,000,000 people of all ages during COVID-19 (Figure 2B).

We estimated the global cumulative excess mortality for all ages over the past 12 months per 1,000,000 people during the COVID-19 pandemic. The central estimate worldwide is 28.88, with an upper limit of 77.45 and a lower limit of 13.63. During this period, the confirmed COVID-19 death rate worldwide was 1.49 per 100,000 people (Figure 2C). A world map illustrates the cumulative excess mortality per 1,000,000 people over the last 12 months, based on our global data (Figure 2D).

All-Ages Cumulative Excess Mortality in the Top 20 Countries

We estimated cumulative excess mortality in all ages the top 20 countries with the highest excess mortality rates during COVID-19, which were the United States of America (USA; Figure S1A, Supplementary Material 1), Brazil (Figure S1B, Supplementary Material 1), India (Figure S1C, Supplementary Material 1), Russian Federation (Figure S1D, Supplementary Material 1), Mexico (Figure S1E, Supplementary Material 1), United Kingdom (UK; Figure S1F, Supplementary Material 1), Peru (Figure S1G, Supplementary Material 1), Italy (Figure S1H, Supplementary Material 1), Germany (Figure S1I, Supplementary Material 1), France (Figure S1J, Supplementary Material 1), Indonesia (Figure S2A, Supplementary Material

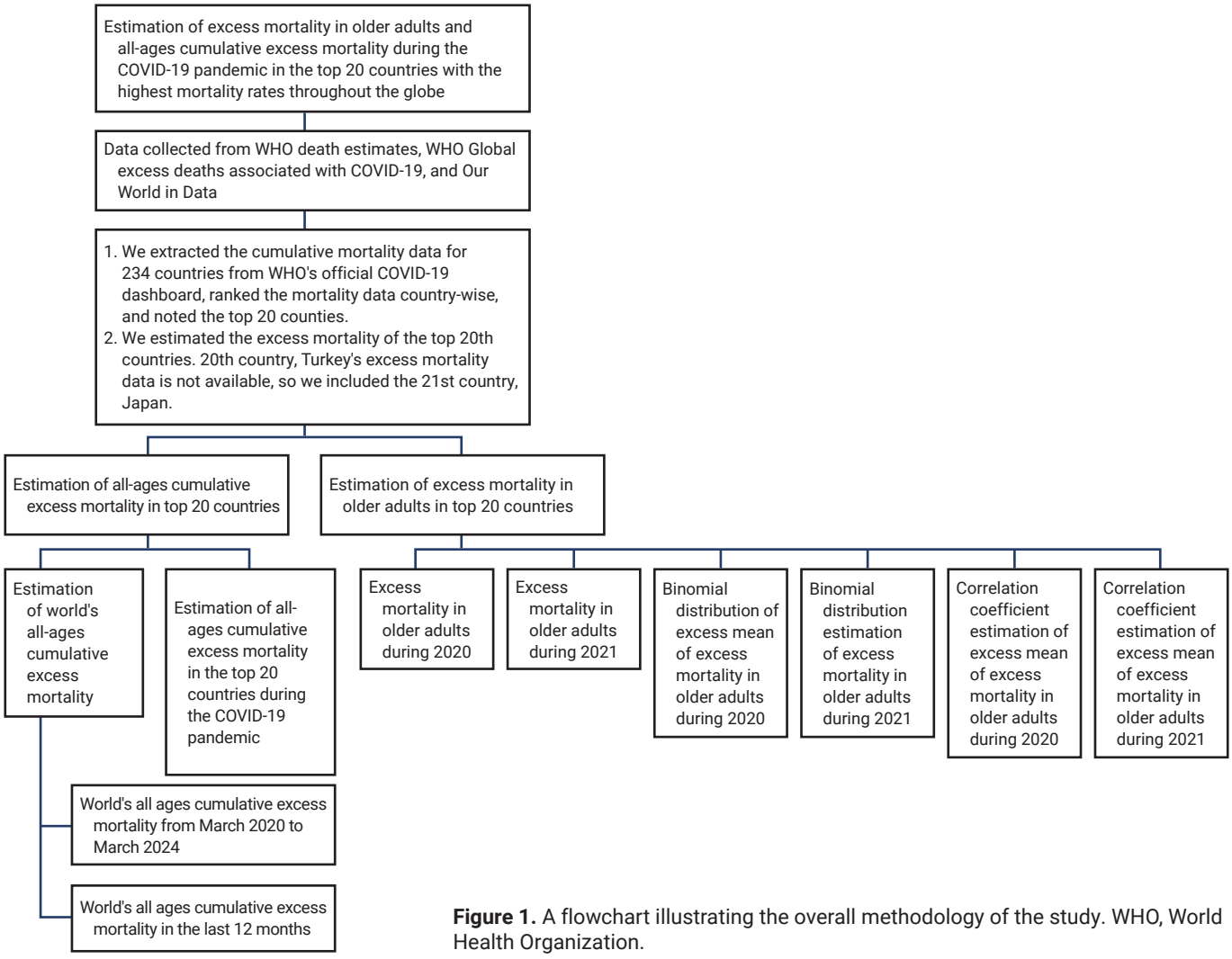

Figure 1. A flowchart illustrating the overall methodology of the study. WHO, World Health Organization.

1), Iran (Figure S2B), Colombia (Figure S2C, Supplementary Material 1), Argentina (Figure S2D, Supplementary Material 1), China (Figure S2E, Supplementary Material 1), Spain (Figure S2F, Supplementary Material 1), Poland (Figure S2G, Supplementary Material 1), Ukraine (Figure S2H, Supplementary Material 1), South Africa (Figure S2I, Supplementary Material 1), and Japan (Figure S2J, Supplementary Material 1).

The central estimate for COVID-19 deaths in the USA was 406.14 per 100,000 people, with an upper bound of 446.79 and a lower bound of 481.78. The confirmed COVID-19 death rate in the USA was 344.18 per 100,000 people at this point. In Brazil, the central estimate stood at 440.12 per 100,000 people, with an upper bound of 448.78 and a lower bound of 432.84. The confirmed COVID-19 death rate in Brazil was 326.9 per 100,000 people at this point. Similarly, India's central estimate was 506.54 per 100,000 people, with an upper bound of 726.17 and a lower bound of 195.07. The confirmed COVID-19 death rate in India was 37.64 per 100,000 people during this period. Russia's central estimate stands at 1,125.13, with an upper bound of 1,318.91 and a lower bound of 861.34. During this period, Russia's confirmed COVID-19 death rate was 277.63 per 100,000 people. Similarly, Japan's central estimate was 1,125.13, with an upper bound of 1,318.91 and a lower bound of 861.34.

Excess Mortality in Older Adults in the Top 20 Countries

Excess mortality in older adults during 2020

Excess mortality among older men in 2020 was recorded in the top 20 countries with the highest mortality rates, specifically within the age groups of 65–74, 75–84, and >85 (Table S1). We observed the highest mean excess mortality in India for the age groups of 65–74 and >85, with figures of 176,308 and 117,279, respectively. Conversely, the lowest mean excess mortality was noted in Japan for the age group >85,

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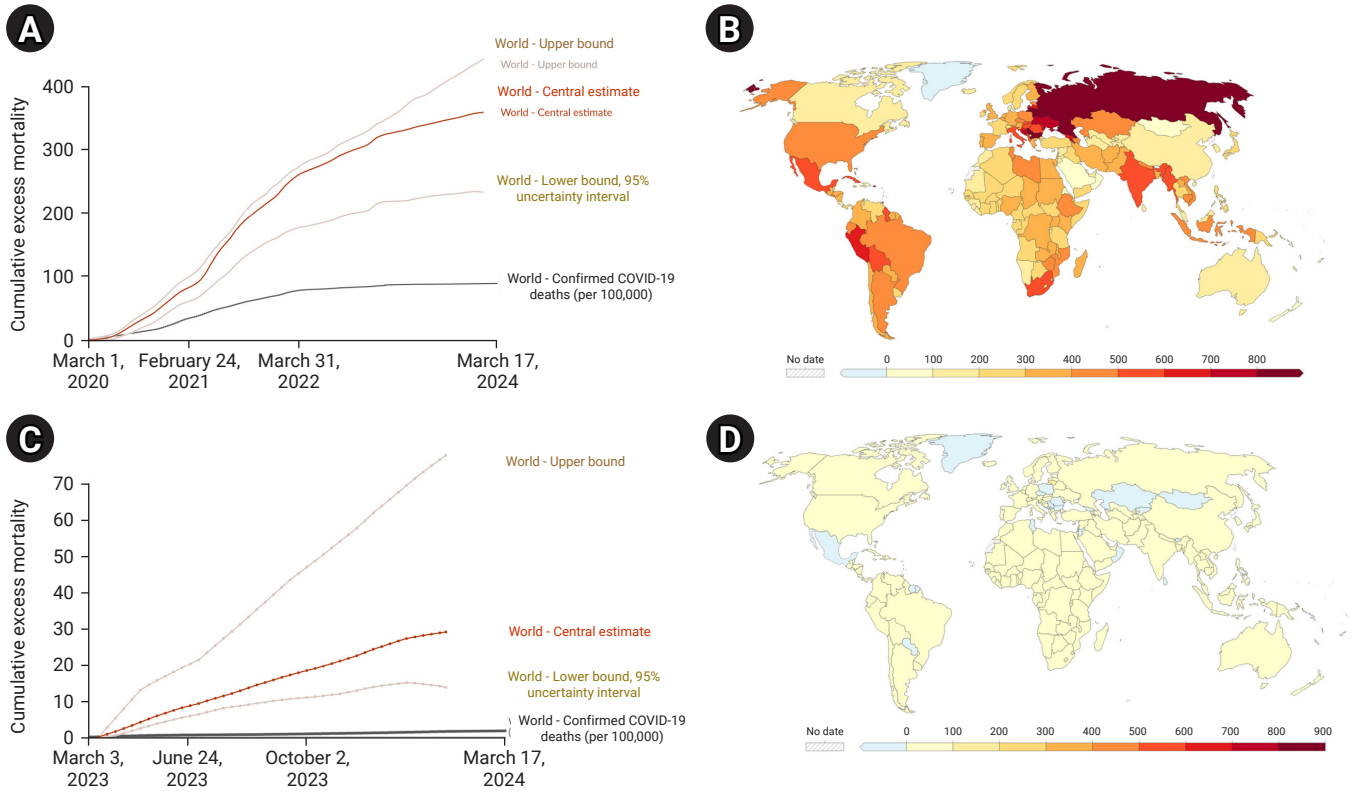

Figure 2. Plot and map showing worldwide cumulative excess mortality for all ages: (A) the plot depicting cumulative excess mortality from March 2020 to March 2024; (B) the map illustrating cumulative excess mortality from March 2020 to March 2024; (C) the plot depicting cumulative excess mortality over the last 12 months; (D) the map illustrating cumulative excess mortality over the last 12 months.

recorded at –450.

In this study, we observed the highest ACM (age-specific mortality count) of excess mortality in China within the age groups of 65–74 and 75–84, with counts of 1,538,960 and 1,530,890, respectively. Conversely, the lowest ACM mean of excess mortality was recorded in South Africa among individuals aged over 85, totaling 15,952.

We observed the highest mean expected deaths from excess mortality in China within the age groups of 65–74 and 75–84, with figures reaching 1,531,352 and 1,529,186, respectively. Conversely, the lowest mean expected deaths from excess mortality were recorded in South Africa for the age group of >85, totaling 12,074.

Excess mortality among older women in 2020 was documented in the top 20 countries with the highest mortality rates, where the average expected deaths, ACM, and average excess deaths were calculated for the age groups 65–74, 75–84, and >85 (Table S2). We observed the highest average excess deaths in America within the >85 age group, totaling 105,646. Conversely, the lowest average excess deaths were recorded in China and Japan for the same age group, with figures of –54,696 and –47,796, respectively.

In this study, we observed the highest average ACM of excess mortality in China within the age groups of 65–74 and 75–84, with figures of 1,228,542 and 1,172,953, respectively. Meanwhile, the lowest average ACM of excess mortality was recorded in South Africa among individuals aged over 85, totaling 32,695. We observed the highest mean expected deaths from excess mortality in China within the age groups of 75–84 and >85, with values of 1,266,743 and 1,227,662, respectively. Conversely, the lowest mean expected deaths from excess mortality were recorded in Peru within the 65–74 age group, totaling 15,557.

However, we observed a significantly higher excess mortality in women over the age of 85 among older adults in 2020.

Excess mortality in older adults during 2021

In 2021, excess mortality among older men was recorded in the top 20 countries with the highest mortality rates, specifically within the age groups of 65–74, 75–84, and over 85, as shown in Table S3. Our analysis revealed that India had the highest mean excess deaths in the 65–74 age group, totaling 588,931. Conversely, China reported the lowest mean excess deaths in the age groups of 75–84 and 65–74, with

figures of –100,092 and –32,014, respectively.

In this study, we observed the highest average ACM of excess mortality in China within the 65–74 age group, totaling 1,733,563. Conversely, the lowest average ACM of excess mortality was recorded in South Africa among individuals aged over 85, with a total of 16,801.

Similarly, we found the highest expected deaths mean for excess mortality in China in the age groups of 65–74 and 75–84, which were 1,578,937 and 1,546,334. Similarly, we found the lowest expected deaths mean for excess mortality in South Africa in the age groups of >85, which was 11,722.

We observed the highest mean expected deaths from excess mortality in China within the age groups of 65–74 and 75–84, with figures reaching 1,578,937 and 1,546,334, respectively. Conversely, the lowest mean expected deaths from excess mortality were recorded in South Africa for the age group of >85, totaling 11,722.

Excess mortality among older women in 2021 was documented in the top 20 mortality countries, where the mean expected deaths, ACM, and mean excess deaths were calculated for the age groups 65–74, 75–84, and >85 (Table S4). We observed the highest mean excess deaths in India within the age groups 65–74 and 75–84, totaling 557,140 and 401,395, respectively. Conversely, the lowest mean excess deaths were recorded in China and Japan. Specifically, in China, the figures for the age groups 65–74 and 75–84 were –26,055 and -78,783, respectively. In Japan, the age group >85 showed a result of –29,934.

We observed the highest average ACM of excess mortality in India and China. In India, the age groups 65–74 and 75–84 had excess mortality figures of 1,515,705 and 1,321,884, respectively. In China, the corresponding figures for the age groups 75–84 and >85 were 1,195,811 and 1,399,316. Conversely, the lowest average ACM of excess mortality was recorded in Spain within the 65–74 age group, totaling 21,167.

We observed the highest mean expected deaths from excess mortality in China within the age groups of 75–84 and >85, with values of 1,263,073 and 1,258,550, respectively. Conversely, the lowest mean expected deaths from excess mortality were recorded in Peru for the age group of 65–74, totaling 16,092.

We also observed a significantly higher excess mortality in women over the age of 85 among older adults in 2021.

Binomial distribution of the mean value of excess mortality in older adults during 2020

The binomial distribution is commonly utilized in biological systems. This model, given a set of parameters, calculates the probability of 1 of 2 possible outcomes and is particularly useful in analyzing population distributions. In our study, we developed various binomial distribution models to represent the average number of excess deaths among older men in 3 age groups: 65–74 (Figure 3A), 75–84 (Figure 3B), and over 85 (Figure 3C) during the year 2020. These models are depicted through histograms that display the distribution of the average excess deaths. Our analysis using the binomial distribution models revealed that the distributions approximated a normal curve for the average excess deaths among these groups of older men. Specifically, we created a model for the 65–74 age group, showing that the histograms were negatively skewed (Figure 3A). A similar approach was taken for the 75–84 age group, which also demonstrated negatively skewed histograms (Figure 3B). The model for the oldest group (over 85) indicated a similar negative skew in the histograms (Figure 3C).

Similarly, we developed binomial distribution models for the mean excess deaths from excess mortality among older women aged 65–74. These models showed that most histograms were negatively stacked (Figure 3D). Similarly, we depicted the binomial distribution models for the mean excess deaths among women aged 75–84, which also showed histograms that were predominantly negatively stacked, although 1 histogram bar was positively stacked (Figure 3E).

The third age group of older adults (those over 85) demonstrated both positive and negative attributes (Figure 3F).

In the context of a binomial distribution, smoothing the lines of a discrete probability distribution can enhance visualization, especially when dealing with large sample sizes. The binomial distribution is, by nature, discrete. It uses a Bernoulli distribution to model the outcomes, representing a random variable with 2 possible results. Each independent experiment in a series may result in 2 possible outcomes, which remain consistent across events. This series of experiments is referred to as Bernoulli's trials [17,18]. Depending on the sample size and the probabilities involved, various methods can be used to smooth lines in a binomial distribution. These include normal approximation, kernel density estimation, or Poisson approximation. For large samples, the most commonly used method is the normal approximation with continuity correction. This approach provides a continuous, smooth curve that closely approximates the underlying binomial distribution.

Binomial distribution of the mean value of excess mortality in older adults during 2021

We employed a binomial distribution model to analyze the mean excess deaths among older men across 3 age groups: 65–74 (Figure 4A), 75–84 (Figure 4B), and over 85 (Figure 4C) during the year 2021. Initially, the model for the 65–74

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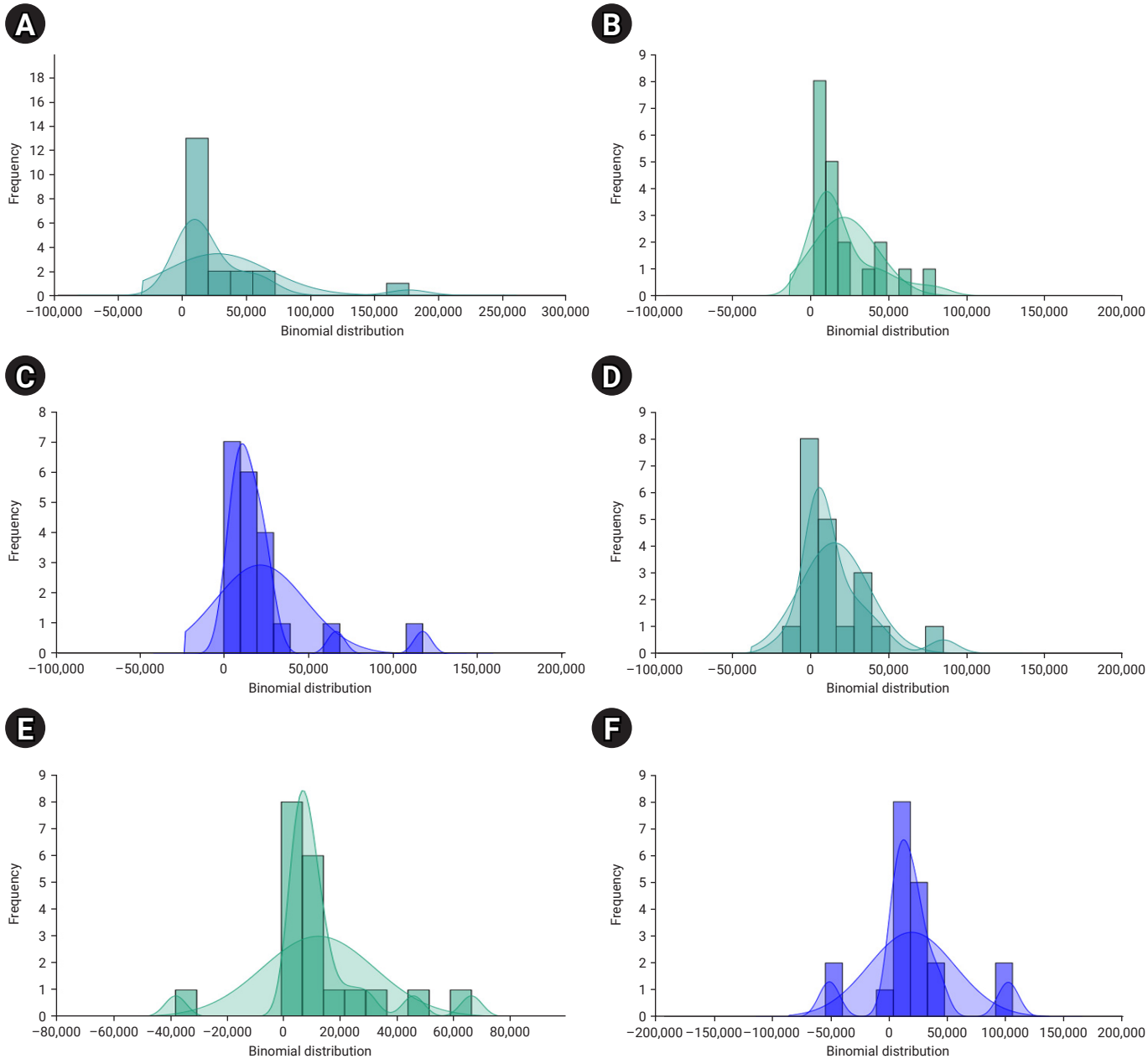

Figure 3. The binomial distribution of the mean excess mortality in older adults during 2020, categorized by age and sex: (A) men aged 65–74, (B) men aged 75–84, (C) men aged 85 or older, (D) women aged 65–74, (E) women aged 75–84, and (F) women aged 85 or older.

age group revealed that, except for 1 positively stacked bar, all histogram bars were negatively stacked (Figure 4A). Similarly, the model for the 75–84 age group showed that all histogram bars were negatively stacked (Figure 4B). For the oldest age group, those over 85, the analysis again indicated that all histogram bars were negatively stacked (Figure 4C).

