OSONG PUBLIC HEALTH
AND RESEARCH PERSPECTIVES
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Vol. 17, No. 4, August 2026

Pages 287-372

Vol. 17, No. 4, August 2026

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OSONG PUBLIC HEALTH
AND RESEARCH PERSPECTIVES

Vol. 17, No. 4, August 2026

pISSN 2210-9099
eISSN 2233-6052

Vol. 17, No. 4, August 2026

Korea Disease Control and
Prevention Agency

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

https://ophrp.org

pISSN 2210-9099
eISSN 2233-6052

Vol. 17, No. 4, August 2026

Published on 31 August 2026

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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Publisher: The Korea Disease Control and Prevention Agency

Editor-in-Chief: Jong-Koo Lee, MD, PhD

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♾ This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 & ANSI/NISO Z39.48-1992 (Permanence of Paper).

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

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pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2026.0615
Osong Public Health Res Perspect 2026;17(4):287-289

Editorial

Resilient public health in a changing world: as threats expand and prevention retreats

Jong-Koo Lee

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Public health depends on acting before illness becomes widespread. Vaccination, surveillance, early detection, environmental control, and effective communication succeed because their benefits are often realized before disease occurs. Yet in 2026, public health is moving in opposing directions: biological, environmental, and social threats are becoming more complex and interconnected, even as institutions and preventive systems face increasing pressure. The result may be a widening public health resilience gap, in which threats evolve faster than our collective capacity—or willingness—to prevent and respond to them.

A recent shift in United States childhood vaccination policy illustrates this tension. On August 10, 2026, a presidential executive order established a framework recommending immunization against 11 diseases for all children, compared with 18 diseases in the 2024 Centers for Disease Control and Prevention (CDC) schedule; several other vaccines were assigned to risk-based or shared clinical decision-making categories [1]. The administration has characterized the change as an effort to align United States recommendations with those of peer countries and expand parental choice; medical and public health experts have raised concerns about its implications for evidence-based immunization policy [2,3].

The central issue is not simply whether a national schedule universally recommends protection against 18 diseases or 11. Vaccination rests on a broader infrastructure of scientific review, surveillance, financing, delivery systems, professional guidance, and public confidence. Changes to any component can have consequences well beyond a single vaccine.

The Republic of Korea's measles experience offers an instructive counterpoint. After the nationwide epidemic of 2000–2001, the Republic of Korea implemented a 5-year elimination strategy combining a school-based catch-up campaign, high 2-dose coverage, vaccination verification at school entry, strengthened epidemiological and virological surveillance, and rapid outbreak response [4]. The Republic of Korea also drew on United States measles-elimination experience, with assistance from the World Health Organization (WHO), United Nations Children's Fund, and the United States CDC [4].

The Republic of Korea declared measles elimination in 2006 and received formal verification from the WHO Western Pacific Region in 2014. This achievement went beyond successful vaccination by strengthening national immunization and surveillance infrastructure [4]. There is therefore a troubling historical irony in seeing elements of an evidence-based prevention system that the United States helped the Republic of Korea build more than 2 decades ago now

Received: August 24, 2026
Accepted: August 25, 2026

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face uncertainty in the United States itself. Public health achievements are reversible: vaccination can achieve elimination, but institutions sustain it.

Several papers in this issue of *Osong Public Health and Research Perspectives* reinforce this point. A commentary on influenza A(H3N2) subclade K shows how viral evolution continually challenges vaccine policy and underscores the need for genomic and antigenic surveillance, vaccine-effectiveness monitoring, timely vaccine-strain selection, and international data sharing. A Perspective on dengue vaccination similarly emphasizes that vaccination should complement, not replace, vector control. Resilience depends on maintaining multiple layers of prevention.

Emerging and re-emerging infections also test these systems. The mpox review describes changing transmission and new diagnostic and prevention challenges, while the national analysis of Lassa fever surveillance in Nigeria demonstrates the importance of sustained surveillance and climatic influences on disease activity. Together, these studies support adaptable One Health surveillance rather than isolated disease-specific systems.

Recent events make this need clear. The 2026 outbreak of Ebola disease caused by Bundibugyo virus in the Democratic Republic of the Congo and Uganda highlighted a less-studied human-pathogenic orthoebolavirus; genomic analysis identified a new variant, while a recent review emphasized gaps between scientific innovation and operational preparedness [5,6]. An Andes virus outbreak aboard an international cruise ship likewise demonstrated the challenges of managing person-to-person transmission in a highly mobile, multinational population [7–9]. Despite their different epidemiology and pandemic potential, both expose weaknesses in surveillance, laboratory capacity, infection control, research pipelines, and cross-border coordination. The investigation of *Kudoa septempunctata* foodborne outbreaks in the Republic of Korea illustrates the same fundamentals: rapid detection, appropriate specimen collection, source identification, and prompt intervention.

Environmental and climate-related hazards further expand the scope of public health protection. The 2025 *Lancet Countdown* highlighted the health burden associated with extreme heat and wildfire smoke [10], and a multicountry European study suggested that conventional methods may substantially underestimate wildfire-attributable mortality [11]. In the Republic of Korea, extreme heat and the devastating 2025 wildfires in Uiseong, Andong, and neighboring areas have highlighted health effects extending beyond the immediate disaster. Investigations following these wildfires underscored the need for long-term, cohort-based follow-up of affected communities [12]. Studies in this issue on ambient temperature and blood pressure in Indonesia and climatic patterns of Lassa fever in Nigeria illustrate why environmental information should be integrated into surveillance of infectious and chronic diseases.

Other papers broaden resilience beyond outbreaks and environmental hazards. Studies of mental disorders in Vietnam, postpartum depression in Indonesia, and lifestyle-related inflammation and quality of life in the Republic of Korea show how social, behavioral, psychological, and biological vulnerabilities intersect. A resilient public health system must identify what threatens health, who is most vulnerable, and how multiple risks interact.

Three priorities follow. First, proven foundations—including vaccination, surveillance, independent scientific review, laboratory networks, and public financing—must be sustained, evaluated, and strengthened. The Republic of Korea's measles-elimination experience shows that prevention depends on durable institutions and international learning, not isolated interventions.

Second, public health systems must detect change and adapt to it. As pathogens evolve, vectors shift, environmental exposures intensify, and population vulnerability changes, surveillance should link epidemiological, genomic, environmental, and population-health information. One Health should function as an operational principle rather than merely an aspiration.

Third, public health protection must encompass infectious diseases, environmental hazards, chronic disease risks, mental and maternal health, behavioral risk, and social vulnerability—particularly when these threats occur simultaneously.

The defining challenge may be a widening resilience gap: biological, environmental, and social risks are changing faster than the institutions designed to anticipate, prevent, and respond to them. Retreating from prevention as new threats emerge would move public health in precisely the wrong direction. The task is not only to prepare for the next outbreak, but also to preserve, connect, and strengthen the institutions capable of protecting populations from multiple threats at once.

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.

Funding
None.

https://doi.org/10.24171/j.phrp.2026.0615

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phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0402
Osong Public Health Res Perspect 2026;17(4):290-299

Review Article

Rethinking mpox: epidemiology, clinical variants, diagnosis, and response

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ABSTRACT

Monkeypox disease, now commonly referred to as mpox, was once considered a geographically restricted zoonotic disease but has emerged as a global public health concern. The 2022 multinational outbreak marked a turning point, with notable shifts in transmission dynamics, affected populations, and clinical manifestations. Classical cases typically involve fever, lymphadenopathy, and a centrifugal vesiculopustular rash; however, recent outbreaks have revealed atypical presentations, including genital and perianal lesions, minimal or absent prodromal symptoms, and asynchronous rash evolution. These variations have complicated early clinical recognition and may contribute to delayed diagnosis and onward transmission. This review synthesizes current evidence on the evolving epidemiology of mpox, highlights differences between endemic and non-endemic outbreaks, and describes the full spectrum of typical and atypical clinical features. It also assesses diagnostic approaches, including molecular and point-of-care techniques, and evaluates the efficacy and limitations of current and emerging vaccines, such as JYNNEOS and ACAM2000. Future priorities include improving global surveillance, refining case definitions, expanding diagnostic access, and ensuring equitable vaccine distribution. Understanding the expanding clinical and epidemiological profile of mpox is essential for timely diagnosis, containment, and preparedness against future outbreaks.

Keywords: Atypical; Epidemiology; Mpox, monkeypox; Outbreak

Received: September 28, 2025
Revised: April 19, 2026
Accepted: April 22, 2026

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Introduction

Mpox, historically known as monkeypox, is a zoonotic viral disease caused by mpox virus, a double-stranded DNA virus in the genus *Orthopoxvirus* and family Poxviridae [1,2]. The virus is closely related to variola virus, the causative agent of smallpox [1]. Traditionally, 2 major clades of mpox virus have been recognized: the West African clade and the Congo Basin clade. The West

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African clade has been associated with a milder disease course, less frequent human-to-human transmission, and lower mortality than the Congo Basin clade [1–3].

On 23 July 2022, the World Health Organization (WHO) declared the multinational mpox outbreak a Public Health Emergency of International Concern (PHEIC). The outbreak was considered atypical because many cases occurred in countries without established endemic transmission and had no epidemiological link to historically endemic areas. Transmission predominantly affected men who have sex with men (MSM), although other populations were also affected [4–7]. The PHEIC designation was lifted on May 10, 2023 [4]. Reported cases were found to have originated from the milder West African clade [3,5].

The first European case was identified in the United Kingdom on May 6, 2022 in an individual who had returned from Nigeria [3,8]. Additional cases were reported in the United Kingdom, the United States, Spain, Canada, Belgium, Sweden, Italy, France, Portugal, Germany, the Netherlands, Switzerland, Israel, and Australia in May 2022. Some cases had no known links to one another or to endemic areas. By September 13, 2022, nearly 58,000 confirmed cases had been reported in more than 100 countries, including 20,733 cases in the United States alone [8,9]. As of August 2023, 80,000 cases of atypical mpox had been reported [9]. In India, 30 cases had been reported by September 2024 after the PHEIC declaration [10].

Differences from Classical Mpox

Classical disease begins with a prodrome of fever, lethargy, and lymphadenopathy, followed by a characteristic vesiculopustular rash [11,12]. The clinical manifestations of atypical mpox may differ from classical presentations. Although the characteristic rash and lesions are still present, atypical cases have shown a higher prevalence of genital and perianal lesions, reported in 73% of cases, as well as a higher incidence of proctitis [6]. Single genital ulcers have also been reported in some cases [13]. Several cases have been asymptomatic or mild [3]. Prodromal symptoms may be absent in some cases and prolonged in others [6]. Several case reports have also described atypical mpox in patients with human immunodeficiency virus (HIV) infection. Oral and tonsillar ulcers, epiglottitis, pharyngitis, and dysphagia are common oropharyngeal manifestations [13]. Cutaneous lesions are mainly vesiculopustular (58%), although macular, pustular, vesicular, crusted, and multiphasic lesions have also been observed [4].

The emergence of atypical mpox raised substantial global public health concerns. Its distinct epidemiological and clinical features challenged existing knowledge and preparedness efforts. As cases increased in non-endemic regions, understanding the characteristics, transmission dynamics, and potential impact of atypical mpox became increasingly important. This review provides a comprehensive overview of current knowledge and research on atypical mpox, including contemporary trends in clinical presentation, to reduce unfamiliarity and improve clinician awareness.

HIGHLIGHTS

- The 2022 multinational mpox outbreak marked a shift in transmission dynamics, with sexual contact emerging as the predominant route of transmission.
- Atypical mpox often presents with genital and perianal lesions, absent or minimal prodromal symptoms, and asynchronous rash evolution.
- Molecular diagnosis, primarily polymerase chain reaction testing of lesion swabs, remains the gold standard for confirmation.
- Management focuses on supportive care and symptomatic relief, with antivirals such as tecovirimat available under specific protocols.
- Continued genomic surveillance and equitable vaccine distribution are essential for future outbreak preparedness.

Epidemiological Aspects

Endemic, or typical, mpox is transmitted primarily through large respiratory droplets, followed by fomites and close physical contact with cases or infected animals [3]. In atypical mpox, human-to-human transmission via respiratory droplets is not considered a major route. Early epidemiological data indicated that the atypical mpox outbreak primarily affected MSM, who accounted for approximately 98% of cases, particularly those with multiple or anonymous sexual partners [3,4,14]. However, as the outbreak progressed, cases were also reported in other population groups, including women and children, with evidence suggesting a higher risk of severe disease in these subgroups [15]. A total of 41% of patients were HIV-positive, but most did not have active immunodeficiency and had low viral loads [4]. These data suggest that HIV positivity is better regarded as a coexisting condition than as an independent risk factor. However, HIV infection could be an important comorbidity in patients with immunodeficiency and may influence disease severity.

Progression of the Pandemic

Countries with endemic mpox virus transmission include Cameroon, Sierra Leone, Liberia, Côte d'Ivoire, Benin, Nigeria, Gabon, the Republic of the Congo, the Central African Republic, South Sudan, and the Democratic Republic of the Congo [3,8]. However, the course of atypical mpox has been erratic. Unlike classical mpox, atypical mpox has been estimated to include asymptomatic cases [3]. Such cases may have been present in endemic regions before the 2022 outbreak. The first European case, involving a man who had traveled from Nigeria to the United Kingdom, was detected on May 6, 2022. The virus subsequently spread across Europe and North America, eventually involving more than 100 countries, as shown in Figure 1 [8]. According to the WHO situation report, the caseload as of March 2025 was 124,753, with a steady decline in reported cases [9].

Risk Factors and Transmission

In a case series by Thornhill et al. [4] involving 528 patients with atypical mpox across 16 countries, sexual contact was identified as the predominant risk factor associated with transmission. Overall, 95% of cases were considered to have been acquired through sexual contact, and 98% of patients were MSM [4,16–20]. This finding is supported by the detection of mpox DNA in seminal fluid and the presence of anogenital lesions [4,7,21]. Seventy-five percent of patients were White. The age of affected individuals ranged from 21 to 62 years, with a median age of 38 years. Approximately 35.5%–47% of patients had coexisting HIV infection, but 95% of these patients had low viral loads [4,5,16–19,22–27]. Recent international travel was also frequently reported; 25%–28% of patients had traveled abroad within 1 month before diagnosis [4,5,22]. A total of 32% of patients had visited sex-on-site venues, 20% had attended large gatherings, and 20% had engaged in sexual intercourse while under the influence of substances. Non-sexual or unknown contact histories were reported in approximately 5% of patients [4,5]. Although infection has been identified in women and children, there is no evidence of sustained transmission in these groups [28].

Case Definition

According to the Centers for Disease Control and Prevention (CDC), mpox cases can be classified as suspected, probable, or confirmed [29]. These definitions are summarized in Table 1. The CDC also provides epidemiological criteria for suspected mpox. These include contact with a person with confirmed or probable mpox within 21 days before illness onset; close or intimate contact with persons in social groups with high mpox activity, including MSM or persons attending relevant social events; travel to a country with endemic or confirmed mpox cases; or contact with a live or dead animal, exotic pet, or animal-derived product from an mpox-endemic area in Africa.

Pathogenesis

Viral entry is thought to occur through macropinocytosis, endocytosis, or cell membrane fusion. Several proteins are associated with viral attachment, including H3 and A27, which bind to heparan sulfate; D8, which binds to chondroitin sulfate; and A26, which binds to laminin. H3 is conserved among poxviruses. Another protein, A17, helps anchor A27, which interacts with A26 [30]. Up to 12 proteins have been implicated in formation of the viral entry complex [30,31].



Figure 1. Timeline of the spread of atypical mpox.

https://doi.org/10.24171/j.phrp.2025.0402

Table 1. Case definitions of human mpox according to the Centers for Disease Control and Prevention

Case type	Criteria
Suspect case	• New characteristic rash OR • Meeting an epidemiological criterion as discussed above and has a high clinical suspicion for mpox.
Probable case	• No evidence of recent other *Orthopoxvirus* infection AND • Demonstration of *Orthopoxvirus* DNA by PCR or immunohistochemical or IgG antibody against *Orthopoxvirus* • The IgG antibody should be demonstrated 4–56 days after rash onset.
Confirmed case	• Demonstration of mpox DNA by PCR or next-generation sequencing OR • Isolation of mpox in culture
Suspect reinfection case	• New characteristic rash OR • Meeting an epidemiological criterion as discussed above and has a high clinical suspicion for mpox.
Probable reinfection case	• A suspect case that demonstrates positive *Orthopoxvirus*/mpox DNA or immunohistochemical or IgG antibody • The IgG antibody should be in paired serum samples- one sample within 3 days of symptom onset and the second 7–14 days after onset. • Applicable only for patients with no prior vaccination or vaccination ≥180 days prior.
Confirmed reinfection case	• Meets criteria from probable reinfection AND • Has significant single nucleotide polymorphisms or genetic variation between mpox genetic sequences from samples obtained from 2 or more separate episodes punctuated by complete resolution of symptoms.

PCR, polymerase chain reaction; IgG, immunoglobulin G.

After infection, viral replication occurs in the cytoplasm and involves the Golgi apparatus. Cell fusion may also occur, leading to syncytium formation. Viral replication is mediated by the F8-A22-E4 polymerase. This holoenzyme is also involved in proofreading, thereby contributing to replication fidelity (Figure 2). However, specific original research examining the viral entry and replication of atypical mpox remains scarce at the time of writing.

After local replication of mpox virus at the inoculation site, the virus spreads to the lymph nodes, leading to primary viremia during an incubation period lasting 1–3 weeks [12,32]. In an aerosol transmission model using cynomolgus monkeys, lymphatic spread through monocyte-associated viremia was demonstrated. Necrotic lesions and intracytoplasmic inclusions were also observed. The study further showed increased viral dissemination associated with secondary bacterial infection [33]. After the initial spread, clinical symptoms begin with the prodrome, which corresponds to secondary viremia.

Clinical Manifestations

Prodromal Symptoms

The incubation period of mpox ranges from 5 to 24 days, with an average of 12 days [14,22]. In classical mpox infection, common systemic features often precede the development of a generalized rash. In atypical mpox, prodromal symptoms have been reported in 36% to 74.8% of patients [6,13,14]. Prodromal symptoms may be completely absent, as described in case reports of patients with itchy vesicular genital lesions who had no prodromal symptoms and were initially misdiagnosed with herpes [7,24,34]. When present, prodromal symptoms include fever, which occurs in 59%–62% of cases and may have sudden onset; lethargy, reported in 41%; myalgia, reported in 31%; sore throat, reported in 22%; and headache, reported in 27%. Lymphadenopathy has been observed in 50.6%–64.9% of cases and may be painful [5,7,13,20–22,24,35–41]. The prodrome may also be prolonged in some individuals [6]. Case reports have also described mild diarrhea, pruritus, throat pain, generalized aches including chest pain, asthenia, and chills [7,36,39–43].

Lesions and Other Clinical Features

The characteristic rash of classical mpox usually begins as macular lesions and progresses through papular, vesicular, pustular, and crusting stages [13,36]. In atypical mpox, this typical evolution may not occur, and macular rashes may also be present [7,22]. Patients may present at any stage of lesion development, with asynchronous lesions or mixed crops [14,16,22,24,26,41,44–47]. In 2 large case series, skin lesions were present in 77%–95% of infected individuals [4,5]. The anogenital area was the most common site

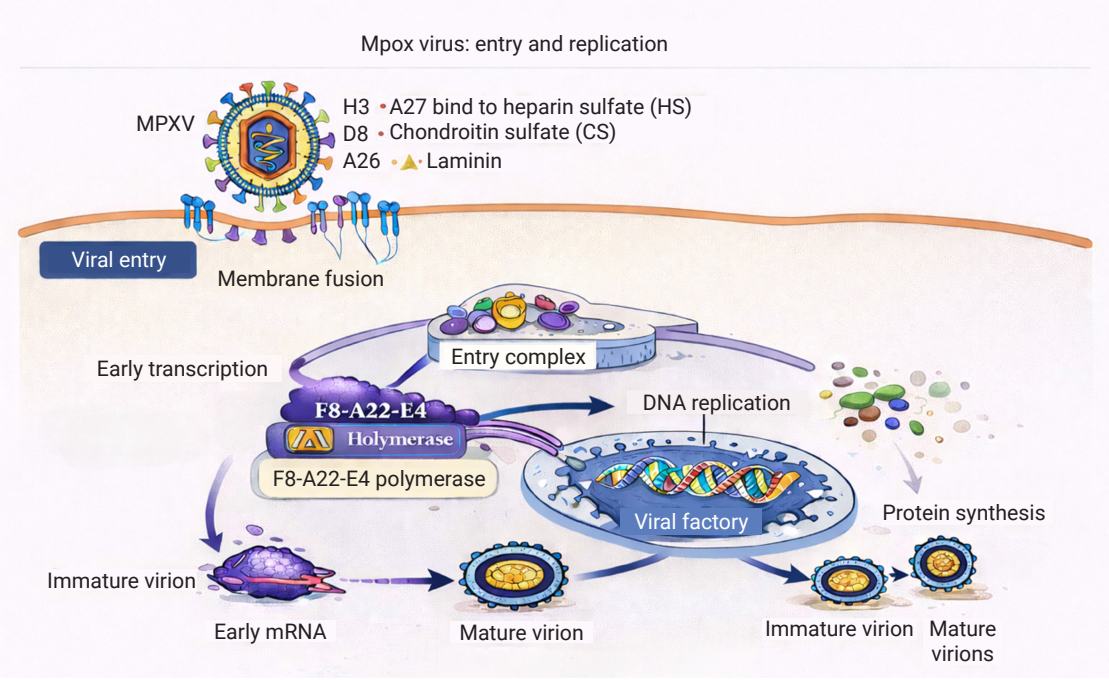


Figure 2. Entry of mpox virus into the host cell and subsequent replication. The figure was enhanced using artificial intelligence.

of these lesions, affecting 73% of patients with rashes [4,7,22,23,25,34,47–49]. Anogenital rashes were distributed as follows: genital lesions, 53%–56.4%; perianal lesions, 34%–41.6%; and genital and/or perianal lesions, 73%–88.3% [13,21]. Other commonly affected sites included the eyes, oropharynx, trunk, arms, or legs (55%); face (25%); and palms and soles (10%). In rare cases, paronychia has also been reported [4,13,23,24,36,50,51].

A variety of lesion types have been observed, with vesiculopustular lesions being the most common (58%). Most patients reported fewer than 20–25 lesions (85%–93%) [13]. Itching was associated with lesions in some cases [7,22]. Morphologically, pseudopustules, defined as whitish papules with a necrotic center, have been identified at the inoculation site in some cases. These are solid inflammatory lesions rather than true pustules containing purulent fluid [13]. Public erythema, diarrhea, and odynophagia have also been reported [7,23]. Some individuals presented with a single genital ulcer or genital vesicular lesions, which could lead to misdiagnosis as another sexually transmitted infection [4,22,35]. Verrucous lesions have also been reported [25,42].

Complications have been reported in approximately 13% of cases. These include severe pain at the site of anogenital lesions, proctitis, penile edema, phimosis or paraphimosis, secondary infections, pharyngitis, bronchopneumonia, encephalitis and other neurological complications, ocular complications including vision loss, acute kidney injury, abscess, sepsis, and myocarditis [4,19,22,48,52–55]. Differences from classical mpox, absence of prodromal symptoms, and clinical overlap with sexually transmitted infections make diagnosis and treatment of atypical mpox challenging. Patients often present to dermatology clinics, sexually transmitted infection clinics, and emergency departments [4,22]. These clinical settings are potential targets for enhancing early diagnosis and management of atypical mpox.

Diagnostic Approaches

Because atypical mpox differs clinically from classical disease, clinicians should recognize its key differential diagnoses. Patients presenting with vesicular lesions have been misdiagnosed with herpes or varicella-zoster virus infection and treated accordingly, often without substantial improvement [7,35,56]. Single genital lesions have also been reported in several cases and may be misdiagnosed as syphilis [4]. Case reports have described umbilicated lesions mimicking molluscum contagiosum [36], impetigo, and erythema multiforme [52]. The rash may also be confused with drug reactions, which can present as polymorphic eruptions. Therefore, a detailed history and a high degree of clinical suspicion in susceptible patients may reduce unnecessary laboratory investigations and facilitate diagnosis of atypical mpox.

The definitive diagnostic modality for atypical mpox

https://doi.org/10.24171/j.phrp.2025.0402

is polymerase chain reaction (PCR). Because PCR is highly specific, clinicians must maintain a high degree of suspicion to diagnose atypical cases reliably. Samples for PCR can be obtained from crusts, lesion fluid, or swabs of cutaneous and anogenital lesions, which have a positivity rate of 97%. Other sample types include nasopharyngeal specimens, urine, semen, and blood, with positivity rates of 26%, 3%, 90%, and 7%, respectively. Thus, mucocutaneous lesion specimens are the most reliable samples, followed by those from seminal fluid [4,5,7,21,35,39,57].

Dermoscopy has identified lesions with varying degrees of vascularity [58]. Morphologically, lesions have shown a hemorrhagic center surrounded by a whitish ring, which is further surrounded by erythema. Pustular and vesicular lesions have also been observed. Histologically, Guarnieri inclusion bodies are seen in the cytoplasm. Lymphocytic infiltrates are present in lesions, along with full-thickness epidermal necrosis and ballooning degeneration of keratinocytes [13,59].

Serological tests, such as enzyme-linked immunosorbent assay and fluorescent antibody testing, can also be performed. Immunoglobulin M can be detected from day 5 to day 56 after rash onset, whereas immunoglobulin G can be identified from the end of the first week of illness [52]. Recently, a method for rapid identification of antibodies against A29L, a surface antigen of mpox virus, was developed using high-throughput B-cell sequencing [60]. However, these tests are not suitable for screening because they are typically performed only after rash onset. A transient decrease in T cells and atypical lymphocytes has also been reported [61–63]. In addition, leukocytosis, thrombocytopenia, decreased serum albumin levels, elevated transaminase levels, and increased blood urea nitrogen levels may be observed [39]. Viral isolation and cell culture can be performed for research purposes in specialized high-biosafety-level laboratories [21,39,64], but they have a limited role in routine diagnosis. Microbial cell-free DNA (mcfDNA) sequencing has also been explored for mpox diagnosis. This approach relies on peripheral blood examination and therefore can be performed before active lesions appear. Sequencing using mcfDNA can also accurately identify coinfections with other viruses and bacteria [65].

Management Strategies

Treatment

Because clinical presentations vary, patients may require extensive supportive and symptomatic management. Isolation and home-based treatment are recommended for patients with mild symptoms [4]. Pain control remains the mainstay of management for proctitis and lesion-associated pain [5,29,66]. One report described a patient who required patient-controlled intravenous analgesia, whereas gabapentin and opioids have been used for short-term management of severe pain [22,29]. Topical lidocaine and stool softeners have also been used to manage proctitis [66]. Oropharyngeal lesions may be managed with salt-water rinses, chlorhexidine mouthwash, or local analgesic mouthwash [29,66]. Topical and systemic antimicrobials, such as mupirocin, may be useful for mucocutaneous lesions with secondary bacterial infection, and corticosteroids may be used to manage local swelling around genital lesions [17,35,66]. Antibiotics have been used for secondary bacterial infections [5,17,29,66]. Pruritic rashes have been managed with antihistamines [5]. Several cases, accounting for 27%–29% of patients, have also involved concomitant sexually transmitted infections, which should be managed according to their respective protocols and treatment strategies [4,5,18,19,26,27,67,68]. Coinfection with cytomegalovirus has also been reported [69].

Beyond symptomatic management, no treatment options are specifically approved for human mpox infection [29]. Antivirals such as tecovirimat, cidofovir, and the cidofovir prodrug brincidofovir have been considered for treatment of human mpox and have been used in some cases [16,49,70]. However, no clinical studies have confirmed the efficacy and safety of these antivirals for human mpox. Several new drugs are being investigated preclinically for mpox management [70]. Tecovirimat, which is approved by the US Food and Drug Administration (FDA) for smallpox, is under investigation for treatment of mpox [29,70]. In the United States, it is available only through the Study of Tecovirimat for Human Monkeypox Virus (STOMP) trial [29,71]. The study is being conducted in the United States, Brazil, Peru, and Thailand. Tecovirimat has also been used successfully in some case reports [4,70]. Brincidofovir is another antiviral approved for use against smallpox and has shown promising results in preclinical studies [29,70]. In the United States, brincidofovir is available to clinicians only through FDA authorization for single-case emergency investigational new drug use. It may be authorized for adult and pediatric patients, including neonates, who have severe disease or are at high risk for severe disease or recrudescence [29]. Cidofovir is another antiviral under consideration for mpox management. It is approved for treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome. No studies have demonstrated the efficacy of cidofovir for mpox, and its use is further limited by severe renal toxicity [29]. Vaccinia immune globulin intravenous (VIGIV) is also FDA-approved for management of vaccinia-related complications during immunization. Although no data are available on the safety and efficacy of VIGIV in human mpox

infection, it has been reserved under the CDC expanded access protocol for management of orthopoxvirus outbreaks [70]. It is also available on a case-by-case basis with CDC approval [29,70]. Trifluridine has been used with some success as adjunctive topical therapy in patients with ocular manifestations [70].

Vaccination

Although no mpox-specific vaccine was initially available, the emergence of atypical mpox prompted efforts to deploy existing smallpox vaccines, which provide some cross-protection against mpox virus because of similarities between orthopoxviruses. Two orthopoxvirus vaccines, JYNNEOS (Bavarian Nordic A/S) and ACAM2000 (Emergent BioSolutions Inc.), are discussed by the CDC for use under specific conditions during human mpox outbreaks [29,70]. Both vaccines are live vaccines. JYNNEOS is based on a live attenuated vaccinia strain, modified vaccinia Ankara, whereas ACAM2000 contains replication-competent live vaccinia virus. JYNNEOS has been approved in various countries for mpox and smallpox. Two doses are recommended 28 days apart, with extension up to 35 days when necessary. In the United States, JYNNEOS has been approved for individuals at high risk for mpox. These include individuals with a new diagnosis of 1 or more sexually transmitted infections within the previous 6 months, more than 1 sexual partner, a history of sex at a commercial sex venue, or sexual intercourse associated with a large public gathering in an area where mpox transmission is occurring. Their sexual partners and people anticipating these exposures are also eligible for vaccination. Post-exposure prophylaxis is recommended within 4 days of exposure but may provide some benefit up to 14 days after exposure. Repeated doses are not recommended except for occupational exposure to orthopoxviruses; in such cases, booster doses can be given every 2–10 years. JYNNEOS is considered safer for immunocompromised individuals and pregnant patients because it does not replicate efficiently in humans. In contrast, ACAM2000 received emergency approval in the United States for the 2022 outbreak. ACAM2000 has more adverse effects and contraindications than JYNNEOS and carries a risk of vaccinia replication-related adverse events [29,70]. The MVA-BN and LC16M8 vaccines have been prequalified by WHO for use against mpox in Africa [72,73].

Challenges and Future Directions

The identification and management of atypical mpox face several major challenges, including divergent clinical presentations, stigma affecting populations at risk, limited clinician awareness, and the absence of mpox-specific treatment options [74]. Atypical presentations, such as single lesions, asynchronous lesions, absent prodromal symptoms, and atypical rashes, complicate prompt recognition and diagnosis [14,16,22,24,41,44,45]. Diagnosis is further hampered by co-occurring sexually transmitted infections. Healthcare providers in non-endemic regions often have limited familiarity with atypical mpox, which may delay diagnosis and treatment. Physicians in endemic areas generally have a higher degree of suspicion for mpox than those in non-endemic areas. Stigma and discrimination affecting certain communities, particularly MSM, may discourage individuals from seeking medical care until complications arise and may hinder contact tracing [74]. In addition, limited access to diagnostic testing and the lack of mpox-specific antivirals may hamper case management.

Because large randomized controlled trials are lacking, several knowledge gaps remain regarding atypical mpox. Understanding the roles of asymptomatic and presymptomatic transmission and environmental contamination is necessary for establishing protocols to prevent mpox transmission comparable to that observed during the 2022 outbreak. Primary prevention measures for mpox infection also need to be better established; this requires clearer understanding of the pathophysiological mechanisms underlying transmission through various routes, particularly sexual contact. Although seminal fluid has tested positive in several studies, lesion swabs and lesion fluid also have high viral loads. Therefore, it is important to determine whether barrier protection during sexual contact would be effective in patients with anogenital lesions. Continuous genomic surveillance remains limited but is necessary to monitor viral evolution and its implications for transmissibility, virulence, and vaccine effectiveness. The long-term health consequences of atypical mpox are not yet fully understood, particularly in high-risk populations, because of the recency of the outbreak. As with coronavirus disease 2019, potential long-term complications and residual morbidities may occur and should be investigated in longitudinal studies.

The global spread of atypical mpox emphasizes the need for effective risk communication, efforts to combat stigma and discrimination, equitable access to healthcare, and strengthened surveillance systems. Collaboration among public health authorities, healthcare providers, researchers, and communities is necessary to address these challenges. International organizations and collaborations also play a crucial role in addressing knowledge gaps and ensuring effective global coordination.

This review is limited by its narrative design, reliance on predominantly observational studies and case reports, heterogeneity among published reports, and the rapidly

https://doi.org/10.24171/j.phrp.2025.0402

evolving nature of the mpox literature, which may limit the generalizability and durability of some conclusions.

Future research priorities include ongoing genomic surveillance to monitor viral evolution, large-scale epidemiological studies to characterize transmission dynamics and zoonotic sources, and investigations of the long-term effects and potential complications of infection. Continued development of novel antiviral agents, immunomodulatory therapies, and next-generation vaccines is essential. Studies should also explore combination therapies for synergistic effects, assess asymptomatic transmission and environmental contamination, and evaluate long-term vaccine effectiveness and the need for booster doses. Measuring the effects of public health interventions and community engagement on outbreak control will help strengthen preparedness for future mpox outbreaks and other emerging infectious diseases. Through sustained research and comprehensive public health strategies, the global community can better address the challenges posed by atypical mpox.

Notes

Ethics Approval
Not applicable.

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

Funding
None.

Availability of Data
All data generated or analyzed during this study are included in this published article. Other data may be requested through the corresponding author.

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

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0426
Osong Public Health Res Perspect 2026;17(4):300-309

Original Article

Molecular and genetic characterization of *Kudoa septempunctata* from foodborne outbreaks in the Republic of Korea, 2016–2024: a retrospective public-health surveillance investigation

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ABSTRACT

Objectives: *Kudoa septempunctata* is a marine myxosporean parasite implicated in seafood-borne acute gastroenteritis, predominantly associated with the consumption of raw olive flounder. This study aimed to characterize the molecular and genetic features of *K. septempunctata*-associated with foodborne outbreaks in the Republic of Korea from 2016 to 2024.

Methods: We reviewed 415 suspected foodborne outbreaks reported through national surveillance between 2016 and 2024. Among these, 37 outbreaks with complete clinical, epidemiological, and laboratory data from 2020 to 2024—including *K. septempunctata* testing and genotyping—were analyzed in detail.

Results: Diarrhea (88.8%) and vomiting (61.2%) were the most common symptoms. The detection rate of *K. septempunctata* was significantly higher in specimens collected ≤24 hours after raw fish consumption (69.8%) than in those collected >24 hours after consumption (35.9%). Outbreak occurrence was higher during warmer months (May–October) than during other periods, although this difference was not statistically significant. All sequences obtained from patient specimens belonged to sequence type 3 (ST3) of *K. septempunctata*.

Conclusion: Since 2020, the proportion of reported outbreaks associated with *Kudoa* has increased, indicating its continued public health relevance. The timing of specimen collection is a key determinant of *K. septempunctata* detection, as diagnostic yield declines significantly when specimens are collected more than 24 hours after exposure. These findings highlight the need for standardized rapid investigation protocols and an integrated surveillance system linking clinical data with seafood supply-chain information.

Keywords: Disease outbreaks; Gastroenteritis; Genotype; *Kudoa septempunctata*; Republic of Korea; Seafood

Received: October 2, 2025
Revised: February 12, 2026
Accepted: March 29, 2026

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The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

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Introduction

Kudoa septempunctata, a myxosporean parasite originally identified in olive flounder (*Paralichthys olivaceus*), has been implicated in foodborne gastroenteritis associated with the consumption of raw olive flounder. In 2012, the Ministry of Health, Labour and Welfare of Japan designated *K. septempunctata* as a foodborne pathogen [1–3]. Previous epidemiological reports have described vomiting, diarrhea, and abdominal pain as the principal symptoms of foodborne illness caused by *K. septempunctata*, with most patients recovering within 24 hours [3]. Humans are considered accidental hosts and are exposed through the ingestion of infected fish tissue, particularly when fish is consumed raw or undercooked [4,5]. Although *K. septempunctata* demonstrates high host specificity for olive flounder, sporadic infections have been reported in other species, including wild grass puffer (*Takifugu alboplumbeus*), Japanese whiting (*Sillago japonica*), and black scraper (*Thamnaconus modestus*) [6,7]. Because the spore density of *K. septempunctata* in these incidental hosts is relatively low, their potential to cause human illness appears limited. Nevertheless, olive flounder remains the primary vector implicated in human foodborne outbreaks associated with *K. septempunctata*.

K. septempunctata belongs to the class Myxosporea and possesses 6 or 7 shell valves with polar capsules [8]. Its natural life cycle has not been fully elucidated. Although many myxosporeans use annelids as alternate hosts, no definitive intermediate host has been identified for *K. septempunctata*; therefore, general myxosporean life-cycle paradigms are referenced without proposing a specific annelid host [9–11]. Animal experiments involving *K. septempunctata* have demonstrated transient gastrointestinal symptoms in some models, whereas others have shown little or no histological evidence of tissue injury [3,12–14]. Therefore, polymerase chain reaction (PCR) positivity for *K. septempunctata* in stool or vomit indicates recent exposure but does not, by itself, establish that the parasite caused the illness [4].

Mitochondrial sequence types of *K. septempunctata*, defined by *cox1*/*rnl* haplotypes, are classified as sequence type 1 (ST1; *cox1*-1/*rnl*-1), sequence type 2 (ST2; *cox1*-2/*rnl*-2), and sequence type 3 (ST3; *cox1*-3/*rnl*-2), with ST3 predominating in the Republic of Korea (ROK) [15,16]. Although genotype-phenotype relationships are well established for other enteric pathogens, such as *Cryptosporidium* and norovirus [17,18], the clinical relevance of *K. septempunctata* sequence types, particularly ST3, remains unclear. This uncertainty underscores the need for integrated epidemiological and molecular analyses.

HIGHLIGHTS

- *Kudoa septempunctata* is a causative agent of seafood-borne gastroenteritis.
- We analyzed 415 disease outbreaks reported in the Republic of Korea from 2016 to 2024.
- Outbreaks were most common in August, consistent with fish consumption data.
- All isolates belonged to the ST3 genotype of *K. septempunctata*.

In the ROK, *K. septempunctata* has been monitored as a foodborne pathogen since 2015 and was incorporated into the National Water and Foodborne Disease Guidelines in 2017 [19,20]. From 2016 to 2019, surveillance focused on laboratory detection (presence or absence of *Kudoa*) and lacked standardized clinical and epidemiological data. To address this gap, standardized investigation workflows for foodborne illness caused by *K. septempunctata* were implemented in 2020.

Accordingly, this study aimed to elucidate the molecular and genetic characteristics of *K. septempunctata* outbreaks and to provide a scientific basis for effective public health interventions in the ROK. By analyzing nationwide surveillance data from 2016 to 2024, focusing on and conducting in-depth analyses of specific outbreaks from 2020 to 2024, we sought to determine the predominant *K. septempunctata* sequence types, evaluate seasonal outbreak trends, and assess the effect of the interval between consumption and specimen collection on pathogen detection rates.

Materials and Methods

Outbreak Criteria

We defined a *Kudoa*-associated outbreak as the occurrence of 2 or more epidemiologically linked cases with compatible gastrointestinal symptoms after the consumption of raw fish, typically raw olive flounder. Confirmed outbreaks required at least 1 case to be PCR-positive for *K. septempunctata* rRNA, with alternative enteric pathogens excluded through laboratory testing or deemed unlikely on the basis of incompatible incubation periods. Events that did not satisfy all of these criteria were classified as possible *Kudoa*-associated outbreaks. Among the total reported cases, we analyzed 37 outbreaks occurring between 2020–2024 and evaluated standardized variables, including outbreak date, number of patients, and symptom types [20]. Outbreaks

were categorized geographically according to the location where cases were identified and field investigations were conducted, as determined by the investigating public health centers (PHCs) or health and environment research institutes (HERIs), rather than by the production origin of the implicated seafood.

Specimen Collection and Ethical Statement

A total of 1,200 clinical specimens (stool and/or vomitus) were tested to identify pathogens in patients presenting with diarrhea or vomiting after suspected seafood-borne illness outbreaks during 2016–2024. This study focused exclusively on the molecular detection and genetic typing of *K. septempunctata* in clinical specimens because food samples, including leftover raw fish, were not included in the analysis. This study was conducted as a retrospective public-health surveillance investigation using specimens collected after symptom onset, and leftover fish from the exposure meal was not available for collection or testing. Clinical specimens were collected primarily at PHCs from suspected cases and were then referred to provincial HERIs under cold-chain conditions for testing [21].

In this study, a retrospective analysis was performed using data collected during routine public health investigations for outbreak diagnosis. Institutional review board approval was waived because the data had been collected for diagnostic purposes during public health practice rather than for human participant research.

DNA Extraction and PCR Assays

Total DNA was extracted from approximately 250 mg of each clinical specimen (stool and/or vomitus) using the FastDNA SPIN Kit for Soil (MP Biomedicals) after mechanical disruption with a FastPrep-24 instrument (MP Biomedicals) at 6.0 m/s for 40 seconds. To detect *K. septempunctata*, nested PCR targeting the 18S and 28S rRNA genes was performed using a thermal cycler (C1000 Touch Thermal Cycler; Bio-Rad Laboratories) (Table 1) [22]. The cycling conditions for the primary PCR were 95 °C for 5 minutes; 35 cycles of 95 °C for 30 seconds, 60 °C for 45 seconds, and 72 °C for 30 seconds; followed by 72 °C for 5 minutes. The cycling conditions for the secondary PCR were 95 °C for 5 minutes; 35 cycles of 95 °C for 30 seconds, 58 °C for 45 seconds, and 72 °C for 30 seconds; followed by 72 °C for 5 minutes. From 2021 onward, a multiplex real-time PCR assay (PowerChek *K. septempunctata* 18S/28S rRNA Real-time PCR Kit II; Kogene Biotech) was used for screening.

Determination of Sequence Type

For mitochondrial typing of *K. septempunctata*, the cytochrome c oxidase subunit I (*cox1*) and large-subunit rRNA (*rnl*) genes were amplified by nested PCR [16]. The amplified DNA fragments were sequenced, and phylogenetic trees were constructed using the maximum-likelihood method with the Kimura 2-parameter model in MEGA 11 and 1,000 bootstrap replicates to determine the sequence type (ST1, ST2, or ST3).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Corp.), with statistical significance set at $\alpha = 0.05$. Seasonality was assessed by comparing the proportion of *Kudoa*-positive outbreaks between May–October and November–April using Pearson's χ^2 test. The effect of specimen collection timing on *K. septempunctata* detection was analyzed using Fisher's exact test by comparing specimens collected ≤24 hours with those collected >24 hours after contaminated food consumption. Relative risk (RR) with 95% confidence intervals (CIs) was calculated for both analyses.

Results

Detection of *K. septempunctata* in Clinical Specimens

Of the 415 outbreaks linked to olive flounder sashimi, 237 events (57.1%) met the prespecified definition of *Kudoa*-associated outbreaks. The proportion of outbreaks confirmed as *Kudoa*-associated increased from 2016 and peaked at 77.8%

Table 1. Polymerase chain reaction primers for the diagnosis of *Kudoa septempunctata*

Gene		Primer	Sequence (5'→3')	Size (bp)	Reference
18S rRNA	1st	K18-1st-F	GGTGGGAGCATTTATTAGAGCT	648	[22]
		K18-1st-R	AATCGAGACCACTGTCAAC		
	2nd	K18-2nd-F	AGAAATACCGGAGTGGACCGTAAAATG	333	
		K18-2nd-R	GTTCCATGCTATAACATTCAAGCGTTCG		
28S rRNA	1st	K28-1st-F	TGCGAGTGAAGCGGGAAAA	717	
		K28-1st-R	GTGTTTCAAGACGGGTCGG		
	2nd	K28-2nd-F	GTGTGTGATCAGACTTGATATG	356	
		K28-2nd-R	AAGCCAAAACTGCTGGCCATTT		

https://doi.org/10.24171/j.phrp.2025.0426

in 2020. During 2021–2024, although the number of reported outbreaks decreased, *K. septempunctata* was consistently identified in nearly all tested outbreaks (e.g., 5/7 in 2023 and 10/12 in 2024; Figure 1A). By region, the number of outbreaks was highest in Gyeonggi-do, followed by Gyeongsangbuk-do and Seoul (Table 2). Overall, 431 of 1,200 clinical specimens (35.9%) tested positive for *K. septempunctata*. Except for 2 outbreaks in which enteropathogenic *Escherichia coli* (EPEC) was identified and 1 outbreak in which norovirus was detected in 2020, no other pathogens were identified in specimens during the study period.

Epidemiological Analysis of Outbreaks

An epidemiological analysis was performed for 37 *Kudoa*-associated foodborne outbreaks identified between 2020 and 2024 (Table 3). All outbreaks involved the consumption of raw fish, primarily olive flounder. The mean attack rate across outbreaks was 87.5% (range, 25%–100%). The mean symptom onset time was 5 hours (range, 1.2–11 hours) after consumption of the contaminated food. The most common symptom was diarrhea, reported in 88.8% of patients, followed by vomiting (61.2%) and abdominal pain (32.7%). Outbreaks tended to occur more frequently during warmer months (May–October; Figure 2) than during colder months, with a notable peak in August (14.8%). However, this seasonal difference was not statistically significant (RR, 1.14; 95% CI, 0.93–1.39; $p = 0.115$). The clinical-specimen detection rate of *K. septempunctata* averaged 53.6%, ranging from 16.7% to 100.0% across outbreaks.

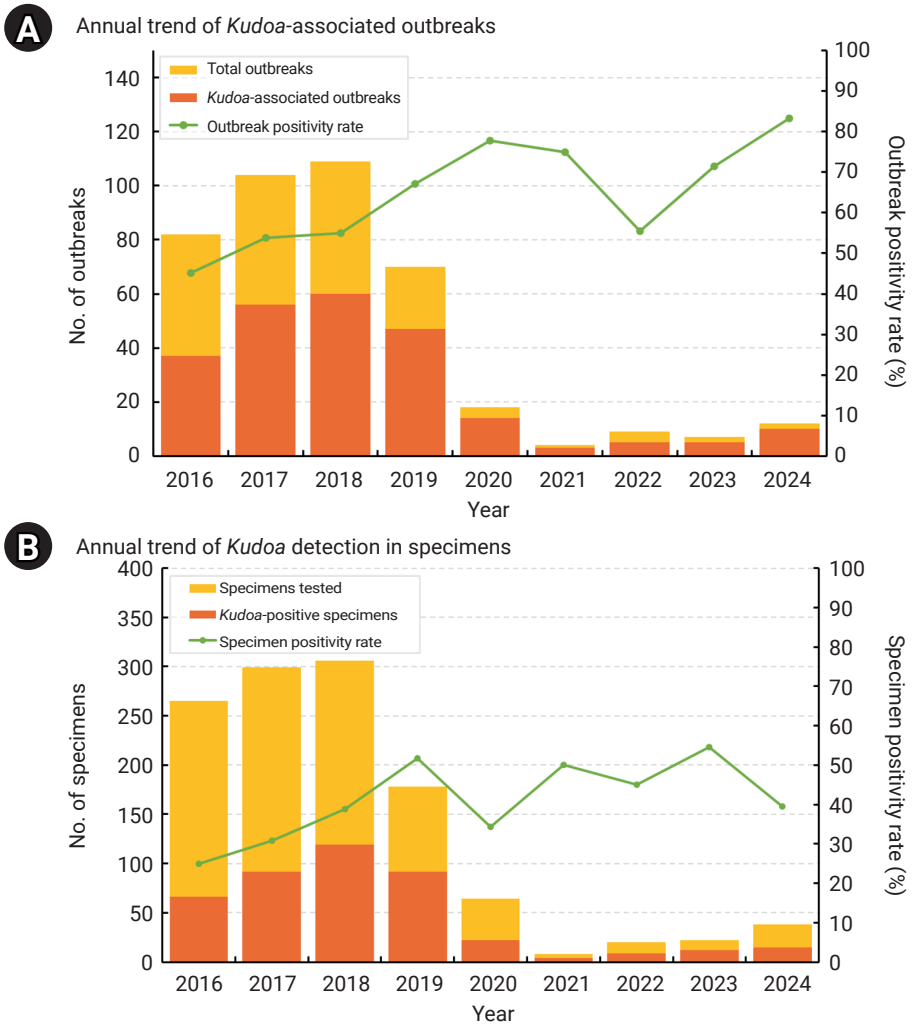


Figure 1. Epidemiological trends in *Kudoa septempunctata*-associated foodborne outbreaks and clinical-specimen testing in the Republic of Korea, 2016–2024. (A) Annual trends in *Kudoa*-associated outbreaks. The bars represent the total number of suspected outbreaks (yellow) and confirmed *Kudoa*-associated outbreaks (orange), and the line indicates the outbreak positivity rate (green). (B) Annual trends in *Kudoa* detection in clinical specimens. The bars represent the total number of specimens tested (yellow) and *Kudoa*-positive specimens (orange), and the line indicates the specimen positivity rate (green).

Table 2. Regional summary of outbreaks and clinical specimens from investigations of *Kudoa*-associated gastroenteritis linked to raw olive flounder, 2016–2024

Region	Total outbreaks (*n*)	*Kudoa*-associated outbreaks (*n*, %)[a]	Specimens tested (*n*)	*Kudoa*-positive specimens (*n*, %)[b]
Gyeonggi-do	123	67 (54.5)	344	116 (33.7)
Gyeongsangbuk-do	65	33 (50.8)	223	59 (26.5)
Seoul	54	31 (57.4)	156	53 (34.2)
Gyeongsangnam-do	35	28 (80.0)	120	63 (52.5)
Daegu	25	19 (76.0)	53	31 (58.5)
Busan	25	12 (48.0)	64	19 (29.7)
Chungcheongnam-do	17	12 (70.6)	47	36 (76.6)
Jeju	16	10 (62.5)	32	14 (43.8)
Chungcheongbuk-do	24	6 (25.0)	76	11 (14.5)
Gangwon	5	5 (100.0)	14	8 (57.1)
Ulsan	5	4 (80.0)	11	8 (72.7)
Daejeon	9	3 (33.3)	15	3 (20.0)
Jeollabuk-do	3	3 (100.0)	5	3 (60.0)
Incheon	2	2 (100.0)	6	5 (83.3)
Jeollanam-do	6	2 (33.3)	32	2 (6.3)
Gwangju	1	0 (0)	2	0 (0)
Total	415	237 (57.1)	1,200	431 (35.9)

[a]*Kudoa*-associated outbreak rate (%) = (no. of *Kudoa*-associated outbreaks/total no. of outbreaks)×100.[b]*Kudoa*-positive specimen rate (%) = (no. of *Kudoa*-positive specimens/no. of specimens tested)×100.

Correlation Between Specimen Collection Interval and Pathogen Positivity

To assess the effect of the interval between contaminated food consumption and specimen collection on diagnostic yield, we analyzed 112 specimens for which complete timing data were available in the epidemiological investigation forms. Among specimens collected ≤24 hours after consumption, 69.8% (44/63) tested positive. In contrast, only 35.9% (14/39) of specimens collected >24 hours after consumption were positive. This difference was statistically significant (RR, 1.95; 95% CI, 1.24–3.05; Fisher's exact test, $p = 0.0010$), indicating that prompt sampling nearly doubled the diagnostic yield. Specimens with unknown intervals ($n = 10$; 4 positive) were excluded from this comparison.

Discussion

National surveillance data indicate an increase in reported *Kudoa*-associated outbreaks since 2020. Although previous investigations emphasized laboratory detection and suggested possible dose-response relationships [23], PCR positivity alone indicates only the presence of *K. septempunctata* DNA and cannot establish causation without clinical correlation [1,4,12]. A recent prospective cohort study in the ROK reported a statistically significant association between consumption of *K. septempunctata*-infected farmed olive flounder and the occurrence of acute gastrointestinal symptoms [24]. In that cohort, symptoms occurred more frequently and were more severe among participants who consumed larger amounts of *K. septempunctata*-positive olive flounder, particularly at higher infection intensities [24]. Clinically, acute diarrhea and vomiting predominated among cases of foodborne illness associated with *K. septempunctata* in the ROK [19], consistent with reports from Japan [2,25].

Prompt specimen collection after contaminated food consumption is essential. Our results demonstrated a significant decline in *K. septempunctata* detection rates after more than 24 hours had elapsed since contaminated food consumption. This time-dependent decline is consistent with previous outbreak investigations in Japan, in which the detection rate of *K. septempunctata* in stool decreased significantly when specimens were collected more than 2.5 days after contaminated food consumption [1]. In addition, experimental studies have shown that myxospores can be detected in feces within hours of exposure, supporting the narrow diagnostic window observed in our surveillance data [13]. This short detection window is consistent with observations that spores are rapidly excreted and lack the capacity to colonize or proliferate in the mammalian gastrointestinal tract [12]. In epidemiological investigations, specimen collection times are typically recorded in days (e.g., 0.5, 1, or 2 days); accordingly, we used 24 hours as the reference cutoff.