Similarly, we developed binomial distribution models for the mean excess deaths from excess mortality among older women aged 65–74. This model showed that all histogram bars were negatively stacked (Figure 4D). We also conducted binomial distribution models for the mean excess deaths among women aged 75–84. All histogram bars were negatively stacked, except for 2 bars that were positively stacked (Figure 4E).

The third age group of older adults (over 85) was predominantly represented by negative values, except for 1 bar that was positively stacked (Figure 4F).

The binomial distribution models consistently revealed 2

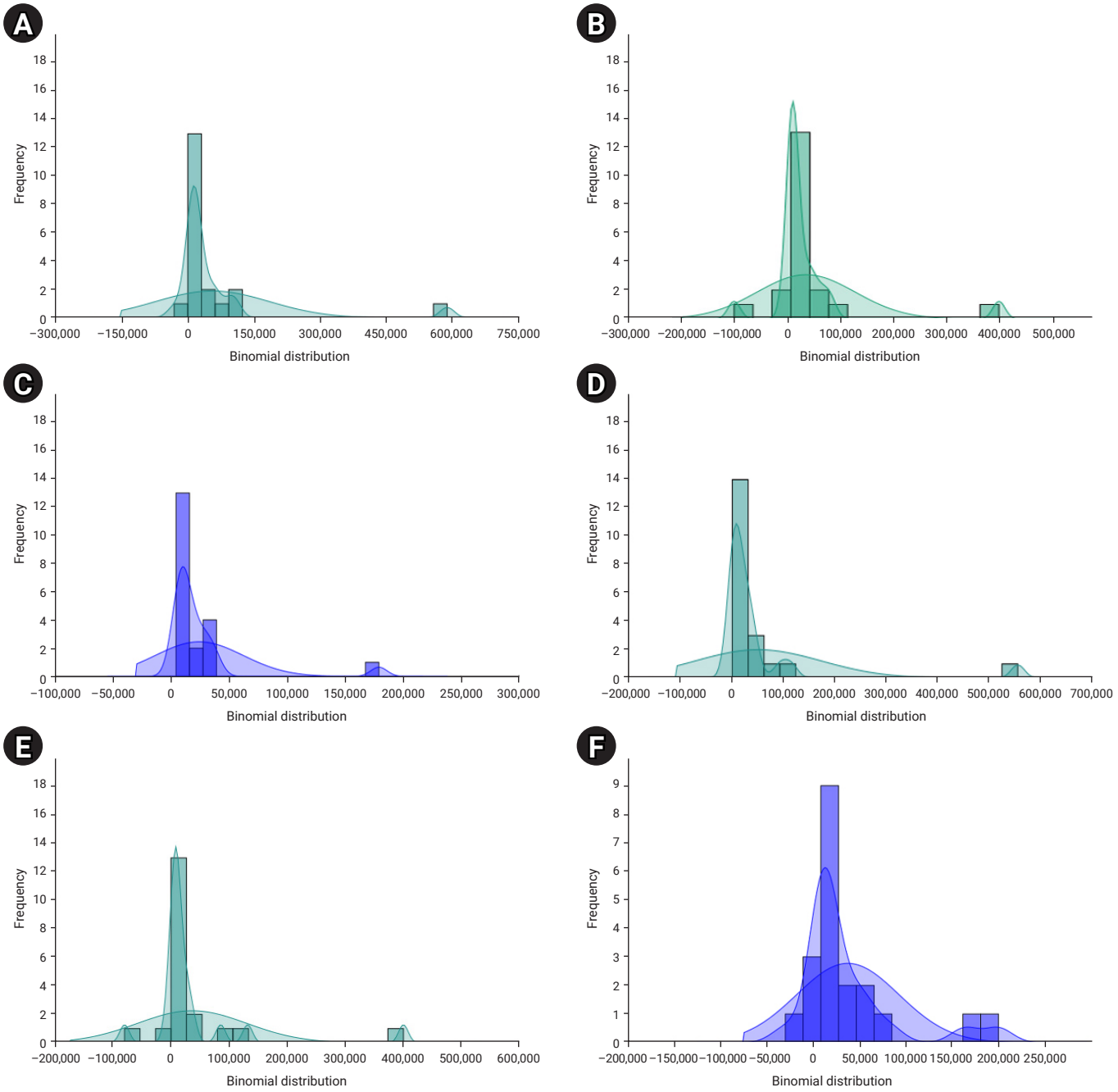

Figure 4. The binomial distribution of the mean excess mortality in older adults during 2021, categorized by age and sex: (A) men aged 65–74, (B) men aged 75–84, (C) men aged 85 and older, (D) women aged 65–74, (E) women aged 75–84, and (F) women aged 85 and older.

distinct classes of data.

Correlation coefficient estimation for excess mortality in older adults during 2020

The study analyzed the correlation coefficient of the mean excess deaths from excess mortality among older adult men and women. We calculated the correlation coefficients for men aged 65–74 (Figure 5A), 75–84 (Figure 5B), and over 85 (Figure 5C) during 2020. For men aged 65–74, the correlation coefficient of the mean excess deaths was 0.7628 (Figure 5A). For the 75–84 age group, the correlation coefficient was 0.8916 (Figure 5B). Similarly, for men aged over 85, the correlation coefficient was 0.7791 (Figure 5C).

Using the mean excess deaths as a measure of excess

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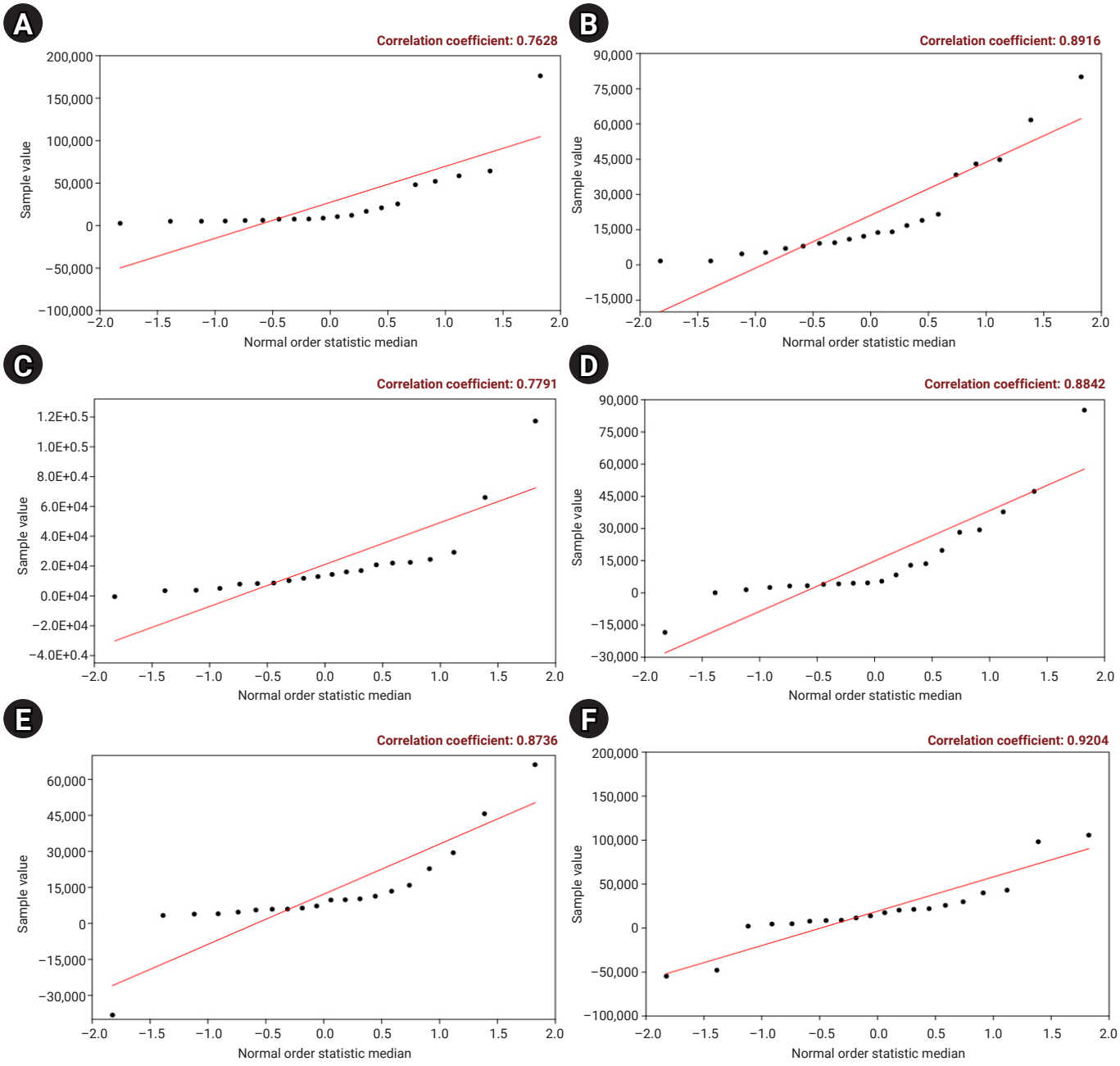

Figure 5. Correlation coefficients for the mean excess mortality among older adults in 2020, categorized by age and sex: (A) men aged 65–74, (B) men aged 75–84, (C) men aged 85 and older, (D) women aged 65–74, (E) women aged 75–84, and (F) women aged 85 and older.

mortality among older women, we estimated the correlation coefficients for the age groups 65–74 (Figure 5D), 75–84 (Figure 5E), and >85 (Figure 5F) during 2020. The mean excess deaths for women aged 65–74 indicate a correlation coefficient of 0.8842 (Figure 5D). Similarly, for women aged 75–84, the correlation coefficient is 0.8736 (Figure 5E). For the age group >85, the correlation coefficient is 0.9204 (Figure 5F).

The estimation of the correlation coefficients indicated a positive linear correlation among all variables.

Figure 5 illustrates the correlation coefficient of the mean excess deaths from excess mortality in older adults (both male and female categories) during 2020. This study examines the relationship between age groups and mortality, indicating that a strong positive correlation would imply an increase in mortality as age increases, which could inform preventative healthcare strategies.

The correlation coefficient is fundamental for identifying and quantifying linear relationships between 2 variables. However, it requires careful interpretation, especially in recognizing its limitations to linear relationships and the potential for other variables or outliers to skew the perceived strength of a relationship. Understanding the direction, strength, and context of the correlation enables researchers and decision-makers to draw meaningful conclusions. Consequently, our correlation coefficient model indicates that excess mortality in older adults (Figure 5) is significant.

Correlation coefficient estimation for excess mortality in older adults during 2021

The study analyzed the correlation coefficient of the mean excess deaths from excess mortality among older men and women during 2021. We calculated the correlation coefficients

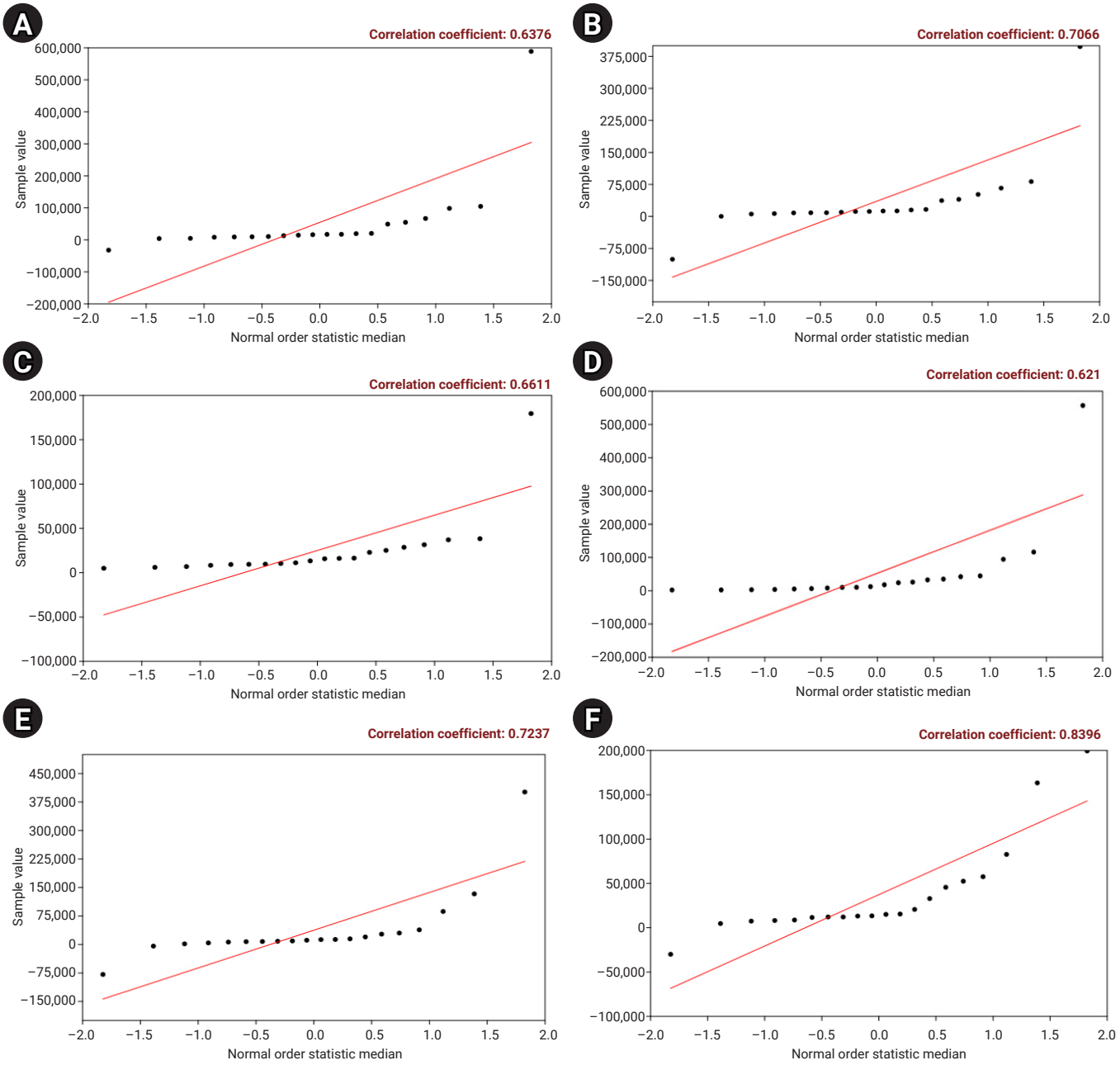

Figure 6. Correlation coefficient of the mean excess deaths in older adults during 2021, categorized by age and sex: (A) men aged 65–74, (B) men aged 75–84, (C) men aged 85 or older, (D) women aged 65–74, (E) women aged 75–84, and (F) women aged 85 or older.

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for the mean excess deaths from excess mortality among older men in the age groups of 65–74 (Figure 6A), 75–84 (Figure 6B), and over 85 (Figure 6C) during 2021. For men aged 65–74, the correlation coefficient of the mean excess deaths from excess mortality was 0.6376 (Figure 6A). For the 75–84 age group, the correlation coefficient was 0.7066 (Figure 6B). Similarly, for men aged over 85, the correlation coefficient was 0.6611 (Figure 6C).

Using the mean excess deaths as a measure of excess mortality among older women, we estimated the correlation coefficients for the age groups 65–74 (Figure 6D), 75–84 (Figure 6E), and >85 (Figure 6F) during 2021. The mean excess deaths for women aged 65–74 yielded a correlation coefficient of 0.621 (Figure 6D). For women aged 75–84, the correlation coefficient was 0.7237 (Figure 6E). Similarly, for women aged over 85, the correlation coefficient was 0.8396 (Figure 6F).

The estimation of the correlation coefficient indicated a positive linear correlation among all variables.

Like Figure 5, Figure 6 illustrates the correlation coefficient of excess deaths, indicating excess mortality among older adults (both male and female) during 2021. Thus, our correlation coefficient model for excess deaths, representing excess mortality in older adults in 2021, is also significant (Figure 6).

Discussion

Our study is the first, to our knowledge, to evaluate the excess mortality of older adults worldwide during the pandemic period. We divided the older population into 3 age groups: 65–74, 75–84, and above 85, to assess their excess mortality. Previous research has explored excess mortality in Sweden during the first wave of the pandemic by level of care [13]. In contrast, our study dealt with global excess mortality. We examined cumulative mortality data from 234 countries using the WHO's official COVID-19 dashboard. We then categorized the mortality data by country and identified the top 20 countries with the highest rates. In these countries, we estimated the excess mortality among older adults. Our analysis covered 2 complete years of the pandemic, from early 2020 to the end of 2021, focusing on 3 key parameters: average ACM, expected deaths, and excess deaths. Additionally, we developed 2 statistical models using the mean excess deaths: a binomial distribution model and a correlation coefficient model. Concurrently, we analyzed all-age excess mortality globally, specifically in these top 20 countries. Several researchers have studied excess deaths during the pandemic, focusing on specific counties or regions [19–24]. Our study, however, estimates excess mortality among older adults in 3 age groups and all-age excess mortality during the COVID-19 pandemic in the top 20 countries with the highest mortality rates worldwide. Thus, our research provides a comprehensive overview of the impact of the pandemic on global mortality rates.

Excess mortality accounts for all deaths and includes factors both directly and indirectly related to it. Directly associated factors encompass the impact of the virus, while indirect factors include disruptions to travel and essential health services, among others. In this context, WHO data on excess mortality encompasses ACM. However, the absence of ACM data for many countries complicates the straightforward evaluation of excess mortality globally. The WHO typically collects mortality data annually or over longer intervals. In our analysis of mortality data across 234 countries, it was noted that WHO does not provide excess mortality data for Turkey, which ranks 20th. Therefore, we included Japan, which ranks 21st, in our datasheet [14]. Msemburi et al. [10] faced similar challenges due to the unavailability of ACM data in many countries. They devised 3 categories of models: countries with complete ACM data for the entire period analyzed (such as the USA), countries with mixed ACM data (such as India), and countries lacking ACM data (such as Pakistan and Ethiopia). In our study, we have divided the ACM excess mortality of older adults into 3 age groups: 65–74, 75–84, and above 85 years, with ACM recorded in all instances (Tables S1–S3).

Figures 2A and B illustrate global excess mortality, as presented by Our World in Data for the years 2020 to 2024. Concurrently, Figures 2B and C focus on the world's excess mortality over the past 12 months. It has been observed that, with the exception of the last 12 months, excess mortality during the pandemic was more pronounced. However, excess mortality worldwide in the last 12 months has been lower. Figure 2B highlights that significant excess mortality occurred in Russia and moderate excess mortality was observed in Mexico, India, Peru, and other countries. The COVID-19 Excess Mortality Collaborators have estimated excess deaths at various national and regional levels due to COVID-19. At the country level, the most cumulative excess deaths were recorded in the USA (1.13 million), Russia (1.07 million), India (4.07 million), Indonesia (736,000), Brazil (792,000), Pakistan (664,000), and Mexico (798,000). Regionally, South Asia, the Middle East, Eastern Europe, and North Africa experienced notably higher excess deaths due to the pandemic.

Our study on excess deaths among older adults during the pandemic made several key observations: First, the research demonstrated that COVID-19 has led to significant excess mortality among older adults across 20 countries. We analyzed excess deaths in these countries by examining 3 components: excess mean, ACM mean, and expected mean. In most cases, these components showed positive values, although negative

values were observed in a few instances. It was observed that the impacts of COVID-19 led to notable excess mortality in older adults across these 3 categories in the 20 regions studied. Second, the study revealed higher excess mortality among women over the age of 85, suggesting that the impact of the SARS-CoV-2 virus is particularly severe in older women. This finding aligns with the observations made by Kontopantelis et al. [25], who also reported increased excess mortality in this demographic. However, their analysis during the first wave was limited to overall age groups in Wales and England. Third, our models indicate trends of excess mortality in these 20 countries, highlighting both the direct and indirect effects of COVID-19 on the health of older adults. Several studies have attempted to quantify the excess mortality attributable to the COVID-19 pandemic [9,25,26], with some specifically focusing on older adults and identifying underlying causes [13,27,28]. Our findings are consistent with these global trends, with only a few exceptions.

One study analyzed the age profiles (single year of age) for England, Wales, and the USA, concluding that each COVID-19 variant exhibits a distinct mortality age profile [29].

The age profile of COVID-19 mortality varies with different virus variants, influenced by factors such as immune response, comorbidities, and vaccination status. The study highlights a crucial observation: each COVID-19 variant distinctly impacts various age groups, particularly in terms of mortality rates in countries like England, Wales, and the USA.

2020: Mortality due to Wuhan+Alpha Variants

In 2020, the initial Wuhan strain and the Alpha variant accounted for the majority of COVID-19-related deaths [30]. During this time, the highest mortality rates were observed in older adults, particularly those aged 65 and older. This age group exhibited a weaker immune response, and the presence of pre-existing conditions such as cardiovascular disease, diabetes, and respiratory issues increased their vulnerability [31]. In England and Wales, the older population, especially those residing in care homes or suffering from multiple comorbidities, faced significant mortality rates. This was prior to the implementation of extensive vaccination programs, leaving older adults particularly prone to severe outcomes [25].

2021: Mortality due to Alpha+Delta Variants

In 2021, while the Alpha variant was still circulating, the Delta variant emerged as a more transmissible and aggressive strain. Delta notably had a more pronounced impact on younger populations compared to earlier variants. Concurrently, there was a slight shift in the age profile for mortality, with an increase in deaths among individuals under 65, although older adults continued to be at high risk.

Delta disproportionately affected younger populations because initial vaccination campaigns prioritized older and more vulnerable groups [32]. By the time Delta emerged as a prevalent variant, many younger adults remained unvaccinated, increasing their susceptibility. Furthermore, Delta's heightened transmissibility and its potential to cause severe illness resulted in increased hospitalization rates among middle-aged and younger adults [33,34].