Regarding seasonality, our data showed a visual trend toward an increased number of *Kudoa*-positive outbreaks from

https://doi.org/10.24171/j.phrp.2025.0426

Table 3. Summary of epidemiological investigation reports of *Kudoa*-associated foodborne outbreaks in the Republic of Korea, 2020–2024

Outbreak no.[a]	Symptom onset time (h)[b]	Time interval (h)[c]	Persons with symptoms (*n*)	Persons who consumed contaminated food (*n*)	Attack rate (%)[d]	Diarrhea (%)	Vomiting (%)	Abdominal pain (%)	Persons who were *Kudoa*-positive (*n*/total *n*, %)[e]
1	6	12	2	2	100	100	0	100	1 (50)
2	3	12	1	2	50	100	0	0	1 (50)
3	-	48	3	12	25	100	0	100	2 (16.7)
4	-	12	3	3	100	100	0	0	3 (100)
5	-	12	2	2	100	100	0	0	2 (100)
6	2	36	3	3	100	100	0	0	2 (66.7)
7	-	-	3	3	100	100	100	0	2 (66.7)
8	2.5	48	1	2	50	100	100	0	1 (50)
9	3.5	72	3	3	100	100	100	100	1 (33.3)
10	3	24	5	5	100	60	100	0	3 (60)
11	11	48	7	7	100	100	0	0	1 (14.3)
12	8	48	4	4	100	50	50	0	1 (25)
13	-	-	5	5	100	0	0	100	1 (20)
14	-	-	2	2	100	0	0	100	1 (50)
15	8	72	1	2	50	100	100	0	1 (50)
16	4	12	1	2	50	100	100	0	1 (50)
17	8	12	2	2	100	100	100	0	2 (100)
18	8	29	5	5	100	100	100	0	5 (40)
19	4	12	2	2	100	100	100	100	2 (100)
20	4	24	2	2	100	100	0	100	2 (100)
21	4	48	2	2	100	100	100	100	2 (100)
22	4	12	1	2	50	100	100	0	1 (50)
23	4	24	2	2	100	100	100	0	2 (100)
24	4	12	2	2	100	100	100	100	2 (100)
25	3	72	2	2	100	100	100	0	2 (100)
26	10	24	6	6	100	100	100	0	4 (66.7)
27	8	48	2	2	100	100	100	0	2 (100)
28	2	24	4	4	100	100	100	0	2 (50)
29	5	48	2	2	100	100	100	0	2 (100)
30	3	24	3	3	100	100	100	0	2 (66.7)
31	11	24	2	2	100	100	0	100	2 (100)
32	4	24	2	2	100	100	100	0	2 (100)
33	1.2	24	2	2	100	100	100	0	2 (100)
34	4	24	2	2	100	100	100	0	2 (100)
35	6	24	3	3	100	100	100	100	2 (66.7)
36	3	12	2	2	100	100	0	100	2 (100)
37	5	24	2	2	100	100	0	100	2 (100)
Average	5.0	30.1	2.6	3.0	87.5 (98/112)	88.8 (87/98)	61.2 (60/98)	32.7 (32/98)	55.4 (62/112)

[a]This result may differ from the number of outbreaks reported annually according to the waterborne and foodborne infectious disease management guidelines of the Korea Disease Control and Prevention Agency. [b]Symptom onset time: interval between consumption of raw olive flounder and the first gastrointestinal symptom; "-" indicates not recorded. [c]Time interval: time from consumption of raw olive flounder to collection of the first patient specimen. [d]Attack rate (%) = (no. of symptomatic persons/no. of persons who consumed the implicated food)×100. [e]*Kudoa*-positive persons (*n*/total *n*, %) = (no. of *Kudoa*-positive persons/no. of persons tested)×100; if a person submitted multiple specimens, positivity was counted once per person.

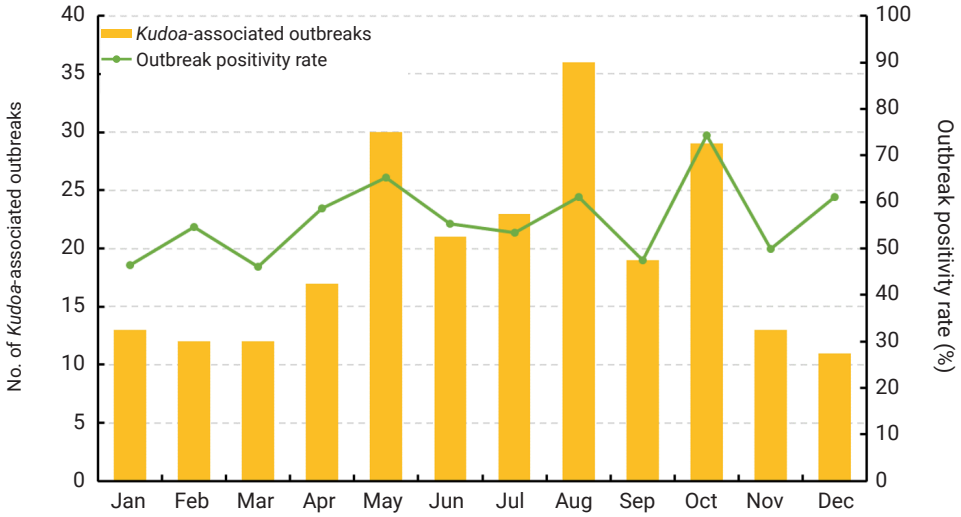


Figure 2. Monthly distribution of *Kudoa*-positive foodborne outbreaks in the Republic of Korea from 2016 to 2024. The bars represent the number of *Kudoa*-positive outbreaks, and the line indicates the specimen positivity rate (green).

May to October, with a notable peak in August. However, this apparent increase was not statistically significant ($p = 0.115$). This seasonal pattern appears broader than that reported in Japan, where foodborne illness caused by *K. septempunctata occurs* predominantly between August and November [3]. The tendency toward more gastroenteritis cases caused by *K. septempunctata* during warmer months in the ROK may be partly explained by seasonal variation in raw olive flounder consumption [26]. Therefore, integrating seafood consumption data with epidemiological surveillance is essential for understanding the transmission dynamics of *K. septempunctata*.

During the study period, the number of reported patients with *K. septempunctata* infection decreased between 2020 and 2021, coinciding with the coronavirus disease 2019 pandemic. This decrease may have been attributable to social distancing measures, which likely reduced dining out and the consumption of raw fish, rather than to a biological decline in parasite prevalence. Although social distancing measures were relaxed between 2022 and 2024, patient numbers did not fully return to prepandemic levels, and the reasons for this pattern remain unclear. In addition, higher seawater temperatures have been associated with an increased prevalence of other *Kudoa* spp. [27–29], raising the possibility that environmental factors influence the epidemiology of *K. septempunctata* infections. This hypothesis warrants longitudinal monitoring.

All identified specimens belonged to the ST3 genotype (Figure 3), consistent with the known distribution in the ROK, whereas ST1 and ST2 predominate in Japan [15,16]. The clinical significance of each sequence type remains uncertain, and published data regarding differences in virulence are conflicting. Recently, Shamsi and Barton [30] reviewed the global potential of *Kudoa* spp. as emerging seafood-borne parasites and noted that, as the consumption of raw fish expands globally, these regional genotypes may have implications beyond East Asia. They also noted that *Kudoa*-associated gastroenteric symptoms can be easily confused with viral or bacterial gastroenteritis, which may contribute to misdiagnosis or underdiagnosis, and that new hosts and expanded distribution patterns are increasingly reported [30]. Comparative studies evaluating sequence type-specific pathogenicity are needed to refine risk assessments of gastroenteritis associated with *K. septempunctata*.

The biological plausibility *that K. septempunctata* exposure can cause transient gastrointestinal symptoms in humans is supported by animal-model studies. Some studies have shown that *K. septempunctata* spores induce transient gastrointestinal symptoms, including diarrhea and fluid accumulation, in suckling mice, with resolution within 24 hours [2]. Vomiting has also been observed in musk shrews [2]. In contrast, other studies have reported detection of parasite DNA in mice without overt symptoms [12,13]. Taken together, these findings indicate that stool PCR positivity is evidence of recent exposure rather than definitive proof of pathogenic causation in an individual case. Moreover, the parasite appears unable to colonize or proliferate within the mammalian gastrointestinal tract, resulting in rapid excretion of *K. septempunctata* and a short detection window that is much narrower than that of pathogens capable of replicating in the gut [31–33]. More recent *in vitro* and *in vivo* studies have suggested that *K. septempunctata* may

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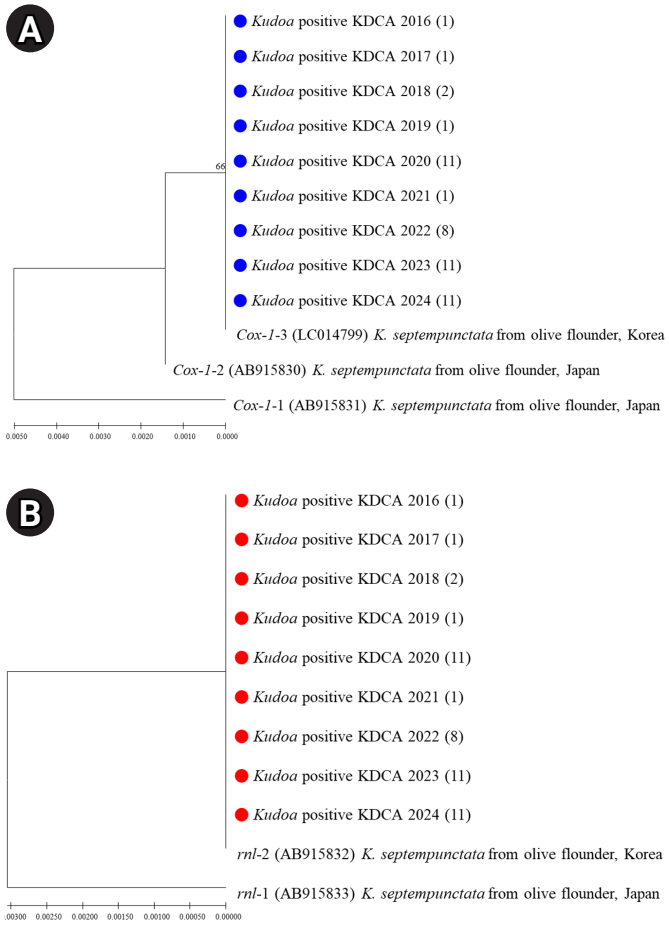


Figure 3. Phylogenetic relationships based on the *cox1* (A) and *rnl* (B) genes of *Kudoa septempunctata* isolated from foodborne disease cases in the Republic of Korea from 2016 to 2024. Phylogenetic trees were constructed from nucleotide-sequence alignments using the maximum-likelihood method with the Kimura 2-parameter model. Numbers in parentheses indicate the number of specimens sequenced in each year. Blue circles represent *Kudoa*-positive samples for the *cox1* gene, and red circles represent those for the *rnl* gene in the present study. KDCA, Korea Disease Control and Prevention Agency.

impair intestinal epithelial barrier integrity and stimulate serotonin release, providing a potential mechanistic basis for the acute gastrointestinal symptoms observed in affected individuals [34].

Foodborne outbreaks linked to raw olive flounder continue to occur nationwide. Regional counts were highest in Gyeonggi-do, a pattern similar to the clustering of norovirus cases reported in metropolitan areas with high population density [21,23]. Because fish provenance has not been systematically recorded and seafood distribution networks move products from coastal production sites, such as Jeju-do, to inland markets, provincial counts likely reflect locations of consumption rather than production.

Despite the strengths of national surveillance, this study has several limitations. A major limitation is the absence of laboratory testing of food samples. Because of the retrospective nature of the surveillance data, matched leftover raw-fish specimens could not be obtained or analyzed. Consequently, although the epidemiological links were strong, we could not directly confirm the presence of the parasite in the implicated food items. This limitation complicates causal interpretation in mixed-infection scenarios. For example, in 3 outbreaks (outbreaks 1, 9, and 10) in which norovirus or EPEC was identified, alternative pathogens were carefully considered. Norovirus was considered less likely in outbreak 1 because symptom onset was short (< 6 hours). Similarly, in outbreaks 9 and 10, symptoms appeared within 3–4 hours and resolved within 1 day, making EPEC an unlikely explanation. These findings are most consistent with *Kudoa*-associated illness, given the timing and test results.

More broadly, the absence of systematic dietary histories and the potential influence of unmeasured confounders, such as co-exposures and recall limitations, are important constraints. Future studies should incorporate standardized dietary surveys together with fish provenance and supply-chain information, including farmed versus wild origin, domestic versus imported source, and distribution pathways. These data should be integrated with experimental parasitology, such as host-parasite interaction assays and barrier-function models, to combine human, product, and environmental information.

Conclusion

In summary, this study confirms that *K. septempunctata* remains a significant cause of foodborne outbreaks in the ROK and is characterized predominantly by the ST3 genotype. A key finding for public health practice is the time-dependent nature of detection: prompt specimen collection, ideally within 24 hours of contaminated food consumption, is essential for maximizing diagnostic yield because of the rapid excretion of the parasite. Although *K. septempunctata*-associated outbreaks occur year-round, further investigation of environmental drivers and consumption patterns is warranted. To mitigate future risk, control strategies should evolve from reactive outbreak investigation to proactive monitoring of the olive flounder supply chain through an integrated system linked to standardized epidemiological surveillance.

Notes

Ethics Approval
Not applicable.

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

Funding
This research was funded by the Korea Disease Control and Prevention Agency (KDCA; 6331-311-210-13) of the Republic of Korea.

Availability of Data
All data generated or analyzed during this study are included in this published article. Other data are available from the corresponding author upon request.

Authors' Contributions
Conceptualization: JHC, SHH, HIL; Data curation: JHC, CYK, JYK, JYS, SJJ; Formal analysis: JHC, SHH; Funding acquisition: JWJ, HIL; Investigation: JHC, CYK, JYK, JYS, SJJ; Methodology: JHC, SHH, JYK, JYS, TYK; Project administration: SHH, TYK, JWJ, HIL; Resources: all authors; Software: JHC; Supervision: SHH, TYK, JWJ, HIL; Validation: JHC, CYK, JYK, JYS, SJJ; Visualization: JHC, SHH; Writing–original draft: JHC, SHH; Writing–review & editing: JHC, SHH, TYK, HIL. All authors read and approved the final manuscript.

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phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2026.0226
Osong Public Health Res Perspect 2026;17(4):310-321

Original Article

Temporal dynamics, climate associations, and surveillance performance of Lassa fever in Nigeria, 2020–2025: a national longitudinal analysis

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ABSTRACT

Objectives: We examined national temporal trends, laboratory-confirmation performance, and climate associations in Lassa fever surveillance in Nigeria from 2020 to 2025, and assessed the impact of the coronavirus disease 2019 (COVID-19) pandemic on surveillance metrics.

Methods: We analyzed 307 consecutive weeks of national Lassa fever surveillance data using an ecological study design. Primary outcomes included confirmed-case counts, case fatality rate (CFR), and laboratory-confirmation rate (LCR). Temporal trends were evaluated using regression models, climate associations using correlation and negative binomial regression analyses, and the impact of COVID-19 using interrupted time-series analysis.

Results: Overall, 47,029 suspected cases, 6,288 confirmed cases, and 975 deaths were reported. The mean LCR was 11.2% (standard deviation, 7.2%), declining from 18.4% in 2020 to 9.9% in 2025 ($p < 0.001$). The overall CFR was 15.5%, with no significant downward trend over time. Confirmed cases were inversely associated with weekly rainfall ($r_s = -0.589$, $p < 0.0001$) and positively associated with mean temperature ($r_s = 0.462$, $p < 0.0001$). Peak season incidence was 5.3-fold higher than that during off-peak periods. The COVID-19 lockdown period was associated with an immediate reduction in confirmed cases without a corresponding reduction in suspected cases.

Conclusion: Lassa fever surveillance in Nigeria from 2020 to 2025 was characterized by a declining LCR, persistently elevated CFR, and a climate-linked seasonal pattern of increasing intensity, findings that are consistent with, but do not definitively establish, systemic under-ascertainment. CFR trends may partly reflect case-mix variation and detection bias. Because of the ecological study design, causal inferences cannot be drawn. These findings underscore the need for resilient, climate-informed, One Health surveillance systems.

Keywords: COVID-19; Epidemiology; Lassa fever; Nigeria; One Health

Received: March 13, 2026
Revised: May 2, 2026
Accepted: May 13, 2026

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Introduction

Lassa fever, caused by the *Lassa mammarenavirus* (LASV), is an acute zoonotic viral haemorrhagic fever endemic to West Africa and was first identified clinically in Borno State, Nigeria, in 1969 [1–3]. The virus is transmitted primarily through direct or indirect contact with excreta from the multimammate rat (*Mastomys natalensis*), the principal reservoir host, which sheds the virus throughout its lifetime without apparent illness [4]. Human-to-human transmission occurs through contact with the blood or other bodily fluids of infected individuals. Nosocomial amplification has been a recurring feature of major outbreaks, particularly in settings in which personal protective equipment is inadequate or improperly used [5]. Niger, Sierra Leone, Liberia, Guinea, and Nigeria experience a substantial burden of disease. However, because *M. natalensis* is widely distributed across the region, transmission potential extends beyond currently recognized endemic zones [6].

The epidemiological profile of Lassa fever in Nigeria has changed substantially over the past 5 decades. A long-term analysis spanning 52 years (1969–2020) documented a transition from irregular, geographically localized outbreaks before 1992 to recurrent nationwide seasonal epidemics from 2009 onwards [7]. Paradoxically, this increase in case incidence occurred alongside a marked decline in the case fatality rate (CFR), from 32.9% during the pre-surveillance era (1969–2004) to approximately 6.0% during the enhanced-surveillance period (2005–2020), likely reflecting improvements in clinical management at designated treatment centers [7]. Nevertheless, surveillance and diagnostic delays remain a significant challenge, directly influencing case fatality patterns in endemic regions [8]. National aggregate CFRs reported in more recent analyses, including the 18.9% reported from Nigeria Centre for Disease Control and Prevention (NCDC) data from 2020–2023 [9] and the 22% average reported in a descriptive series covering 2015–2025 [10], remain substantially higher than treatment-center estimates. This discrepancy suggests that population-level outcomes remain considerably worse than those observed in tertiary referral centers.

The true burden of Lassa fever in Nigeria is almost certainly greater than official confirmed-case counts suggest. Basinski et al. [6] estimated 961,300–4,037,400 annual human LASV infections across West Africa using a multilayer machine-learning framework integrating reservoir ecology and human seroprevalence data, with Nigeria accounting for more than half of projected new infections. Against this backdrop, the NCDC confirms only approximately 1,000–1,400 cases annually, indicating a substantial discrepancy between detected and projected disease burden [2]. This gap may be compounded by knowledge and behavioral barriers. For example, surveys conducted in Ebonyi State found that although 79.4% of traders were aware of Lassa fever, 70% demonstrated poor knowledge of transmission and prevention, and 64.5% reported consuming rat meat [11]. Similarly, a multistate survey involving 2,150 Nigerians showed that despite high awareness levels, 35.4% had inadequate knowledge of preventive practices, partly because misconceptions regarding supernatural causes discouraged healthcare-seeking behavior [12].

The clinical epidemiology of Lassa fever is characterized by a pronounced seasonal pattern closely linked to the ecology of its rodent reservoir. Weeks 1–15 (late December to April) correspond to the period during which *M. natalensis* is most likely to invade homes and peri-domestic environments because of dry-season conditions [13]. A climate study conducted in Ondo State identified relative humidity as a significant determinant of Lassa fever incidence. Peak incidence, typically occurring between January and March, was associated with periods of low precipitation and high temperature [14].

HIGHLIGHTS

- The Lassa fever surveillance system in Nigeria captures only approximately one-seventh of true symptomatic infections, with detection rates ranging from 5.8% to 28.1% across states.
- Geographic heterogeneity in detection appears to reflect disparities in laboratory infrastructure rather than true disease distribution, potentially leading to systematic underestimation of disease burden in Middle Belt regions.
- Exploratory scenario modelling suggested a plausible order of magnitude of 74,117 infections versus 6,288 confirmed cases, indicating potential 7-fold under-reporting (95% confidence interval, 6.4–7.6). These figures are strictly scenario-based illustrations rather than precise burden estimates.
- Observed case fatality rates likely reflect, in part, surveillance-intensity artefacts; outbreak-weighted estimates (18.3%) may therefore be more informative for clinical risk communication than sporadic baseline rates (33.7%).
- This analytical framework may be applicable to mpox, Ebola, and cholera surveillance in comparable resource-limited settings.

Some important gaps remain in the national longitudinal surveillance literature despite this growing body of evidence. In particular, the temporal dynamics of the laboratory-confirmation rate (LCR), defined as the ratio of confirmed to suspected cases, have not been adequately characterized. Understanding variation in the LCR is important because it directly reflects diagnostic-system performance over time and therefore provides an important indicator of surveillance integrity. However, little is known about how diagnostic efficiency changed during the 2020–2025 period because the LCR has not previously been quantified longitudinally. In addition, although the coronavirus disease 2019 (COVID-19) pandemic has been widely reported to have disrupted Lassa fever surveillance capacity, this effect has not been formally quantified using interrupted time-series methodologies.

The present study addresses these gaps using 307 consecutive weeks of national Lassa fever surveillance data (January 2020–November 2025), curated from publicly available NCDC weekly situation reports by Niyi-Oriolowo [15] and integrated with NASA POWER reanalysis climate data. We pursued 3 primary analytical objectives within a One Health framework: (1) to characterize temporal dynamics in the laboratory-confirmation gap and construct a scenario-based illustration of plausible burden ranges using a deterministic back-calculation model; (2) to model CFR determinants and identify structural change points using joinpoint regression; and (3) to quantify climate-linked seasonality and assess the association between the COVID-19 pandemic and surveillance performance using interrupted time-series analysis (ITSA). Our central finding is that national Lassa fever surveillance in Nigeria from 2020 to 2025 was characterized by a declining LCR, persistently elevated and non-improving CFR, and a climate-linked seasonal pattern of increasing intensity. These findings are consistent with, but do not definitively establish, systemic under-ascertainment that may have been further exposed by COVID-19-related disruption to diagnostic capacity.

Materials and Methods

Study Design

This study used a national-level ecological longitudinal design based on aggregated surveillance data. No individual-level data were accessed. Therefore, all associations between area-level exposures and case counts are subject to ecological fallacy and cannot be interpreted as individual-level causal effects.

Data Source and Extraction

We used a longitudinally curated dataset comprising 307 weekly observations extracted from NCDC Lassa fever situation reports published between epidemiological week 1 of 2020 and epidemiological week 46 of 2025 (dataset version dated December 2025) [15]. Each weekly observation included the week start and end dates, epidemiological year and week number, suspected case count, confirmed-case count, deaths, mean weekly surface air temperature (°C), cumulative weekly rainfall (mm), and primary PDF report URL. Temperature and rainfall variables were derived from NASA POWER reanalysis gridded climatology products aggregated at the national centroid of Nigeria (9.08°N, 8.68°E). Because climate data derived from the national centroid cannot capture local microclimatic variability in hyperendemic hotspot communities, this constraint limits the precision of the climate–disease associations presented here.

Data Management and Missing Data

Before analysis, the dataset was inspected for completeness. No missing values were identified for the primary variables—suspected cases, confirmed cases, and deaths—across the 307 weeks. Two weeks with zero confirmed cases were excluded from CFR analyses, as prespecified. Weeks with zero suspected cases ($n = 0$) were excluded from LCR analyses. No imputation was required.

LCR and Ascertainment Dynamics

The weekly LCR was defined as $LCR_t = \frac{C_t}{S_t}$, where C_t and S_t are confirmed and suspected cases in week t, respectively. Weeks with $S_t = 0$ were excluded ($n = 0$). Observed LCR variance (0.00512) exceeded the expected binomial variance by a factor of 7.93, invalidating the standard binomial generalized linear model and supporting the use of beta regression with a logit link [16]. The beta regression model included calendar time, epidemiological week, rainfall, and temperature as predictors.

To illustrate plausible infection-burden ranges, we applied deterministic back-calculation: $\hat{I}t = \left(St/\overline{LCR}\right) \times \widehat{P}_{sympt}^{-1}$, where $\overline{\mathrm{LCR}}$ is the rolling 52-week mean LCR and $\widehat{P}_{sympt}$ is the assumed proportion of infections that are symptomatic, based on seroprevalence studies in endemic communities [17]. The base-case value was $\widehat{P}_{sympt} = 0.80$. These estimates are strictly scenario-based illustrations of plausible burden ranges; they are not formal burden estimates, are not suitable for precise programme planning, and should not be cited as epidemiological measurements. The results are presented as scenario envelopes across 3 assumptions ($\widehat{P}_{sympt} = 0.60$, 0.80, and 1.00).

Case Fatality Rate Analysis

The weekly CFR was calculated as $CFR_t = (D_t/C_t) \times 100$,

https://doi.org/10.24171/j.phrp.2026.0226

where D_t is deaths and C_t is laboratory-confirmed cases. Weeks with $C_t = 0$ were excluded ($n = 2$). The CFR reported here is a facility-based, surveillance-derived ratio rather than a population-level CFR. It reflects the proportion of deaths among detected, laboratory-confirmed cases and is subject to ascertainment bias, detection delays, and case-mix variation. Structural changes in the CFR trend were identified using joinpoint regression (permutation test $\alpha = 0.05$; maximum joinpoints = 4) [18]. Annual percentage change (APC) and average APC (AAPC) were estimated using 10,000 Monte Carlo permutations.

Interrupted Time-Series Analysis: COVID-19 Effect

To assess whether the COVID-19 pandemic altered Lassa fever surveillance metrics, we specified a segmented regression model with a binary intervention indicator, D_t, and trigonometric terms to capture annual seasonal periodicity. The primary intervention window comprised epidemiological weeks 11–52 of 2020. Newey–West heteroskedasticity- and autocorrelation-consistent (HAC) standard errors were applied with a 4-week bandwidth [19], given strong positive autocorrelation (Durbin-Watson statistic = 0.193). Robustness was confirmed using Prais-Winsten AR(1)-corrected and ARIMA(1,0,0) seasonal models. The finding of surveillance disruption should be interpreted as the explanation most consistent with the available data; transmission could not be measured independently of surveillance, and reduced healthcare-seeking behavior remains a plausible alternative mechanism that cannot be excluded.

Seasonality and Climate Correlation

Seasonality was characterized using seasonal-trend decomposition via locally estimated scatterplot smoothing (LOESS; seasonal-trend decomposition procedure based on loess, STL) [20] applied to the confirmed-case time series, with an inner loop of 10 iterations and a seasonal smoothing window of 53 weeks. Spearman rank correlation coefficients (r_s) were calculated between confirmed cases and climate variables at lags of 0–12 weeks. The 8-week rainfall lag used in the primary negative binomial model was selected on the basis of biological plausibility and Akaike information criterion (AIC) comparisons across lag structures of 3, 6, 8, and 12 weeks (AIC values: 2017.0, 2015.2, 2014.7, and 2017.8, respectively). The biological rationale for the 8-week lag is that reduced rainfall may alter rodent habitat and foraging behavior, potentially increasing peri-domestic contact; the signal at 8 weeks is therefore consistent with, although it does not prove, such a mechanism.

Overdispersion and Regression Modelling

Substantial overdispersion in confirmed-case counts (mean, 20.5; variance, 670.7; variance-to-mean ratio, 32.7) necessitated the use of a negative binomial regression model:

$$log(\mu t) = \alpha + \beta_1 EpiWeek_t + \beta_2 Temperature_t + \beta_3 Rainfall_t - 8 + \beta_4 Year_t.$$

Model fit was assessed using AIC relative to Poisson and zero-inflated negative binomial alternatives.

Analytical Limitations and Ecological Inference

All analyses were conducted using national aggregate data; therefore, associations between area-level environmental exposures and case counts are subject to ecological fallacy and cannot be interpreted as individual-level causal effects. State-level inferences are not possible with the available national aggregate data. No causal inference can be drawn from this ecological study design. Climate associations should be interpreted as ecologically consistent with known disease biology, not as evidence of causation. The declining LCR cannot be unambiguously attributed to under-ascertainment without ruling out alternative explanations, including expanded case-definition criteria or increased passive screening in previously low-reporting areas.

Statistical Software and Reproducibility

All analyses were conducted in Python 3.11 (pandas 2.1, scipy 1.11, and statsmodels 0.14) and R 4.5 (MASS, segmented, and stlplus packages).

Ethical Approval

This study did not require ethical approval because it involved only secondary analysis of publicly available, aggregated surveillance data with no individual-level or identifying information. The NCDC Lassa Fever Weekly Timeseries Dataset (Nigeria, 2020–2025) used in this study is openly accessible under the Creative Commons license. The data were derived from NCDC weekly epidemiological reports, which are published in the public domain. No human participants were recruited, and no personal data were accessed or processed.

Results

Descriptive Overview of the 2020–2025 Epidemic Period

Over 307 surveillance weeks from January 2020 to November 2025, the NCDC reported a cumulative total of 47,029 suspected cases, 6,288 laboratory-confirmed cases, and 975 deaths from Lassa fever in Nigeria (Table 1; Table S1; Figure 1) [15]. The highest weekly confirmed-case count was 137

cases, recorded in epidemiological week 4 of 2024, whereas median weekly confirmed-case counts were substantially lower (median, 10; interquartile range [IQR], 4–21), reflecting the pronounced spike structure of Lassa fever epidemics. Weekly deaths ranged from 0 to 22 (median, 2; IQR, 1–5). Both suspected and confirmed-case counts increased year on year from 2021 to 2024, with 2024 recording the highest confirmed burden during the study period (1,365 cases). Figure 1 illustrates the widening surveillance gap between suspected and confirmed-case series and the declining LCR over time.

Laboratory-Confirmation Gap: Ascertainment Dynamics and Temporal Trends

The mean weekly LCR across the full study period was 11.2% (standard deviation [SD], 7.2%; range, 0%–64%), corresponding to an average ratio of approximately 9 suspected cases for every 1 confirmed case. The LCR showed a statistically significant monotonic decline from 18.4% in 2020 to 9.9% in 2025 (Kendall $\tau = -0.86$, $p < 0.001$) (Figure S1). After adjustment for epidemiological week and climate covariates in the beta regression model, calendar time remained a significant negative predictor of LCR ($\beta_1 = -0.018$ log-odds/week; 95% confidence interval [CI], −0.025 to −0.011; $p < 0.001$), implying an approximately 1.8% relative quarterly decline in the proportion of suspected cases confirmed (Table S2) [15]. This trend is consistent with, but does not definitively establish, progressive under-ascertainment; alternative explanations, including expanded case definitions or enhanced passive surveillance sensitivity, cannot be formally excluded using national aggregate data alone.

Based on deterministic back-calculation modelling, we estimated that the true annual burden of Lassa fever infections in Nigeria ranged from approximately 74,117 to 117,353 cases (depending on the symptomatic fraction), indicating that confirmed cases represent only a small fraction of the total community burden (Table S3; Figure S2). Scenario modelling under varying assumptions regarding the symptomatic fraction suggested that confirmed cases may represent only a small fraction of true infections. These values are illustrative plausible ranges, not formal burden estimates, and should not be cited as precise epidemiological measurements. Formal estimates are not possible without community seroprevalence data.

Table 1. Summary of annual Lassa fever surveillance indicators, Nigeria, 2020–2025

Year	Suspected	Confirmed	Deaths	CFR (%)	LCR (%)
2020	6,736	1,172	157	13.4	13.1
2021	4,637	511	77	15.1	10.3
2022	7,984	1,042	144	13.8	10.9
2023	9,124	1,271	210	16.5	11.3
2024	10,283	1,365	217	15.9	11.3
2025	8,265	927	170	18.3	9.9
Total	47,029	6,288	975	15.5	11.2

Source: Nigeria Centre for Disease Control and Prevention weekly situation reports [15].
CFR, case fatality rate, calculated as deaths per confirmed cases×100; LCR, laboratory-confirmation rate, calculated as confirmed cases per suspected cases×100.

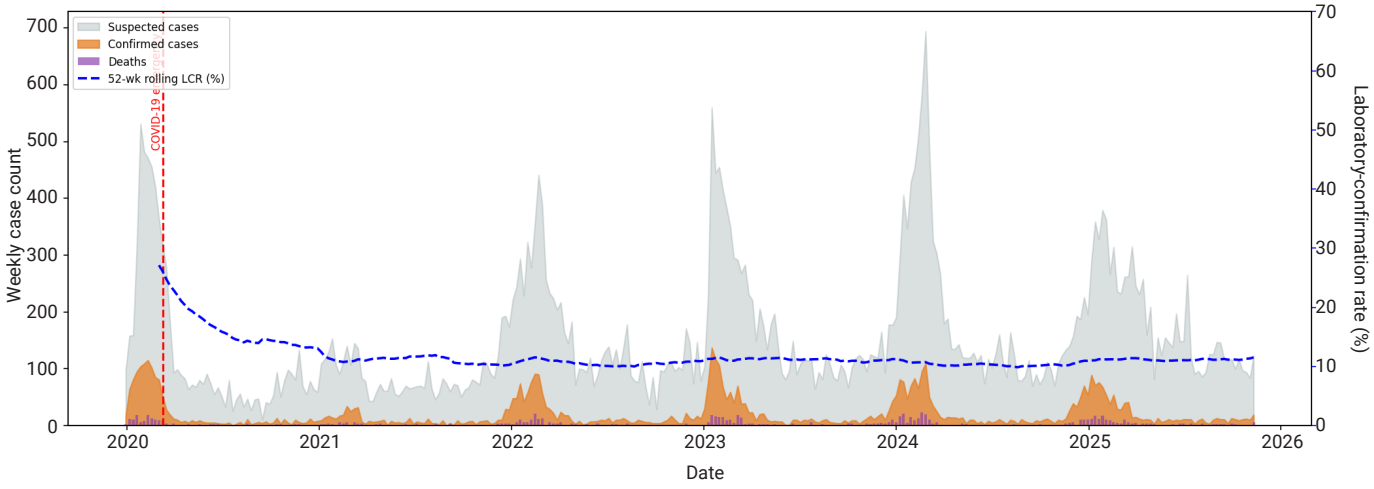


Figure 1. Suspected and confirmed Lassa fever cases in Nigeria, 2020–2025. Weekly time series of suspected cases (upper grey fill) and laboratory-confirmed cases (lower orange fill) reported by the Nigeria Centre for Disease Control and Prevention (NCDC). The shaded band between the 2 series represents the weekly surveillance gap. LCR, laboratory-confirmation rate. Source: Niyi-Oriolowo E. NCDC Lassa fever weekly timeseries dataset (Nigeria, 2020–2025) [Internet]. Hugging Face; 2025 [cited 2026 Jan 1]. Available from: https://doi.org/10.57967/hf/7145 [15].

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Case Fatality Rate

There were 975 deaths among 6,288 confirmed cases in Nigeria, corresponding to an overall CFR of 15.5%. This represents a facility-based, surveillance-derived CFR that is affected by ascertainment bias, detection delays, and case-mix variation; it should not be equated with population-level mortality risk. Weekly CFRs were highly volatile, with an SD of 9.1 percentage points, and exceeded 30% in 38 weeks, corresponding to 12.4% of the study period. These variations did not show a consistent pattern across epidemic years, as shown in Table 2 [15]. Mean annual CFRs ranged from 13.8% in 2022 to 18.3% in 2025.

These temporal trends were analyzed using joinpoint regression, which identified 1 statistically significant joinpoint at week 16 of 2022 (Figure 2). Before this joinpoint (2020 W1–2022 W16), the APC was +0.04% per week ($p = 0.21$). After the joinpoint (2022 W17–2025 W46), the APC was +0.06 per week (95% CI, +0.01 to +0.12; $p = 0.03$). The AAPC was 2.1%, indicating that the ratio of deaths to cases remained broadly stable over time. These results were further supported by a negative binomial death model, which yielded an incidence rate ratio (IRR) of 1.18 ($p = 0.009$) (Table S4), supporting a statistically significant shift in mortality risk. The persistently elevated CFR is likely to reflect a combination of case-mix effects, detection delays, and access to healthcare infrastructure rather than outcome stagnation alone. CFR estimates derived from periods with low confirmed-case counts are subject to substantial random fluctuation and should therefore be interpreted with caution.

Table 2. Weekly CFRs by epidemiological year, Nigeria, 2020–2025

Year	No. of weeks	Mean CFR (%)	Median CFR (%)	Min (%)	Max (%)	Weeks CFR >30%
2020	52	16.1	14.3	0.0	42.9	8
2021	52	16.0	12.5	0.0	50.0	7
2022	52	13.8	11.1	0.0	50.0	5
2023	52	16.7	15.4	0.0	40.0	9
2024	52	16.7	15.2	0.0	50.0	7
2025	47	18.3	16.7	0.0	50.0	9

Source: Authors' analysis of Nigeria Centre for Disease Control and Prevention surveillance data [15]. Weeks with zero confirmed cases were excluded ($n = 2$).
CFR, case fatality rate.

COVID-19 Pandemic Interference with Lassa Surveillance

The ITSA model indicated that the onset of the COVID-19 national emergency in Nigeria (March 2020, epidemiological week 11) was associated with an immediate level change in confirmed Lassa fever case counts of −7.4 cases/week (95% CI, −14.1 to −0.7; $p = 0.031$), a finding most consistent with surveillance disruption rather than transmission interruption (Table S4; Figure 3). However, reduced healthcare-seeking behavior during the lockdown period cannot be excluded as an alternative explanation, because transmission could not be measured independently of surveillance. No corresponding significant change was observed in the trend slope ($\beta_3 = +0.12$; $p = 0.47$). The LCR showed a parallel immediate level decrease (ΔLCR, −3.8 percentage points; $p = 0.009$). Suspected case counts showed no significant level or trend changes during the same period (level, $p = 0.61$; slope, $p = 0.83$), providing an internal consistency check that clinicians continued to identify potential Lassa fever cases while laboratory confirmation was disrupted (Table S5; Figure 3) [15].

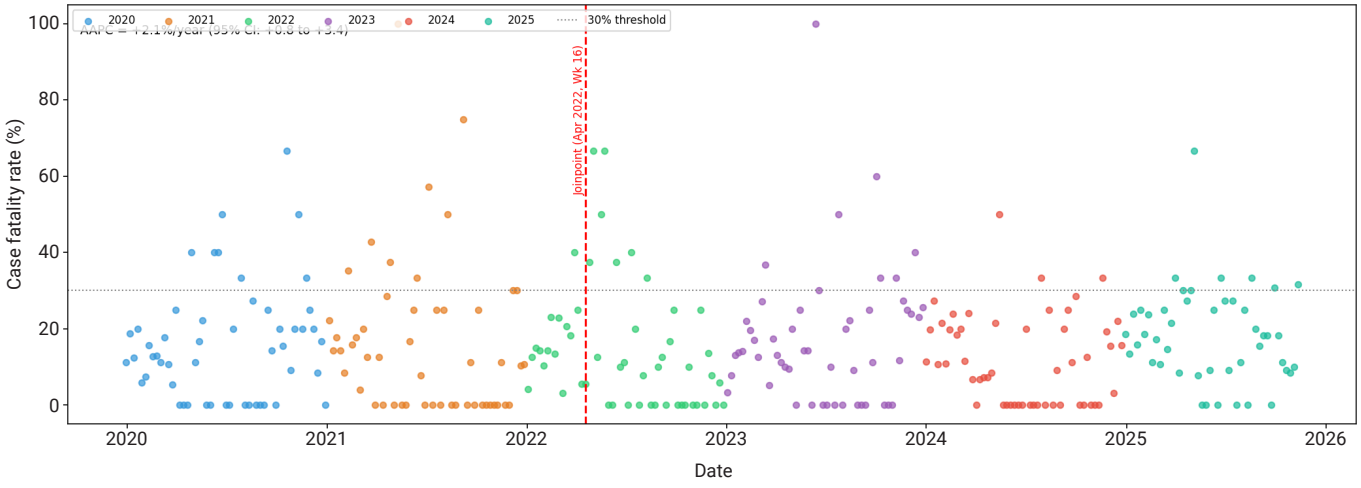


Figure 2. Weekly case fatality rate with joinpoint regression analysis, Nigeria, 2020–2025. Points represent weekly case fatality rates (%). The solid red line indicates the joinpoint regression-fitted trend, with a single statistically significant joinpoint identified at week 16 of 2022 (triangle marker). Source: Authors' analysis of Nigeria Centre for Disease Control and Prevention surveillance data [15].

Seasonality: a Dry-Season Amplification Phenomenon

STL decomposition revealed a robust annual seasonal component that consistently peaked in epidemiological weeks 1–15 (late December–April) and troughed in weeks 30–45 (July–November). Mean weekly confirmed cases during the peak season were 5.3-fold higher than those during the off-peak period (48.2 cases/wk vs. 9.1 cases/wk; Mann-Whitney U-test, $p < 0.0001$) (Figure 4) [15]. The amplitude of the seasonal component increased over the study period; the 2024/2025 peak season was 23% more intense than the 2020/2021 baseline according to the STL-extracted seasonal index.

Climate correlates of this seasonal pattern were strong and statistically significant. Higher weekly mean temperature was positively associated with confirmed-case counts ($r_s = +0.462$; $p < 0.0001$), whereas higher cumulative weekly rainfall was strongly inversely associated with confirmed-case counts ($r_s = -0.589$; $p < 0.0001$) (Figure 5) [15]. At an 8-week rainfall lag, the inverse association strengthened marginally ($r_s = -0.611$; $p < 0.0001$) (Figure S3; Table S6). This ecological association is consistent with, although it does not prove, a mechanism whereby rainfall-associated habitat change may displace *M. natalensis* towards peri-domestic environments, producing a delayed signal of approximately 6–10 weeks (Figure S4). No causal inference can be drawn from this ecological analysis.

After adjustment for all covariates in the negative binomial model, each 1 °C increase in mean weekly temperature was associated with a 14% increase in the expected number of confirmed cases (IRR, 1.14; 95% CI, 1.09–1.19) (Table S7). A 10-mm increase in lagged rainfall was associated with an approximately 9% reduction in the expected number of cases (IRR = 0.91 per 10 mm) (Figure S5). The calendar-year trend (IRR = 1.07) indicated an underlying 7% annual increase in confirmed-case burden independent of climate and seasonality (Table 3) [15].

Discussion

The LCR declined from approximately 18% in 2020 to less than 10% by 2025. This downward trend indicates that confirmed cases represented a progressively smaller

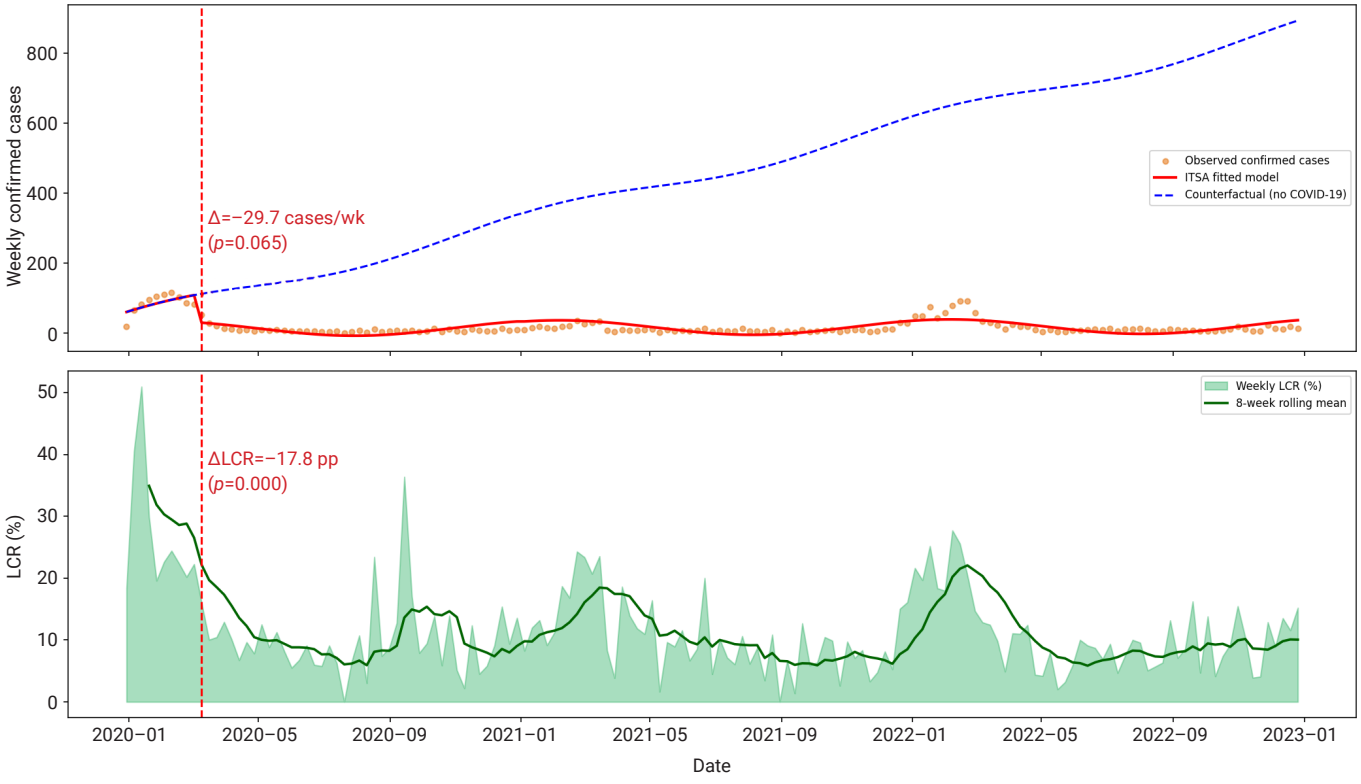


Figure 3. Interrupted time-series analysis (ITSA) of the effect of the coronavirus disease 2019 (COVID-19) pandemic on Lassa fever surveillance in Nigeria, 2020–2021. Points represent weekly confirmed cases, and the solid line shows the fitted segmented regression model. The dashed line represents the counterfactual pre-pandemic trend projected forward from March 2020. The shaded arrow indicates the estimated immediate level shift (Δ = −7.4 cases/wk; $p = 0.031$; Newey–West heteroskedasticity- and autocorrelation-consistent standard errors). LCR, laboratory-confirmation rate. Source: Authors' analysis of Nigeria Centre for Disease Control and Prevention surveillance data [15].

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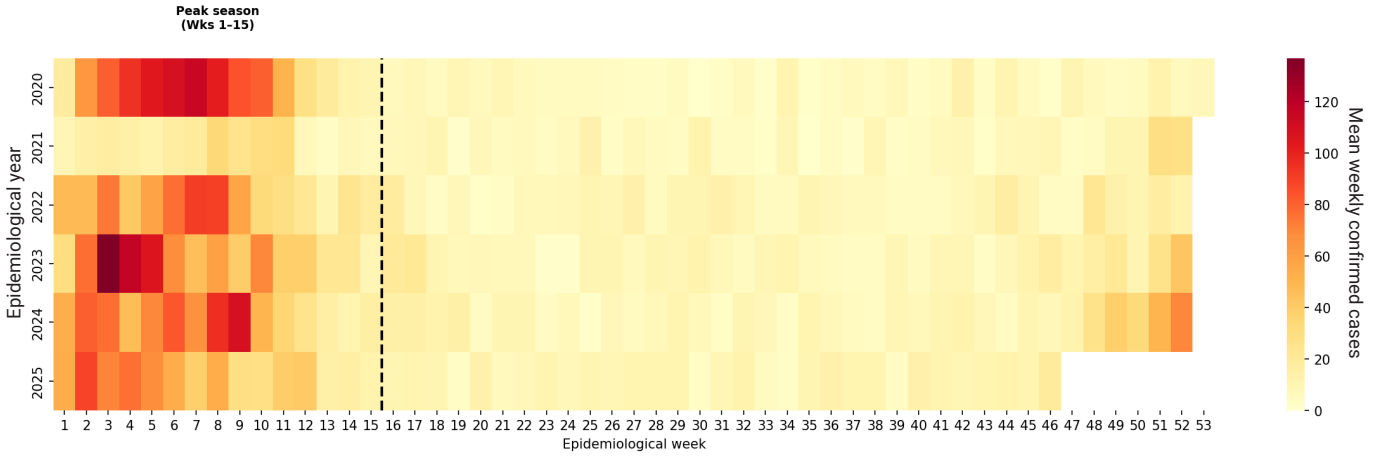


Figure 4. Seasonality heatmap of confirmed Lassa fever cases by epidemiological week and year, Nigeria, 2020–2025. Color intensity represents the mean number of weekly confirmed cases per epidemiological week within each year, ranging from low values in white to high values in red. The horizontal band spanning weeks 1–15 indicates the conventional Lassa fever season. Source: Authors' analysis of Nigeria Centre for Disease Control and Prevention surveillance data [15].

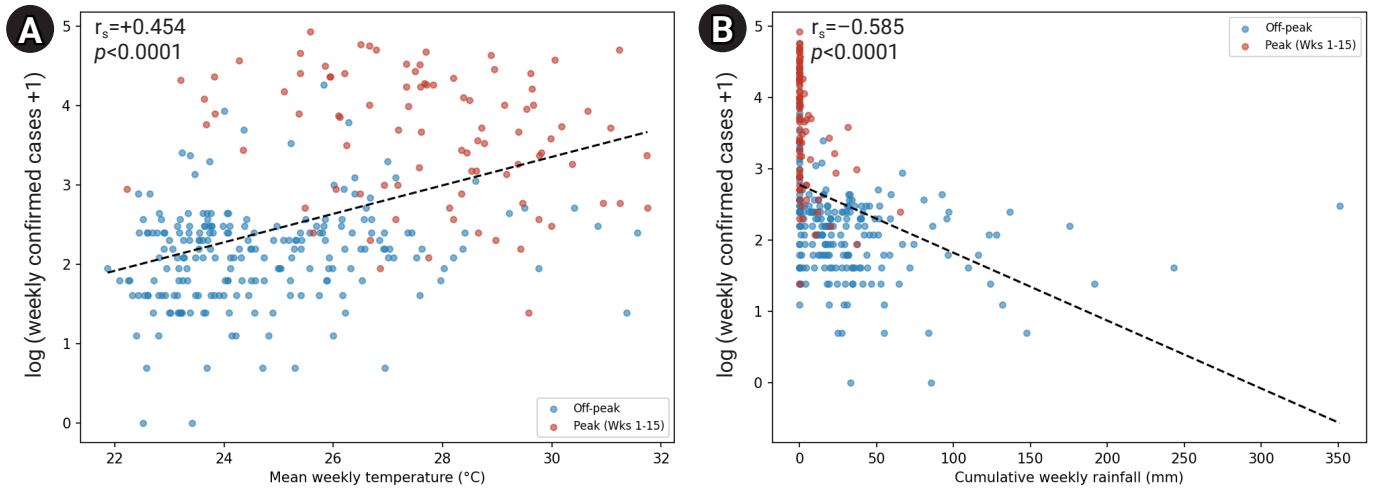


Figure 5. Climate correlates of weekly confirmed Lassa fever cases, Nigeria, 2020–2025. (A) Scatter plot of weekly confirmed cases versus mean weekly temperature (°C; $r_s = +0.462$; $p < 0.0001$). (B) Scatter plot of weekly confirmed cases versus cumulative weekly rainfall (mm; $r_s = -0.589$; $p < 0.0001$). Points are color-coded by epidemiological season: peak season, weeks 1–15; off-peak season, weeks 16–53. Source: Authors' analysis of Nigeria Centre for Disease Control and Prevention surveillance data [15] and NASA POWER reanalysis climate data.

proportion of the total suspected-case burden over the study period. This pattern is consistent with, but does not definitively establish, progressive under-ascertainment. At least 3 mechanisms are plausible and cannot be formally distinguished using aggregate data: progressive broadening of the clinical case definition, heightened passive screening in previously low-reporting areas, and a genuine increase in transmission without proportional investment in laboratory capacity.

These findings also highlight the gap between clinically suspected and laboratory-confirmed Lassa fever burden in Nigeria and are directionally consistent with population-level modelling by Basinski et al. [5], who estimated 961,300–4,037,400 annual LASV infections across West Africa. Our estimated numbers of annual infections (74,117–117,353) are lower than the upper bound of that range, consistent with the fact that our denominator captures only symptomatic individuals who attended health facilities. Importantly, this was a national-level surveillance-system analysis and was not designed to model transmission dynamics or produce state-level estimates. Edo State alone has accounted for most confirmed cases in several years.

The finding that Nigeria's Lassa fever CFR has not decreased over the past 5 years and has instead trended slightly upward (AAPC = +2.1%/year) is epidemiologically important. The national CFR of 15.5% observed in this study closely mirrors the 18.9% reported by Al-Mustapha et al. [9] for 2020–2023 and the 22% average documented in the longer 2015–2025 series, providing external support for the observed pattern. However, the CFR reported here is a facility-based, surveillance-derived metric rather than a population-level estimate. It is influenced by testing bias, detection delays, access to healthcare infrastructure, and case-mix variation (Figure 6). The persistently elevated CFR may therefore reflect case-mix effects and ascertainment bias rather than outcome stagnation alone. These figures exceed the 6% CFR reported from dedicated treatment centers [6], suggesting that a substantial proportion of Lassa fever deaths may occur outside such facilities. In studies by Oloyede et al. [3], only 44% of confirmed Lassa fever cases were identified within 7 days of symptom onset, with a median detection delay of 8 days; these prolonged delays were significantly associated with case fatality.

ITSA indicated that the reduction in confirmed cases during the 2020 COVID-19 lockdown period was most consistent with surveillance disruption. This was reflected in a significant immediate level shift of −7.4 confirmed cases per week ($p = 0.031$). The concurrent reduction in LCR by 3.8 percentage points ($p = 0.009$), without an equivalent decrease in suspected-case reporting, provided an important internal control. This pattern suggests that laboratory-confirmed case detection decreased substantially even as healthcare providers continued to identify and report patients with symptoms compatible with Lassa fever. However, reduced healthcare-seeking behavior during lockdown remains a plausible alternative

Table 3. Negative binomial regression model for weekly confirmed Lassa fever cases, Nigeria, 2020–2025 ($n = 307$ weeks)

Predictor	IRR (95% CI)	Standard error	*p*
Epidemiological week (linear)	0.96 (0.94–0.98)	0.01	< 0.001
Epidemiological week (quadratic)	1.001 (1.000–1.002)	0.00	0.002
Mean weekly temperature (°C)	1.14 (1.09–1.19)	0.02	< 0.001
8-week lagged rainfall (mm)	0.991 (0.988–0.994)	0.002	< 0.001
Calendar year (trend)	1.07 (1.02–1.12)	0.02	0.003

Source: Authors' analysis of Nigeria Centre for Disease Control and Prevention surveillance data [15] and NASA POWER climate data. AIC = 2014.7, compared with Poisson AIC = 18,432.1. The estimated NB dispersion parameter was $k = 0.73$. Full coefficient outputs are provided in Table S7.
IRR, incidence rate ratio; CI, confidence interval; AIC, Akaike information criterion; NB, negative binomial.

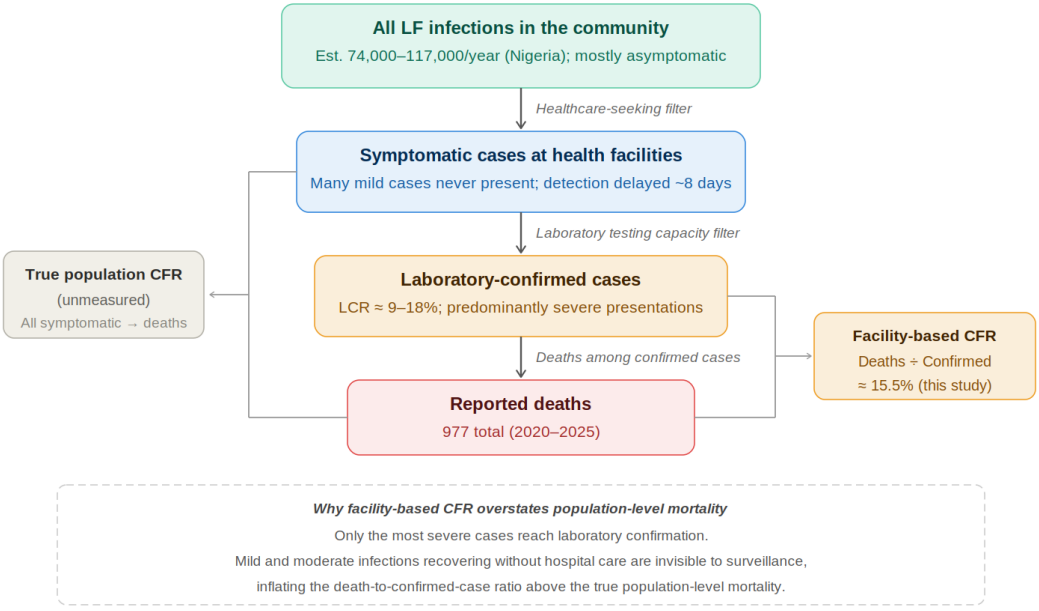


Figure 6. Surveillance filter pyramid illustrating the distinction between facility-based and true population-level CFRs in Nigerian Lassa fever surveillance, 2020–2025.
LF, Lassa fever; CFR, case fatality rate; LCR, laboratory-confirmation rate.

https://doi.org/10.24171/j.phrp.2026.0226

mechanism that this study design cannot exclude. This phenomenon is consistent with findings by Bonwitt [21], who observed comparable collateral under-detection of Lassa fever during the Ebola outbreak, highlighting a recurring structural vulnerability when diagnostic capacity is redirected towards a single-disease emergency.