The unique age profiles associated with illness or mortality for each variant can be explained by considering the characteristics of the variant, the immune responses across different age groups, and the initial focus of vaccine rollouts on protecting older adults and high-risk individuals.

We have analyzed excess mortality by examining ACM, expected deaths, excess deaths, and adverse excess deaths in accordance with WHO guidelines. Other researchers have also attempted to analyze excess mortality from this perspective [1,35–37]. Consequently, our analysis holds significant importance. Some researchers present excess mortality as a percent increase over the number of deaths in 2019. Calculating excess mortality as a percentage of 2019 deaths, however, offers a more nuanced perspective, providing a clearer understanding of the pandemic's relative impact. This approach accounts for demographic variations and can alter the rankings, frequently placing countries with younger populations or less robust healthcare systems higher on the list [38]. Additionally, it underscores how specific variants, such as Delta, can disproportionately impact younger demographics, leading to significant increases in mortality that may not be as apparent when only absolute death counts are considered.

Measuring excess mortality as a percentage increase over the number of deaths in 2019 significantly alters the ranking of countries in terms of the pandemic's impact, particularly when compared to using absolute numbers of excess deaths. This approach accounts for variations in population size, age demographics, and baseline mortality rates, facilitating a more uniform comparison [9,39]. For instance, countries like the USA may exhibit a relatively moderate percentage increase in excess mortality, partly because the older, more vulnerable segments of the population received vaccinations early [40]. Our study, however, calculates excess mortality by analyzing ACM, expected deaths, and adverse excess deaths in accordance with WHO guidelines. This method is considered 1 of the standard approaches, which is why we adhere to the WHO procedure.

The age distribution of COVID-19 fatalities is critical in shaping public health strategies, including lockdowns and vaccination drives. By focusing on the age groups most

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at risk of severe outcomes, public health officials can use resources more efficiently, minimize disruptions to society, and potentially save more lives. At the onset of the pandemic, older adults were significantly more likely to suffer from severe illness and death. This disparity led to age-specific lockdown measures, imposing stricter restrictions on older adults while allowing younger, healthier individuals more freedom due to their lower risk [41]. Such measures, including targeted lockdowns or isolation for those at higher risk, were particularly relevant in countries like Italy, which have substantial older populations and experienced considerable losses in care homes. Strategically isolating older adults while granting younger people more liberties to sustain economic activities could help reduce both mortality and broader societal damage [42].

Young adults and children, while less susceptible to fatal outcomes, still contributed to the spread of the disease. Consequently, age-specific restrictions might have differed based on the national context, enabling younger individuals to resume work and educational activities with appropriate precautions. For instance, some countries considered protecting older adults and other vulnerable groups while permitting younger, working-age adults to continue economic activities. However, this approach was not broadly adopted due to uncertainties regarding the transmission dynamics at the time [43,44].

It has been observed that there is a correlation between the extent of COVID-19 testing and the number of reported deaths. Research indicates that the number of tests conducted per population is directly related to the reported death counts [45–47]. Notably, regions conducting fewer tests tend to report fewer deaths.

Exploration of Gender-Specific Vulnerabilities

The findings indicate a disproportionately high mortality rate among older women due to the COVID-19 pandemic, particularly in those aged 85 and older. This observation is crucial, yet further investigation into the underlying causes of this trend is necessary. Exploring potential gender-specific vulnerabilities, such as biological factors, social conditions, or differences in access to healthcare, could offer more profound insights into why this particular demographic is more severely impacted by the pandemic. Therefore, our study is essential for informing public health decisions. The insights gained will assist policymakers in developing targeted strategies for the care and protection of older adults.

Strengths of This Study

This study may represent the first investigation into excess mortality among older adults. It offers a comprehensive overview of excess mortality in this demographic, utilizing WHO data and Our World in Data for 20 countries. The findings depict the state of patient care during the COVID-19 pandemic in these countries and identify patterns of excess mortality among the most vulnerable groups. The study reveals that the pandemic poses a significant threat to older adults, potentially overwhelming healthcare systems in certain countries. It clearly demonstrates the increased risk of mortality for older adults, which has escalated over the course of 2 years in the pandemic.

Limitations

The study has several limitations. First, it was conducted using comprehensive data analysis, which means our estimates are dependent on the scope and availability of the data. Second, due to the reliance on available data, the research cannot determine the causes of increased mortality among women over 85 years old. Third, although various modeling strategies are closely related, we utilized data from WHO and Our World in Data. Consequently, our calculations of global excess mortality and the excess mortality in these 20 countries for all age groups are based on Our World in Data, while we rely on WHO data to calculate different components of excess mortality, such as excess mean, ACM mean, and the expected mean for older adults. Fourth, our analysis focused on 20 countries, examining excess mortality during the pandemic period without extending the analysis to other countries.

Issues regarding methodology have occasionally been raised during the calculation of excess mortality. Concurrently, conflicts in this area have also been reported [48–51]. However, in this analysis, we utilize the WHO data and the methodologies outlined by Our World in Data for calculating excess mortality.

Future Directions

Further research is required using the excess mortality data of older adults from around the world. Our future studies will focus on this data. Additionally, it is necessary to estimate the excess mortality among older adults throughout the pandemic period, utilizing the complete data sets from 2020, 2021, 2022, and 2023. We will concentrate on analyzing these data for the specified years. Furthermore, we aim to develop predictive models for forecasting excess mortality among older adults in any forthcoming pandemic.

Conclusion

Our estimates of excess mortality during this crisis period suggest that the impact on mortality has been particularly severe. It is crucial for the global community to monitor excess

mortality among older adults using reliable sources to discern patterns. In this study, we analyze excess mortality data from the WHO, which may reveal trends in the excess mortality of older adults during a pandemic. Understanding these patterns from our comprehensive analysis will aid in the development of public healthcare policies tailored for older adults, potentially mitigating the effects of future pandemics. This understanding will also inform the design of post-pandemic healthcare policies and facilitate a gap analysis of emergency medical care resources related to ACM. Ultimately, our study will contribute to the enhancement of emergency medical care resources.

Supplementary Material

Supplementary Material 1. Comprehensive definitions of all-cause mortality, expected deaths, excess deaths, and negative excess deaths; **Figure S1.** Excess mortality across all ages in the top 20 mortality countries. This figure includes the first 10 countries: (A) USA, (B) Brazil, (C) India, (D) Russian Federation, (E) Mexico, (F) UK, (G) Peru, (H) Italy, (I) Germany, (J) France; **Figure S2.** Excess mortality across all ages in the top 20 mortality countries. This figure includes the remaining 10 countries: (A) Indonesia, (B) Iran, (C) Colombia, (D) Argentina, (E) China, (F) Spain, (G) Poland, (H) Ukraine, (I) South Africa, (J) Japan; **Table S1.** Excess mortality, expected deaths mean, ACM mean, and excess deaths mean in older men (age groups 65–74, 75–84, and >85) during 2020; **Table S2.** Excess mortality, expected deaths mean, ACM mean, and excess deaths mean in older women (age groups 65–74, 75–84, and >85) during 2020; **Table S3.** Excess mortality, expected deaths mean, ACM mean, and excess deaths mean in older men (age groups 65–74, 75–84, and >85) during 2021; **Table S4.** Excess mortality, expected deaths mean, ACM mean, and excess deaths mean in older women (age groups 65–74, 75–84, and >85) during 2021. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0186.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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Availability of Data
Data are already available in the manuscript.

Authors' Contributions
Conceptualization: CC; Data curation: CC; Formal analysis: MB, SSL; Investigation: CC; Methodology: CC; Project administration: CC; Resources: CC, MB; Software: CC, MB; Supervision: CC; Validation: MB, SSL; Visualization: MB, SSL; Writing–original draft: CC; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Effectiveness of a brain exercise program using game-based cognitive enhancement to reduce mild cognitive impairment among older adults in Pathum Thani Province, Thailand: a quasi-experimental study

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ABSTRACT

Objectives: Mild cognitive impairment (MCI) is prevalent among older adults and may progress to dementia. This study evaluated the effectiveness of a game-based brain exercise program in reducing MCI among older adults.

Methods: A quasi-experimental study was conducted with 2 groups of older participants in Pathum Thani Province, Thailand. A total of 96 individuals with Thai mental state examination (TMSE) scores between 12 to 23, indicating MCI but no dementia diagnosis, were recruited. Using multi-stage sampling, participants were divided into an intervention group ($n=48$) and a control group ($n=48$). The intervention group participated in a 6-week game-based brain exercise program, while the control group received a self-administered brain exercise manual. Face-to-face interviews assessed outcomes at baseline, post-intervention, and 3-month follow-up. Data were analyzed using descriptive statistics and repeated-measures analysis of variance.

Results: Significant differences were observed in mean TMSE scores and MCI knowledge between the intervention and control groups at the 3-month follow-up ($p<0.001$). The intervention group showed significant increases in TMSE scores and MCI knowledge post-intervention and at 3-month follow-up ($p<0.001$).

Conclusion: The findings suggest that a game-based brain exercise program can improve cognitive function in older adults. Healthcare professionals can implement such programs to reduce MCI by addressing planning, management, and related issues in the future.

Keywords: Aged; Brian exercise program; Cognitive dysfunction

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Introduction

Thailand's population of older adults has grown rapidly due to improvements in the public health system [1]. Related health issues have become a significant concern, prompting the government to implement measures to enhance older adults' quality of life [2]. These strategies are integrated into the National Economic and Social Development Plan, which includes healthcare services and social welfare programs for older adults [3].

Dementia is a syndrome characterized by the loss of brain function, leading to declines in memory, learning, personality, behavior, language, calculation, comprehension, creativity, concentration, and intelligence [4]. Symptoms include forgetfulness and difficulty recalling recent events. Brain function deteriorates gradually, eventually affecting daily life. While dementia can occur at any age, it is most common among older adults [5,6]. According to the Department of Health, dementia is the fifth leading cause of death among individuals aged 65 and over. Over 1 million older adults in Thailand suffer from dementia, with a higher prevalence among women. The condition increases with age, affecting 7.1% of those aged 60 to 69, 14.7% of those aged 70 to 79, and 32.5% of those aged 80 and above [7].

Mild cognitive impairment (MCI) is considered an early stage of dementia [8]. Its prevalence varies depending on population characteristics, ranging internationally from 21.5% to 71.3% [9]. In Thailand, MCI prevalence is reported at 18.1% to 33.9%, with rates of 18.7%, 28.5%, 26.4%, and 33.9% among individuals aged 65 to 69, 70 to 74, 75 to 79, and 80 and above, respectively [10]. Risk factors for MCI include non-modifiable factors such as genetics, age, gender, and a history of brain injury, as well as modifiable factors like education, exercise, nutrition, chronic disease management, and avoiding smoking and excessive alcohol consumption [11,12].

Strategies to reduce MCI risk and promote brain capacity include learning new skills, engaging in brain-stimulating activities, regular exercise, stress management, and maintaining mental well-being [13]. Previous interventions for MCI have included memory training, cognitive stimulation therapy, exercise programs, nutrition interventions, social interaction support, and the use of applications and devices for daily routine management and memory reminders [14]. Game-based brain exercise programs are an innovative approach to improving cognitive function in MCI. These programs aim to stimulate brain activity, enhance neuroplasticity, and engage cognitive functions in an enjoyable and interactive way. Games are designed to target multiple cognitive domains, such as memory, attention, executive function, and problem-solving. Research suggests that game-based programs are a promising intervention for preventing MCI and slowing its progression [15,16].

HIGHLIGHTS

- Mild cognitive impairment is recognized as an early stage of dementia.
- A game-based brain exercise program was developed based on cognitive training research. These activities were simple, culturally relevant, and progressively challenging to maintain engagement and motivation among older participants. The games targeted multiple cognitive functions, including memory, attention, executive function, and problem-solving.
- The results suggest that the game-based brain exercise program has the potential to improve cognitive function in older adults.

This study's brain exercise program was developed using the knowledge, attitude, and practice (KAP) model [17], which educates participants about cognitive health, the risks of cognitive impairment, and the benefits of cognitive exercises, particularly game-based activities. The program also incorporates self-efficacy theory to boost participants' confidence and commitment to engaging in cognitive exercises [18]. The study addresses a gap in research, as Thailand's growing population of older adults, including in Pathum Thani, increases the likelihood of MCI development [19]. While cognitive enhancement programs have been studied globally, there is limited localized research on game-based interventions tailored to the cultural, social, and environmental context of older individuals in Thailand, particularly in Pathum Thani [20]. Region-specific interventions are essential to address the unique demographic and lifestyle factors of this population [21]. In summary, games provide an engaging, enjoyable, and potentially effective method for improving cognitive functions in older adults [17]. However, there is a lack of research emphasizing preventive measures through early interventions. This program aims to enhance memory, attention, and problem-solving skills by engaging participants in stimulating mental activities through games, thereby slowing cognitive decline.

Materials and Methods

Study Design and Setting

This quasi-experimental study employed a repeated-

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measures design with 2 groups to evaluate Thai mental state examination (TMSE) scores and MCI knowledge. The intervention group participated in a 6-week brain exercise program featuring weekly game-based cognitive enhancement sessions, followed by a 3-month follow-up period. The control group received a self-administered brain exercise manual for the same duration. Both groups were assessed at 3 time points: baseline, post-intervention, and 3-month follow-up, with data collection occurring between August and December 2023.

The researcher obtained permission from the directors of the hospital and primary healthcare unit to conduct the study. After approval, the research team collaborated with these institutions to recruit participants for the intervention and control groups. Healthcare professionals at the hospital and primary healthcare units identified potential participants based on specific criteria, including age, TMSE score history, and general health status. They provided a list of individuals who met the inclusion criteria. Recruitment was conducted within the participants' local community. After compiling the list of eligible individuals, the researcher scheduled appointments to contact the sample group. Participants were invited to the sub-district health promotion hospital for a second screening, which involved administering the TMSE assessment form and evaluating additional characteristics based on the inclusion and exclusion criteria. Eligible participants were then provided with informed consent forms to sign. Data were collected through face-to-face interviews conducted by the researchers and assistant researchers.

The 6-week brain exercise program for the intervention group consisted of weekly game-based cognitive enhancement sessions, followed by a 3-month follow-up period. The control group received a self-administered brain exercise manual for the same duration. Both groups were assessed at baseline, post-intervention, and 3-month follow-up through 30-minute face-to-face interviews. The same research team conducted all assessments to ensure consistency and uniformity in evaluation procedures throughout the study.

Participants

The study population comprised 175,287 older adults in Pathum Thani Province, Thailand [20]. Participants were selected based on TMSE scores ranging from 12 to 23 and a diagnosis of MCI by medical doctors. A multi-stage sampling method was employed to recruit participants in 2 steps: First, Pathum Thani Province was divided into 7 districts. One district was randomly selected for the intervention group, and another for the control group using a lottery method without replacement to ensure equal probability of selection. Khlong Luang district was assigned to the intervention group, and Lam Luk Ka district to the control group. Both districts shared similar demographic profiles, proportions of older adults in the population, and lifestyles. Then, using purposive sampling, 48 participants from Khlong Luang district were recruited for the intervention group, and 48 participants from Lam Luk Ka district were recruited for the control group, based on the inclusion criteria outlined in Figure 1.

Inclusion criteria

Participants were individuals aged 60 years or older residing in Pathum Thani Province. They had TMSE scores between 12 and 23, were diagnosed with MCI by a medical doctor, could communicate and interact effectively, and voluntarily consented to participate. Exclusion Criteria: Individuals diagnosed with severe dementia, those who were disabled or bedridden, and those with underlying conditions (e.g., heart disease, osteoarthritis, or cancer) that hindered program participation were excluded.

Intervention Details

The brain exercise program utilized a game-based cognitive enhancement approach to reduce MCI among the participants, who were older adults. The program was developed based on the KAP model [17] and self-efficacy theory [18], and drew on cognitive training research using games [22]. The activities were designed to be easy to understand, culturally appropriate, and progressively challenging to maintain participant engagement and motivation [23]. The program tailored activities to participants' baseline KAP model regarding cognitive health, providing information about MCI [17]. By incorporating self-efficacy theory [18], the program aimed to build participants' confidence in their ability to improve cognitive health through consistent engagement in brain exercises.

Community involvement was integrated into the intervention to ensure the program's sustainability and enrich its content. Focus groups with key stakeholders, including the participants, healthcare providers, and village health volunteers, contributed to the program's development and design. Stakeholders provided feedback on the study objectives and content relevance, which informed adjustments to the intervention. Five experts in medicine, education, public health, geriatric nursing, and behavioral science reviewed the intervention draft to assess content validity using the content validity index (CVI). The program achieved a CVI of 0.90, indicating excellent content validity.

The program employed 2 strategies: (1) providing knowledge about MCI and (2) practicing brain exercises

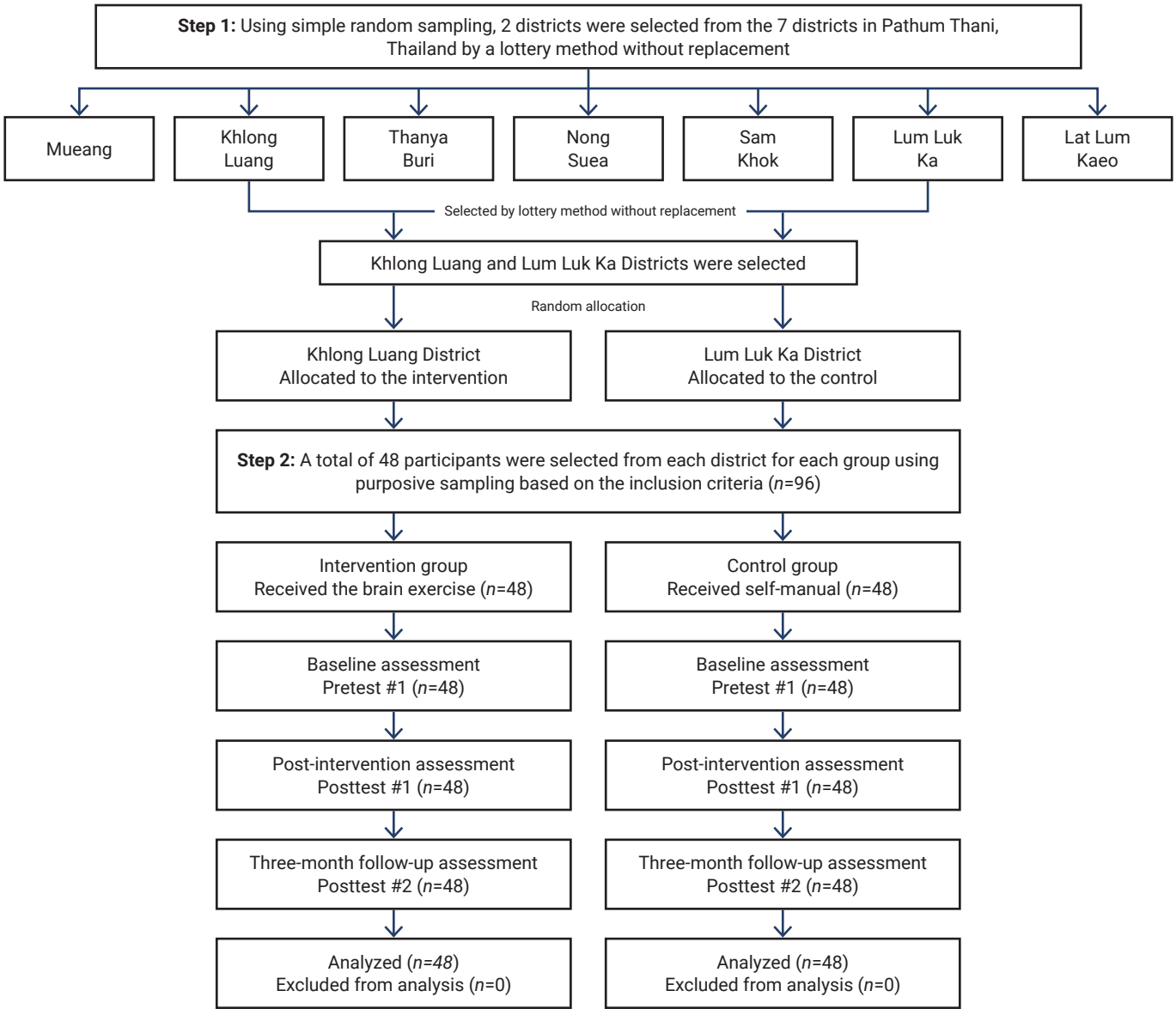

Figure 1. The flowchart of sampling and measurements timeline.

through game-based activities targeting cognitive functions such as memory, attention, executive function, and problem-solving [24]. These activities aimed to restore normal cognitive function and ensure continuous mental stimulation. The research team, along with trained public health staff and nurses, conducted and supervised the intervention. Personnel underwent training to familiarize themselves with the program's details, measurement techniques, and follow-up procedures. The intervention was delivered over 6 weeks, with 1-hour sessions held weekly on Mondays at the hospital. The program consisted of 6 sessions, with baseline assessments conducted before the first session using assessment and interview forms.

Session 1: enhancing knowledge and interaction activity

This session introduced and explained the program's purpose and process while stimulating the brain's left and right hemispheres and engaging the 5 senses. It provided information on MCI, including its symptoms, risk factors, and prevention methods, through slide presentations and short video clips. A discussion activity on MCI knowledge was facilitated to encourage participant interaction and engagement. The session also included the "One Brain, Two Hands" game, designed to improve executive function and attention. This game required participants to plan, switch between actions, and control movements, directly engaging cognitive flexibility, inhibitory control, and task-switching. Participants focused on

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specific instructions for hand coordination, such as raising the thumb on the right hand and the pinky on the left hand, then switching hands, or holding the tip of the nose with the right hand and the right ear with the left hand, then switching hands. These activities helped improve selective attention and sustained attention by requiring participants to follow precise instructions and coordinate their movements effectively.

Session 2: play a memory-stimulating game

This session aimed to improve memory and executive function through a series of games. The first game, "Who Is This?," involved playing audio clips of well-known individuals, such as actors, artists, and singers, and asking participants to guess their identities. This activity enhanced memory recall and recognition. Next, the "Fill in the Clock Hands" game was introduced to train executive functions. Participants were instructed to write down a specific time and draw the corresponding clock hands on a clock face, improving their planning and organizational skills. The final activity, the "Sequence of Events" game, required participants to arrange a series of images in the correct chronological order. This task enhanced problem-solving abilities and task execution by challenging participants to logically sequence events.

Session 3: play a visual training game

This session focused on enhancing attention and visual perception through 3 activities. The "Color Confusion" game, required participants to identify the color of written words (e.g., the word "red" written in blue ink) without reading the text. This activity improved selective and sustained attention by forcing participants to focus on color identification rather than word recognition. The "Spot the Differences" game involved comparing 2 similar images and identifying subtle differences. This task enhanced visual discrimination, a key aspect of visual processing. The "What's in This Picture" game, engaged visual memory and processing. Participants observed a picture for 10 seconds and then answered questions about its details, challenging them to recall and describe visual information accurately.

Session 4: play a brain-stimulating game

This session aimed to improve attention and memory functions through a variety of activities. Slow dancing encouraged mindfulness and body awareness, indirectly enhancing attention. Imaginative drawing required participants to draw freely based on their imagination. This task encouraged divergent thinking and visual expression, directly engaging attention function. Short film reflection, involved watching a short film about dementia and answering related questions. This activity fostered attention and thematic processing as participants analyzed the film's content and themes.

Session 5: play a memory training game

This session focused on enhancing memory through 2 activities. The first, the "Missing Half" game, required participants to complete the missing half of an image, stimulating visual memory and detail retention. The second activity, the "Color Ladder" game, involved memorizing and recalling a sequence of colors. Participants were shown a series of colored images and asked to identify which color was missing, improving working memory and the ability to store and manipulate information over short periods.

Session 6: play a thinking process training game

This session aimed to improve cognitive functions, including memory and attention, through a series of activities. The "Fun Math" game required participants to solve mathematical problems involving addition, subtraction, multiplication, and division, engaging attention and cognitive flexibility. The "Picture Association" game involved showing participants a set of related images and asking them to identify the missing associated image from options A, B, C, or D. This activity enhanced associative memory and recall. The "Your Perspective, My Perspective" game required participants to observe an arrangement of cube blocks and answer questions about the shape's top-down view and the total number of cubes. This task demanded sustained attention and spatial processing. The final activity, a group discussion, allowed participants to synthesize information, share insights, and suggest improvements. They reviewed knowledge about MCI, analyzed the program's outcomes, and created a Line group for ongoing communication and Q&A. The session concluded with scheduling, follow-up instructions, and post-intervention assessments using the same instruments as at baseline.

After the 6-week program, participants practiced brain exercises at home during a 3-month follow-up period. The research team and village health volunteers conducted biweekly home visits to monitor progress, provide MCI information, and ensure continued engagement with brain exercises. Post-intervention and 3-month follow-up assessments were conducted using the TMSE and MCI knowledge evaluation forms. The control group received a self-administered brain exercise manual covering MCI definitions, symptoms, causes, impacts, diagnosis, and prevention. They underwent the same assessments as the intervention group at baseline, post-intervention, and 3-month follow-up, using interview forms for general data, the TMSE, and MCI knowledge assessments.

Measurement

Participants completed a semi-structured interview form administered by the researcher and written in Thai. The instruments used in this study were developed based on a comprehensive literature review and related studies [16,17,25], and a standard tool was employed to measure MCI in older adults [26]. The tools were divided into 3 parts.

Part 1: baseline characteristics interview form

This tool, developed by the researcher, assessed baseline characteristics through 9 items in both open-ended and closed-ended formats. The questionnaire covered aspects such as sex, age, marital status, education level, occupation, membership in a club for older adults, caregiver status, family type, and chronic diseases.

Part 2: TMSE

The TMSE is a widely accepted and valid assessment tool developed by the Train the Brain Forum Committee [26] to evaluate MCI in older adults in community or clinical settings. It is simple to use, efficient, highly sensitive, and validated for use in the Thai language. The test consists of questions and tasks divided into 6 sections: orientation, registration, attention, calculation, language, and recall. The TMSE has a total score of 30 points, with scores of 23 or below indicating MCI.

Part 3: knowledge about MCI assessment form

This tool, developed by the researcher based on relevant literature [27], assessed knowledge of MCI in older adults. It comprised 15 questions with "correct" or "incorrect" response options. Each correct answer earned 1 point, while incorrect answers earned zero points. Scores were interpreted using Bloom's criteria [28]: 0–8 indicated low knowledge, 9–11 indicated moderate knowledge, and 12–15 indicated high knowledge of MCI.

The validity of the tools was assessed by 3 experts—a geriatrician, a public health specialist, and a geriatric nurse—using the index of item-objective congruence (IOC). The IOC values ranged from 0.90 to 1.00. Reliability was tested through a pilot study involving 30 older adults from the same districts as the study sample, though they were not included in the actual study. The data were analyzed for reliability, resulting in a Cronbach's alpha coefficient of 0.90 for the TMSE and a Kuder-Richardson-20 (KR-20) value of 0.95 for knowledge of MCI.

Bias

The researchers implemented several strategies to minimize potential bias. First, they clearly defined participant selection criteria to avoid favoring specific characteristics, such as health status or familiarity with games. Second, baseline characteristics were controlled using statistical testing to ensure no significant differences between the intervention and control groups at the study's outset. The chi-square test (or Fisher exact test) was used to compare baseline characteristics, and the results showed no significant differences ($p > 0.05$), indicating demographic similarity between the groups and reducing the potential for confounding variables. Third, evaluators were trained to administer tests consistently, minimizing discrepancies in measurement. Fourth, both baseline and post-intervention assessments, along with follow-ups, were used to measure changes over time. Finally, incentives and regular encouragement were provided to retain participants throughout the study period.

Study Size

The sample size was calculated using the G*Power program, with an effect size of 0.80 [29], an alpha level of 0.05, a power of 0.95, and an allocation ratio (N2/N1) of 1. The calculation determined that 48 participants were needed for each group.

Statistical Methods

Data analysis was conducted using IBM SPSS ver. 29.0.1 (IBM Corp.), with a significance level set at 0.05. Descriptive statistics, including minimum and maximum values, frequency, percentage, mean, and standard deviation (SD), were employed. The chi-square test (or Fisher exact test) was used to compare baseline characteristics between the intervention and control groups before the experiment. Repeated-measures analysis of variance (ANOVA) was used to examine the effect of the brain exercise program on TMSE scores and knowledge of MCI among participants, both between and within groups, at 3 time points. The assumption of normality was assessed using the Kolmogorov–Smirnov test, which confirmed that the dependent variables, including TMSE scores ($p = 0.22$) and knowledge of MCI scores ($p = 0.20$), were normally distributed ($p > 0.05$). The assumption of sphericity was tested using the Mauchly test, which was significant ($p < 0.001$), indicating a violation of the sphericity assumption. Therefore, the Greenhouse-Geisser correction was applied to adjust the degrees of freedom for ANOVA. *Post-hoc* comparisons were performed using Bonferroni correction, with *i*-values adjusted for multiple comparisons to control for family-wise error.

Ethics Statement

The study protocol was approved by the Institutional Review Board of Valaya Alongkorn Rajabhat University under the Royal Patronage (IRB No: 0028/2023), with certification granted on August 4, 2023. The IRB confirmed informed

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consent, and participants were required to provide informed consent before participating in the research.

Results

Participants

A total of 48 older adults were initially recruited for both the intervention and control groups, selected from 2 randomly assigned districts. All 48 participants in the intervention group and 48 in the control group completed the study, with no dropouts. Post-intervention and 3-month follow-up evaluations were conducted using the same assessment tools for both groups.

Descriptive Data of Baseline Characteristics Variables

Table 1 shows that the baseline characteristics were comparable between the intervention and control groups, with no significant differences ($p > 0.05$). Among the 96 participants, 57.3% were female, and 71.9% were aged 60–69 years, with an average age of 68.9 years (SD = 6.4). Most participants were married (67.7%), had completed primary school (66.7%), and were employed (70.8%). Additionally, 55.2% were members of a club for older adults, 69.8% had a caregiver, and 84.4% lived in nuclear families. Chronic diseases were prevalent (89.6%), with hypertension (47.9%), dyslipidemia (41.7%), diabetes (33.3%), dyspepsia (8.3%), knee osteoarthritis (8.3%), heart disease (6.3%), and glaucoma/cataracts (5.2%) being the most common conditions.

Effects of the Brain Exercise Program on MCI by TMSE Between and Within Groups

Table 2 presents the results of a repeated-measures ANOVA analyzing the effectiveness of the brain exercise program on

Table 1. The baseline characteristics of the intervention and control group ($n = 96$)

Variable	Total ($n = 96$)	Intervention group ($n = 48$)	Control group ($n = 48$)	p
Sex				0.84[a]
Male	41 (42.7)	21 (43.8)	20 (41.7)	
Female	55 (57.3)	27 (56.3)	28 (58.3)	
Age (y)				0.09[b]
60–69	69 (71.9)	32 (66.7)	37 (77.1)	
70–79	20 (20.8)	14 (29.2)	6 (12.5)	
≥80	7 (7.3)	2 (4.1)	5 (10.4)	
Marital status				0.97[a]
Married	65 (67.7)	32 (66.7)	33 (68.8)	
Single	19 (19.8)	10 (20.8)	9 (18.8)	
Widowed/divorced/separated	12 (12.5)	6 (12.5)	6 (12.5)	
Occupational				0.07[a]
Unemployed	28 (29.2)	18 (37.5)	10 (20.8)	
Employed	68 (70.8)	30 (62.5)	38 (79.2)	
Education level				0.66[a]
Primary school	64 (66.7)	31 (64.6)	33 (68.8)	
Secondary school or higher	32 (33.3)	17 (35.4)	15 (31.3)	
Membership in elderly club				0.30[a]
Yes	53 (55.2)	24 (50.0)	29 (60.4)	
No	43 (44.8)	24 (50.0)	19 (39.6)	
Caregiver status				0.50[a]
Having a caregiver	67 (69.8)	35 (72.9)	32 (66.7)	
Not having a caregiver	29 (30.2)	13 (27.1)	16 (33.3)	
Family type				0.40[a]
Nuclear family	81 (84.4)	39 (81.3)	42 (87.5)	
Extended family	15 (15.6)	9 (18.8)	6 (12.5)	
Having chronic diseases				0.18[a]
Yes	86 (89.6)	41 (85.4)	45 (93.8)	
No	10 (10.4)	7 (14.6)	3 (6.3)	

Data are presented as n (%).
[a]Chi-square test, [b]Fisher exact test; significant difference $p < 0.05$.

Table 2. Repeated-measures ANOVA of MCI by TMSE and knowledge of MCI between and within groups ($n = 96$)

Outcome variable	ss	df	MS	F-test	p
TMSE score					
Between subject					
Intervention	2,502.78	1	2502.78	208.25	< 0.001[a]
Error (between-group-error)	1,129.72	94	12.02		
Within subject					
Time	2,062.76	1.40	1477.44	163.23	< 0.001[a]
Intervention x time	1,050.02	1.40	752.07	83.09	< 0.001[a]
Error (within-group-error)	1,187.89	134.02	12.64		
Knowledge of MCI					
Between subject	355.56	1	355.56	24.70	< 0.001[a]
Intervention	1,353.09	94	14.39		
Error (between-group-error)					
Within subject					
Time	287.17	1.85	155.05	28.50	< 0.001[a]
Intervention x time	188.42	1.85	101.73	18.70	< 0.001[a]
Error (within-group-error)	947.07	174.10	5.44		

ANOVA, analysis of variance; MCI, mild cognitive impairment; ss, sum of squares; df, degrees of freedom; MS, mean of square; TMSE, Thai mental state examination.
[a]Statistically significant at $p < 0.05$.

MCI, as measured by TMSE scores. A statistically significant difference was found between the intervention and control groups ($F(1,94) = 208.25$, $p < 0.001$). Within-subjects testing revealed significant changes in TMSE scores over the 3 time points ($p < 0.001$), indicating a significant interaction between time and intervention. *Post-hoc* pairwise comparisons using the Bonferroni correction (Table 3) showed no significant differences in TMSE scores between the intervention group (mean ± SD, 17.46 ± 2.80) and control group (mean ± SD, 16.96 ± 2.89) at baseline ($p > 0.05$). However, significant differences were observed at post-intervention, with the intervention group scoring higher (mean ± SD, 26.33 ± 3.43) than the control group (mean ± SD, 17.94 ± 2.87; $p < 0.001$). This difference persisted at the 3-month follow-up, with the intervention group (mean ± SD, 27.81 ± 2.41) outperforming the control group (mean ± SD, 19.02 ± 2.86; $p < 0.001$). These findings indicate that the intervention group showed significantly greater improvement in MCI, as measured by TMSE scores, than the control group (Figure 2).

Effects of the Brain Exercise Program on Knowledge of MCI Between and Within Groups

Table 2 also presents the results of repeated-measures ANOVA analyzing the effectiveness of the brain exercise program on knowledge of MCI. A statistically significant difference was found between the intervention and control groups ($F(1,94) = 24.70$, $p < 0.001$). Within-subjects testing revealed significant changes in knowledge of MCI scores over the 3 time points ($p < 0.001$), indicating a significant interaction between time and intervention. *Post-hoc* pairwise comparisons using Bonferroni correction (Table 3) showed no significant differences in knowledge of MCI scores between the intervention group (mean ± SD, 9.17 ± 3.69) and control group (mean ± SD, 8.73 ± 2.28) at baseline ($p > 0.05$).

However, significant differences were observed post-intervention, with the intervention group scoring higher (mean ± SD, 11.69 ± 3.16) than the control group (mean ± SD, 9.81 ± 2.69; $p = 0.002$). This difference further increased at the 3-month follow-up, with the intervention group (mean ± SD, 13.46 ± 1.96) outperforming the control group (mean ± SD, 9.10 ± 3.02; $p < 0.001$). These results demonstrate that the intervention group achieved significantly higher knowledge of MCI than the control group (Figure 3).

Discussion

The brain exercise program utilizing game-based cognitive enhancement effectively reduced MCI and increased knowledge of MCI among older adults in Thailand. The findings are discussed below.

This study demonstrated that the brain exercise program successfully improved participants' knowledge of MCI. Significant differences in knowledge scores were observed between the intervention and control groups, with notable improvements in the intervention group before and after the program. These findings align with Xue et al. [30], who found that a game-based training intervention significantly enhanced participants' understanding of MCI. Similarly,

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Table 3. *Post-hoc* pairwise comparison with Bonferroni correction of outcome variables between the intervention and control group ($n = 96$)

Time	Group		Mean difference	SE	*p*
TMSE scores					
Baseline	Intervention	Control	0.500	0.581	0.392
Post-intervention	Intervention	Control	8.396	0.647	< 0.001[a]
3-month follow-up	Intervention	Control	8.792	0.521	< 0.001[a]
Knowledge of MCI					
Baseline	Intervention	Control	0.438	0.626	0.486
Post-intervention	Intervention	Control	1.875	0.598	0.002[a]
3-month follow-up	Intervention	Control	4.354	0.519	< 0.001[a]

SE, standard error; TMSE, Thai mental state examination; MCI, mild cognitive impairment.
[a]Statistically significant at $p < 0.05$.

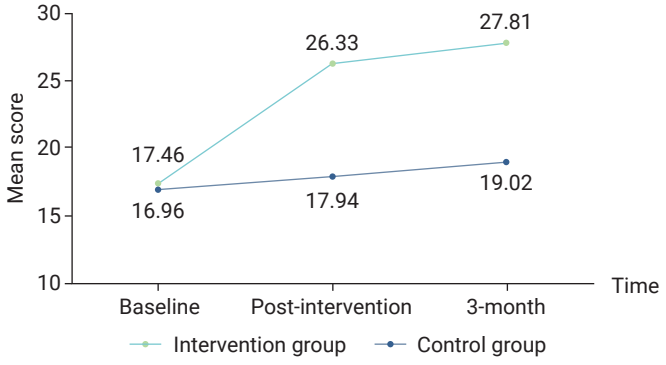

Figure 2. Mean scores of mild cognitive impairments as measured by Thai mental state examination (TMSE) scores between the intervention and control group in 3 tests.

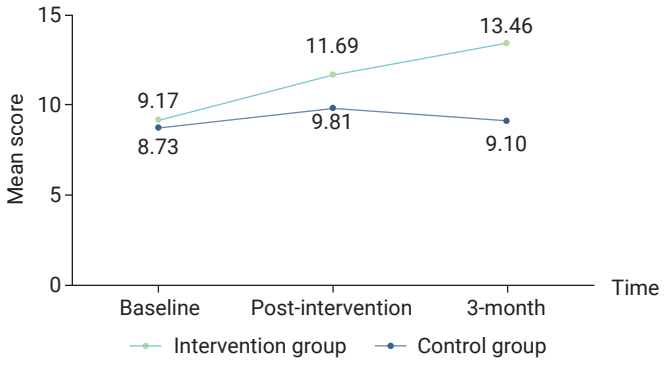

Figure 3. Mean scores of knowledge of mild cognitive impairment (MCI) between the intervention and control group in 3 tests.

Phirom et al. [29] reported that participants in the intervention group showed significant cognitive improvements, as measured by Montreal cognitive assessment scores ($p = 0.001$), compared to the control group. The combination of interactive physical-cognitive, game-based training, and MCI education proved effective in boosting knowledge and cognitive function among community-dwelling older adults. This is consistent with Ishibashi et al. [14], who demonstrated that cognitive interventions involving video games improved processing speed and working memory by increasing knowledge of MCI and encouraging brain exercises among older adults.

These findings suggest that the intervention program effectively motivates older adults to gain a deeper understanding of MCI [31]. The program was designed with a strong educational focus, delivering knowledge about MCI through slide presentations and short video clips. These materials covered key topics, including (1) symptoms of MCI, (2) risk factors, and (3) preventive measures. Following the presentations, participants engaged in discussion activities, which allowed them to ask questions, clarify doubts, and reflect on what they had learned [32]. This interactive format reinforced knowledge retention and ensured participants understood and remembered the information [27]. By integrating these educational components, the program made learning about MCI both informative and enjoyable, ultimately increasing participants' knowledge of the condition.

The findings also revealed that the brain exercise program effectively reduced MCI, as evidenced by changes in TMSE scores across 3 time periods. The intervention group showed greater increases in TMSE scores compared to the control group. This aligns with Arshad et al. [33], who found significant improvements in Mini-Mental State Examination scores after a 6-week brain training game intervention. Similarly, Boonkerd et al. [34] reported that a neurobic exercise-based brain training program resulted in higher cognitive ability scores in the intervention group compared to the control group. These findings are further supported by Wang et al. [16], who demonstrated that game-based brain training can enhance cognitive functions in older adults, and Dell'Osso et al. [35], who highlighted video games as a promising method

for cognitive training and neurorehabilitation. Additionally, Sanghuachang et al. [36] identified neurobic exercise programs as effective nursing interventions for improving memory performance in older adults with MCI. Systematic reviews on exergaming, which combines exercise with gaming, also highlighted its innovative, enjoyable, and safe nature, with statistically significant improvements in cognitive function for individuals with MCI [37].

These results can be attributed to the program's design, which was based on cognitive training research and incorporated games specifically tailored to improve cognitive abilities. These games were not only engaging but also supported by evidence demonstrating their efficacy in enhancing brain function [38]. By utilizing games, the program created an interactive environment where participants could strengthen cognitive skills in a non-tedious and stress-free manner [39,40]. While this study did not evaluate cognitive improvement in individual domains, it compared overall cognitive function between the intervention and control groups using the TMSE, a comprehensive tool measuring memory, attention, executive function, and problem-solving. The games targeted key cognitive domains affected by MCI: (1) Memory: Games involving word, pattern, or sequence recall improved short-term and working memory. (2) Attention: Games requiring focus on details or tasks with increasing difficulty enhanced sustained attention and concentration. (3) Executive Function: Games targeting planning, decision-making, and flexible thinking strengthened higher-level cognitive processes. (4) Problem-Solving: Games involving logical reasoning and puzzle-solving encouraged critical thinking and adaptive problem-solving skills. The program fostered the development of new neural pathways, enhancing the brain's resilience against MCI progression [41]. The improvement in TMSE scores reflected this enhanced cognitive function, demonstrating that regular engagement with these games contributed to better cognitive performance over time. Higher TMSE scores indicated improved cognitive function and reduced MCI severity.

The interactive and playful nature of the games kept participants highly engaged, a critical factor in the program's success. Older adults are more likely to adhere to a program they find enjoyable, which was a key strength of this intervention [42–44]. This finding aligns with self-efficacy theory [18], which emphasizes an individual's belief in their ability to perform behaviors necessary to achieve specific outcomes. The mastery experiences provided by the game-based program played a significant role in enhancing self-efficacy. As participants completed games targeting specific cognitive functions—such as memory, attention, and problem-solving—they gained a sense of accomplishment [45,46]. These positive experiences boosted participants' confidence in their cognitive abilities, reinforcing their belief in the possibility of cognitive improvement, which ultimately contributed to higher TMSE scores and reduced MCI symptoms [47].