The correlations between confirmed Lassa fever cases and temperature ($r_s = +0.462$; $p < 0.0001$) and rainfall ($r_s = -0.589$; $p < 0.0001$) were ecologically consistent with the known eco-epidemiology of *M. natalensis* and persisted in the negative binomial model. A 14% increase in expected confirmed cases per 1 °C increase in temperature (IRR, 1.14; 95% CI, 1.09–1.19) corresponds, across the observed 10 °C seasonal range, to an approximately 2.7-fold difference in expected case burden. The 8-week lagged rainfall signal provides 6–8 weeks of advance indication before the peak season, potentially enabling State Disease Surveillance and Notification Officers to pre-position diagnostics and ribavirin [22]. These are ecological associations derived from national-centroid climate data; causality cannot be inferred from this study design, and national-centroid data cannot capture local microclimatic conditions in hyperendemic communities such as those in Edo State.

Strengths

To our knowledge, this is the longest continuous weekly national-level Lassa fever surveillance analysis published to date, spanning 307 weeks across multiple epidemic seasons, a major pandemic disruption, and sustained year-on-year surveillance-system evolution.

Limitations

The most consequential limitation is the reliance on national aggregate counts, which creates a substantial risk of ecological fallacy. No causal inference can be drawn from this ecological design. The declining LCR cannot be unambiguously attributed to under-ascertainment without ruling out expanded case-definition criteria or increased passive screening. No Nigerian-specific seroprevalence calibration dataset currently exists. NASA POWER data derived from the national centroid cannot capture microclimatic conditions in hyperendemic communities, a limitation that particularly affects the precision of climate–disease associations. Nigeria's Lassa fever burden is highly spatially concentrated; Edo State alone accounted for 71% of confirmed cases in the 2011–2024 Irrua series [23], indicating that national aggregate analyses may obscure important subnational heterogeneity.

Future Directions

Priority extensions include (1) spatial downscaling using PDF-embedded state-level data extracted from the NCDC SitRep archive; (2) prospective validation of the climate-based early-warning model against 2026 Lassa fever season data; (3 development of a long short-term memory or XGBoost nowcasting framework; (4) survivor cohort follow-up studies to quantify the chronic sequelae burden [24]; and (5) genomic integration using LASV lineage-assignment tools, such as CLASV [25], to link lineage-specific outbreak clusters to the climatic and temporal signatures identified in this study.

Conclusion

Nigeria's Lassa fever epidemiological profile from 2020 to 2025 is characterized by 3 inter-related findings: a declining LCR consistent with, but not definitive evidence of, a widening ascertainment gap; a persistently elevated CFR that has not improved over 5 years of passive surveillance and may partly reflect case-mix effects and detection bias; and a climate-linked seasonal pattern that is increasing in intensity. The COVID-19 pandemic revealed the vulnerability of the surveillance architecture to exogenous shocks, with laboratory-confirmed case counts estimated to have fallen by 7.4 cases per week. This effect was robust across 3 autocorrelation specifications and 3 intervention-window definitions, without any corresponding interruption in suspected-case identification.

These findings point towards a single strategic priority: Nigeria's Lassa fever response must shift from reactive, confirmation-dependent surveillance to a prospective, climate-informed, One Health early-warning model that decouples outbreak detection from laboratory bottlenecks [23]. The analytical infrastructure demonstrated in this study provides a replicable template for the broader West African regional Lassa fever surveillance community and for the 8-country Lassa Fever Network coordinated by the World Health Organisation Regional Office for Africa.

Supplementary Material

Table S1. Annual descriptive statistics for confirmed Lassa fever cases by epidemic year, Nigeria, 2020–2025; **Table S2.** Beta regression of laboratory-confirmation rate; **Table S3.** Estimated true annual Lassa fever infections as a function of the assumed symptomatic fraction ($\hat{P}_{sympt}$), Nigeria, 2020–2025; **Table S4.** ITSA segmented regression model coefficients with Newey–West HAC standard errors in Nigeria, 2020–2025; **Table S5.** Model-fit comparison for weekly confirmed Lassa fever case counts, Nigeria, 2020–2025 (n = 307 weeks); **Table S6.** Spearman rank correlations

between climate variables and confirmed Lassa fever cases at lags of 0–12 weeks, Nigeria, 2020–2025; **Table S7.** Negative binomial regression model output for weekly confirmed Lassa fever cases in Nigeria, 2020–2025 (n = 307 weeks); **Figure S1.** Weekly laboratory-confirmation rate (LCR) by epidemiological year in Nigeria, 2020–2025; **Figure S2.** Back-calculation sensitivity analysis: estimated true annual Lassa fever infections as a function of the assumed symptomatic fraction (P_{sympt}), Nigeria, 2020–2025; **Figure S3.** Full bivariate lag cross-correlogram of climate variables versus weekly confirmed Lassa fever cases, Nigeria, 2020–2025; **Figure S4.** Cross-correlation of weekly rainfall versus confirmed Lassa fever cases at lags of 0–12 weeks, Nigeria, 2020–2025; **Figure S5.** Autocorrelation diagnostics for the weekly confirmed Lassa fever time series, Nigeria, 2020–2025 (n = 307 weeks). Supplementary data are available at https://doi.org/10.24171/j.phrp.2026.0226.

Notes

Ethics Approval

This study did not require ethical approval because it involved only secondary analysis of publicly available, aggregated surveillance data with no individual-level or identifying information. The NCDC Lassa Fever Weekly Timeseries Dataset (Nigeria, 2020–2025) used in this study is openly accessible under the Creative Commons license. The data were derived from NCDC weekly epidemiological reports, which are published in the public domain. No human participants were recruited, and no personal data were accessed or processed.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The dataset analyzed in this study is publicly available on Hugging Face at: https://huggingface.co/datasets/EmanuelN/ncdc_lassa_fever_timeseries (https://doi.org/10.57967/hf/7145). The dataset, compiled by Niyi-Oriolowo (2025), contains weekly Lassa fever surveillance data for Nigeria (2020–2025) extracted from NCDC epidemiological reports, and is released under the Creative Commons license.

Authors' Contributions

Conceptualization: AJT; Data curation: AJT; Formal analysis: AJT, OAA; Funding acquisition: FMN; Investigation: AJT, FMN; Methodology: AJT, OAA; Project administration: FMN; Resources: OAA, FMN; Software: AJT, FMN; Supervision: AJT; Validation: OAA; Visualization: AJT, OAA; Writing–original draft: AJT, FMN; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0544
Osong Public Health Res Perspect 2026;17(4):322-325

Perspective

Dengue vaccine: a hidden risk to *Aedes aegypti* control in Brazil

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The approval and implementation of dengue vaccines in Brazil represent a major advance in the fight against this severe disease, which has imposed a substantial public health burden for decades. The dengue vaccines currently approved in Brazil are Dengvaxia (Sanofi Pasteur) and QDenga (Takeda Pharmaceutical), both of which use recombinant DNA technology [1], while the Butantan-DV vaccine remains under clinical evaluation. Brazil is the first country in the world to offer dengue vaccination through its public health system. The national immunization program began in February 2024 and has already reached 1,921 municipalities [2]. However, despite this important achievement and the expansion of vaccination coverage, a critical epidemiological question arises: could the introduction of the vaccine induce risk compensation behaviors, thereby reducing community vigilance and adherence to *Aedes aegypti* vector control measures (Table 1) [3–8].

Table 1. Comparison of dengue vaccines currently available and those under development in Brazil

Vaccine	Indication (y)	Overall efficacy (%)	Highlights and challenges	Reference
Dengvaxia	9–45 (HIV-positive)	44–65	Risk in HIV-negative individuals, restricted use.	[3–5]
QDenga (TAK-003)	4–60	62–84	Widespread use, strong protection against hospitalization.	[6–8]
Butantan-DV	2–59 (in testing)	79.6	Single dose, promising results.	[7,8]

HIV, human immunodeficiency virus.

Received: December 1, 2025
Revised: May 4, 2026
Accepted: May 12, 2026

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Although *A. aegypti* has a long history in Brazil, the modern dengue challenge began with the reintroduction of the virus in the early 1980s, facilitated by the resurgence of vector populations. Since the establishment of the species in the country, Brazil has experienced numerous dengue outbreaks, with endemic cycles occurring every 3–5 years, and disease incidence has increased 30-fold over the past 50 years [9–11]. This mosquito is a vector for multiple clinically important arboviruses, including chikungunya, Zika, and yellow fever. Although yellow fever vaccination is available, widely available and effective vaccines for Zika and chikungunya remain limited; consequently, vector control remains essential.

Unlike these diseases, dengue now has available vaccines; however, the perceived protection conferred by vaccination may reduce vigilance and weaken efforts by both the public and health

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authorities to control *A. aegypti*. Boccia et al. [12] hypothesized this possibility in 2013, before vaccines became available, suggesting that the population might relax vector control practices following vaccine introduction. Hadisoemarto and Castro [13] reached a similar conclusion in a study conducted in Indonesia. The concern extends beyond dengue itself to its vector. If public authorities reduce efforts to eliminate breeding sites and scale back public awareness campaigns, mosquito populations could increase, thereby elevating the incidence of diseases such as chikungunya and Zika, which continue to cause serious neurological and congenital complications and for which vaccines are still unavailable.

Although a vaccine against Zika virus infection is not yet available, several prophylactic vaccine candidates are under development [14]. Current clinical trials include the VRC5283 vaccine in Phase II studies [15–17] and ChAdOx1-based candidates [14,18]. For chikungunya, the IXCHIQ vaccine, produced by the Butantan Institute (Brazil) in partnership with the pharmaceutical company Valneva using recombinant attenuated strains, is currently undergoing Phase III clinical trials. Notably, 100% of previously infected individuals developed neutralizing antibodies after a single dose [19]. These findings reinforce the importance of maintaining efforts to eliminate mosquito breeding sites. This concern also has a historical basis. One need only recall the Rockefeller Foundation's campaign to eradicate yellow fever, exemplified by the creation of the National Yellow Fever Service under Decree-Law No. 1,975 of January 23, 1940 [20].

Following the success of vector elimination campaigns, the Pan American Health Organization formally declared the disease eradicated in 1958 [21], and Brazil was considered free of *A. aegypti*. Subsequently, vector control measures ceased to be a public health priority and were progressively relaxed. However, *A. aegypti* persisted in the environment and, years later, facilitated the reintroduction of dengue fever into the country during the 1980s. This re-emergence may have resulted from reinfestation originating in regions where the mosquito had not been eliminated, such as Venezuela, the United States, and several Caribbean islands [22], from the resurgence of remnant mosquito populations, or from a combination of these factors. In 2013 and 2014, Zika and chikungunya viruses crossed the country's borders and became transmissible through the same vector responsible for dengue and yellow fever transmission [23].

The coronavirus disease 2019 (COVID-19) pandemic highlighted the relationship between vaccination and behavioral change. Specifically, it illustrated the phenomenon of risk compensation, in which individuals adjust their behavior in response to perceived reductions in risk. Early in the pandemic, individuals who perceived the novel coronavirus as a significant threat were more likely to wear masks, practice hand hygiene, and avoid large gatherings as case numbers increased. However, the effects of risk compensation tend to diminish over time as the perceived novelty and threat of the disease decline [24–26].

Transmission dynamics provide another example of trade-offs associated with perceived risk. COVID-19 spreads primarily through the air, with rapid propagation in enclosed environments and strong dependence on immediate behavioral interventions. In contrast, Zika, dengue, and chikungunya require sustained environmental management to eliminate breeding sites and reduce mosquito populations over time.

A specific manifestation of risk compensation is the Peltzman effect. This effect describes a compensatory behavioral response to safety interventions, whereby reductions in perceived risk may encourage individuals to adopt riskier behaviors, potentially attenuating or even reversing some of the expected benefits of the intervention [27]. In the context of dengue fever, this mechanism could occur if expanded vaccination coverage—which reduces the individual risk of severe disease in many circumstances—leads to reduced adherence to vector prevention practices, such as decreased surveillance, less frequent elimination of household breeding sites, reduced use of protective screens, or diminished participation in community campaigns. Such behavioral changes could contribute to the maintenance or expansion of *A. aegypti* populations and thereby reduce the overall population-level impact of vaccination compared with predictions based solely on biological efficacy.

Two critical considerations emerge. First, the scientific

HIGHLIGHTS

- Dengue vaccines represent a major health advance in Brazil but may induce risk compensation behaviors.
- Perceived protection following immunization could critically reduce community adherence to *Aedes aegypti* vector control measures.
- Relaxed environmental management might expand mosquito populations, paradoxically increasing Zika and chikungunya transmission risks.
- Public health policies must ensure sustained funding and rigorous environmental interventions alongside ongoing vaccination campaigns.

literature regarding risk compensation following vaccination remains heterogeneous. El-Gilany and Abou-elwafa [28] did not identify a consensus regarding the presence of the Peltzman effect during the pandemic, whereas Henk et al. [26] suggested that the effect may occur but is attenuated when individuals perceive greater risk to others, indicating that collectivist values may mitigate the phenomenon. To address this issue, public health authorities could implement communication strategies emphasizing collective responsibility for eliminating breeding sites by engaging neighbors, schools, and community leaders to counteract individual complacency and sustain community participation. Second, dengue presents an additional biological consideration: heterogeneity in risk according to prior serological status and the potential for increased disease severity in seronegative individuals receiving certain vaccines, a distinct immunologically mediated phenomenon related to antibody-dependent enhancement (ADE) [29,30]. This relationship should be explicitly acknowledged because reduced vector control resulting from behavioral changes after vaccination may increase mosquito exposure. When increased exposure is combined with the immunological risk associated with ADE in specific subgroups, public health outcomes may paradoxically worsen, reinforcing the need to maintain rigorous environmental control measures even after vaccine implementation.

In summary, dengue vaccination may foster a sense of security that could contribute to the relaxation of other preventive measures. Individuals who believe they are protected may neglect actions such as eliminating breeding sites, thereby allowing *A. aegypti* populations to proliferate and increasing the risk of chikungunya and Zika outbreaks. As observed during the COVID-19 pandemic, public health communication should emphasize that vaccination must complement, rather than replace, ongoing vector control measures. Health policies should ensure sustained funding for vector control programs regardless of vaccination coverage targets so that environmental interventions are not weakened after vaccine introduction. It is therefore essential to recognize that dengue vaccination is a valuable tool, but not a standalone solution. Effective arbovirus control requires coordinated strategies, including continuous vaccination campaigns involving media outlets, schools, community health workers, and young people to encourage immunization; implementation of community incentive programs to eliminate potential breeding sites; use of real-time data to identify high-risk areas and guide interventions; maintenance or expansion of vector control resources after vaccine introduction; and continued investment in studies evaluating population behavior following vaccination.

Brazil has become a global leader in incorporating dengue vaccines into public health practice and has achieved substantial progress; however, several challenges remain, including variable vaccine uptake, differences in efficacy among vaccines and serotypes, and inconsistent public adherence to measures for eliminating natural and artificial breeding sites. Available and investigational vaccines, such as Dengvaxia, QDenga, and Butantan-DV, expand the prospects for disease control but require integrated strategies that combine surveillance, public education, and vector control to achieve sustainable impact. Public health authorities must prioritize these integrated measures because, even in the presence of effective vaccines, environmental management remains the primary defense against *A. aegypti*.

Notes

Ethics Approval
Not applicable.

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

Funding
None.

Availability of Data
All data generated or analyzed during this study are included in this published article. For other data, these may be requested through the corresponding author.

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phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0226
Osong Public Health Res Perspect 2026;17(4):326-336

Original Article

Association between ambient temperature and blood pressure in hypertensive adults in Bogor City, Indonesia: a 6-year longitudinal cohort study

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ABSTRACT

Objectives: Climate variability, particularly ambient air temperature, is an emerging environmental determinant of blood pressure (BP); however, evidence from tropical low- and middle-income countries (LMICs) remains limited. We examined associations between monthly average ambient temperature with systolic BP (SBP) and diastolic BP (DBP) among adults in Bogor City, Indonesia.

Methods: This longitudinal cohort analysis used secondary data collected between 2011 and 2018 from 1,648 participants with repeated BP measurements (19 assessments over 6 years). Average ambient temperature data were matched to the month of BP measurement. Generalized estimating equations models were used to assess the association between temperature and BP after adjustment for age, sex, education, and socioeconomic status.

Results: Mean ambient temperature ranged from 24.6 °C to 28.9 °C. SBP varied more than DBP and tended to increase as ambient temperature decreased. The overall main effect of temperature on BP was not statistically significant. However, several visit-specific temperature–time interactions were negative and significant, suggesting inverse patterns between lower temperatures and higher SBP or DBP. Marginal effects plots demonstrated time-varying associations, with predicted SBP and DBP differences of approximately −4 to +3 mmHg across follow-up visits at representative temperatures. Socioeconomic status and education were associated with SBP, whereas age and female sex were associated with DBP.

Conclusion: Temperature variations were associated with time-varying BP changes among adults with hypertension in Bogor City during 2011–2018. Although the main temperature effect was non-significant, temperature–time interactions suggested modest inverse patterns within clinically plausible ranges. These findings support the need for updated, multi-site studies in tropical LMIC settings.

Keywords: Blood pressure; Climate change; Hypertension; Temperature

Received: June 16, 2025
Revised: December 26, 2025
Accepted: March 25, 2026

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Introduction

Non-communicable diseases (NCDs) are chronic conditions driven by genetic, physiological, environmental, and behavioral factors. Although they are often associated with aging, NCDs also affect younger populations, with 17 million people younger than 70 years dying annually from these diseases [1]. Globally, NCDs represent a major health burden, and without innovative interventions, achieving the Sustainable Development Goal target of reducing premature NCD mortality by one-third by 2030 appears unlikely [2].

According to the Global Burden of Disease Study, cardiovascular diseases were the leading cause of NCD-related death globally and in Indonesia from 1990 to 2019. Elevated systolic blood pressure (SBP) accounted for approximately 10.8 million deaths, representing 19.2% of all deaths in 2019 [3].

Climate change is projected to exacerbate environmental hazards such as heat waves, heavy rainfall, and droughts, all of which substantially affect human health. These changes are associated with increased risks of cardiovascular, respiratory, and infectious diseases and may also threaten health infrastructure [4].

Although numerous studies have examined temperature variability and cardiovascular mortality [5–11], fewer have investigated its specific association with blood pressure (BP). Cross-sectional studies have shown strong associations between ambient temperature and both SBP and diastolic BP (DBP) [12–15]. However, longitudinal evidence remains limited. A study in Scotland found that temperature-sensitive individuals experienced notable effects on mortality and SBP [16], while research from Asian countries with 4 distinct seasons reported a 5.7 mmHg increase in SBP per 10 °C decrease in temperature [17]. Most of these studies were conducted in high-income countries with temperate or subtropical climates, leaving an important gap in the evidence from tropical low- and middle-income countries (LMICs) such as Indonesia.

The human body can adapt to ambient temperatures, but extreme heat may induce physiological stress, increase heart rate, and raise hypertension risk via hormonal and nervous system activation [18]. In Indonesia, the burden of NCDs—especially hypertension, heart disease, and stroke—continues to rise. Data from the Basic Health Research (Riskesdas) surveys show that the prevalence of hypertension among adults increased from 25.8% in 2013 to 34.1% in 2018, while coronary heart disease and stroke also displayed upward trends [19].

Despite growing global attention to environmental temperature and cardiovascular health, research in Indonesia's tropical setting remains limited. Local evidence from Banjarmasin showed a correlation between indoor temperature and hypertension [20], and national data from 2015–2016 indicated higher numbers of outpatient visits for diabetes and cardiovascular diseases on days when temperatures exceeded 29.5 °C [21].

Indonesia has developed national health sector guidelines to address climate-related health risks, reflecting growing recognition of the health impacts of climate variability [22]. Nevertheless, the available studies remain inconsistent in methodology and outcomes, which limits their generalizability [23]. Most of the existing evidence still originates from high-income countries with temperate climates, leaving a critical knowledge gap in tropical LMICs. Although the global literature on the health effects of climate change has expanded, evidence from LMICs has changed little over the past decade and remains concentrated in a small number of countries and climate-sensitive diseases [24].

To address this gap, this study investigated the relationship between ambient temperature and BP variability using 6 years of cohort data from Bogor City collected between 2011 and 2018. Although the dataset provides rare longitudinal evidence from a tropical LMIC context, the period of data collection may limit its direct applicability to the current policy environment, a limitation discussed later in this paper. This study aimed to clarify how temperature fluctuations were associated with BP as an intermediate cardiovascular risk factor.

HIGHLIGHTS

- Ambient temperature showed no overall effect on blood pressure but varied across time.
- Lower temperatures were associated with modest increases in systolic blood pressure.
- Effect sizes were small but biologically plausible in tropical populations.
- Associations were time-dependent rather than uniform across follow-up visits.
- Results emphasize temporal variability in climate–health relationships.

Materials and Methods

Study Design

This longitudinal study used data from the Non-Communicable Disease Risk Factor Cohort Study conducted in Bogor City by

the Center for Research and Development of Public Health Efforts, Ministry of Health, Indonesia, between 2011 and 2018. These data were linked with ambient temperature data obtained from the Indonesian Agency of Meteorological, Climatological, and Geophysical (BMKG).

Study Participants

A total of 5,296 individuals were originally enrolled in the Bogor City cohort. BP measurements were obtained at least once during follow-up from 4,896 participants. Attendance varied across scheduled visits, which were conducted 3 times per year, resulting in intermittent missing measurements. A subset of 1,648 participants completed all 19 scheduled BP assessments over the 6-year follow-up period and was classified as having complete BP data.

Missing measurements primarily resulted from irregular attendance, as well as attrition due to illness, death, or relocation. The primary longitudinal analyses used a complete-case approach restricted to participants with BP measurements at all scheduled visits, thereby ensuring consistency in the repeated-measures analysis.

BP Measurement

BP was measured repeatedly over the 6-year follow-up period. Measurements were obtained every 4 months, resulting in 3 assessments per year and a total of 19 measurements per participant, including 1 baseline assessment in 2011 and 18 follow-up assessments.

Hypertension was defined according to the 2018 guidelines of the European Society of Cardiology/European Society of Hypertension, the Eighth Joint National Committee, and the Indonesian Society of Hypertension, all of which classify hypertension as SBP ≥140 mmHg and/or DBP ≥90 mmHg [25].

BP was measured by trained paramedical staff from the Bogor City Health Office using a validated automated digital sphygmomanometer and a standardized protocol designed to minimize random error and systematic measurement bias. Participants were instructed to avoid smoking, eating, and physical activity for at least 30 minutes before measurement and to remain seated quietly for 5–15 minutes before assessment. Measurements were obtained in a calm indoor environment with participants seated, their feet flat on the floor, their legs uncrossed, and their right arm supported at heart level.

An appropriately sized cuff was placed on the right upper arm, with the lower edge positioned 1–2 cm above the antecubital fossa and the bladder centered over the brachial artery. Either 2 or 3 consecutive readings were obtained at 5-minute intervals, and their average was used for analysis. The right arm was used consistently for all participants to reduce inter-arm variability.

To reduce variability related to the timing of measurement, BP assessments were conducted during scheduled examination sessions using the same protocol and setting across all study visits. Although the exact clock time of measurement was not recorded, standardized premeasurement resting conditions and uniform measurement procedures were applied consistently throughout the study period to enhance comparability across follow-up visits [26].

Temperature Measurement

Ambient air temperature data were obtained from the BMKG. Monthly average temperatures from the West Java Climatology Station, the only station providing complete and validated long-term records for Bogor City, were used for the 2011–2018 study period. This station serves as the official reference for local climate monitoring.

The monthly mean ambient temperature was selected to represent medium-term thermal exposure relevant to BP regulation. BP reflects an integrated physiological state influenced by sustained autonomic activity, vascular resistance, and volume regulation over days to weeks rather than acute responses to short-term temperature fluctuations. Because BP measurements were obtained at scheduled cohort visits approximately every 4 months, monthly averages provided a temporally aligned exposure metric and reduced random variability associated with day-to-day temperature changes.

Temperature exposure was matched to the calendar month of each BP measurement to ensure temporal correspondence between environmental conditions and clinical assessments. This approach assumes broadly similar ambient exposure across participants and does not capture neighborhood-level microclimatic variation or individual indoor–outdoor activity patterns. No missing values were reported in the BMKG temperature dataset during the study period.

Lagged temperature structures were not applied because the study was not designed to evaluate acute heat or cold effects within narrow physiological windows, such as daily lags. Instead, the analysis focused on medium-term exposure patterns and their time-varying associations with repeated BP measurements. Within the observed narrow temperature range, introducing multiple lag terms would have increased model complexity without clear physiological interpretability.

Covariates

Baseline covariates included age, sex, education level, and socioeconomic status (SES). Age was defined at cohort entry and categorized as 30–44 years, 45–59 years, and ≥60 years to capture baseline age-related differences in BP risk. Sex was classified as male or female. Education level reflected

https://doi.org/10.24171/j.phrp.2025.0226

the highest level attained at baseline, was categorized as less than high school or high school and above, and was assumed to remain stable throughout follow-up.

SES was derived from baseline household income relative to the Bogor City municipal minimum wage (3,557,146 Indonesian Rupiah [IDR] in 2018), in accordance with official government standards. SES was categorized as below or above the municipal minimum wage and was treated as a baseline, time-invariant covariate. Annual changes in income or SES were not assessed because repeated measurements were not available in the cohort dataset. Accordingly, SES was modeled as an indicator of long-term socioeconomic position rather than short-term economic fluctuation.

Several established individual-level determinants of BP, including body mass index, smoking status, alcohol consumption, physical activity, dietary intake, comorbidities such as diabetes or kidney disease, and antihypertensive medication use, were unavailable in the dataset and therefore could not be included in the models. In addition, information on individual-level cooling access, such as air conditioning use, ventilation, housing characteristics, and indoor temperature, was unavailable. These variables were excluded because of data limitations.

Statistical Analysis

To estimate the longitudinal association between ambient temperature and BP, generalized estimating equation (GEE) models were used to account for repeated measurements within individuals. Follow-up visits, including baseline in 2011 and 18 subsequent assessments through 2018, were represented as indicator variables, with baseline as the reference category. Therefore, the visit-specific coefficients reflect contrasts relative to baseline rather than direct physiological changes. All models were adjusted for age, sex, education level, and SES.

An unstructured working correlation matrix was specified to allow maximum flexibility in modeling within-individual correlations across repeated BP measurements. This choice was motivated by the long follow-up period, irregular visit spacing inherent to cohort field implementation, and the absence of strong a priori assumptions regarding correlation decay over time, which could have made more parsimonious structures such as exchangeable or autoregressive (AR-1) overly restrictive. Alternative working correlation structures—independent, exchangeable, and AR-1—were formally compared using the quasi-likelihood under the independence model criterion (QIC) and its small-sample correction (QICC). Because QIC and QICC values were broadly comparable across structures, the unstructured correlation matrix was retained for the primary analyses (Table S1). Additional details on the comparison of working correlation structures and sensitivity analyses are provided in Supplementary Material 1.