Cultural aspects significantly influenced the design of the games and activities, making the intervention more effective. The brain exercises were culturally relevant, tailored to the context of Pathum Thani. Activities incorporated culturally familiar themes, symbols, or references to ensure engagement and relatability. For example, images in activities like "Spot the Differences" or "What's in This Picture?" featured local landmarks, traditional markets, or religious symbols familiar to participants. Cultural practices and values also influenced activity selection. For instance, slow-dancing activities incorporated Thai music or traditional rhythms, resonating with cultural preferences and encouraging participation. Thai culture's emphasis on social harmony and community engagement was leveraged to create a supportive learning environment. For example, participants were encouraged to share insights or reflect on a short film about dementia, aligning with communal values. In conclusion, cultural adaptation played a pivotal role in the program's success, particularly for populations of older adults with unique social, linguistic, and cognitive needs.

In summary, the game-based brain exercise program successfully improved TMSE scores, reflecting enhanced cognitive functioning and reduced MCI severity among older adults [48]. However, this study had several limitations. First, both the intervention and control groups were located in rural areas, limiting the generalizability of the findings to urban populations due to differences in lifestyle, sociodemographic factors, and economic conditions. Second, the program's short duration (6 weeks with a 3-month follow-up) limits insights into its long-term effects. Future studies should extend the follow-up period to 6 or 12 months to assess sustainability. Third, the non-randomized study design introduces potential selection bias. To address this, future studies should employ matching techniques to pair participants based on key variables like age, gender, baseline cognitive function, or health status. Statistical methods such as analysis of covariance can also control for baseline differences. Fourth, the program focused primarily on game-based cognitive enhancement and may have overlooked other factors influencing cognitive health, such as physical exercise, nutrition, social interaction, and mental health.

Conclusion

In conclusion, the brain exercise program utilizing game-

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based cognitive enhancement successfully improved participants' knowledge of MCI and cognitive performance, as demonstrated by increased TMSE scores. These improvements indicated enhanced cognitive abilities and reduced MCI severity, suggesting that game-based brain exercise programs can be valuable tools in addressing cognitive decline and promoting mental well-being among older adults. As recommendations for practice, the program can be integrated into comprehensive geriatric care services in hospitals or clinics. Physicians and geriatric specialists could recommend it to older patients showing early signs of cognitive decline, using it as a cognitive rehabilitation tool alongside other therapies. Further research should explore developing the brain exercise program through mobile applications to promote cognitive health in older adults. Additionally, future studies could examine the benefits of integrating physical activity or social interaction elements into the program. Lastly, domain-specific assessments should be used to explore how different cognitive areas are affected by the intervention.

Notes

Ethics Approval

The study received approval from the Research Ethics Committee on Human Research at Valaya Alongkorn Rajabhat University. The project was assigned identification numbers REC No. 0028/2023 and COA No. 0028/2023 and obtained certification on August 4, 2023. The study was performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: PK, PT, NK; Data curation: PK, SR, WP; Formal analysis: PT, SM, CP; Investigation: PK, PT, SR, WP; Methodology: all authors; Project administration: PK, PT; Resources: PT, CP; Supervision: PK, PT; Validation: PT, NK; Visualization: PT; Writing–original draft: PT; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Altered eotaxin-1 and interleukin-34 levels in obsessive-compulsive disorder: a case-control observational study in Bangladesh

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ABSTRACT

Objectives: Obsessive-compulsive disorder (OCD) is a prevalent mental health condition that impacts daily life. It is thought to be associated with genetic, biological, and structural brain changes, serotonergic abnormalities, altered neuromodulation, and environmental factors. Limited observational studies have examined cytokines in Bangladeshi patients with OCD. This study aimed to assess the levels of eotaxin-1 and interleukin (IL)-34 in individuals with this disorder.

Methods: This case-control observational study included 58 patients with OCD and 30 healthy controls (HCs) matched for age, sex, and body mass index. The severity of OCD was assessed using the Yale-Brown obsessive-compulsive scale (Y-BOCS). Psychiatrists evaluated participants according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Serum levels of eotaxin-1 and IL-34 were measured using enzyme-linked immunosorbent assay kits.

Results: Patients with OCD exhibited significantly higher serum eotaxin-1 levels (121.13 ± 7.84 pg/mL) than HCs (85.52 ± 9.42 pg/mL). Conversely, IL-34 levels were considerably lower in patients than in HCs (119.02 ± 14.53 pg/mL vs. 179.96 ± 27.88 pg/mL). The Cohen d values for eotaxin-1 and IL-34 were 0.55 and −0.48, respectively. Among patients with OCD, a significant positive correlation was found between serum eotaxin-1 level and Y-BOCS score, along with a negative correlation between serum eotaxin-1 and IL-34 levels.

Conclusion: The findings suggest that altered eotaxin-1 and IL-34 levels may be associated with OCD. These chemokines and cytokines could serve as primary tools for assessing the risk of OCD, warranting further clinical investigation. This could potentially support more extensive research and the development of diagnostic and therapeutic strategies targeting these pathways.

Keywords: Chemokine CCL-11; Eotaxin-1; Interleukin-34; Mental disorders; Obsessive-compulsive disorder

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Introduction

Obsessive-compulsive disorder (OCD) is characterized by recurring obsessions—repetitive, peculiar, and intrusive thoughts or images related to various issues—and compulsions, which are repetitive mental acts or rituals typically performed to reduce the anxiety associated with obsessions and to provide temporary relief [1–3]. These obsessions and compulsions can lead to functional impairment, ultimately affecting the quality of life of individuals with OCD [4]. OCD typically emerges early in life, from childhood to early adulthood, and the severity of symptoms can fluctuate over time [5,6]. The global prevalence of OCD is estimated to be between 1.5% and 3% across all age groups, affecting individuals regardless of age, sex, or socioeconomic background [7]. The National Mental Health Survey of Bangladesh reported that 0.7% of Bangladeshi adults had an OCD diagnosis in 2018–2019 [8]. The World Health Organization ranks OCD as the fourth most common mental disorder and among the top 10 leading causes of disability worldwide [9]. Without proper diagnosis and treatment, OCD can become chronic, leading to prolonged disability and an increased health burden [10]. Furthermore, OCD can exacerbate economic strain by reducing productivity and frequently requiring medical treatment, counseling, and medication, thereby imposing a greater financial burden on society [11,12].

In recent years, the pathogenesis of OCD has been researched across various dimensions. Nevertheless, its complete pathogenesis remains elusive due to the complex interplay of genetic, biological, and environmental factors [13,14]. Evidence suggests that neuroinflammation, marked by increased levels of proinflammatory cytokines and immune dysregulation, may play a role in the development and progression of OCD [15]. Elevated immune markers have been observed in some patients with OCD, indicating a potential link between peripheral inflammation and inflammation of the brain [15]. This immune dysregulation may impact brain circuits implicated in OCD, such as the orbitofrontal cortex, cortico-striato-thalamo-cortical loop, and anterior cingulate cortex, as well as the caudate nucleus and thalamus. These regions are involved in decision-making, impulse control, habit formation, and cognitive processing [16]. Neuroimaging studies have revealed structural and functional abnormalities in these brain areas among individuals with OCD [17,18]. Furthermore, alterations in the levels of neurotransmitters, including serotonin, dopamine, and glutamate, have been implicated in the pathophysiology of this condition [19].

Immune dysregulation, characterized by altered chemokine and cytokine levels, may play a role in the pathophysiology of OCD. Eotaxin-1, a chemokine involved in the selective recruitment of eosinophils to sites of inflammation, has been found to exhibit altered levels in the pathogenesis of OCD. This change is attributed to immune dysregulation and subsequent neuroinflammation [20,21]. Factors such as aging, reduced neurogenesis, neurodegeneration, and immune dysregulation may contribute to the pathophysiology of OCD through altered levels of eotaxin-1 [22,23]. Research has shown an increased level of eotaxin-1 in patients with OCD compared to healthy controls (HCs), although the difference was not statistically significant [24]. While the precise mechanisms are not fully understood, immunomodulation and resulting neuroinflammation are prevalent in OCD. Consequently, the level of eotaxin-1 is elevated due to the selective recruitment of eosinophils to the inflammatory sites of the brain [25].

Interleukin (IL)-34 is a cytokine with a multifaceted role in both proinflammatory and anti-inflammatory processes. It is implicated in the differentiation, survival, and function of macrophages. IL-34 promotes the activation of macrophages and microglia, contributing to the immune response through increased secretion of inflammatory mediators such as tumor necrosis factor alpha, IL-6, and IL-1β [26,27]. This positions IL-34 as a key player in autoimmune diseases and neuroinflammatory disorders. Conversely, IL-34 can also display anti-inflammatory effects by inducing regulatory macrophages and boosting the production of IL-10, a cytokine known for its anti-inflammatory properties [28]. Although IL-34 has been associated with cognitive impairment in vascular dementia and Alzheimer's disease and is crucial in modulating the immune system by influencing various

HIGHLIGHTS

- The role of cytokines in obsessive-compulsive disorder (OCD) remains unclear, with few observational studies exploring eotaxin-1 and interleukin (IL)-34 levels in patients with OCD.
- The present study observed altered levels of eotaxin-1 and IL-34 in patients with OCD relative to healthy controls.
- Among these patients, we noticed a significant positive correlation between serum eotaxin-1 levels and OCD symptoms and a negative correlation between serum eotaxin-1 and IL-34 levels.
- The findings indicate that altered levels of eotaxin-1 and IL-34 could be utilized in the diagnosis and treatment of OCD.

signaling pathways, its direct relationship with OCD has not been established [29]. Nevertheless, several studies have suggested a potential link between IL-34 and OCD, given its role in neuroprotection and the activation of different immune system target cells [30–34].

The current absence of specific assessment techniques for diagnosing and monitoring OCD necessitates heavy reliance on clinical assessments, which can be biased and variable. Consequently, the development of robust diagnostic methods that incorporate biomarkers could facilitate the early detection and diagnostic precision of OCD [35,36]. Potential biomarkers, such as serum markers, genetic markers, and neuroimaging findings, could also assist in differentiating OCD from other psychiatric disorders. These biomarkers may provide valuable insights into the neurobiological mechanisms underlying OCD, ultimately leading to more effective therapies through the creation of targeted treatment plans [37].

Recently, several studies have aimed to identify potential biomarkers for OCD. The discussions above suggest a possible association between eotaxin-1 and IL-34 with OCD. However, research on these biomarkers in relation to OCD remains inconclusive. Therefore, this study was designed to evaluate and compare the serum levels of eotaxin-1 and IL-34 in patients with OCD and HCs. The goal is to explore their viability as early risk assessment tools and to understand their role in the pathophysiology of OCD.

Materials and Methods

Study Population

This observational case-control study was conducted between July 1, 2023, and December 31, 2023. It included 58 individuals diagnosed with OCD according to the International Classification of Diseases code of F42 for OCD, with F42.1 indicating predominantly compulsive acts, F42.2 denoting mixed obsessional thoughts and acts, and F42.9 representing unspecified OCD. Additionally, 30 HCs were included in the study. To ensure statistical power, the odds ratio, alpha risk, and exposed controls were considered. The patients with OCD were recruited from a tertiary care teaching hospital in Dhaka, Bangladesh, while the HCs were sourced from various areas within Dhaka. All participants underwent diagnosis and evaluation by experienced psychiatrists at the hospital. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and the Yale-Brown obsessive-compulsive scale (Y-BOCS) were utilized to diagnose OCD and assess symptom severity, respectively. A comprehensive matching process was employed to ensure consistency in age, sex, and sociodemographic variables between groups. Sociodemographic and clinical data were collected from both patient and HC groups using standardized questionnaires. All participants were between 18 and 60 years old. Exclusion criteria encompassed cognitive impairment, other comorbid psychiatric disorders such as anxiety and depression, severe medical conditions including any acute medical or physical condition, history of kidney or liver failure, concomitant psychosis, and prior use of antipsychotic drugs. Furthermore, individuals who were receiving medications, supplements, or blood transfusions that could influence the blood levels of the target biomarkers were also excluded from the study.

Sample Collection

A 5-mL blood sample was drawn from the cephalic vein of each participant. The samples were left to clot in Falcon tubes at room temperature for 1 hour. Subsequently, the tubes containing the clotted blood were centrifuged at 3,000 rpm for approximately 15 minutes at room temperature to separate the serum. The serum was then carefully transferred to Eppendorf tubes and refrigerated at −80 °C to ensure optimal preservation.

Measurement of Serum Eotaxin-1 and IL-34

Commercially available enzyme-linked immunosorbent assay (ELISA) kits from Boster Bio were used to measure the serum levels of eotaxin-1 and IL-34. The serum concentrations of eotaxin-1 and IL-34 were determined following the manufacturer's instructions for the ELISA kit (Picokine; Boster Bio) [38,39]. The manufacturer provided intra-assay coefficients of variation, which were 5% for eotaxin-1 and 5.7% for IL-34. To maintain consistency and minimize potential bias, all experiments were performed by the same researchers, who were blinded to the potential outcomes.

Yale-Brown Obsessive-Compulsive Scale

The Y-BOCS is a widely utilized clinical instrument for evaluating the severity of symptoms in OCD, covering 2 primary domains: obsessions and compulsions. Each domain is scored on a scale ranging from 0 to 4. Obsessions are rated based on factors such as the time spent on intrusive thoughts, the degree to which these obsessions interfere with daily life, the distress they cause, efforts to resist them, and the individual's control over them. Similarly, compulsions are evaluated based on the time dedicated to repetitive behaviors, the level of interference with daily activities, the anxiety experienced when compulsions are resisted, attempts to resist them, and the degree of control. The overall Y-BOCS score categorizes OCD severity into 4 distinct levels: scores of 8–15 indicate mild OCD, 16–23 moderate,

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24–31 severe, and 32–40 extremely severe. This essential tool is instrumental in the diagnosis and monitoring of OCD [40,41]. A study conducted with a Bangladeshi cohort found that the Bengali version of the dimensional Y-BOCS demonstrates excellent internal consistency and good to excellent interrater reliability [42]. To gather clinical and sociodemographic data, the local language and English versions of the Y-BOCS, along with all questionnaires, were employed.

Statistical Methods

IBM SPSS ver. 25.0 (IBM Corp.) and Microsoft Excel (Microsoft Corp.) were utilized for data processing and statistical analysis. The independent samples t-test and the chi-square test were employed to differentiate between groups and evaluate the relationships between variables. The Cohen d was calculated to determine the effect sizes for significant findings. Spearman correlation analysis was conducted to explore the associations among various study parameters in patients with OCD, with Bonferroni adjustments applied to correct for multiple comparisons. Box plot graphs were employed to visually represent the results. Descriptive analysis was used to outline the sociodemographic profiles of the participants, and results were presented as mean ± standard error of the mean. Receiver operating characteristic (ROC) curve analysis was performed to quantify the diagnostic accuracy of the altered serum parameters. A 2-tailed *p*-value less than 0.05 was considered to indicate statistical significance.

Ethics Statement

The Research Ethics Committee (REC) of the University of Asia Pacific (UAP) approved the study protocol (UAP/REC/2023/207). Informed written consent was obtained from all participants prior to data collection. Written informed consent was also secured for the publication of these anonymous study results. The investigations were conducted in accordance with the principles outlined in the Helsinki Declaration.

Results

Participants and Descriptive Data

The characteristics of the study population are detailed in Table 1. Regarding age distribution, the most common age range for both patients and HCs was 18 to 25 years, with 65.5% of patients and 50.0% of HCs falling within this category ($p = 0.112$). When considering marital status, patients had a slightly higher percentage of unmarried patients compared to HCs (patients with OCD, 53.4%; HCs, 50.0%; $p = 0.759$). In

Table 1. Characteristics of the study population

Parameter	Patients with OCD (*n* = 58)	Healthy controls (*n* = 30)	*p*
Age (y)	25.57 ± 0.78	27.70 ± 1.01	0.112
18–25	38 (65.5)	15 (50.0)	
26–35	15 (25.9)	11 (36.7)	
36–45	5 (8.6)	4 (13.3)	
Sex			0.653
Male	30 (51.7)	14 (46.7)	
Female	28 (48.3)	16 (53.3)	
BMI (kg/m^2)	22.56 ± 0.32	23.47 ± 0.46	0.130
Below 18.5 (CED)	1 (1.7)	1 (3.3)	
18.5–25.0 (normal)	47 (81.0)	23 (76.7)	
Above 25.0 (obese)	10 (17.2)	6 (20.0)	
Marital status			0.759
Married	27 (46.6)	15 (50.0)	
Unmarried	31 (53.4)	15 (50.0)	
Education level			0.428
Illiterate	3 (5.2)	0 (0)	
Primary	10 (17.2)	4 (13.3)	
Secondary	24 (41.4)	11 (36.7)	
Graduate and above	21 (36.2)	15 (50.0)	
Occupation			0.156
Business	9 (15.5)	4 (13.3)	
Service	8 (13.8)	8 (26.7)	
Housewife	15 (25.9)	7 (23.3)	
Student	17 (29.3)	8 (26.7)	
Unemployed	9 (15.5)	3 (10.0)	
Economic status			0.971
High	5 (8.6)	3 (10.0)	
Medium	36 (62.1)	18 (60.0)	
Low	17 (29.3)	9 (30.0)	
Area of residence			0.785
Rural	23 (39.7)	11 (36.7)	
Urban	35 (60.3)	19 (63.3)	
Smoking history			0.968
Non-smoker	54 (93.1)	28 (93.3)	
Smoker	4 (6.9)	2 (6.7)	
Family history of OCD			0.004
Yes	12 (20.7)	0 (0)	
No	46 (79.3)	30 (100.0)	

Data are presented as mean ± standard deviation or *n* (%).
OCD, obsessive-compulsive disorder; BMI, body mass index; CED, chronic energy deficiency.

and IL-34 between patients with OCD and HCs. Serum eotaxin-1 levels were significantly higher in the OCD group than in HCs, with a significant positive correlation observed between eotaxin-1 level and the severity of OCD. Conversely, serum IL-34 levels were significantly lower in patients, but these levels did not correlate significantly with OCD severity. Additionally, a significant negative correlation was found between eotaxin-1 and IL-34 levels. ROC analysis suggests

terms of education, the largest proportion of both patients and HCs had reached the secondary level (patients with OCD, 41.4%; HCs, 36.7%; $p = 0.428$), and the most common occupation was student. Participants predominantly lived in urban areas (patients with OCD, 60.3%; HCs, 63.3%; $p = 0.785$). Finally, 20.69% of the patients had a previous history of OCD.

Clinical Profile and Laboratory Findings

The mean ages of the patient group and the HC group were 25.57 ± 0.78 years and 27.70 ± 1.01 years, respectively ($p = 0.112$). The mean body mass indices for the patient and HC groups were 22.56 ± 0.32 kg/m^2 and 23.47 ± 0.46 kg/m^2, respectively ($p = 0.107$).

Serum levels of eotaxin-1 were higher in patients (121.13 ± 7.84 pg/mL) than in HCs (85.52 ± 9.42 pg/mL), a statistically significant difference ($p = 0.007$) with a Cohen d effect size of 0.55. In contrast, serum levels of IL-34 were considerably lower in patients (119.02 ± 14.53 pg/mL) compared to HCs (179.96 ± 27.88 pg/mL), with this difference also displaying statistical significance ($p = 0.035$) and a Cohen d effect size of −0.48. Figure 1 compares serum eotaxin-1 and IL-34 levels between patients with OCD and HCs.

Correlation Analysis

The Spearman correlations among various parameters are presented in Table 2. We observed a significant positive correlation between serum eotaxin-1 level and the Y-BOCS score in patients with OCD (r = 0.287, $p = 0.029$). Conversely, we found a negative correlation between serum IL-34 levels and Y-BOCS scores in these patients (r = −0.018, $p = 0.894$), although this finding was not statistically significant. Additionally, a significant negative correlation was observed between serum eotaxin-1 and IL-34 levels (r = −0.273, $p = 0.038$).

ROC Curve Analysis

The results of the ROC curve analysis for serum eotaxin-1 and IL-34 levels are presented in Table 3 and illustrated in Figure 2. According to the analysis, the cut-off values for serum eotaxin-1 and IL-34 levels were determined to be 83.04 pg/mL and 175.62 pg/mL, respectively. The sensitivity for serum eotaxin-1 was found to be 72.4%, with a specificity of 76.3%. For serum IL-34, the sensitivity was 73.3%, and the specificity was 77.2%. The area under the curve for serum eotaxin-1 was 0.717, and for IL-34, it was 0.719 ($p < 0.001$ for both).

Discussion

In the present study, we compared serum levels of eotaxin-1

Table 2. Spearman correlation analysis of research parameters in patients with OCD

Correlation parameter	*r*	*p*[a]
Age and Y-BOCS score	−0.059	0.660
Age and eotaxin-1	0.154	0.250
Age and IL-34	0.024	0.860
BMI and Y-BOCS score	0.102	0.447
BMI and eotaxin-1	−0.094	0.482
BMI and IL-34	−0.141	0.290
Eotaxin-1 and Y-BOCS score	0.287	0.029
IL-34 and Y-BOCS score	−0.018	0.894
Eotaxin-1 and IL-34	−0.273	0.038

OCD, obsessive-compulsive disorder; Y-BOCS, Yale-Brown obsessive-compulsive scale; IL, interleukin; BMI, body mass index.
[a]Bonferroni-corrected *p*-values.