Potential non-linear temperature effects were considered a priori, given previous evidence of U- or J-shaped associations between temperature and cardiovascular outcomes. However, the observed temperature range during the study period was relatively narrow (24.6 °C–28.9 °C), which limited statistical power to detect meaningful non-linearities or threshold effects. Exploratory analyses using alternative parameterizations, including temperature percentiles and spline-based terms, did not indicate substantial departures from linearity and yielded unstable estimates. Therefore, ambient temperature was modeled as a continuous linear term, with temporal heterogeneity captured through temperature–visit interaction terms.

Ethical Approval

The study protocol was approved by the Ethics Committee of the National Institute of Health Research and Development, Ministry of Health, Indonesia (approval numbers: KE.01.05/EC/394/2012 for baseline and LB.02.01/2/KE.076/2018 for follow-up assessments).

Results

During the 2011–2018 follow-up period in Bogor City, monthly mean ambient temperature varied within a relatively narrow range, from 24.6 °C to 28.9 °C. Within this context, 1,648 hypertensive adults aged ≥30 years completed all 19 scheduled BP assessments and were included in the analysis. Given the limited exposure contrast, temperature-related BP effects were expected to be modest and to primarily reflect temporal variability rather than responses to extreme temperatures.

The analytical sample was predominantly female (77.2%), and most participants were 45–59 years of age (46.4%). More than half had less than a high school education (58.9%), and most lived below the municipal minimum wage threshold (Table 1).

As shown in Figure 1, within-person variability was greater for SBP than for DBP, with mean within-person standard deviations of 10.0 mmHg and 6.4 mmHg, respectively, indicating greater temporal fluctuation in SBP. Simple Pearson correlation analyses showed near-zero associations between ambient temperature and BP (data not shown), reflecting between-individual correlations averaged across repeated measurements. In contrast, the GEE framework explicitly accounts for within-individual correlation over time and estimates population-averaged associations based

on repeated measures, making it more sensitive to detecting time-dependent relationships driven by within-person changes across follow-up visits.

Regression coefficients from the GEE models represent the estimated change in BP per 1 °C difference in monthly mean ambient temperature at a given follow-up visit. To facilitate clinical interpretation, these coefficients were translated into predicted BP values at representative temperature levels corresponding to the 25th percentile (24.6 °C), median (26.8 °C), and 75th percentile (28.9 °C) of the observed temperature distribution.

Table 1. Descriptive characteristics of participants in the Non-Communicable Disease Risk Factor Cohort, Bogor City, 2011–2018 (n = 1,648)

Characteristic	Frequency (n, %)
Age group (y)	
30–44	603 (36.6)
45–59	764 (46.4)
≥60	281 (17.1)
Sex	
Male	376 (22.8)
Female	1,272 (77.2)
Education level	
<High school	970 (58.9)
≥High school	678 (41.1)
Economic status	
Low (<UMK)	1,501 (91.1)
High (≥UMK)	147 (8.9)

The table shows the distribution of participants by age group, sex, education level, and economic status. Most participants were female (77.2%) and 45–59 years of age (46.4%). The majority had less than a high school education (58.9%) and household income below the municipal minimum wage threshold (91.1%).
UMK, Upah Minimum Kota (municipal minimum wage).

Figure 2 summarizes the time-varying temperature effects across all follow-up visits and highlights periods during which lower ambient temperatures were associated with higher BP. Several visits (e.g., visits 3–5 and 14–18) showed negative and statistically significant slopes, indicating higher SBP and DBP at relatively cooler temperatures during these periods. However, rather than emphasizing isolated visit-specific coefficients, the primary inference was based on global Wald tests, which confirmed statistically significant time effects and temperature–visit interactions for both SBP (Wald χ^2 = 272.9, degrees of freedom [df] = 18, p < 0.001) and DBP (Wald χ^2 = 373.5, df = 18, p < 0.001), indicating that temperature–BP associations varied across follow-up visits.

Marginal effects plots further illustrate these patterns by translating the coefficients into clinically interpretable predicted BP values at representative temperature contrasts (Figures 3, 4). These predicted values correspond to the 25th percentile (24.6 °C), median (26.8 °C), and 75th percentile (28.9 °C) of the observed temperature distribution, facilitating interpretation of the time-varying effects. Across visits, predicted SBP differences associated with lower versus higher temperatures ranged from approximately −4 to +3 mmHg, whereas the corresponding DBP differences were smaller but followed similar time-varying patterns.

Sensitivity analyses excluding the second follow-up visit, which showed the largest visit-specific coefficient, yielded similar time-varying patterns, indicating that the

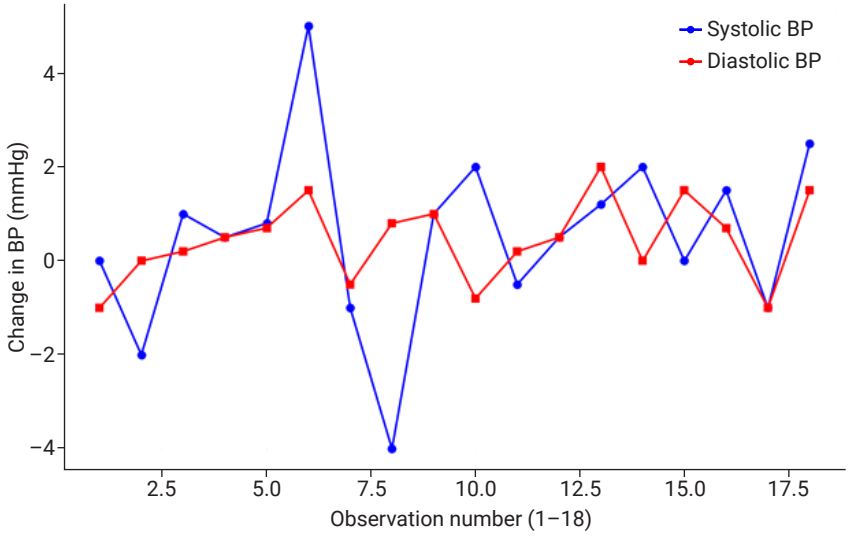


Figure 1. Temporal changes in systolic and diastolic blood pressure (BP) across follow-up visits, Bogor City cohort, 2011–2018. Mean systolic BP (blue) and diastolic BP (red) across 18 follow-up visits. Each point represents the average value across all participants at each visit, illustrating between-person mean trends and temporal fluctuations in BP over the 6-year study period.

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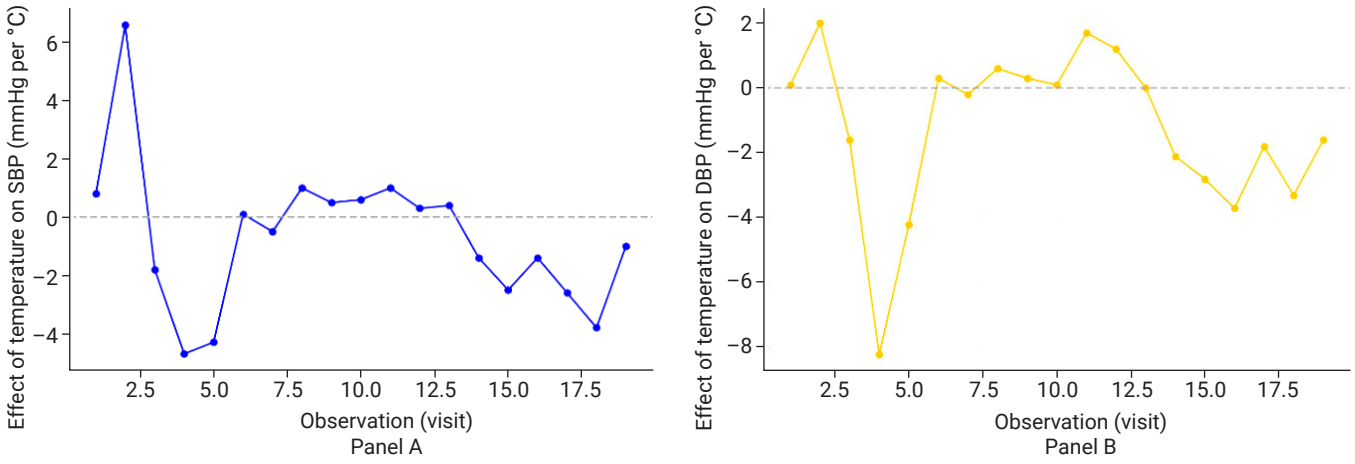


Figure 2. Time-varying temperature effects on systolic and diastolic blood pressure across follow-up visits, Bogor City cohort, 2011–2018. Panel A shows the estimated effect of ambient temperature on systolic blood pressure (SBP), and panel B shows the corresponding effect on diastolic blood pressure (DBP). Each point represents the temperature coefficient (°C) from the generalized estimating equation model for each follow-up visit, with positive values indicating higher blood pressure at warmer temperatures. The dashed horizontal line at 0 represents the null effect and illustrates how the direction and magnitude of temperature–blood pressure associations varied across the 19 observation points.

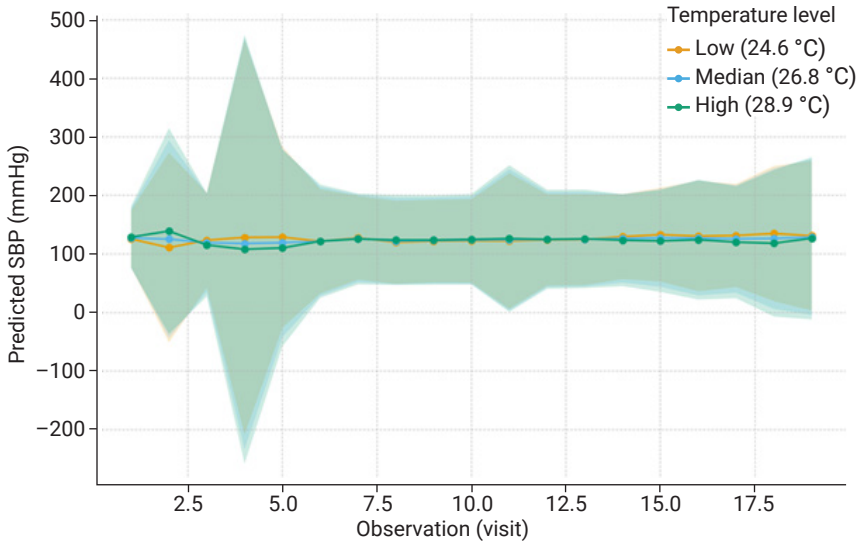


Figure 3. Predicted systolic blood pressure (SBP) from the generalized estimating equation models across 19 follow-up visits (Bogor City, Indonesia, 2011–2018) at 3 representative ambient temperature levels (24.6 °C, 26.8 °C, and 28.9 °C), with 95% confidence intervals. Each line represents the estimated mean SBP at low, median, and high ambient temperature levels derived from the fitted model. Shaded ribbons indicate the 95% confidence intervals. The x-axis corresponds to the sequence of follow-up visits (baseline plus 18 subsequent visits), and the y-axis shows model-predicted SBP (mmHg).

findings were not driven by a single influential visit. Overall, no clear evidence of non-linear or threshold effects was observed within the narrow temperature range, and linear specifications provided stable and interpretable estimates.

Covariate effects were modest. Higher SES was associated with slightly higher SBP, whereas higher educational attainment was associated with lower SBP; corresponding patterns for DBP were less consistent. Model comparisons based on the QIC and QICC supported the use of an unstructured working correlation matrix for both SBP and DBP outcomes (Table S1). Detailed visit-specific regression coefficients are presented in Tables S2 and S3, with additional model diagnostics and sensitivity analyses provided in Tables S1–S4.

Overall, when expressed in clinically interpretable terms, the observed associations corresponded to small BP

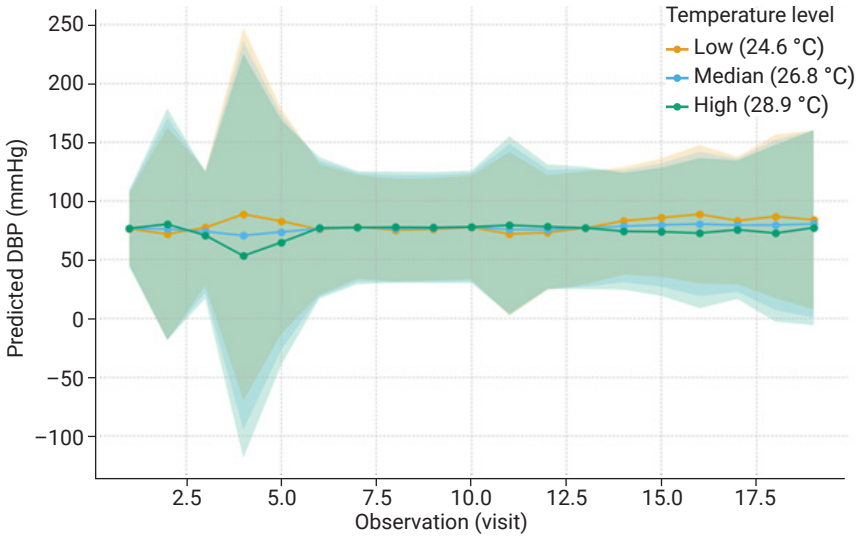


Figure 4. Predicted diastolic blood pressure (DBP) from the generalized estimating equation models across 19 follow-up visits (Bogor City, Indonesia, 2011–2018) at 3 representative ambient temperature levels (24.6 °C, 26.8 °C, and 28.9 °C), with 95% confidence intervals. Each line represents the estimated mean DBP at low, median, and high ambient temperature levels derived from the fitted model. Shaded ribbons indicate the 95% confidence intervals. The x-axis corresponds to the sequence of follow-up visits (baseline plus 18 subsequent visits), and the y-axis shows model-predicted DBP (mmHg).

differences on the order of a few mmHg across representative temperature contrasts. These modest effect sizes varied over time, and the primary inference was supported by joint tests of temporal heterogeneity rather than isolated visit-specific estimates.

Discussion

This longitudinal cohort study suggests that associations between ambient temperature and BP in a tropical urban setting varied over time rather than remaining uniform throughout follow-up. Although the main temperature effects were not statistically significant, significant time effects and temperature–time interactions indicate that BP responses to temperature differed across visits. These findings suggest that the association between ambient temperature and BP is context-dependent and shaped by temporal, physiological, and environmental factors rather than by a single stable exposure–response relationship.

Notably, the absence of a statistically significant overall temperature effect does not imply a lack of physiological relevance. Within the relatively narrow temperature range observed in this tropical environment, even modest variations in ambient temperature may affect BP regulation. Predicted differences in SBP across representative temperature contrasts were small, on the order of a few millimeters of mercury, but were physiologically plausible and consistent with gradual cardiovascular adaptation [17,27,28]. Such modest effect sizes would be expected in tropical populations, in which long-term acclimatization and behavioral adaptation may attenuate the magnitude of temperature-related BP changes relative to temperate or cold climates [29].

Several biological mechanisms may explain the inverse associations observed at specific follow-up visits between lower ambient temperature and higher BP. Even in tropical climates without extreme cold exposure, relatively cooler temperatures may trigger peripheral vasoconstriction, increased sympathetic nervous system activity, and elevated vascular resistance, leading to transient increases in BP [27,30]. Cold-related impairment of endothelial function, including reduced flow-mediated dilation, increased blood viscosity, and activation of the renin–angiotensin system, has been documented across diverse climatic settings and provides biologically plausible pathways linking lower temperatures to higher BP [30–32]. These mechanisms operate along a continuum and are not restricted to extreme cold conditions.

Temporal heterogeneity in the temperature–BP association may also reflect physiological acclimatization and changes in individual susceptibility over time. Repeated exposure to seasonal patterns may modify autonomic and vascular responses, whereas aging, disease progression, and changes in healthcare access may alter BP sensitivity to environmental stressors during follow-up [17,33]. In addition, tropical meteorological conditions vary across months and years in ways not fully captured by mean temperature alone, including changes in humidity, rainfall, cloud cover, and perceived thermal stress, all of which may modulate cardiovascular strain at specific time points [34].

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The use of monthly mean temperature captures cumulative thermal exposure relevant to BP regulation, which reflects integrated autonomic, vascular, and volume-related processes operating over days to weeks rather than acute responses to short-term temperature fluctuations [17,35]. Within this framework, the observed time-varying associations are best interpreted as reflecting relative thermal stress within a stable climatic range rather than responses to extreme heat or cold. Accordingly, modeling temperature as a linear exposure with time-varying interactions was both methodologically appropriate and biologically plausible in this cohort.

Socioeconomic and housing-related factors may also modify temperature–BP relationships in tropical urban populations. Variations in housing quality, ventilation, and behavioral responses to cooler periods may influence individual exposure and vulnerability over time [35]. Because information on indoor environments and adaptive behaviors was unavailable in this study, the observed associations should be interpreted as average population-level effects and may underestimate temperature sensitivity among individuals with limited adaptive capacity. Future studies incorporating indoor environmental data, higher-resolution meteorological exposure measures, and individual adaptive behaviors are needed to better characterize vulnerability to temperature-related BP changes in tropical settings.

In this study, participants with higher educational attainment tended to have slightly lower SBP, whereas those with higher SES had marginally higher SBP. These associations should be interpreted cautiously and should not be construed as evidence of a direct causal relationship. Importantly, individual-level behavioral factors such as dietary patterns, physical activity, smoking, alcohol consumption, and healthcare utilization were not measured and therefore could not be directly evaluated.

The observed pattern may reflect broader social and environmental gradients associated with socioeconomic position rather than the intrinsic effects of income or education alone. In several LMIC settings undergoing epidemiological and nutritional transition, higher SES has been associated with a higher prevalence of hypertension. For example, studies from Nepal have reported higher BP and hypertension prevalence among employed and higher-income groups, potentially reflecting shifts toward more sedentary occupations and increased consumption of processed or energy-dense foods [36–38].

Alternative explanations may include differences in occupational stress, work-related demands, healthcare access, or other unmeasured lifestyle factors associated with socioeconomic position. In contrast, higher educational attainment may confer modest protective effects through improved health literacy, greater awareness of cardiovascular risk, and healthier long-term behaviors, even in contexts in which income-related exposures increase. Given the absence of detailed behavioral and clinical covariates, these findings should be interpreted as descriptive associations that highlight the social patterning of BP rather than causal pathways.

DBP was 3.5–3.7 mmHg higher among participants aged 45–59 years and ≥60 years than among those aged 30–44 years, and it was 1.2 mmHg higher in women than in men. These findings are consistent with research from China reporting a 6.4 mmHg increase in SBP per decade of age [39]. Age is a well-established determinant of BP, with both baseline age and aging positively associated with higher values [40]. However, Khajavi et al. [40] found stronger aging effects in men, whereas other studies have shown that postmenopausal women experience steeper increases in SBP that eventually exceed those in men [41].

The associations observed in this study reflect short- to medium-term physiological responses to ambient temperature variability during 2011–2018 rather than long-term climate change trends. The analysis captured routine fluctuations in monthly mean temperature and did not assess gradual warming trajectories or future climate scenarios. Accordingly, these findings should not be interpreted as direct evidence of climate change effects but rather as evidence that temperature variability may influence BP regulation in a tropical urban setting [34,35].

Nevertheless, these findings remain relevant to public health. Increasing climate variability and the growing frequency of extreme weather events are expected to intensify population exposure to fluctuating thermal conditions, especially in rapidly urbanizing tropical regions [34]. Understanding short- to medium-term physiological responses to temperature may therefore help generate hypotheses regarding population vulnerability and adaptive capacity under changing climatic conditions, even in the absence of extreme heat or cold exposure [35].

From a public health perspective, the modest magnitude of the observed BP changes suggests that these results should be interpreted as hypothesis-generating rather than immediately actionable. Future studies using updated cohorts, higher-resolution climate data, and information on indoor environments and adaptive behaviors will be needed to better understand how increasing climate variability may interact with hypertension risk in tropical populations [34,35].

Strengths and Limitations

This 6-year cohort study (2011–2018) from Bogor City provides one of the few longitudinal analyses of ambient temperature

and BP in a tropical LMIC setting. By leveraging repeated BP measurements and population-based cohort data, the study contributes valuable historical evidence on time-varying climate–health relationships in an understudied context.

However, several limitations should be acknowledged. First, the dataset did not include several individual-level factors, such as body mass index, smoking, alcohol consumption, physical activity, dietary patterns, comorbidities (e.g., diabetes or kidney disease), or antihypertensive medication use, which may have contributed to residual confounding. These factors are well-established determinants of BP and may also modify physiological responses to ambient temperature; failure to account for them may therefore have attenuated or distorted the estimated associations. In addition, SES and education were treated as baseline characteristics; therefore, potential changes in income or social position during follow-up could not be evaluated, which may have introduced additional residual confounding. Second, the primary analyses were restricted to participants with complete BP measurements at all follow-up visits. If participants with incomplete follow-up differed systematically from those retained in the analytical sample, this complete-case approach may have introduced selection bias. Third, because the cohort was drawn from an urban population in Bogor City, the findings may have limited generalizability to rural populations or to other regions with different climatic, socioeconomic, or health-system contexts.

Fourth, temperature exposure was derived from monthly averages obtained from the official BMKG Data Online system. For Bogor City, only 1 meteorological station, the West Java Climatology Station, provides complete long-term records. Although this reflects national meteorological infrastructure rather than a weakness of the study design, reliance on a single station may have resulted in nondifferential exposure misclassification because it could not capture microclimatic variation, occupational exposure, or indoor–outdoor temperature differences. Such nondifferential misclassification would most likely bias the estimated associations toward the null, potentially leading to underestimation of the true temperature–BP association. Fifth, humidity and other indicators of seasonal variation were unavailable, limiting the ability to disentangle temperature-specific effects from broader seasonal influences. Although BP measurement procedures were standardized, information on short-term behavioral factors such as caffeine intake or smoking immediately before measurement was unavailable, which may have introduced nondifferential measurement variability across study visits.

Sixth, time in the GEE models was specified as indicator variables for each follow-up visit, resulting in multiple temperature–time interaction terms and increased model complexity. Although this approach allowed a flexible representation of temporal heterogeneity, it also introduced a potential risk of overfitting. To mitigate this concern, the interpretation emphasized global Wald tests and marginal effects summaries rather than isolated visit-specific coefficients, and the overall interaction pattern remained consistent across sensitivity analyses. Seventh, the observed ambient temperature range (24.6 °C–28.9 °C) was relatively narrow, and the study was not designed to evaluate extreme heat or cold thresholds. Because daily temperature data and short-term lag structures were not examined, potential non-linear or acute BP responses to short-term temperature extremes could not be assessed. The findings should therefore be interpreted as reflecting medium-term exposure patterns rather than immediate physiological effects within the context of gradual temperature variability typical of tropical urban environments. Eighth, stratified subgroup analyses (e.g., by sex or age) were not conducted because the study was not powered for such comparisons.

Finally, the study analyzed data collected between 2011 and 2018 and should therefore be interpreted as historical evidence. Subsequent changes in climate patterns, lifestyle behaviors, and hypertension management in Indonesia, including those during the coronavirus disease 2019 period, may influence the current magnitude or direction of temperature–BP associations.

Despite these limitations, the study strengthens understanding of temporal variability in BP in a tropical urban cohort and provides hypothesis-generating evidence to inform future multi-site longitudinal investigations incorporating richer individual-level covariates and higher-resolution environmental data. Overall, this study offers historical cohort evidence indicating that, although the main temperature effect on BP was not statistically significant, temperature–time interactions revealed modest, time-varying associations within clinically plausible ranges.

Conclusion

This 6-year cohort study (2011–2018) in Bogor City provides one of the few longitudinal analyses examining the relationship between ambient temperature and BP in a tropical LMIC. Although the main temperature effects on SBP and DBP were not statistically significant, several temperature–time interactions were observed, indicating that the associations varied across follow-up visits. Lower ambient temperatures were generally associated with higher BP, and these fluctuations, although modest (approximately −4 to +3 mmHg for SBP), fell within clinically plausible ranges.

https://doi.org/10.24171/j.phrp.2025.0226

SES and educational attainment were associated with SBP, whereas age and sex were associated with DBP. These findings highlight that both environmental and sociodemographic factors shape BP variability in tropical urban populations. Although temperature exposure itself is not modifiable, its interaction with population vulnerability and adaptation capacity should be considered when developing strategies for hypertension prevention and control.

Future studies should incorporate individual-level information on cooling access and indoor thermal environments to better characterize vulnerability to temperature-related BP changes.

This study contributes valuable historical evidence from Indonesia's tropical setting and underscores the need for updated multi-site studies with richer individual- and environmental-level data. Such research will be critical to understanding how increasing climate variability and urban heat exposure interact with chronic disease risk, particularly in resource-limited settings.

Supplementary Material

Supplementary Material 1. Supplementary methods and results; **Table S1.** Comparison of working correlation structures using QIC and QICC; **Table S2.** Estimated effects of ambient temperature and covariates on systolic blood pressure (SBP) from generalized estimating equation (GEE) models, Bogor City cohort, 2011–2018; **Table S3.** Estimated effects of ambient temperature and covariates on diastolic blood pressure (DBP) from generalized estimating equation (GEE) models, Bogor City cohort, 2011–2018; **Table S4.** Net temperature effects across follow-up visits for systolic blood pressure (SBP) and diastolic blood pressure (DBP). Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0226.

Notes

Ethics Approval

This study was approved by the Ethics Committee of the National Institute of Health Research and Development, Ministry of Health, Indonesia (approval numbers KE.01.05/EC/394/2012 for baseline and LB.02.01/2/KE.076/2018 for follow-up assessments).

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: PSH, WR; Data curation: PSH, WR, ID; Formal analysis: PSH, WR, ID, PWD; Investigation: NEWS, NS; Methodology: WR, PWD, YT; Supervision: WR, PWD, YT; Validation: PWD, YT; Visualization: NEWS, NS; Writing–original draft: PSH, WR, NEWS, NS; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Acknowledgements

The authors express their sincere appreciation to the Research and Development Center for Public Health Efforts, Ministry of Health of the Republic of Indonesia, and to the Meteorology, Climatology, and Geophysics Agency (BMKG) for providing access to the datasets used in this study. The authors also extend their gratitude to the Non-Communicable Disease Risk Factor Cohort research team for their dedication and hard work in conducting the cohort study, which made it possible to use these valuable data for this analysis. Constructive comments from the anonymous reviewers are also gratefully acknowledged for improving the quality and clarity of this manuscript.