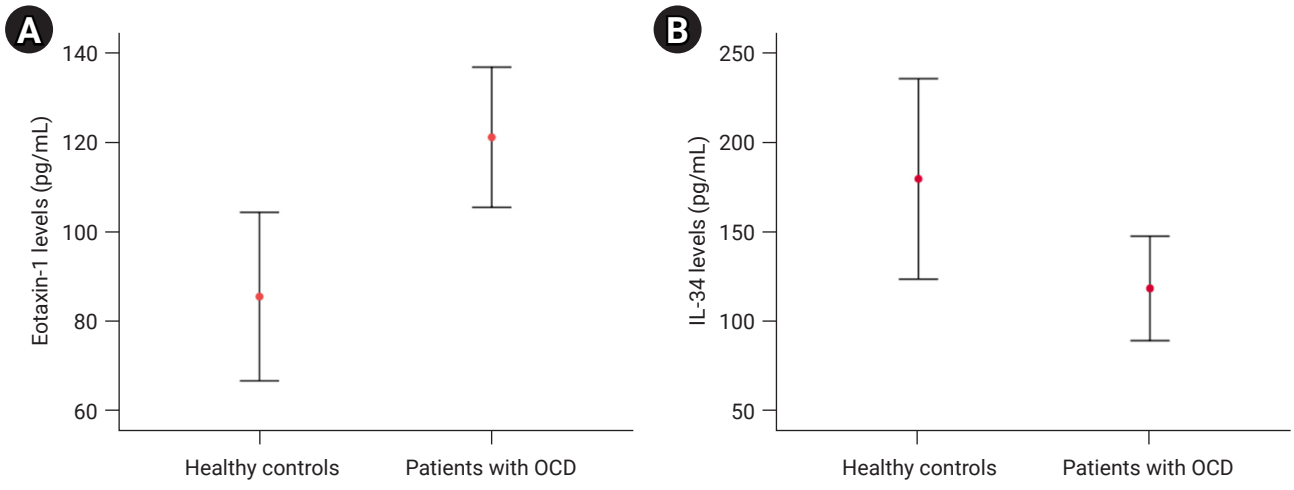

Figure 1. Comparison of serum eotaxin-1 (A) and interleukin (IL)-34 (B) levels between patients with obsessive-compulsive disorder (OCD) and healthy controls.

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Table 3. Receiver operating characteristic curve analysis of serum eotaxin-1 and IL-34 levels

Parameter	Cut-off value (pg/mL)	Sensitivity (%)	Specificity (%)	AUC	95% CI	*p*
Eotaxin-1	83.04	72.4	76.3	0.717	0.598–0.836	<0.001
IL-34	175.62	73.3	77.2	0.719	0.612–0.826	<0.001

IL, interleukin; AUC, area under the curve; CI, confidence interval.

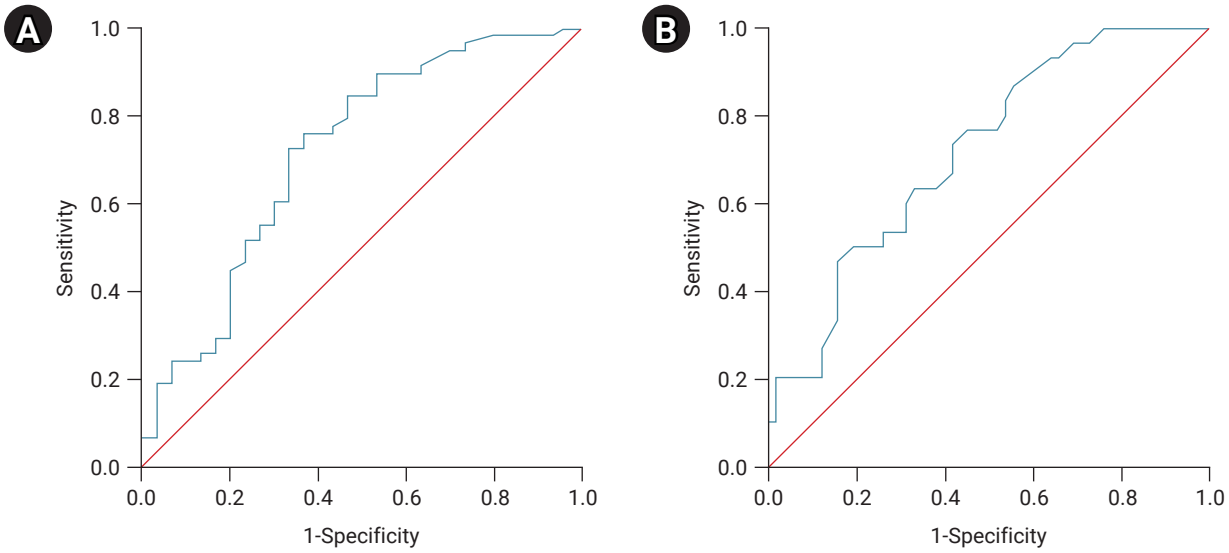

Figure 2. Receiver operating characteristic curves of serum eotaxin-1 levels (A) and serum interleukin 34 levels (B) among the study population.

that both eotaxin-1 and IL-34 exhibit good sensitivity and specificity for distinguishing between patients with OCD and HCs. The study also included no significant differences in sociodemographic and biophysical evaluations between the OCD patients and HCs, suggesting that these factors did not significantly influence the laboratory findings.

Consistent with the findings of this study, previous research has also reported elevated levels of eotaxin-1 in patients with OCD compared to HCs; however, the increase observed in the earlier study was not statistically significant [24]. Studies have suggested that eotaxin-1 plays a critical role in the recruitment of eosinophils to sites of inflammation, which is believed to be a key component of OCD pathophysiology [24,43]. As a chemoattractant, eotaxin-1 binds to the CCR3 receptor on eosinophils, directing them to sites of inflammation where they release inflammatory mediators that contribute to central inflammation [44]. Eotaxin-1 has also been associated with aging, decreased neurogenesis, and neurodegeneration, affecting neural progenitor cells and microglia, which could potentially lead to cognitive impairments associated with OCD [24,45]. Additionally, studies have highlighted the effects of aging, reduced neurogenesis, and mitochondrial dysregulation on OCD [46,47].

Although the current study found statistically significant decreases in serum IL-34 levels, previous research did not establish a direct correlation between IL-34 and OCD. Instead, it reported that IL-34 was involved in inflammation and immune responses. IL-34 acts as a ligand for the colony-stimulating factor 1 receptor, playing a crucial role in the survival, proliferation, and differentiation of macrophages and microglia, which are thought to contribute to the pathophysiological circumstances of OCD [25,32,33]. By promoting microglial activation, IL-34 contributes to the inflammatory response within the central nervous system (CNS) [26]. IL-34 is also found to play a vital role in exerting anti-inflammatory effects by altering leukocyte adhesion and transendothelial migration, and by reducing the secretion of proinflammatory cytokines [48,49]. Additionally, IL-34 has been shown to restore blood-brain barrier integrity by upregulating tight junction proteins, which are often downregulated by proinflammatory cytokines. Thus, decreased IL-34 levels are associated with increased proinflammatory cytokines in the CNS, leading to neuroinflammation, which is involved in the pathogenesis of OCD [50]. In OCD, ongoing neuroinflammation and consequent oxidative stress lead to a predominance of proinflammatory cytokines, further

rationalizing the decreased levels of IL-34 due to its anti-inflammatory nature [16,43,51,52].

The current lack of reliable quantitative diagnostic methods and established biomarkers for mental disorders, such as OCD, is notable [53–56]. Research into these biomarkers can markedly improve our understanding of OCD by illuminating the roles of immunomodulation, neuroinflammation, neurodegeneration, and oxidative stress in the development and persistence of the condition. Overall, investigating eotaxin-1 and IL-34 as potential biomarkers for OCD may improve diagnostic precision, advance new treatment options, and enrich our understanding of the mechanisms underlying this disorder.

The present study has several notable strengths. It represents the first investigation to examine eotaxin-1 and IL-34 levels among patients with OCD within a homogeneous population, achieved through stringent application of exclusion criteria. Globally, only a limited number of studies have explored these chemokines and cytokines in individuals with OCD, with inconclusive results. This research utilized ROC analysis, which demonstrated good sensitivity and specificity, indicating that the altered parameters have diagnostic accuracy for differentiating patients from healthy individuals. As such, this study offers new insights to the existing body of knowledge in the field. Additionally, the study specifically selected patients who had not been exposed to medication, ensuring that the biomarker levels were not influenced by pharmaceutical interventions. This approach supports the generalizability and reliability of the research findings.

The current research also has certain limitations that should be acknowledged. First, as with any cross-sectional study that employs random sampling, the findings may exhibit some degree of variability. The limited sample size and the inclusion of individuals with a history of smoking could introduce confounding factors that affect the analysis of biomarkers. Additionally, this study did not account for variables such as diet, physical activity, and sleep patterns. The correlation coefficients between variables were moderate, indicating that the observed relationships should be interpreted with caution. Therefore, the findings of this research should be considered preliminary. To improve the robustness of the results, further investigations are necessary. These should explore a broader range of cytokines and involve a larger and more homogeneous population, taking into account any potential confounding factors associated with OCD.

The results of this study suggest that eotaxin-1 and IL-34 may be valuable as diagnostic biomarkers for OCD. By measuring the levels of these biomarkers, clinicians may gain key insights into the processes of immunomodulation, neuroinflammation, neurodegeneration, and oxidative stress that are associated with OCD. Incorporating eotaxin-1 and IL-34 into the evaluation process, such as in interventional studies, could improve clinical decision-making and facilitate the delivery of more personalized and targeted treatments for patients with OCD.

The present findings highlight the relationship between serum eotaxin-1 and IL-34 levels and the pathophysiology and progression of OCD. A thorough understanding of the disease's pathogenesis, including the relevant immune and inflammatory markers, is essential for effective patient management. Based on the results of this study, we recommend the following: (1) the use of serum eotaxin-1 and IL-34 levels as risk assessment tools for evaluating patients with OCD; (2) the recognition of the significance of eotaxin-1 and IL-34 through ROC analysis; (3) the development of targeted therapeutic interventions that address alterations in cytokines and chemokines in patients with OCD; and (4) the provision of dietary recommendations that may be beneficial in managing OCD symptoms.

Conclusion

Altered levels of eotaxin-1 and IL-34 in patients with OCD may be linked to the condition. The significant increase in eotaxin-1 and decrease in IL-34 observed in this study suggest that these cytokines play a role in OCD. By providing new insights into this psychiatric disorder, the findings could lead to the development of practical and reliable diagnostic tools. Identifying these specific biomarkers in OCD could increase diagnostic precision, enable targeted treatments, and ultimately improve patient outcomes. These results not only contribute to the growing body of knowledge about OCD but also highlight the importance of further research to validate these findings and discover new information that could lead to more effective diagnostic and therapeutic strategies for this challenging disorder.

Notes

Ethics Approval

The Research Ethics Committee (REC) of the University of Asia Pacific (UAP) has approved the study protocol (UAP/REC/2023/207). Informed written consent was obtained from all participants prior to data collection. Additionally, we secured written informed consent for the publication of these anonymous study results. The investigations were conducted in accordance with the principles outlined in the Helsinki Declaration.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data
The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: SIH, RS, MRI; Data curation: SIH, RS; Formal analysis: SIH, SMAI; Funding acquisition: MRI; Investigation: MRI, SIH; Methodology: MRI; Project administration: MRI; Supervision: MRI; Validation: MAB; Visualization: MMASQ; Writing–original draft: SIH, RS; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Short Communication

Characteristics and trends of severe/critical COVID-19 cases in the Republic of Korea (January 2020 to August 2023)

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ABSTRACT

Objectives: We analyzed the demographic and clinical characteristics of patients diagnosed with coronavirus disease 2019 (COVID-19), focusing specifically on severe/critical cases, and assessed the trends and rates of severity and fatality among these patients in the Republic of Korea.

Methods: Clinical data on patients with COVID-19 from January 20, 2020 to August 30, 2023 were collected from the Korea Disease Control and Prevention Agency's database. We identified patients who progressed to severe/critical conditions and analyzed their demographic and clinical profiles. Severity and fatality rates were calculated and compared annually to track the disease progression over time.

Results: During the surveillance period, 34,572,554 COVID-19 cases were confirmed, among whom 38,112 (0.11%) progressed to severe/critical conditions. Most severe/critical cases occurred in individuals aged ≥60 years, with a notable increase in patients aged ≥80 years from 2022. The overall severity rate was 0.19%, with a fatality rate of 0.10%. However, the severity of cases gradually diminished during the study period. In 2022, the severity and fatality rates decreased to 0.14% and 0.09%, respectively. In 2023, while the severity rate remained stable at 0.15%, the fatality rate further decreased to 0.06%. Notably, throughout the study period, individuals aged ≥80 years had a significantly higher severity rate (2.44%), with a fatality rate of 1.75%.

Conclusion: These findings underscore the importance of prioritizing protection and management strategies for older adults and high-risk groups to mitigate the impact of COVID-19. Continued surveillance and analysis are essential to effectively control COVID-19 and minimize its burden on public health.

Keywords: COVID-19; Fatality rate; Severe/critical cases; Severity rate

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 [1]. Since its initial outbreak in Wuhan, China, in December 2019, COVID-19 has led to over 770 million confirmed cases worldwide, with more than 6.9 million deaths reported as of August 27, 2023, corresponding to a fatality rate of 0.9% [2]. In the Republic of Korea, from the first confirmed case on January 20, 2020, to August 30, 2023, there have been a total of 34,572,554 confirmed cases and 35,605 deaths, yielding a significantly lower fatality rate of 0.10% [3].

The World Health Organization declared a public health emergency of international concern on January 31, 2020 [4], and later classified the situation as a pandemic on March 12, 2020 [5]. In the Republic of Korea, following a 1-month delay after the first confirmed case on January 20, 2020, authorities elevated the crisis alert to the highest level, "serious," on February 23 [6]. Initially, COVID-19 was categorized as a class 1 statutory infectious disease under the category of emerging infectious diseases. Thanks to effective measures such as a high vaccination rate and the availability of oral medications, the disease was reclassified to class 2 on April 25, 2022, and subsequently downgraded further to class 4 on August 31, 2023.

Severity classification is critical for the development and management of effective medical response systems. It informs decisions regarding the allocation of hospital beds, options for home treatment, distribution of healthcare resources, and the formulation of treatment plans. During the early stages of the COVID-19 outbreak in the Republic of Korea, the government enforced stringent control measures. These included mandatory isolation, hospitalization, and daily health monitoring for all infected individuals, symptomatic or not, to prevent the virus from spreading. As the strategy shifted towards adapting to life with COVID-19 ("with COVID"), the focus on managing severe and critical patients intensified. Prompt identification and treatment of these high-risk cases are crucial to avoid a significant rise in mortality rates as normal activities resume. Proactive measures are particularly important, considering the potential for rapid increases in cases, as observed in other countries.

In the Republic of Korea, continuous assessments of severity throughout the pandemic have guided the allocation of hospital beds, the estimation of healthcare resources, and the production of weekly reports on severity and fatality rates. This data is a vital indicator for public health strategies, aiding in the reduction of COVID-19's impact on community health, healthcare systems, lifestyles, and economic conditions [7].

HIGHLIGHTS

- We collected demographic and clinical characteristics of confirmed coronavirus disease 2019 cases from January 20, 2020 to August 30, 2023 to assess trends in health status related to the virus.
- The severity and fatality rates were 0.19% and 0.10%, respectively.
- The majority of severe/critical cases occurred in individuals aged ≥60 years, with more than half (52.8%, 20,136 cases) identified during the 2022 surveillance period.
- Intensive protection and management of older adults and high-risk groups, as well as prompt and accurate surveillance and analysis of severe/critically ill patients, are crucial for reducing severity and fatality rates.

Therefore, we analyzed the characteristics, severity, and fatality rates of patients with severe/critical COVID-19 in the Republic of Korea, from the first confirmed case in January 2020 to the conclusion of mandatory surveillance on August 30, 2023. This analysis aims to inform future pandemic control policies, resource allocation, and healthcare preparedness.

Materials and Methods

Study Population

This study examined the magnitude of outbreaks and the demographic characteristics of patients who developed severe/critical illness among confirmed COVID-19 cases, as reported by the Korea Disease Control and Prevention Agency (KDCA) COVID-19 Information Management System. The analysis covered the period from January 20, 2020, the date of the first confirmed case in the Republic of Korea, to August 30, 2023. A confirmed COVID-19 case was defined as an individual with a confirmed infection identified either through COVID-19 gene detection or virus isolation, regardless of clinical symptoms. This definition also included individuals who exhibited COVID-19 symptoms and had a confirmed infection determined by rapid antigen testing (implemented by experts since March 14, 2022) or emergency screening tests [8].

We classified the severity of COVID-19 into 8 stages: stages 1 to 2, mild/less severe illness (stage 1, no interference with daily life; stage 2, interference with daily life, but no need for oxygen therapy); stages 3 to 4, moderate illness

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requiring oxygen therapy (stage 3, oxygen therapy with nasal prongs; stage 4, oxygen mask); stages 5 to 7, severe/critical illness involving advanced oxygen support or organ failure (stage 5, non-invasive mechanical ventilation/high-flow oxygen therapy; stage 6, invasive mechanical ventilation; stage 7, multi-organ damage, extracorporeal membrane oxygenation, and continuous renal replacement therapy); and stage 8, death [8].

We primarily analyzed data from stages 5 to 7 (severe/critical) and stage 8 (death) to calculate the severity and fatality rates. However, we recognize the potential for underreporting of severe/critical cases, particularly regarding deaths at long-term care facilities. To account for this possible underestimation, we included death data in our adjustments [7].

The clinical status of confirmed cases was monitored through the KDCA COVID-19 Information Management System and the Integrated Reporting Portal for Health and Medical Resources. When necessary, phone calls and emails were utilized. Data concerning COVID-19 fatalities were gathered using the KDCA system in accordance with the Infectious Disease Prevention and Management Act in the Republic of Korea. Reported death cases were subject to expert review, and those attributed to other diseases or external causes were excluded to maintain data accuracy [9].

All collected data were anonymized to protect patient privacy. Personal information was removed, and unique identification numbers were assigned to each dataset. The anonymized data were then stored on encrypted computers with restricted external access.

Data Analysis

To analyze the characteristics of severe/critical patients, we conducted a frequency analysis based on demographics such as sex, age, and reported region, with the data categorized by year. We assessed community severity by classifying cases into 2 categories: severe/critical and death. We then calculated severity and fatality rates by year and age group. The severity rate indicates the percentage of confirmed cases that were classified as severe, critical, or deceased during the mandatory surveillance period. This rate was determined by calculating the proportion of severe, critical patients, and deaths among the confirmed cases and then multiplying by 100% to generate a percentage (%). Similarly, the fatality rate was calculated as the proportion (%) of deaths among confirmed cases during the same period. To compute age-standardized severity and fatality rates, we used mid-year population data, which reflects the population distribution for the respective years [10]. Age groups were divided into 10-year intervals to enable a comparison of severity rates across different ages. Basic statistical analyses were conducted using Microsoft Excel ver. 2018 (Microsoft Corp.).

Ethics Approval

The study protocol was approved by the Institutional Review Board (IRB) of the KDCA (IRB-2022-10-03-PE-A). Obtaining informed consent was exempted by the IRB as there was no personal information in the study.

Results

General Characteristics

During the mandated COVID-19 surveillance period from January 20, 2020, to August 30, 2023, a total of 34,572,554 confirmed cases were recorded. Among these, 38,112 (0.11%) progressed to a severe/critical condition. Notably, the highest number of confirmed cases was observed in 2022, accounting for 52.8% (20,136) of all severe/critical cases identified during the monitoring period (Table 1).

Daily monitoring of severely/critically ill patients showed a peak in new severe/critical cases on March 29, 2022, with 244 reported cases. However, the number of hospitalized severe/critical cases reached a peak of 1,315 on March 31, 2022, with a daily average of 285. This is more than 10 times the daily average of new severe/critical cases (Table 1; Figure 1).

Men constituted the majority of severe/critical cases, totaling 22,005 cases or 57.7%. The average age of patients in severe/critical conditions over the period was 71.3 years, with a standard deviation (SD) of 15.7 years. This average age showed slight variations annually: it was 70.6 years (SD, 12.2 years) in 2020, dropped to 65.7 years (SD, 15.3 years) in 2021, and increased to 73.2 years (SD, 15.6 years) in 2022 and 73.8 years (SD, 15.4 years) in 2023. Notably, except for 2021, the average age consistently remained in the 70s.

In terms of age distribution, individuals aged ≥80 years constituted the largest group, accounting for 34.7% (13,218 cases), followed by those aged 70 to 79 years at 26.4% (10,072 cases), and 60 to 69 years at 20.7% (7,893 cases). Notably, individuals aged ≥60 years comprised 81.8% (31,183 cases) of all severe/critical patients (Table 1).