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https://doi.org/10.24171/j.phrp.2025.0226

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2026.0101
Osong Public Health Res Perspect 2026;17(4):337-350

Original Article

Burden and trends of mental disorders in Vietnam, 1990–2023: insights from the Global Burden of Disease Study 2023

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ABSTRACT

Objectives: This study evaluated the epidemiological burden and temporal trends of mental disorders in Vietnam from 1990 to 2023 and projected the future burden through 2040.
Methods: Global Burden of Disease Study 2023 data were used to analyze the age-standardized prevalence rate (ASPR), age-standardized incidence rate (ASIR), and age-standardized disability-adjusted life-year rate (ASDAR) by age, sex, and diagnostic subtype. Temporal trends were quantified using the estimated annual percentage change (EAPC), and Pearson correlation analysis examined associations with Vietnam's human development index (HDI). Bayesian structural time series (BSTS) models were used to forecast the burden through 2040.
Results: In 2023, approximately 9.1 million individuals in Vietnam had mental disorders, with 2.94 million annual incident cases and 1.41 million disability-adjusted life-years. Depressive disorders ranked highest across all metrics, and females consistently had higher age-standardized rates than males. Age-standardized rates increased significantly from 1990 to 2023: ASIR, 1.10% EAPC (95% confidence interval [CI], 0.87%–1.33%); ASPR, 0.27% EAPC (95% CI, 0.21%–0.33%); and ASDAR, 0.52% EAPC (95% CI, 0.46%–0.58%). Mental disorder burden was strongly positively correlated with HDI ($r = 0.773–0.909$, all $p < 0.001$). BSTS models projected continued increases through 2040 (ASPR, 9,003.75; ASIR, 3,307.11; ASDAR, 1,408.05 per 100,000 population).
Conclusion: Mental disorders constitute an escalating public health challenge in Vietnam, with the burden increasing steadily over 3 decades and projected to continue rising through 2040. Reorientation toward an integrated, community-based care model, alongside targeted workforce expansion and systematic integration of mental health services into primary care, is essential to mitigate this growing burden.

Keywords: Global Burden of Disease; Mental disorders; Vietnam

Received: January 28, 2026
Revised: April 3, 2026
Accepted: May 11, 2026

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The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

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Introduction

Mental health is foundational to individual well-being and effective functioning, extending beyond the absence of mental disorders to encompass cognitive clarity, learning capacity, emotional awareness, and interpersonal understanding. Mental health also reflects a dynamic balance among physical, psychological, social, cultural, and spiritual dimensions, with mental and physical health inextricably linked [1].

Mental disorders are characterized by clinically significant disruptions in cognition, emotion regulation, or behavior that result in distress or functional impairment. These disorders encompass diverse conditions, including depression, bipolar affective disorder, schizophrenia, dementia, intellectual disabilities, and autism spectrum disorder [2]. In 2019, approximately 970 million individuals—1 in 8 people globally—were living with mental disorders, with anxiety and depressive disorders predominating [3]. The coronavirus disease 2019 (COVID-19) pandemic substantially increased this burden; anxiety disorders and major depressive disorder rose by 26% and 28%, respectively, in 2020 alone [4].

Mental disorders represent a substantial public health challenge and impede economic development, particularly in low- and middle-income countries (LMICs) [5]. Accordingly, improving population mental health has emerged as a core pillar of the United Nations 2030 Agenda for Sustainable Development, reflecting a global shift toward recognizing mental well-being as inseparable from physical health and macroeconomic stability. Sustainable Development Goal (SDG) Target 3.4 commits member states to reducing premature mortality from non-communicable diseases by one-third through prevention and treatment, while also promoting mental health and well-being as a necessary component of achieving universal health coverage under SDG Target 3.8 [6]. Mental health is also increasingly recognized as a cross-cutting catalyst for SDG 8, Decent Work and Economic Growth, because psychological stability and cognitive resilience are essential prerequisites for a productive workforce, human capital development, and long-term economic stability [6]. However, substantial gaps remain among epidemiological research, public health priorities, and clinical practice, particularly in settings where research capacity and evidence-based information remain limited.

Vietnam exemplifies this evidence gap. According to the World Health Organization (WHO), prevalence data from Vietnam's National Mental Hospital indicated that, in 2014, 14.2% of the population had at least 1 of 10 common mental disorders, with alcohol-related disorders (5.3%), anxiety disorders (2.6%), and depressive disorders (2.45%) being the most prevalent [1]. The Vietnam Adolescent Mental Health Survey (V-NAMHS) documented that 1 in 5 adolescents (21.7%) reported a mental health problem in the preceding 12 months; anxiety disorders were the most prevalent at 18.6%, followed by depression at 13.6% [7]. Despite its substantial impact on population well-being, mental health continues to receive less policy attention and fewer resources than other health sectors. Vietnam also faces concurrent pressures from rapid population aging, a high neurological disability burden, and the sustained mental health effects of the COVID-19 pandemic.

Understanding temporal trends in the burden of mental disorders, the relationship between disease burden and socioeconomic development, and projected future trajectories are essential for informing evidence-based national mental health policy, allocating resources effectively, and building institutional capacity to address population mental health needs. This study characterized the epidemiology of mental disorders in Vietnam from 1990 to 2023 by examining temporal trends and disease burden and by exploring associations with socioeconomic development, aiming to provide evidence to support mental health policy development and service planning.

HIGHLIGHTS

- In 2023, approximately 9.1 million individuals in Vietnam were living with a mental disorder, accounting for 1.41 million disability-adjusted life-years.
- The age-standardized incidence rate in Vietnam exhibited a 1.10% estimated annual percentage change from 1990 to 2023, exceeding the global average increase of 0.92%.
- Mental disorder burden metrics showed strong positive correlations with Vietnam's human development index during 1990–2023 ($r \geq 0.773$, $p < 0.001$).
- Without appropriate policy interventions, the burden of mental disorders in Vietnam is projected to continue increasing through 2040.

Materials and Methods

Data Sources

Mental disorders were defined according to the Global Burden of Disease (GBD) Study categorization, which aligns with the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders. Data on the burden of mental disorders in Vietnam were obtained

https://doi.org/10.24171/j.phrp.2026.0101

from the GBD Study 2023 (GBD 2023) results tool (https://vizhub.healthdata.org/gbd-results/). Data was accessed in November 2025.

GBD 2023 provides comprehensive estimates of disease burden across 204 countries and territories over time. These estimates were generated by the Institute for Health Metrics and Evaluation using Bayesian meta-regression tools, primarily DisMod-MR 2.1 and DisMod-AT for specific mental health causes [8]. For Vietnam, GBD estimates for mental disorders were informed by 8 primary data sources identified through systematic reviews of national health surveys and local epidemiological studies. To produce a continuous time series and bridge intervals between available primary inputs, the GBD framework uses spatiotemporal Gaussian process regression and hierarchical Bayesian modeling. This estimation strategy incorporates regional epidemiological patterns and country-specific socioeconomic covariates to synthesize internally consistent modeled outcomes.

In this study, incidence, prevalence, and disability-adjusted life-years (DALYs) were extracted to assess the burden of mental disorders in Vietnam from 1990 to 2023. Vietnam's human development index (HDI) data for the same period were obtained from the United Nations Development Programme.

Data Analysis

Age-standardized incidence, prevalence, and DALY rates were calculated to enable valid temporal comparisons. Temporal trends in disease burden from 1990 to 2023 were quantified using the estimated annual percentage change (EAPC). The EAPC was derived from the following log-linear regression model:

$$\ln(\mathrm{ASR}) = \alpha + \beta x + \varepsilon,$$

where ASR denotes the age-standardized rate and x represents the calendar year. The EAPC summarizes the average annual percentage change and was computed as follows:

$$\mathrm{EAPC} = 100 \times [\exp(\beta) - 1].$$

The 95% confidence interval (CI) was computed similarly, using the upper and lower limits of the regression coefficient β obtained from the model [9]. To assess the robustness of the trend estimates to uncertainty in the GBD 2023 data, sensitivity analyses were performed by recalculating the EAPCs for Vietnam using the upper and lower bounds of the 95% uncertainty intervals (UIs) for the age-standardized rates. For each indicator—prevalence, incidence, and DALYs—the EAPC was re-estimated from the respective time series of the upper and lower UI bounds using the same log-linear regression model.

Future trends in the age-standardized incidence rate (ASIR), age-standardized prevalence rate (ASPR), and age-standardized disability-adjusted life-year rate (ASDAR) were projected through 2040 using Bayesian structural time series (BSTS) models [10]. The models used a semi-local linear trend state-space component and included an exogenous regressor to account for the impact of the COVID-19 pandemic during 2019–2023. The COVID-19 effect was specified as a pulse intervention for ASIR and as a step intervention for both ASPR and ASDAR. Posterior estimates were obtained through Markov chain Monte Carlo (MCMC) sampling with 20,000 iterations, including a 2,000-iteration burn-in period, using the default prior distributions in the bsts package in R. Model performance was evaluated using Bayesian R^2 and mean absolute percentage error (MAPE). The complete R code for BSTS model specification, fitting, and projection is provided in Supplementary Material 1. In addition to the baseline projection, a policy intervention scenario was modeled that assumed a cumulative 17% relative reduction in ASIR, ASPR, and ASDAR by 2040. This 17% target was established as a pragmatic, resource-adjusted proxy aligned with the spirit of United Nations SDG 3.4 [6], which calls for reducing the non-communicable disease burden and promoting mental health. Calibration of this target reflects the long-term implementation trajectory and evolving healthcare infrastructure following Vietnam's recent transition to upper-middle-income country status. This scenario also builds on the foundational service-coverage milestones established by Vietnam's Prime Ministerial Decision No. 155/QĐ-TTg, the National Plan for the Prevention and Control of Non-Communicable Diseases and Mental Health Disorders, 2022–2025 [11], and Prime Ministerial Decision No. 1929/QĐ-TTg, the Program for Community-Based Social Assistance and Rehabilitation for People With Mental Disorders, Children With Autism, and People With Mental Health Problems, 2021–2030 [12]. These policy anchors were used to ensure that the projection remained ambitious in its public health goals while remaining feasible within Vietnam's national socioeconomic context through 2040 [13].

Pearson correlation analysis was conducted to evaluate correlations between mental disorder burden metrics and Vietnam's HDI. Statistical significance was defined as $p < 0.05$. All analyses were performed using R ver. 4.1.3 (R Foundation for Statistical Computing).

Ethics Approval

This study used publicly available, de-identified data from

the GBD 2023 study. Therefore, institutional review board approval and informed consent were not required.

Results

Burden of Mental Disorders in Vietnam in 2023

In 2023, mental disorders affected more than 9.1 million individuals in Vietnam (95% UI, 8.24–10.09 million), corresponding to a crude prevalence rate of 8,823.62 per 100,000 population (95% UI, 7,993.82–9,788.06) (Table 1). Annual incidence exceeded 2.94 million cases (95% UI, 2.65–3.30 million), with a crude incidence rate of 2,858.71 per 100,000 population (95% UI, 2,576.25–3,200.33). Mental disorders accounted for an estimated 1.41 million DALYs (95% UI, 1.03–1.82 million), corresponding to a crude DALY rate of 1,366.15 per 100,000 population (95% UI, 999.36–1,770.19).

Substantial age-related disparities were observed across all disease burden metrics (Figure 1). Crude prevalence rates increased from 1,510.7 per 100,000 among children younger

Table 1. Mental disorder burden in Vietnam, 2023

	Number (95% UI)	Crude rate per 100,000 population (95% UI)
Prevalence	9,101,872.35 (8,245,900.57–10,096,724.33)	8,823.62 (7,993.82–9,788.06)
Incidence	2,948,862.53 (2,657,488.67–3,301,255.16)	2,858.71 (2,576.25–3,200.33)
DALYs	1,409,228.07 (1,030,869.56–1,826,010.80)	1,366.15 (999.36–1,770.19)

UI, uncertainty interval; DALYs, disability-adjusted life-years.

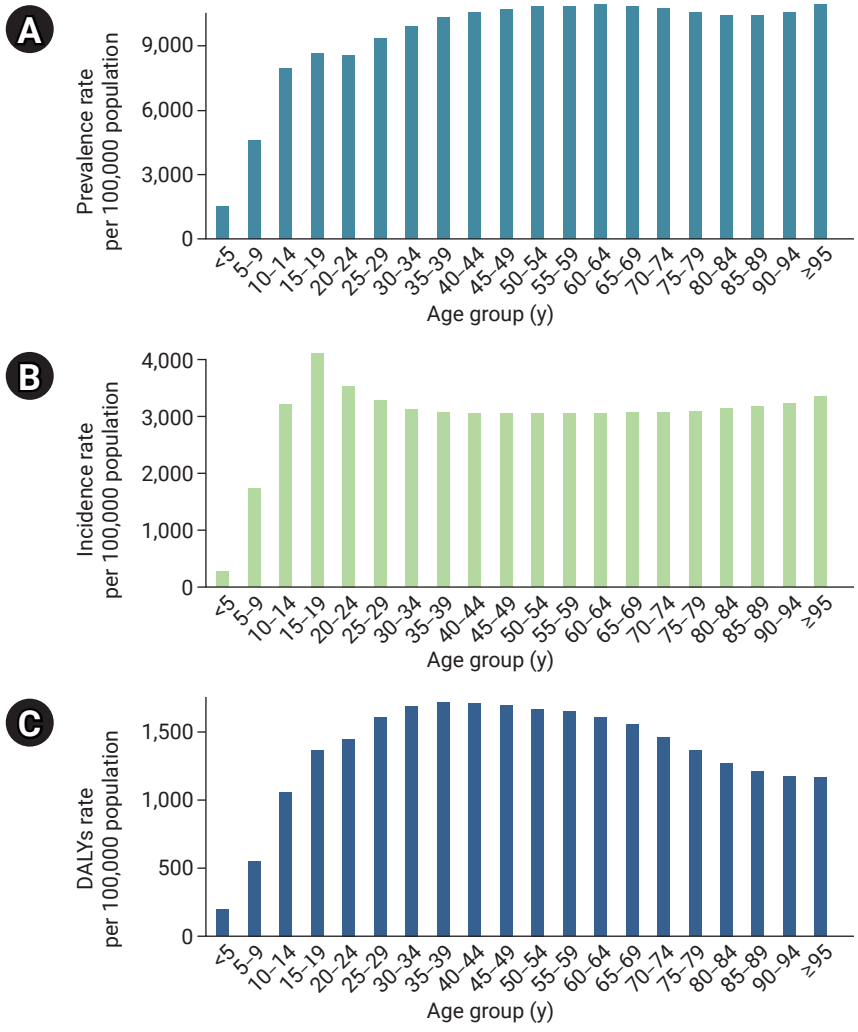


Figure 1. Age-specific mental disorder burden for prevalence (A), incidence (B), and DALYs (C) across the life course in Vietnam, 2023. DALYs, disability-adjusted life-years.

https://doi.org/10.24171/j.phrp.2026.0101

than 5 years to 7,941.2 per 100,000 among those aged 10–14 years, rose further to a peak of 10,914.2 per 100,000 in the 60–64-year age group, declined across older age groups, and then increased again to 10,938.3 per 100,000 among those aged 95 years or older. In contrast, crude incidence rates followed a distinct trajectory. Incidence was lowest among young children, at 278.6 per 100,000 among those younger than 5 years, increased sharply through childhood and early adolescence, and peaked at 4,125.3 per 100,000 in the 15–19-year age group. Incidence rates subsequently declined to approximately 3,000–3,400 per 100,000 from age 20 years onward and remained relatively stable across middle and older adulthood. Crude DALY rates increased progressively from childhood, rising from 203.3 per 100,000 among children younger than 5 years to a peak of 1,727.1 per 100,000 in the 35–39-year age group, before gradually declining in older age groups and reaching 1,168.9 per 100,000 among those aged 95 years or older.

The GBD 2023 estimates demonstrated pronounced sex disparities in the burden of mental disorders in Vietnam (Table 2). Age-standardized rates were consistently higher among female than male individuals across all measures. The ASPR was 9,036.97 versus 7,817.77 per 100,000, respectively, corresponding to a 15.6% higher prevalence among female individuals. A similar pattern was observed for disability burden, with an ASDAR of 1,381.26 versus 1,216.94 per 100,000, corresponding to a 13.6% higher rate among female individuals. ASIR also differed substantially by sex, reaching 3,328.56 per 100,000 annually among female individuals and 2,249.85 per 100,000 among male individuals.

In subtype-specific estimates, depressive disorders were the leading contributor to the burden of mental disorders in Vietnam across all metrics in 2023 (Table 3). For depressive disorders, the ASPR was 2,489.70 per 100,000 and the ASIR was 2,137.42 per 100,000; this subtype also accounted for the highest disability burden, with an ASDAR of 422.92 per 100,000. Anxiety disorders had the second-highest ASPR, at 2,177.50 per 100,000, with an ASIR of 256.44 per 100,000 and an ASDAR of 259.66 per 100,000. Schizophrenia had a substantially lower ASPR, at 318.70 per 100,000, but still contributed to a considerable disability burden, with an ASDAR of 205.99 per 100,000. Bipolar disorder had an ASPR of 313.83 per 100,000, an ASIR of 23.39 per 100,000, and an ASDAR of 68.38 per 100,000. Autism spectrum disorders had an ASPR of 601.15 per 100,000, an ASIR of 17.70 per 100,000, and an ASDAR of 114.01 per 100,000. Idiopathic developmental intellectual disability had an ASPR of 554.93 per 100,000 and an ASDAR of 27.31 per 100,000. Behavioral

Table 2. Sex-stratified burden of mental disorders in Vietnam, 2023

Indicators	Male (95% UI)	Female (95% UI)
ASIR per 100,000 population	2,249.85 (2,038.04–2,523.77)	3,328.56 (2,979.33–3,752.32)
ASPR per 100,000 population	7,817.77 (7,079.54–8,744.94)	9,036.97 (8,092.39–10,108.74)
ASDAR per 100,000 population	1,216.93 (903.58–1,557.31)	1,381.26 (1,009.14–1,817.36)

UI, uncertainty interval; ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; ASDAR, age-standardized disability-adjusted life-year rate.

Table 3. Burden of mental disorders by subtype in Vietnam, 2023

Mental disorder subtype	ASIR per 100,000 population (95% UI)	ASPR per 100,000 population (95% UI)	ASDAR per 100,000 population (95% UI)
Anxiety disorders	256.44 (192.83–340.30)	2,177.49 (1,676.29–2,675.90)	259.66 (173.00–377.39)
Depressive disorders	2,137.41 (1,871.87–2,448.59)	2,489.69 (2,065.12–3,041.30)	422.92 (276.90–618.13)
Schizophrenia	21.04 (17.00–25.61)	318.70 (251.13–390.16)	205.99 (145.66–267.60)
Bipolar disorder	23.38 (18.38–29.29)	313.83 (249.37–397.91)	68.37 (40.53–100.47)
Autism spectrum disorders	17.70 (8.68–33.22)	601.14 (440.37–861.10)	114.00 (71.08–174.66)
Attention-deficit/hyperactivity disorder	18.01 (11.41–27.22)	284.30 (195.77–400.18)	12.36 (6.97–18.49)
Conduct disorder	135.32 (89.86–180.69)	383.21 (274.36–497.86)	47.18 (25.74–73.96)
Eating disorders	187.92 (122.77–286.11)	148.71 (115.07–194.73)	31.95 (18.33–47.63)
Idiopathic developmental intellectual disability	NA[a)]	554.93 (243.26–1,027.49)	27.30 (11.98–51.89)
Other mental disorders	0[b)]	1,504.34 (1,179.82–1,884.32)	112.58 (74.36–160.80)

ASIR, age-standardized incidence rate; UI, uncertainty interval; ASPR, age-standardized prevalence rate; ASDAR, age-standardized disability-adjusted life-year rate.
[a)]Incidence was not estimated by the Global Burden of Disease Study (GBD) for this condition. [b)]The estimated value rounds to zero in the GBD data.

conditions, including conduct disorder and attention-deficit/hyperactivity disorder, had lower disability impacts, with ASDARs of 47.18 and 27.31 per 100,000, respectively. Eating disorders had the lowest age-standardized burden, with an ASPR of 148.71 per 100,000 and an ASDAR of 31.95 per 100,000.

Temporal Trends in Mental Disorder Burden in Vietnam, 1990–2023

From 1990 to 2019, age-standardized rates increased modestly both in Vietnam and globally (Figure 2). Vietnam's ASPR increased from 7,481.7 to 7,669.1 per 100,000, while the global ASPR increased from 11,442.6 to 12,046.2 per 100,000. Vietnam's ASIR increased from 2,218.1 to 2,575.6 per 100,000, while the global ASIR increased from 4,231.9 to 4,815.4 per 100,000. Similarly, Vietnam's ASDAR increased from 1,073.9 to 1,173.0 per 100,000, while the global ASDAR increased from 1,605.8 to 1,740.0 per 100,000.

During 2020–2023, incidence rates showed synchronized patterns in Vietnam and globally (Figure 2). Vietnam's ASIR increased from 2,575.6 per 100,000 in 2019 to 3,946.3 per 100,000 in 2021, before declining to 2,797.3 per 100,000 by 2023. Global incidence rates increased from 4,815.4 per 100,000 in 2019 to 7,389.3 per 100,000 in 2021, before declining to 4,862.8 per 100,000 in 2023. Prevalence and DALY rates followed different post-2020 trajectories. Globally, both ASPR and ASDAR increased continuously during 2020–2023: ASPR rose from 12,046.2 per 100,000 in 2019 to 14,210.7 per 100,000 in 2023, and ASDAR increased from 1,740.0 to 2,070.5 per 100,000 over the same period. In Vietnam, ASPR increased from 7,669.1 per 100,000 in 2019 to 8,287.6 per 100,000 in 2021, declined to 8,142.4 per 100,000 in 2022, and then recovered to

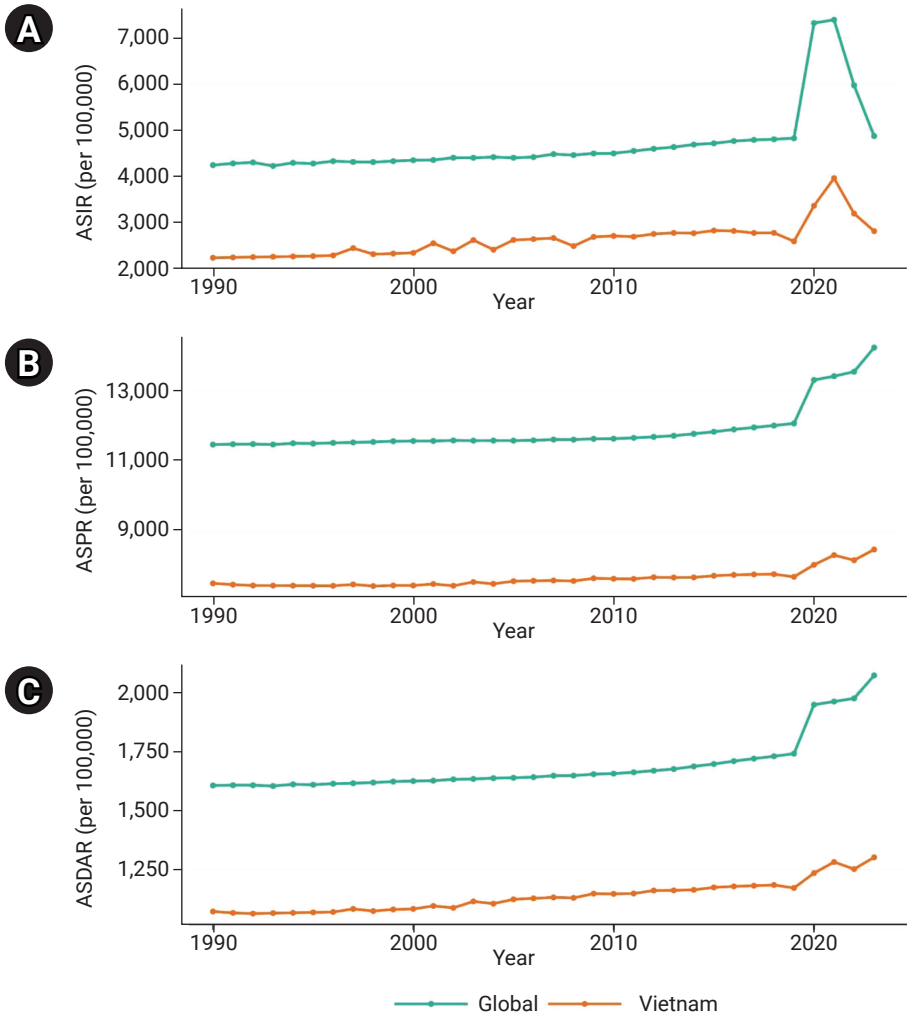


Figure 2. Temporal trends in age-standardized prevalence (A), incidence (B), and disability-adjusted life-year (C) rates in Vietnam versus globally, 1990–2023.
ASIR, age-standardized incidence rate; ASPR, age-standardized prevalence rate; ASDAR, age-standardized disability-adjusted life-year rate.

https://doi.org/10.24171/j.phrp.2026.0101

8,447.8 per 100,000 in 2023. ASDAR followed a similar pattern, increasing from 1,173.0 per 100,000 in 2019 to 1,282.6 per 100,000 in 2021, declining to 1,252.8 per 100,000 in 2022, and then increasing to 1,302.4 per 100,000 in 2023.

From 1990 to 2023, age-standardized rates for all 3 metrics increased both in Vietnam and globally (Table 4). Vietnam's ASIR had an EAPC of 1.10% (95% CI, 0.87%–1.33%), compared with a global EAPC of 0.92% (95% CI, 0.58%–1.26%). Vietnam's ASPR EAPC was 0.27% (95% CI, 0.21%–0.33%), compared with the global EAPC of 0.39% (95% CI, 0.26%–0.52%). For ASDAR, Vietnam's EAPC was 0.52% (95% CI, 0.46%–0.58%), closely paralleling the global EAPC of 0.52% (95% CI, 0.38%–0.66%). Sensitivity analyses using the upper and lower bounds of the 95% UIs for Vietnam produced similar estimates: EAPC values ranged from 0.27% to 0.28% for prevalence, 1.06% to 1.13% for incidence, and 0.57% to 0.62% for DALYs (Table 5). These findings support a consistently increasing trend in age-standardized mental disorder burden.

Correlation Between Mental Disorders and HDI in Vietnam

Mental disorder burden in Vietnam was strongly positively correlated with HDI. ASDAR showed the strongest correlation ($r = 0.909$, $p < 0.001$), while ASPR ($r = 0.773$, $p < 0.001$) and ASIR ($r = 0.799$, $p < 0.001$) also showed strong positive correlations, although these correlations were slightly lower than that observed for ASDAR (Figure 3).

Forecasted Epidemiological Burden of Mental Disorders through 2040

The BSTS models demonstrated strong predictive accuracy and goodness of fit, with Bayesian R^2 values of 0.9918 for ASPR, 0.9653 for ASIR, and 0.9952 for ASDAR, supported by low MAPE values of 0.17%, 1.48%, and 0.23%, respectively (Table S1). Effective sample size values ranged from 71.9 to 207.3 across indicators, indicating adequate MCMC chain convergence. Diagnostic plots further supported satisfactory convergence and model fit (Figure S1). Under the baseline scenario, the burden of mental disorders in Vietnam was projected to continue increasing through 2040 (Figure 4). ASPR was projected to reach 9,003.75 per 100,000 (95% credible interval [CrI], 7,846.42–10,737.80), ASIR was projected to reach 3,307.11 per 100,000 (95% CrI, 705.16–5,591.76), and ASDAR was projected to reach 1,408.05 per 100,000 (95% CrI, 1,242.67–1,593.63). In contrast, the policy intervention scenario suggested substantial potential for mitigation, lowering the projected 2040 ASPR to 7,473.12 per 100,000 (95% CrI, 6,512.53–8,912.37), ASIR to 2,744.90 per 100,000 (95% CrI, 585.28–4,641.16), and ASDAR to 1,168.68 per 100,000 (95% CrI, 1,031.41–1,322.71) (Figure 4). Compared with the baseline forecasts, these intervention outcomes corresponded to absolute reductions of 1,530.63 in ASPR, 562.21 in ASIR, and 239.37 in ASDAR per 100,000 population.