Over half of the severe/critical cases (61.7%, 23,510 cases) were reported in metropolitan areas (Seoul, Gyeonggi, and Incheon) (Table 1). Non-metropolitan areas contributed 38.0% (14,476 cases) of the cases, with only a negligible 0.3% (126 cases) identified through quarantine procedures. Within the metropolitan regions, Seoul accounted for the highest proportion of cases (27.3%, 10,401 cases), followed by Gyeonggi (26.9%, 10,260 cases) and Incheon (7.5%, 2,849

Table 1. Characteristics of severe and critically ill patients by year

Class	Total (January 20, 2020–August 31, 2023)	2020 (from January 20, 2020)	2021	2022	2023 (until August 31, 2023)
Total	38,112 (100.0)	1,731 (100.0)	10,185 (100.0)	20,136 (100.0)	6,060 (100.0)
Sex					
Male	22,005 (57.7)	1,019 (58.9)	5,978 (58.7)	11,443 (56.8)	3,565 (58.8)
Female	16,107 (42.3)	712 (41.1)	4,207 (41.3)	8,693 (43.2)	2,495 (41.2)
Age (y)	71.3±15.7	70.6±12.2	65.7±15.3	73.2±15.6	73.8±15.4
0–9	212 (0.6)	0 (0.0)	4 (0.0)	145 (0.7)	63 (1.0)
10–19	158 (0.4)	0 (0.0)	27 (0.3)	259 (1.3)	84 (1.4)
20–29	389 (1.0)	8 (0.5)	151 (1.5)	181 (0.9)	49 (0.8)
30–39	903 (2.4)	14 (0.8)	467 (4.6)	338 (1.7)	84 (1.4)
40–49	1,699 (4.5)	60 (3.5)	845 (8.3)	640 (3.2)	154 (2.5)
50–59	3,568 (9.4)	186 (10.7)	1,580 (15.5)	1,406 (7.0)	396 (6.5)
60–69	7,893 (20.7)	464 (26.8)	2,684 (26.4)	3,644 (18.1)	1,101 (18.2)
70–79	10,072 (26.4)	581 (33.6)	2,527 (24.8)	5,297 (26.3)	1,667 (27.5)
≥80	13,218 (34.7)	418 (24.1)	1,904 (18.7)	8,371 (41.6)	2,525 (41.7)
≥60	31,183 (81.8)	1,463 (84.5)	7,115 (69.9)	17,312 (86.0)	5,293 (87.3)
Region					
Metropolitan area	23,510 (61.7)	1,177 (68.0)	7,692 (75.5)	11,641 (57.8)	3,000 (49.5)
Seoul	10,401 (27.3)	673 (38.9)	4,192 (41.2)	4,353 (21.6)	1,183 (19.5)
Gyeonggi	2,849 (7.5)	117 (6.8)	694 (6.8)	1,670 (8.3)	368 (6.1)
Incheon	10,260 (26.9)	387 (22.4)	2,806 (27.6)	5,618 (27.9)	1,449 (23.9)
Non-metropolitan area	14,476 (38.0)	530 (30.6)	2,394 (23.5)	8,493 (42.2)	3,059 (50.5)
Chungcheong	3,251 (8.5)	101 (5.8)	608 (6.0)	1,901 (9.4)	641 (10.6)
Daejeon	898 (2.4)	32 (1.8)	196 (1.9)	490 (2.4)	180 (3.0)
Sejong	86 (0.2)	0 (0.0)	11 (0.1)	56 (0.3)	19 (0.3)
Chungbuk	757 (2.0)	22 (1.3)	156 (1.5)	460 (2.3)	119 (2.0)
Chungnam	1,510 (4.0)	47 (2.7)	245 (2.4)	895 (4.4)	323 (5.3)
Honam	2,325 (6.1)	63 (3.6)	280 (2.7)	1,441 (7.2)	541 (8.9)
Gwangju	829 (2.2)	28 (1.6)	89 (0.9)	545 (2.7)	167 (2.8)
Jeonbuk	728 (1.9)	21 (1.2)	107 (1.1)	443 (2.2)	157 (2.6)
Jeonnam	768 (2.0)	14 (0.8)	84 (0.8)	453 (2.2)	217 (3.6)
Gyeongbuk	2,855 (7.5)	240 (13.9)	409 (4.0)	1,643 (8.2)	563 (9.3)
Deagu	1,820 (4.8)	185 (10.7)	283 (2.8)	1,054 (5.2)	298 (4.9)
Gyeongbuk	1,035 (2.7)	55 (3.2)	126 (1.2)	589 (2.9)	265 (4.4)
Gyeongnam	4,453 (11.7)	99 (5.7)	834 (8.2)	2,568 (12.8)	952 (15.7)
Busan	2,366 (6.2)	62 (3.6)	416 (4.1)	1,394 (6.9)	494 (8.2)
Ulsan	669 (1.8)	15 (0.9)	150 (1.5)	376 (1.9)	128 (2.1)
Gyeongnam	1,418 (3.7)	22 (1.3)	268 (2.6)	798 (4.0)	330 (5.4)
Gangwon	1,361 (3.6)	22 (1.3)	227 (2.2)	825 (4.1)	287 (4.7)
Jeju	231 (0.6)	5 (0.3)	36 (0.4)	115 (0.6)	75 (1.2)
Quarantine station	126 (0.3)	24 (1.4)	99 (1.0)	2 (0.0)	1 (0.0)

Data are presented as *n* (%) or mean±standard deviation.

cases). Among non-metropolitan areas, Busan recorded the highest proportion of cases (6.2%, 2,366 cases), followed by Daegu (4.8%, 1,820 cases) and Chungnam (4.0%, 1,510 cases) (Table 1).

Clinical Characteristics

The average duration from diagnosis to the onset of severe/critical illness was 6.6 days. This duration has decreased over time: from 8.2 days in 2020, to 7.7 days in 2021, 6.4 days in 2022, and down to 5.0 days in 2023, as shown in Table 2. Children aged 0 to 9 years experienced the quickest progression to severe/critical illness, averaging 4.5 days, while patients aged 30 to 39 years had the slowest progression, averaging 7.5 days.

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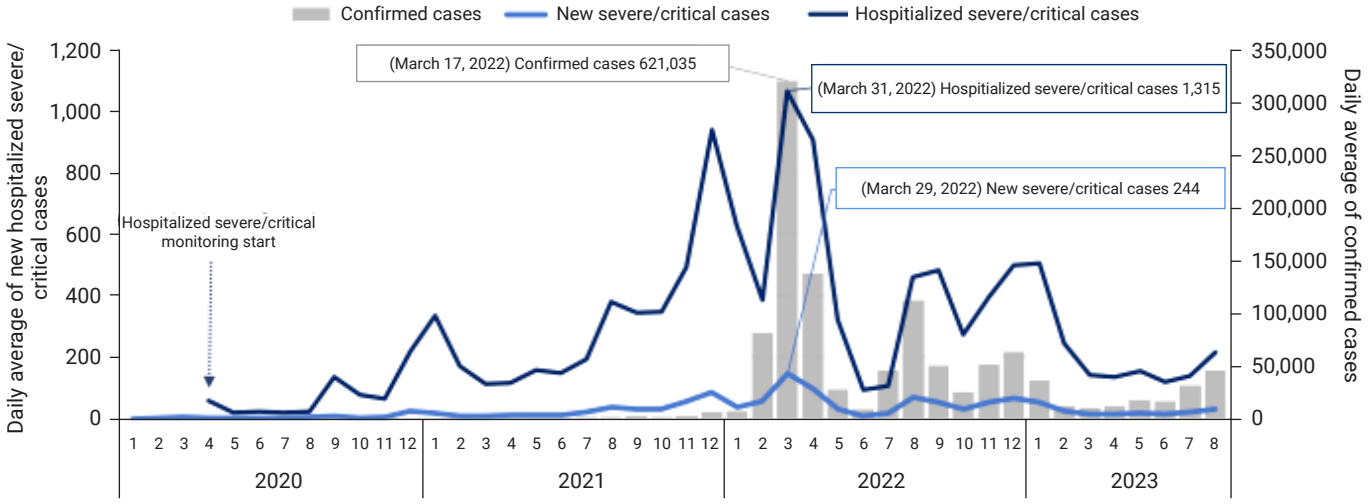

Figure 1. Trends in monthly confirmed cases, severe/critical cases, and deaths due to COVID-19 during the study period. The solid lines represent monthly averages, while the peak values provided above the graphs correspond to the single highest daily value recorded within each month. For example, the maximum number of daily cases was recorded on March 17, 2022, within the monthly trend for March 2022, is represented as "March 17, 2022." This distinction between monthly averages and daily peak values is intended to provide both overall trends and critical peak days during the pandemic.

Table 2. Duration from diagnosis to severe/critical illness and length of isolation treatment by age group

Age group (y)	Period from diagnosis to progression to a severe/critical condition (d)[a]					Period of isolated treatment for severe/critical condition (d)[b]				
	Total[c]	2020[d]	2021	2022	2023[e]	Total[c]	2020[d]	2021	2022	2023[e]
Total	6.6	8.2	7.7	6.4	5.0	9.3	14.0	10.7	8.7	7.8
≤19	5.1	-	8.6	5.1	4.2	7.3	-	7.0	6.0	11.3
20–59	7.3	7.4	8.1	6.8	5.3	8.8	10.7	9.2	8.3	7.6
≥60	6.5	8.3	7.5	6.4	5.0	9.5	14.8	11.6	8.8	7.8
0–9	4.5	-	5.0	4.7	4.0	7.8	-	10.0	5.7	12.5
10–19	6.0	-	9.2	5.6	4.5	6.6	-	6.7	6.5	7.4
20–29	7.2	8.0	8.2	7.2	4.2	6.9	7.3	6.6	7.2	6.4
30–39	7.5	6.9	8.4	6.9	5.4	8.4	7.3	8.8	7.9	8.1
40–49	7.4	8.5	8.1	6.6	6.4	8.5	10.4	8.8	8.2	7.5
50–59	7.1	7.1	7.9	6.8	5.0	9.2	11.2	9.8	8.7	7.7
60–69	6.8	8.0	7.4	6.7	5.1	9.6	12.5	11.0	8.7	7.7
70–79	6.5	7.9	7.2	6.6	5.0	9.9	17.0	12.3	8.8	7.7
≥80	6.3	9.3	8.0	6.1	5.0	9.1	15.1	11.7	8.9	7.9

-, No cases.
[a]Average duration from diagnosis to progression to a severe/critical condition. [b]Average duration from severe/critical condition to release from isolated treatment for severe/critical conditions (excluding deceased patients). [c]January 20, 2020–August 31, 2023. [d]From January 20, 2020. [e]Until August 31, 2023.

The average duration of isolated treatment for severe/critical cases was 9.3 days. This duration decreased over time, similar to the progression to severe/critical illness: from 14.0 days in 2020 to 10.7 days in 2021, 8.7 days in 2022, and 7.8 days in 2023 (Table 2). The shortest average isolated treatment period was observed in individuals aged 10 to 19 years (6.6 days), while the longest was in those aged 70 to 79 years (9.9 days).

Trends in the Severity and Fatality Rates

The overall severity rate of COVID-19 throughout the study period was 0.19%. There was a significant annual decrease,

with the rate dropping from 4.33% in 2020 to 0.14% in 2022 and 0.15% in 2023, compared to 2.25% in 2021. The standardized severity rate remained consistent at 0.19% during the study period. Annually, the rates were 3.19% in 2020, 2.23% in 2021, 0.15% in 2022, and 0.12% in 2023, demonstrating a decreasing trend similar to that of the severity rate.

The overall fatality rate during the outbreak was 0.10%. The severity of the outbreak showed a consistent decline, with fatality rates decreasing to 2.16% in 2020, 0.91% in 2021, 0.09% in 2022, and 0.06% in 2023. Throughout the study period, the standardized fatality rate remained at 0.10%. Over time, this rate also showed a downward trend, falling from 1.58% in 2020 to 0.95% in 2021, 0.10% in 2022, and finally to 0.05% in 2023.

Both severity and fatality rates generally increased with age across all years. However, deviations from this trend were observed in 2021 compared to 2020. Specifically, the severity rate for individuals aged ≤59 years rose in 2021, while it declined for those aged ≥60 years. Similarly, the fatality rate in 2021 decreased relative to 2020 for all age groups, except for those aged 0 to 9, 20 to 29, and 40 to 49 years. These findings indicate that age-related changes in severity may exhibit slight annual variations (Table 3).

Discussion

This study represents the first comprehensive analysis of data on all severe/critical COVID-19 patients in the Republic of Korea, spanning from the initial confirmed case to the conclusion of mandatory surveillance. In 2022, the rise of the Omicron variant precipitated a marked escalation in confirmed cases, especially among high-risk individuals in vulnerable facilities [11,12]. This increase underscores the

Table 3. Case severity and fatality rate by year (based on confirmed diagnosis date) (unit: %)

Class	Total (January 20, 2020–August 31, 2023[a])	2020 (from January 20, 2020)	2021	2022	2023 (until August 31, 2023[a])
Case severity rate[b]					
Age group (y)					
Total	0.19	4.33	2.25	0.14	0.15
0–9	0.01	0.00	0.01	0.01	0.03
10–19	<0.01	0.00	0.04	<0.01	<0.01
20–29	0.01	0.09	0.19	0.01	0.01
30–39	0.02	0.26	0.59	0.01	0.01
40–49	0.04	0.74	1.09	0.02	0.02
50–59	0.10	1.91	2.11	0.06	0.06
60–69	0.27	6.19	3.79	0.18	0.18
70–79	0.76	16.69	9.22	0.60	0.47
≥80	2.44	30.64	19.55	2.31	1.41
Age-standardized severity rate	0.19	3.19	2.23	0.15	0.12
Case fatality rate[c]					
Age group (y)					
Total	0.10	2.16	0.91	0.09	0.06
0–9	<0.01	0.00	0.01	<0.01	<0.01
10–19	<0.01	0.00	0.00	<0.01	<0.01
20–29	<0.01	0.00	0.01	<0.01	<0.01
30–39	<0.01	0.05	0.04	<0.01	<0.01
40–49	0.01	0.08	0.09	0.01	0.01
50–59	0.03	0.38	0.33	0.03	0.02
60–69	0.11	1.68	1.07	0.09	0.05
70–79	0.40	7.76	4.22	0.36	0.16
≥80	1.75	24.06	14.25	1.72	0.73
Age-standardized fatality rate	0.10	1.58	0.95	0.10	0.05

[a]The fatality rate was analyzed by continuously observing the progress of confirmed patients during each respective period. The monitoring period includes confirmed cases up to 2 weeks prior (August 12th, 2023, 12 AM). [b]Case severity rate: (no. of severe/critical cases and deaths among confirmed cases in a specific period)/no. of confirmed cases in a specific period×100. [c]Case fatality rate: (no. of deaths among confirmed cases in a specific period)/no. of confirmed cases in a specific period×100.

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potential for a corresponding rise in severe/critical cases among older adults.

To prepare for this scenario, researchers analyzed the severity and fatality rates of Omicron cases using data from the ongoing monitoring of severe/critical patients [13]. This scientific evidence enabled the government to quickly communicate the necessity for preventive measures, including border restrictions and stricter quarantine protocols, to curb the spread of the variant [14]. The monitoring system implemented for severe/critical cases played a key role in an effective response to infectious diseases, ensuring preparedness and protecting citizens. We also consider it to be a contributing factor in maintaining a relatively stable proportion of older adults among these high-risk patients over time.

An analysis of critically ill patients by age revealed that most were older adults (≥60 years). The proportion of patients aged ≥80 years increased starting in 2022, and pediatric cases (<19 years) began to emerge in 2021. Notably, while individuals aged ≥60 years accounted for only about 20% of the total COVID-19 cases throughout the study period, they represented 70% to 80% of the critically ill patients. This disparity became even more pronounced from 2022 to 2023, with this age group accounting for over 85% of critically ill cases. Interestingly, a similar trend was observed in the United States, where 62.5% of hospitalized patients with COVID-19 from January to August 2023 were aged ≥65 years [15].

The average time from diagnosis to the onset of severe/critical illness was 6.6 days, with the youngest age group (under 19 years) experiencing the shortest duration, averaging 5.1 days. This duration has decreased over time, falling from 8.2 days in 2020 to 5.0 days in 2023 (Figure 1, Figures S1, S2).

The average duration of isolated treatment for severe/critical cases was 9.3 days. Individuals aged ≥60 years experienced the longest isolation period, averaging 9.5 days. This prolonged duration may be attributed in part to policy changes, including modifications to isolation criteria in response to new variants and changes in the severity of the disease over the course of the pandemic.

Additional analyses are necessary to comprehensively assess the factors influencing disease progression. This involves considering patient factors, including underlying conditions, and clinical factors, such as vaccination status and the use of COVID-19 therapeutics. Such analysis is crucial for evaluating the effectiveness of vaccination programs.

This study underscores the importance of rapid and efficient responses to future pandemics, though several limitations persist. First, the current surveillance system for patients with severe COVID-19 depends on data reported by public health centers and medical institutions. Delays in reporting, particularly during spikes in severe cases or patient deaths, can result in an underestimation of the true extent of severe illness. While the Republic of Korea employs various systems to ensure accurate monitoring, challenges in data linkage highlight the necessity for enhanced monitoring systems in future pandemics. Second, this study utilized descriptive statistics to explore overall trends in severity across the entire population. However, the absence of detailed information necessary for comparing urban and rural areas or for analyzing specific types of medical institutions limited the scope of the analysis. Moreover, variations in the definitions of severe/critical cases across different countries complicate international comparisons. For example, while the Republic of Korea uses specific criteria such as intensive care unit admission or ventilator use to classify severe cases, some countries consider all hospitalized cases as severe. These discrepancies hinder uniform analysis and make cross-country comparisons challenging. These constraints underscore the need for integrating diverse datasets and conducting more standardized, in-depth investigations to enable more refined analyses.

Despite the decreasing trends in severity and fatality rates, our findings highlight the ongoing vulnerability of older adults. It is crucial to focus on protective and management strategies, particularly prioritizing vaccination efforts for this age group, to prepare for future outbreaks.

Supplementary Material

Figure S1. Average monitoring period by progression to a severe/critical condition; **Figure S2.** (A) Duration from diagnosis to progression to a severe/critical condition by age group. (B) Duration of isolated treatment for severe/critical conditions by age group (hospitalization period). Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0295.

Notes

Ethics Approval

The study protocol was approved by the Institutional Review Board of the KDCA (IRB-2022-10-03-PE-A). Obtaining informed consent was exempted by the IRB as there was no personal information in the study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: SJJ; Data curation: SJJ, SYP; Formal analysis: SJJ, JHJ; Investigation: SJJ, MS, BR, SYC; Methodology: SJJ, SYP; Project administration: SJJ; Resources: SJJ; Software: SJJ; Supervision: SSK; Validation: SJJ, SYP, JHJ; Visualization: SJJ, JHJ; Writing–original draft: SJJ; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Commentary

Polycystic ovary syndrome, cardiovascular risk, and coffee: a complex interplay

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The recent article by Ildarabadi et al. [1], "Effects of green coffee supplementation on paraoxonase-1 activity and malondialdehyde levels in Iranian women with polycystic ovary syndrome: a randomized clinical trial," published in *Osong Public Health Research Perspectives* (2024), highlights the potential benefits of green coffee in addressing metabolic and oxidative stress-related aspects of polycystic ovary syndrome (PCOS). This compelling research inspires further exploration into the intricate relationships among PCOS, cardiovascular risk, and coffee consumption.

PCOS is a multifaceted endocrine disorder with significant metabolic and cardiovascular implications. Its prevalence among women of reproductive age underscores the importance of understanding and mitigating associated risks [2]. Recent studies have emphasized oxidative stress, dyslipidemia, and insulin resistance as central mechanisms driving cardiovascular complications in PCOS [3,4]. Intriguingly, coffee—a widely consumed beverage with antioxidant properties—has emerged as a potential modulator of these risks [5].

Coffee contains bioactive compounds such as chlorogenic acid, which is known for its antioxidative and anti-inflammatory effects [5]. Evidence suggests that moderate coffee consumption may increase paraoxonase-1 (PON-1) activity, reduce oxidative stress markers like malondialdehyde, and improve the lipid profile [6]. The randomized trial conducted by Ildarabadi et al. [1] demonstrated that green coffee supplementation significantly increased PON-1 levels and lowered cholesterol and triglyceride levels in women with PCOS. These findings align with broader research indicating that coffee has the potential to modulate metabolic pathways implicated in PCOS, including those influencing glucose and lipid metabolism [7].

However, the relationship between coffee and cardiovascular health in PCOS is complex. High caffeine intake can intensify sympathetic nervous system activity, potentially increasing the risk of arrhythmia in predisposed individuals [8]. Moreover, disparities in the effects of coffee may arise due to varying caffeine tolerance, genetic predispositions, and the hormonal milieu specific to PCOS [7,8].

Despite these complexities, integrating coffee or its bioactive components into dietary recommendations offers promise as a complementary strategy for cardiovascular risk reduction in PCOS [9]. Future research should aim to establish dose-response relationships, explore the long-term impacts of coffee consumption, and examine interactions with common pharmacological treatments for PCOS. Such insights will be instrumental in developing

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personalized interventions for this high-risk population [10].

Thank you for the opportunity to share these observations. I hope they contribute to ongoing discourse and encourage further exploration of this pertinent intersection.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
The author has no conflicts of interest to declare.

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None.

Availability of Data
Not applicable.

HIGHLIGHTS

- Bioactive compounds in coffee, such as chlorogenic acid, have antioxidative and anti-inflammatory effects, which may help reduce oxidative stress and metabolic dysfunction commonly seen in polycystic ovary syndrome (PCOS).
- Moderate coffee consumption has been associated with increased paraoxonase-1 (PON-1) activity and improved lipid profiles, which could help mitigate the heightened cardiovascular risk in women with PCOS.
- While coffee may offer benefits, excessive caffeine intake can stimulate the sympathetic nervous system, potentially worsening arrhythmia risk in predisposed individuals with PCOS, necessitating personalized dietary recommendations.

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Instruction for authors

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Osong Public Health and Research Perspectives (PHRP) is the international bimonthly (published at the end of February, April, June, August, October, and December) journal founded in 2010 by the Korea Disease Control and Prevention Agency (KDCA). With the mission of the KDCA, to create a disease-free world, PHRP encourages sharing medical information and knowledge in the areas of public health. PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials and correspondence, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

Before submitting a manuscript, authors should carefully read and follow the instructions for writing an article for PHRP. For issues not addressed in these instructions, authors should refer to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/recommendations/) from the International Committee of Medical Journal Editors (ICMJE). Manuscripts submitted to PHRP that do not follow these instructions will be returned to the authors without further review.

Contact Us

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ARTICLE PROCESSING CHARGES

The author does not have pay publication charges for open access. The KDCA will pay to make the article open access.

RESEARCH AND PUBLICATION ETHICS

The journal adheres to the guidelines and best practices published by professional organizations, including the ICMJE Recommendations and the Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by the Committee on Publication Ethics [COPE], Directory of Open Access Journals [DOAJ], World Association of Medical Editors [WAME], and Open Access Scholarly Publishers Association [OASPA]; https://doaj.org/bestpractice). Furthermore, all processes of handling research and publication misconduct shall follow the applicable COPE guidances (https://publicationethics.org/)

Human and Animal Rights

Clinical research should be conducted in accordance with the World Medical Association's Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) and approved by the Institutional Review Board (IRB) of the institution where the experiment was performed. Animal experiments should also be reviewed by an appropriate committee (Institutional Animal Care and Use Committee [IACUC]) for the care and use of animals. Studies involving pathogens requiring a high degree of biosafety should pass review of a relevant committee (Institutional Biosafety Committee [IBC]). Clinical studies that do not meet the Helsinki Declaration will not be considered for publication.

Statement of Informed Consent and Institutional Approval

The editor of PHRP may request submission of copies of informed consent forms from human subjects in all studies and IRB approval documents. For articles involving human subjects who can be identified through descriptions, photographs, or pedigrees, a signed informed consent statement must be provided. This consent must be obtained from each identifiable participant, or from a parent or legal guardian if the participant is unable to provide consent. The statement should explicitly permit the publication of the relevant descriptions, photographs, and pedigrees in both print and online formats. Articles describing the use of animals in experiments must be approved by the relevant authorities.

Protection of privacy and confidentiality

Patients have a right to privacy that must not be violated without informed consent. Identifying information, such as names, initials, or hospital numbers, should not be published unless essential for scientific purposes and with written informed consent from the patient (or parent or guardian). Nonessential identifying details should be omitted. If there is any doubt about maintaining anonymity, informed consent is necessary, as masking the eye region in photographs is inadequate. If identifying characteristics are deidentified, authors must assure, and editors must confirm, that these changes do not distort scientific meaning.

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Manuscripts are considered with the understanding that no part of the work has been published previously in print or electronic format and the paper is not under consideration by another publication or electronic medium.

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It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication as described in the ICMJE Recommendations (http://www.icmje.org/icmje-recommendations.pdf).

Plagiarism and Duplicate Publication

Attempting to publish substantially similar work more than once without attribution of the original source(s) is considered a redundant publication. The definition of "substantially similar" is as follows: (1) at least one of the authors is common to all reports (it is likely to be plagiarism if there are no common authors); (2) the subject or study populations are the same or similar; (3) the methodology is typically identical or nearly so and; (4) the results and interpretation vary little or not at all.

If all or part of the subject population has been reported previously, it should be declared in the Materials and Methods and must be appropriately referenced. In cases where authors are concerned with any potential overlap with published manuscripts or manuscripts being reviewed, the authors must include a letter explaining how the manuscript submitted to PHRP significantly differs from other materials. For more information, please refer to ICMJE Recommendation (available at: http://www.icmje.org/recommendations/).

Authorship and the Author's Responsibilities

Authorship credit must be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreeing to be accountable for all aspects of the work in ensuring that the questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The authors should meet these 4 conditions. If the number of authors exceeds 3, the specific role(s) of authors should be described at the end of the main text.

- Correction of authorship: Any requests for changes in authorship (adding author(s), removing author(s), or re-arranging the order of authors) after the initial manuscript submission and before publication should be explained in writing to the editor in a letter or e-mail from all authors. This letter must be signed by all authors of the paper. A copyright assignment must be completed by every author.
- Role of the corresponding author: The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. The corresponding author typically ensures that all of the journal's administrative requirements, such as providing the details of authorship, ethics committee approval, clinical trial registration documentation, and conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely manner, and after publication, should be available to respond to critiques of the work and cooperate with any requests from the journal for data or additional information or questions about the article.
- Contributors: Any researcher who does not meet all 4 ICMJE criteria for authorship discussed above but contributes substantively to the study in terms of idea development, manuscript writing, conducting research, data analysis, and financial support should have their contributions listed in the Notes section of the article.
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for Preventing Illegitimate Authorship" by the National Research Foundation of Korea (https://www.nrf.re.kr/eng/).

Conflict of Interest Statement

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Potential conflicts should be reported even if the authors believe they were not influenced in preparing the manuscript. All authors must disclose i.e., (1) financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony), (2) personal relationship, (3) academic competition, and (4) intellectual passion. These disclosures should be included on the title page.

Role of the Funding Source

The author is requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor (s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement, then this should be stated.

Inclusive Language

Authors are encouraged to use inclusive language that acknowledges diversity, respects all individuals, and promotes equal opportunities. Avoid assumptions about the reader's beliefs or identities, and refrain from language that implies superiority based on factors such as age, gender, race, ethnicity, culture, sexual orientation, disability, or health condition. Writing should be free of bias, stereotypes, and cultural assumptions. Gender neutrality is encouraged by using plural nouns (e.g., "patients") instead of gendered pronouns ("he/she"). Descriptors of personal attributes should only be used if relevant and valid.

Process for Managing Research and Publication Misconduct

When the journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and so on, the resolution process will follow the guidances provided by the COPE (https://publicationethics.org/guidance). The editorial boards of PHRP will carry out the discussion and decision for suspected cases. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

Complaints and Appeals Policy

The policies of PHRP are principally intended to protect the authors, reviewers, editors, and the publisher of the journal. The process of handling complaints and appeals follows the guidances of COPE (https://publicationethics.org/guidance).

Editorial Responsibilities

The Editorial Board will continuously work to monitor and safeguard publication ethics, including guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoiding any conflict of interest with respect to articles they reject or accept; promoting publication of corrections or retractions when errors are found; and preservation of the anonymity of reviewers.

EDITORIAL POLICY

Copyright

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permission to use tables or figures published in PHRP in other journals, books, or media for scholarly and educational purposes.

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PHRP is an open access journal, which means that authors who publish with us are able to freely share their research in various ways, including preprint servers, social media platforms, conferences, and educational materials, in accordance with our open access policy.

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• Published version
The final, published version can be shared immediately upon publication. Under the CC BY-NC 4.0 license, this version permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Data Sharing Policy

To foster transparency, we encourage authors to state the availability of their data in your submission.
Subject to ethical and legal considerations, authors are encouraged to:

- Upload research data during the submission process; otherwise, share research data in a relevant public data repository with DOI for the data location.
- Include a data availability statement linking to the data. If it is not possible to share the data, use the statement to confirm why it cannot be shared.

Clinical Trials: PHRP accepts the ICMJE Recommendations for data sharing statement policies. Authors may refer to the editorial, "Data Sharing Statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in the Journal of Korean Medical Science (https://dx.doi.org/10.3346/jkms.2017.32.7.1051).

Archiving Policy

PHRP provides electronic backup and preservation of access to the journal content in the event the journal is no longer published by archiving the journal content in National Library of Korea and PubMed Central (https://www.ncbi.nlm.nih.gov/pmc/journals/2151/) from the first volume, 2010.

Preprint Policy

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. PHRP allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. PHRP recommend authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program—Similarity Check (Crosscheck) or Copy Killer. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in PHRP, including DOI at PHRP. It is strongly recommended that authors cite the article in PHRP instead of the preprint at their next submission to journals.

Use of Artificial Intelligence (AI)-Assisted Technologies

The journal has adopted policies, as specified by the ICMJE, regarding the use of AI in the preparation of materials intended for publication in the journal. Generative AI, including language models, chatbots, image creators, machine learning, or similar technologies, may be employed to enhance readability and language accuracy in scientific writing. However, chatbots or other AI-assisted technologies cannot be listed as authors.

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It must be clearly reported in a dedicated section of the Methods, or in the Acknowledgements section for article types lacking a Methods section. This disclosure should provide details about the specific tools used, including the model name, version, and manufacturer, along with an explanation of the capacity in which they were utilized. Authors should affirm that there is no plagiarism of text or images in materials produced by AI. It is not acceptable to cite AI-generated material as a primary source.

Peer Review Policy

All papers, including those invited by the editor, are subject to peer review. PHRP has adopted a double-blind peer review policy, where the author identities remain anonymous to the reviewers, and vice versa, and the identities of the reviewers and authors are visible to (decision-making) the editor throughout the peer review process. The Editorial Board selects reviewers based on expertise, publication history, and past reviews. During the peer review process, reviewers can interact directly or exchange information (e.g., via submission systems or email) with only an editor, which is known as "independent review." An initial decision will normally be made within 4–6 weeks after the reviewers agree to review a manuscript. No information about the review process or editorial decision process is published on the article page.

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SUBMISSION & PEER REVIEW PROCESS

Online Submission

All manuscripts should be submitted online at https://mc04.manuscriptcentral.com/osongphrp (PHRP online submission system: ScholarOne). The entire process of manuscript submission, peer-review, and resubmission to PHRP is done through the online system.

Manuscripts submitted to PHRP will be preliminarily reviewed by the Editorial Office. Manuscripts not conforming to the instructions will be returned to the corresponding authors without being considered for publication. Submitted manuscripts are also screened for possible plagiarism or duplicate publication using Crossref Similarity Check. If a paper that might be regarded as duplicate or redundant had already been published in another journal or submitted for publication, the author should notify the fact in advance at the time of submission.

Any inquiry concerning manuscript submission should be directed to the editorial office at ophrp@korea.kr.

Peer Review Process

This journal operates a **double-blind** review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of 2 independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. The detailed review process is as follows.

- The Editorial Office of PHRP receives and reviews all submitted manuscripts, and all submitted manuscripts are considered confidential. The submitted manuscripts are initially screened for formatting. Once the manuscript is provisionally accepted, it is sent to the 2 most relevant reviewers for review.
- The reviewers are selected by the editor from the Editorial Board's database or the board members' recommendation. The reviewers are then requested to evaluate the manuscript based on originality, validity, presentation, and importance and interest, and, when considered necessary, statistics.
- Acceptance of a manuscript depends on the evaluation, critiques, and recommended decision made by the reviewers. A reviewer may recommend "accept," "minor revision," "major revision," and "reject." If there are conflicting decisions between reviewers, or between the author and reviewer(s), the Editor-in-Chief has the full right to decide whether the manuscript will be published in the journal. Three repeated decisions of "major revisions" are equivalent to rejection, and rejected papers will not be considered further.
- The reviewed manuscript with comments, recommendations, and revisions is returned to the corresponding author. The corresponding author is to submit the revised manuscript

accompanied by point-to-point replies to the comments given by the editor and how the revisions have been made. There should be a reasonable explanation for any noncompliance with the recommendations. In cases where references, tables, or figures are moved, added, or deleted during the revision process, renumbering must be done so that all references, tables, and figures are cited in numeric order. If the revised paper is not received within 2 months of decision, the manuscript is considered to have been withdrawn.

- When the final decision on the acceptance of the manuscript is made, the Editorial Office notifies the corresponding author. The peer-review process takes approximately 8–12 weeks.

Submission by Editors

Final decisions regarding manuscript publication are made by the editor-in-chief or a designated editor who does not have any relevant conflicts of interest. In the event that an editor has a conflict of interest with a submitted manuscript or with the authors, the manuscript will be handled by one of the other editors who does not have a conflict with the review and who is not at the same institution as the submitting editor. In such circumstances, full masking of the process will be ensured so that the anonymity of the peer reviewers is maintained.

MANUSCRIPT PREPARATION

General Requirements

- All manuscripts must be in grammatically correct English and should be created using MS Word. The manuscript must be double-spaced and written in an A4 page format. Do not leave a space between paragraphs. Only a single font (preferably Times New Roman) should be used in 11 point with margins of 2.5 cm.
- All pages should be paginated consecutively.
- All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
- Abbreviations: Where a term/definition is repeatedly referred to (i.e., 3 times in the text), it is written in full when it first appears, followed by the subsequent abbreviation in parentheses (even if it was previously defined in the abstract); thereafter, the abbreviation is used.
- Gene nomenclature: Current standard international nomenclature for genes should be adhered to. Genes should be typed in italic font and include the accession number. For human genes, use the genetic notation and symbols approved by the HUGO Gene Nomenclature Committee (http://www.genenames.org/) or refer to PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez).
- Units: Système International (SI) units must be used, with the exception of blood pressure values, which are to be reported in mmHg. Please use the metric system for expressions of length, area, mass, and volume. There should be a space between the numerals and the unit symbol. When indicating time, the 24-hour system is to be used.
- Math formulae: Present simple formulae in the line of normal text where possible and use the solidus (/) instead of a horizontal line for small fractional terms, e.g., X/Y. In principle, variables are to be presented in italics. Powers of e are often more conveniently denoted by "exp." Number consecutively any equations that have to be displayed separately from the text (if referred to explicitly in the text).

Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, authors should adhere the reporting guidelines relevant to their specific research design and submit a checklist. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

Manuscript Types

PHPR publishes editorials, original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews.

- **Original articles** are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. These articles should be written in the following format: title page; abstract and keywords; main body (introduction, materials and methods, results, discussion, conclusion [if any]); references; and tables and figure legends. Manuscript limitations are 5,000 words, excluding the abstract,

references, and tables and figure legends.

- **Review articles** provide concise reviews of subjects important to medical researchers, and can be written by an invited medical expert. These have the same format as original articles, but the details may be more flexible depending on the content. Manuscript limitations are 6,500 words from introduction to conclusion, 100 references, 10 figures and 10 tables. The abstract should not exceed 200 words, and must be written as one unstructured paragraph.
- **Systematic reviews** should adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The template for systematic reviews can be downloaded from https://ophrp.org/file/PHRP_Systematic%20Review_PRISMA.docx.
- **Guidelines** are similar to original articles, but provide evidence-based recommendations expected to impact clinical research and practice. This category can include consensus-based statements of reporting standards or clinical practice guidelines.
- **Data Profiles (including Cohort Profiles)** present large data sets from specific populations that could be analyzed in epidemiological studies. Data Profiles should be structured with the following headings in the main text: Introduction, Collection, Data Resource Use, Strengths and Weaknesses, and Access. Cohort Profiles present up-to-date information about large population-based cohorts for which long-term data collection is planned. Data Profiles should be structured with the following headings in the main text: Introduction, Study Participants, Measurements, Key Findings, Strengths and Weaknesses, and Access. The main text of Data and Cohort Profiles is limited to 4,000 words, with an unstructured abstract of up to 200 words, a maximum of 7 tables and figures, and no more than 40 references.
- **Special Articles** deal with topics or issues that are relevant to public health, but without following a traditional study format. For example, articles in this category may address scientific methodology, wide-ranging ethical and social issues, scientific methodology, or other scholarly topics. Reports from consensus committees and working groups can be published as Special Articles. This category has a main text limit of 3,500 words, with an unstructured abstract of no more than 200 words, a maximum of 7 tables and figures, and no more than 40 references.
- **Brief reports** deal with issues of importance to biomedical researchers and follow the general guidelines for original articles. The manuscript should not exceed 2,000 words, excluding references, tables and figures, and must include a structured abstract of no more than 250 words.
- **Short communications** follow the general guidelines for original articles but present original research and/or preliminary findings in a more concise format with fewer details. The manuscript should not exceed 3,000 words, excluding references, tables, and figures, and must include a structured abstract of no more than 250 words.
- **Viewpoints** may deal with almost any topic deemed to be important in the fields of public health, ethics, health law, prevention, or health policy, and are not typically written in response to a specific article. Viewpoints should have a clear focus and present material in a well-organized and scholarly manner, but should not contain novel research findings or previously unpublished data. Although we welcome unsolicited viewpoint contributions, we request that authors contact the Editorial Office (ophrp@korea.kr) prior to submission to confirm that the proposed topic is suitable for the journal. The main text of Viewpoints is limited to 3,000 words, with an unstructured abstract of up to 150 words, a maximum of 4 tables and figures, and no more than 30 references.
- **Editorials** provide invited perspective on an area of PHRP, dealing with very active fields of research, current interests, fresh insights, and debates. An abstract is not required and a brief unstructured text should be prepared. Although editorials are normally invited or written by an editor, unsolicited editorials may be submitted. Manuscript limitations are 1,000 words and 20 references.
- **Commentaries** are brief articles with a narrow focus. The journal commissions most commentaries, but unsolicited commentaries will also be considered. Commentaries may undergo peer review. The length of commentaries should be limited to 500 words, 10 references, and 2 figure or small table.
- **Correspondence** is a comment from readers regarding a published article with a reply from the authors of the article. Manuscript limitations are 500 words, 2 tables/figures, and 5 references.
- **Book reviews** may be published. Please dispatch a book to the editorial office if you think the book is essential to public health personnel.

Key features and limits of articles are summarized in Table 1 below.

Table 1. Key features and limits of articles

Type of article	Abstract (words)	Text (words)*	References	Tables and figures
Original article	Structured, 250	5,000	-	-
Review article	200	6,500	100	10 Tables 10 Figures
Data profile	200	4,000	40	7
Special article	200	3,500	40	7
Brief report	Structured, 250	2,000	-	-
Short communication	Structured, 250	3,000	-	-
Viewpoint	150	3,000	30	4
Editorial	Not required	1,000	20	-
Commentary	Not required	500	10	2
Correspondence	Not required	500	-	2

*Excluding abstract, references, tables, and figure legends.

Title Page

Title page should include (1) the title of the article (less than 50 words); (2) name of the authors (first name, middle initial, last name in capitals) and institutional affiliation including the name of department(s) and institution(s) of each author; (3) name, full address (including the postal code) of the institutional affiliation, telephone and e-mail address of the corresponding author; (4) a running title of 50 characters or less including blank spaces; and (5) notes (disclaimers). Notes include ethics approval and consent to participate, conflict of interest, funding, availability of data, authors' contributions according to the CRediT taxonomy (https://credit.niso.org/), additional contributions, and ORCID of all authors. All contributors who do not meet the criteria for authorship as defined above should be listed in an additional contribution section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chair who provided only general support. Authors should disclose whether they had any writing assistance and identify the entity that paid for this assistance.

Abstract and Keywords

An abstract and 3–6 relevant keywords (in alphabetical order) are required. Abstracts should be no more than 250 words in length. Abstracts should be structured, with the following section headings: Objectives, Methods, Results, Conclusion. For selecting keywords, refer to the MeSH browser (http://www.ncbi.nlm.nih.gov/mesh).

Highlights

All papers must include 3–5 short sentences presenting short summary or findings in the next of title page. The highlight section should be no more than 100 words, including spaces.

Main Body

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name of the manufacturer. All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms "sex" (when reporting biological factors) and "gender" (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was obtained by all participants (or the participant's legal guardian) / Informed consent was waived by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors

should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.
- **Discussion** should contain an interpretation and explanation of the results and important aspects of the study, followed by the conclusions drawn from them. Information already mentioned in the Introduction or Results sections should not be repeated and the main conclusions of the study may be presented in the discussion.
- **Conclusion** (if any) must be linked with the purpose of the study stated in the abstract, and clearly supported by the data produced in the study. New hypotheses may be stated when warranted, but must be clearly labeled.

References

Authors are responsible for the accuracy and completeness of their references and for correct text citations.

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by "et al."
- When citing organizations that are national bodies such as government agencies, if a nationality is not part of the name, place the country in parentheses after the name, using the two-letter ISO country code.
- References cited in tables or figure legends should be included in sequence at the point where the table or figure is first mentioned in the main text.
- Do not cite abstracts unless they are the only available reference to an important concept.
- Uncompleted work or work that has not yet been accepted for publication (i.e., an "unpublished observation" or "personal communication" should not be cited as a reference). In the references list, references should be limited to those cited in the text and listed in the order in which they appear in the text. The journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- Use of DOI is highly encouraged. Note that missing data will be highlighted at the proof stage for the author to correct.
- Other types of references not described below should follow the ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Please refer to the following examples.

- **Journal articles**
  1. Park AK, Kim IH, Kim J, et al. Genomic surveillance of SARS-CoV-2: distribution of clades in the Republic of Korea in 2020. Osong Public Health Res Perspect 2021; 12:37-43.
  2. Hyun J, Lee JH, Park Y, et al. Interim epidemiological and clinical characteristic of COVID-19 28 cases in South Korea. Public Health Wkly Rep 2020;13:464-74. Korean.
  3. Gultekin V, Allmer J. Novel perspectives for SARS-CoV-2 genome browsing. J Integr Bioinform 2021 Mar 15 [Epub]. https://doi.org/10.1515/jib-2021-0001.
- **Books**
  1. Riffenburgh RH, Gillen DL. Statistics in medicine. 4th ed. Academic Press; 2020.
  2. Miller DD. Minerals. In: Damodaran S, Parkin KL, editors. Fennema's food chemistry. 5th ed. CRC Press; 2017. p. 627-80.
  3. Ministry of Employment and Labor (KR). Statistics on occupational injuries and illnesses, 2008. Ministry of Employment and Labor; 2009. Korean.
- **Websites**
  1. World Health Organization (WHO) (CH). COVID-19 vaccines [Internet]. WHO; 2021 [cited 2021 Mar 15]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.
- **Conference papers**
  1. Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, IE. Springer; 2002. p. 182-91.
- **Dissertation**
  1. Park HY. The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]. Yonsei University; 2000.

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