Discussion

Mental disorders impose a substantial burden on the Vietnamese population. In 2023, an estimated 9.1 million individuals were living with a mental disorder in Vietnam, corresponding to a crude prevalence of approximately 8.8%. Annual incidence exceeded 2.94 million cases, contributing to 1.41 million DALYs. Both crude prevalence

Table 4. Estimated annual percentage change of mental disorder rates in Vietnam and globally, 1990–2023

Region	Indicators	Prevalence	Incidence	DALYs
Vietnam	ASR (95% UI), 1990	7,481.69 (6,732.04–8,333.43)	2,218.09 (1,996.56–2,436.39)	1,073.85 (770.50–1,339.34)
	ASR (95% UI), 2023	8,447.76 (7,640.18–9,369.78)	2,797.27 (2,518.72–3,148.19)	1,302.36 (952.74–1,683.69)
	EAPC (95% CI)	0.27 (0.21–0.33)	1.10 (0.87–1.33)	0.52 (0.46–0.58)
Global	ASR (95% UI), 1990	11,442.64 (10,445.44–12,550.46)	4,231.89 (3,786.00–4,703.65)	1,605.79 (1,162.92–2,021.89)
	ASR (95% UI), 2023	14,210.67 (12,849.50–15,940.13)	4,862.84 (4,381.09–5,549.90)	2,070.54 (1,519.08–2,750.50)
	EAPC (95% CI)	0.39 (0.26–0.52)	0.92 (0.58–1.26)	0.52 (0.38–0.66)

DALYs, disability-adjusted life-years; ASR, age-standardized rate; UI, uncertainty interval; EAPC, estimated annual percentage change.

Table 5. Sensitivity analysis of estimated annual percentage change in mental disorder rates in Vietnam, 1990–2023

Analysis scenario	EAPC (95% CI)		
	Prevalence	Incidence	DALYs
Main analysis (mean ASR)	0.27 (0.21–0.33)	1.10 (0.87–1.33)	0.52 (0.46–0.58)
Sensitivity: upper UI bounds	0.27 (0.19–0.35)	1.13 (0.89–1.36)	0.62 (0.55–0.70)
Sensitivity: lower UI bounds	0.28 (0.22–0.34)	1.06 (0.84–1.29)	0.57 (0.52–0.62)

EAPC, estimated annual percentage change; CI, confidence interval; DALYs, disability-adjusted life-years; ASR, age-standardized rate; UI, uncertainty interval.

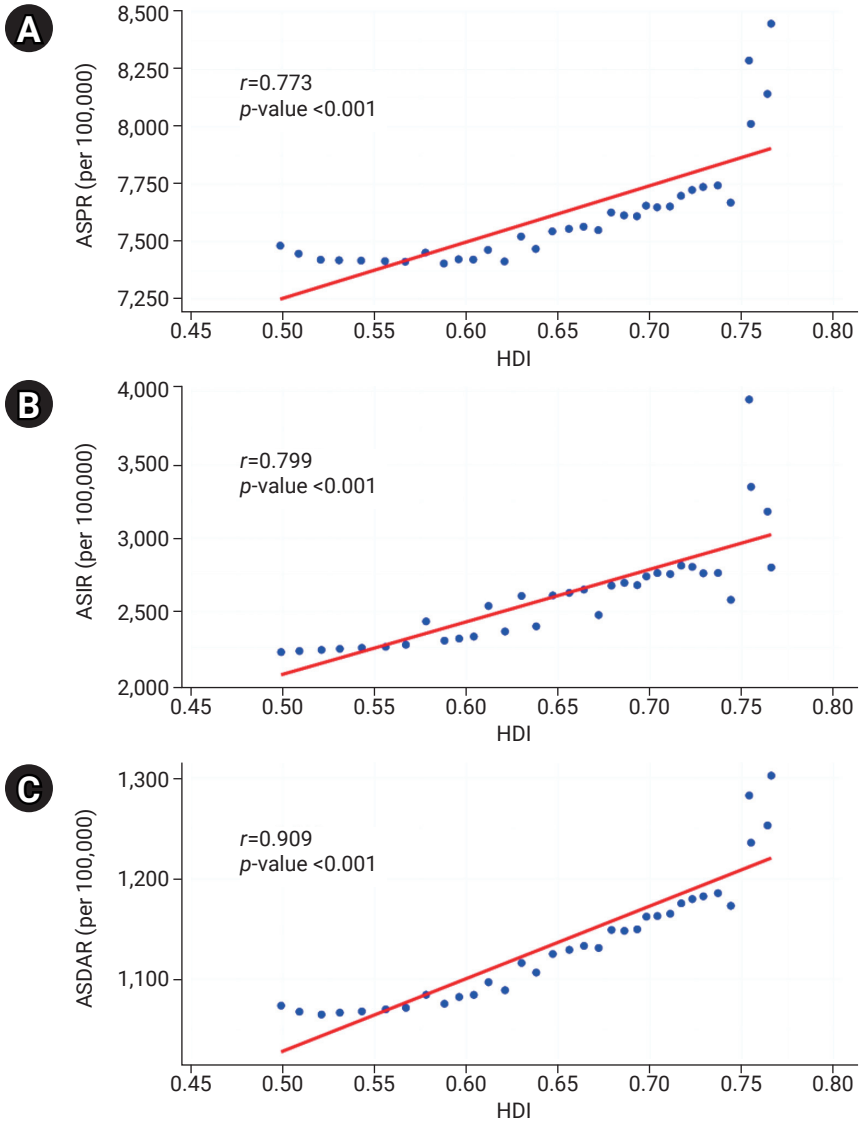


Figure 3. Correlations between mental disorder burden and HDI in Vietnam. (A) ASPR. (B) ASIR. (C) ASDAR.
HDI, human development index; ASPR, age-standardized prevalence rate; ASIR, age-standardized incidence rate; ASDAR, age-standardized disability-adjusted life-year rate.

and DALY rates increased steadily from 1990 to 2023, reflecting Vietnam's demographic transition and evolving epidemiological profile. Notably, Vietnam's ASIR increased by 1.10% annually during this period, exceeding the global average increase of 0.92%. To address uncertainty arising from the limited number of Vietnam-specific primary data sources informing GBD estimates, sensitivity analyses recalculated EAPCs using the lower and upper bounds of the 95% UIs (Table 5). These analyses showed that temporal trends were highly robust to parameter uncertainty: the EAPC for prevalence varied only from 0.27% to 0.28%, the EAPC for incidence remained consistently positive at 1.06% to 1.13%, and the EAPC for DALYs ranged from 0.57% to 0.62%. Although the absolute levels of GBD estimates for mental disorders may be affected by differences in diagnostic thresholds and cross-walk adjustments in the GBD framework, these findings suggest that the upward trend in Vietnam's mental disorder burden likely reflects an epidemiological pattern rather than a modeling artifact.

The 2020–2023 period, which coincided with the COVID-19 pandemic, revealed a marked divergence in epidemiological patterns. Specifically, ASIR increased from 2,575.6 to 3,946.3 per 100,000 between 2019 and 2021, indicating an acute shock to national mental health. This sharp increase in 2021 coincided temporally with the implementation of Directive 16 and stringent social-distancing measures across major

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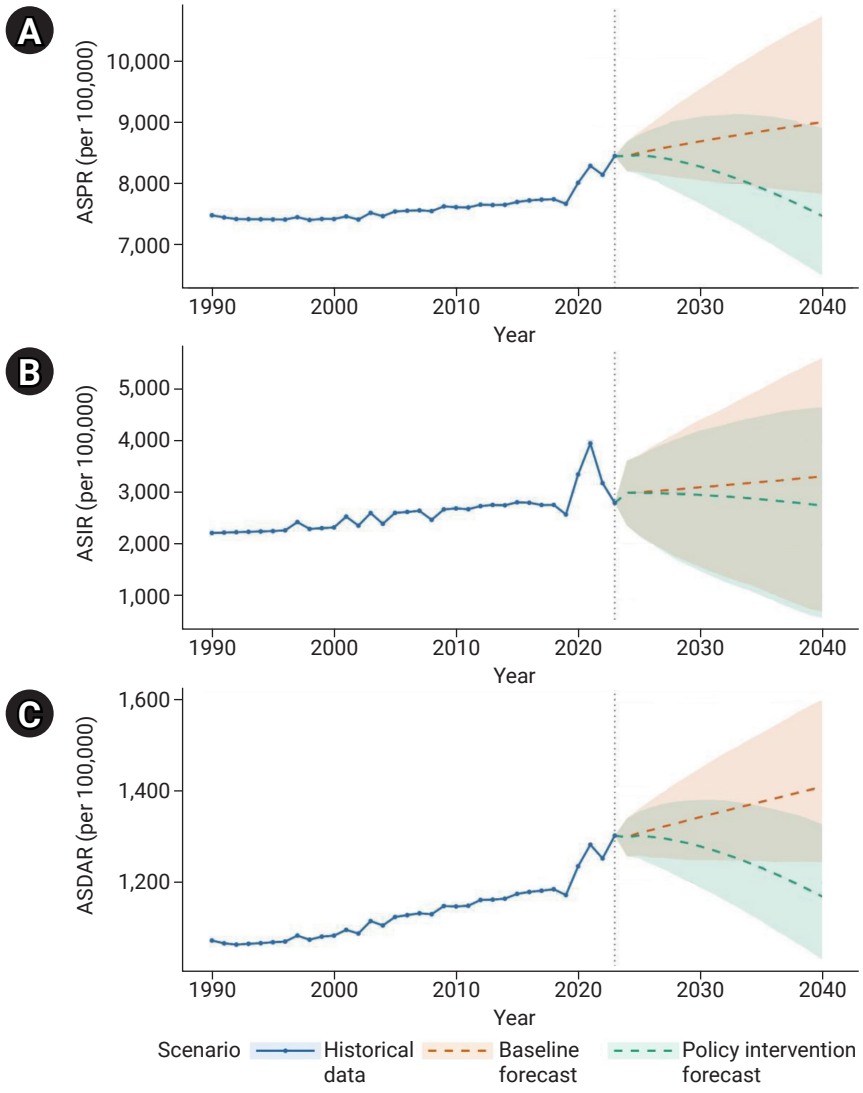


Figure 4. Baseline and policy intervention projections of mental disorder burden in Vietnam through 2040. (A) ASPR. (B) ASIR. (C) ASDAR.
ASPR, age-standardized prevalence rate; ASIR, age-standardized incidence rate; ASDAR, age-standardized disability-adjusted life-year rate.

southern provinces [14]. This pattern also coincided with a convergence of potential stressors, including fear of infection, sudden income loss, and psychological strain from prolonged confinement [15–17]. Meanwhile, ASPR and ASDAR showed a stepwise pattern, rising sharply and remaining elevated through 2023. This divergence may suggest that cases identified during the pandemic were associated with a higher chronic prevalence burden, potentially reflecting sustained population-level effects beyond transient psychological distress [16].

In Vietnam, the age distribution of mental disorder burden reveals distinct life-stage patterns. Crude incidence peaked sharply at 4,125.3 per 100,000 in the 15–19-year age group, aligning with global evidence that approximately 48% of mental disorders begin by age 18 years and 62.5% begin by age 25 years [18]. In contrast, crude disability burden, measured as DALYs, peaked at 1,727.1 per 100,000 in the 35–39-year age group, corresponding to the working-age population, while crude prevalence accumulated across the life course and peaked at 10,914.2 per 100,000 in the 60–64-year age group. This stratification across the life course indicates that new disorder onset is concentrated in adolescence, cumulative disability is most pronounced during working ages, and long-term prevalence increases with age. These distinct patterns have important implications for prevention and intervention strategies.

Adolescence, defined as ages 10–19 years, represents a critical developmental window of mental health vulnerability in Vietnam, with crude incidence peaking in the 15–19-year age group at 4,125.3 per 100,000. This elevated burden is likely

associated with a combination of traditional and modern psychosocial stressors. Previous research suggests that academic pressures contribute substantially to psychological distress during this period, particularly among female students [19–21]. In addition, pervasive internet and social media use introduced new vulnerabilities; more than 30% of urban adolescents in Vietnam show signs of problematic internet use, which has been closely associated with anxiety symptoms [22,23]. These findings underscore the need for adolescent-focused prevention and early intervention strategies that address both traditional academic stressors and emerging challenges of the digital era.

However, the perceived magnitude of the adolescent burden is highly contingent on the diagnostic thresholds and modeling assumptions used. Based on GBD 2023 estimates, the prevalence of mental disorders was 7,941.2 per 100,000 (7.94%) among adolescents aged 10–14 years and 8,696.2 per 100,000 (8.70%) among those aged 15–19 years. In contrast, V-NAMHS reported a strict clinical prevalence of only 3.3% among adolescents aged 10–17 years using the Diagnostic Interview Schedule for Children, Version 5, case definition [7]. This discrepancy indicates that GBD estimates are approximately 2.4- to 2.6-fold higher than estimates based on this narrow clinical threshold. V-NAMHS also found that 21.7% of adolescents experienced broader mental health problems [7], indicating that the choice of case definition can shift burden estimates by a factor of approximately 6.6. In this context, GBD-modeled prevalence for early adolescence (7.94%) and late adolescence (8.70%) occupies a middle range: it exceeds strict clinical pathology estimates by 2.4- to 2.6-fold but remains 2.5- to 2.7-fold lower than the community-level symptom burden estimate of 21.7%. This positioning likely reflects methodological differences between the two approaches. The GBD framework synthesizes diverse and sparse primary data through cross-walking and spatiotemporal smoothing to produce harmonized estimates, whereas the V-NAMHS provides a nationally representative snapshot using a single, uniform diagnostic instrument.

These methodological differences may be further compounded by substantial gaps in service utilization. The V-NAMHS identified a 91.6% treatment gap among adolescents reporting mental health problems, with only 8.4% of the 1,301 affected adolescents accessing supportive or counseling services in the preceding 12 months [7]. This low level of service use likely contributes to downward bias in some surveys and clinical data inputs used in GBD modeling. Although the upward temporal trajectory, as reflected by the EAPC, remained statistically robust in sensitivity analyses (Table 5), these comparisons confirm that absolute values are highly sensitive to diagnostic thresholds and data availability. Future mental health policy should therefore triangulate standardized GBD trends with domestic empirical data to guide resource allocation more effectively.

Although incidence peaks in adolescence, the burden of disability is concentrated in the 35–39-year age group, during prime working years. This concentration suggests that mental disorders exert their greatest functional impact when economic activity and family responsibilities are highest. Contextual evidence from Vietnam indicates that mental health problems are prevalent among working-age adults, particularly in urban and industrial settings. Studies of industrial workers in Vietnam have reported depressive symptom prevalence ranging from 18.8% to 38.6%, depending on occupational sector and location [24–26]. This accumulation of disability during working ages may generate substantial productivity losses and household dysfunction, thereby magnifying societal costs beyond direct healthcare expenditures.

The prevalence peak among older adults highlights the intersection of mental health burden with Vietnam's rapid demographic aging. The prevalence peak in the 60–64-year age group and the secondary rise among the oldest-old, those aged 95 years or older, likely reflect the cumulative effects of long-term mental disorders alongside increasing physical comorbidity rather than elevated incidence at older ages. Rapid urbanization and labor migration have altered traditional family structures, which may reduce social support for some older adults, particularly in rural areas [27–29]. The rising burden among the oldest-old also aligns with evidence of increasing neurocognitive disorders, including dementia, which contribute substantially to mental health-related disability and caregiving demands in aging populations [30].

GBD 2023 estimates revealed sex disparities in Vietnam's mental disorder burden, with females experiencing 15.6% higher ASPR and 13.6% higher ASDAR than males. This pattern aligns with global GBD findings showing that females bear a disproportionately higher mental health burden across LMICs, driven by biological factors, such as hormonal fluctuations, and psychosocial stressors, such as gender-based violence and caregiving roles [31,32]. In Vietnam, rapid urbanization and economic transitions may exacerbate these vulnerabilities, mirroring Southeast Asian trends in which shifts in social roles amplify sex disparities in mental health burden [33].

Depressive disorders emerged as the leading contributor to Vietnam's mental disorder burden in GBD 2023 estimates, outpacing anxiety disorders and underscoring the need for enhanced detection amid rising psychosocial stressors, including economic pressures and post-pandemic

https://doi.org/10.24171/j.phrp.2026.0101

effects. This pattern is consistent with global evidence showing that these internalizing conditions dominate DALYs in LMICs [8]. Schizophrenia had a disproportionate disability impact despite lower prevalence and incidence, highlighting its chronic and resource-intensive nature and the need for specialized long-term care investments. Neurodevelopmental disorders, including autism spectrum disorders and idiopathic developmental intellectual disability, also highlight persistent early-life gaps in mental health identification in Vietnam. Limited pediatric screening capacity, weak early detection systems, and low adolescent service utilization contribute to under-recognition and substantial unmet need [34,35].

Beyond these demographic patterns, our analysis revealed a strong positive association between Vietnam's HDI and the burden of mental disorders, with correlations of $r = 0.909$ for ASDAR, $r = 0.773$ for ASPR, and $r = 0.799$ for ASIR, all $p < 0.001$. These findings are consistent with global epidemiological evidence showing that, as countries undergo rapid socioeconomic development, the documented burden of mental health conditions often increases in parallel [3]. This association may partly reflect improved healthcare system capacity, which enables better case detection and documentation, as well as potential increases in mental health risk in the context of rapid urbanization, intensifying occupational stress, labor migration, and weakening traditional family support networks [27,29,36]. Demographic aging may also contribute: longer life expectancy associated with development is linked to a higher proportion of older adults at elevated risk for chronic mental conditions, which can further increase the observed population burden of mental disorders [37].

Projections through 2040 using BSTS models—characterized by high predictive accuracy, with R^2 values greater than 0.96 and low MAPE values across all indicators—indicate a steadily increasing age-standardized burden of mental disorders in Vietnam. Under the baseline scenario, age-standardized prevalence is projected to reach 9,003.75 per 100,000 population by 2040, alongside rising incidence and DALY rates. The more pronounced upward trajectories of prevalence and DALYs suggest that the future burden is not explained solely by demographic shifts but may also reflect a stepwise upward shift in baseline burden after the COVID-19 pandemic. This pattern may indicate that, although the spike in new cases coincided with a transient pulse effect, the dominant long-term pattern is sustained disability, placing chronic pressure on an already constrained national healthcare infrastructure. The projected baseline highlights a critical disparity between escalating epidemiological needs and Vietnam's current systemic capacity. According to the latest World Bank reports from 2024, Vietnam's specialized workforce remains substantially constrained, with approximately 0.62 psychiatrists per 100,000 population [38]. Although this ratio is slightly higher than the average for lower-middle-income countries (0.40), it remains below the upper-middle-income country average (1.60) and the global average (1.70) [39], potentially contributing to the reported 90% treatment gap for common mental disorders such as depression and anxiety.

However, the policy intervention scenario demonstrates that this trajectory is not inevitable. A cumulative 17% relative reduction, aligned with United Nations SDG 3.4 and the WHO Comprehensive Mental Health Action Plan 2013–2030, could lower the projected 2040 ASPR to 7,473.12 per 100,000 and the projected ASDAR to 1,168.68 per 100,000. Achieving such targets may require structural reforms focused on decentralizing care from the current hospital-centric model. Although Vietnam's national average of 10.3 psychiatric beds per 100,000 population is comparable to the global average of 10.8, only 7% of these beds are integrated into general hospitals, with the substantial majority concentrated in specialized psychiatric facilities [38]. This concentration within specialized facilities, coupled with marked regional disparities ranging from 1.14 psychiatrists per 100,000 population in the Red River Delta to 0.12 per 100,000 population in the Central Highlands [38], likely hinders equitable access to care and underscores the need to transition toward an integrated, community-based framework. A feasible pathway to bridge this gap involves task-sharing within Vietnam's network of more than 11,000 commune health stations through scaled collaborative care models [38]. In these models, specialized psychiatrists provide remote supervision and technical support to trained grassroots staff, integrating WHO Mental Health Gap Action Programme pathways and evidence-based psychosocial protocols [7,40]. This approach aligns with Vietnam's National Plan for Prevention and Control of Noncommunicable Diseases and Mental Disorders for 2022–2025 (Decision 155/QĐ-TTg) [11], which mandates the integration of mental health into existing non-communicable disease management. Furthermore, implementation of the Community-Based Social Assistance and Functional Rehabilitation Program for People With Mental Illness, Children With Autism, and People With Intellectual Disabilities for 2021–2030 (Decision 1929/QĐ-TTg) [12] may further mitigate social stigma and facilitate patient reintegration. Ultimately, the divergence between the baseline and intervention scenarios emphasizes the cost of inaction: without specific structural reforms to integrate mental healthcare into the primary care framework, Vietnam may face an increasingly

unsustainable escalation of its mental health disability burden through 2040.

To our knowledge, this study provides the first comprehensive assessment of mental disorder burden in Vietnam from 1990 to 2023 using GBD 2023 estimates. By examining temporal trends alongside socioeconomic correlates, this analysis highlights how mental health patterns have evolved in parallel with Vietnam's development. In addition, the use of BSTS modeling allowed quantification of COVID-19-related shock effects in future projections, while detailed stratification by age, sex, and diagnostic subtype provided a granular view of burden across population groups. Several limitations warrant consideration. First, the findings rely on GBD 2023 modeled estimates rather than primary data from a national disease registry or comprehensive population-based surveys in Vietnam. Although the GBD framework uses sophisticated Bayesian meta-regression through DisMod-MR 2.1 to synthesize global evidence, the estimates for Vietnam were informed by a relatively limited base of 8 primary data sources. This low data density may result in wider UIs and potential underestimation or overestimation of the true burden. Consequently, caution is needed when interpreting trends for specific diagnostic subtypes, because estimates for less common disorders may be influenced by regional patterns rather than solely reflecting the epidemiological profile of the Vietnamese population. Second, upstream risk factors—including academic stress, socioeconomic disadvantage, trauma exposure, and substance use—were not examined, which limits causal interpretation. Third, GBD disability weights are largely derived from high-income settings and may not fully capture functional impairment within Vietnam's sociocultural and economic context. Finally, the analysis was restricted to national-level estimates and did not examine subnational heterogeneity; given regional disparities in economic development and health system capacity, mental disorder burden and access to care are likely to vary substantially across regions.

Conclusion

This study demonstrated that the burden of mental disorders in Vietnam increased substantially from 1990 to 2023, alongside economic development and demographic aging. Burden patterns differed across the life course, with new cases concentrated in adolescence, disability peaking during prime working years, and prevalence accumulating among older adults. Females consistently had higher age-standardized rates than males across all metrics. Subtype stratification further showed that, although depressive and anxiety disorders dominated the overall burden, each condition followed a distinct burden trajectory requiring condition-specific responses. The strong positive association between human development and disease burden underscores that Vietnam's socioeconomic progress has been accompanied by intensifying psychosocial stressors that existing services may be insufficiently equipped to address. Vietnam's current health system lacks the capacity and structure needed to address this expanding chronic burden. Reorienting from a hospital-centric model toward an integrated, community-based care model represents a critical structural priority, alongside expansion of the mental health workforce and systematic integration of screening and support services into primary care, school, workplace, and geriatric settings. In the absence of such reforms, projections indicate that Vietnam's mental disorder burden will continue to escalate through 2040.

Supplementary Material

Supplementary Material 1. R code for Bayesian structural time series (BSTS) model specification, fitting, and projection is available as a separate file; **Table S1.** Bayesian structural time series model fit and convergence diagnostics; **Figure S1.** BSTS MCMC convergence and posterior predictive diagnostics for mental disorder burden indicators in Vietnam, 1990–2023. Each row presents 3 diagnostic panels: trace plot (left), residual distribution (center), and normal Q–Q plot (right). (A) ASPR, (B) ASIR, (C) ASDAR. Supplementary data are available at https://doi.org/10.24171/j.phrp.2026.0101.

Notes

Ethics Approval
Not applicable.

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

Funding
This study was supported by the University of Danang–VN-UK Institute for Research and Executive Education through grant No. T2023-VNUK-06.

Availability of Data
All data generated or analyzed during this study are included in this published article. Additional data may be requested from the corresponding author.

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https://doi.org/10.24171/j.phrp.2026.0101

phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2026.0223
Osong Public Health Res Perspect 2026;17(4):351-361

Original Article

Child health problems and social determinants as predictors of postpartum depression: a cross-sectional study using 2023 Indonesia Health Survey data

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ABSTRACT

Objectives: This study examined the predictive role of child health problems and social determinants in postpartum depression (PPD), with the aim of supporting early screening strategies and more comprehensive maternal health policies.
Methods: This cross-sectional study used secondary data from the 2023 Indonesia Health Survey, conducted by the Indonesian Ministry of Health. The analysis included 26,656 postpartum women aged at least 15 years who had given birth within the previous 24 months. PPD was assessed using the Mini International Neuropsychiatric Interview. Multiple logistic regression was used to analyze the data.
Results: Child health problems were among the strongest factors associated with PPD in Indonesia. Having had an unplanned pregnancy was associated with higher odds of PPD (adjusted odds ratio [aOR], 3.90; 95% confidence interval [CI], 2.90–5.25; $p < 0.001$), as was having a child with chronic illness (aOR, 2.30; 95% CI, 1.01–5.26; $p = 0.048$). Social risk factors, including younger maternal age, divorce or separation from a partner, unemployment, and lack of social support, were also associated with PPD in Indonesia.
Conclusion: Child health problems and adverse social conditions were significantly associated with postpartum mental health in Indonesia. Integrating early screening into maternal and child health services and strengthening maternal support systems may help reduce the burden of PPD.

Keywords: Child health; Indonesia; Postpartum depression; Social factors

Received: March 10, 2026
Revised: April 27, 2026
Accepted: April 28, 2026

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Introduction

Background

Postpartum depression (PPD) is a common mental health problem, with a global prevalence

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ranging from 3% to 10% [1]. PPD can contribute to long-term maternal psychological morbidity and adversely affect child development and mothers' social relationships [2]. As shown in a previous review, depression during pregnancy can negatively affect fetal brain development and child developmental outcomes, including emotional, behavioral, cognitive, and language domains [3]. Longitudinal data also indicate that PPD can adversely affect personal relationships and social interactions [4,5].

In Indonesia, perinatal mental health screening has not been implemented consistently in primary health care services [6] and has not been optimally integrated into maternal and child health programs [7]. Health care workers therefore must recognize key indicators that may be associated with PPD.

One less explored indicator of PPD is the role of child health in shaping maternal mental health [8]. In a Chinese study, neonatal incubator care due to infant health problems was associated with PPD, highlighting the potential effect of infant health problems on maternal emotional well-being [8]. In addition to child health, social determinants, such as unplanned pregnancy and lack of social support, may moderate the risk of PPD [9].

To date, most studies of PPD have focused on biological predictors or maternal sociodemographic characteristics without incorporating indicators of child morbidity and birth outcomes. As a result, integrated maternal and child health strategies in Indonesia are not adequately supported by empirical evidence on the joint relevance of maternal social determinants and child health problems.

Objectives

This study examined child health problems and social factors associated with PPD among Indonesian mothers. Using nationally representative data, this study provides evidence on the social determinants of postpartum mental health and the relevance of child health indicators. The findings may inform early screening strategies and policies aimed at strengthening maternal mental health support within maternal and child health care programs.

Materials and Methods

Study Design and Setting

This cross-sectional study used secondary data from the 2023 Indonesia Health Survey (*Survei Kesehatan Indonesia* [SKI]), a national health survey conducted by the Indonesian Ministry of Health. The survey is conducted every 5 years and collects basic health indicators describing community health at the district/city, provincial, and national levels. The survey includes data on demographic and socioeconomic characteristics, communicable and noncommunicable diseases, mental health, disability, child health, and maternal health. Survey data were collected using a probability proportional to size approach. Ten households in each census block were selected using a 2-stage systematic linear sampling procedure. All members of selected households who had lived in the household for at least 1 year and shared the same source of funds for daily needs were invited to participate in the survey [10].

HIGHLIGHTS

- Of the studied factors, child health problems are among the strongest predictors of postpartum depression in Indonesia.
- Having had an unplanned pregnancy and caring for a child with chronic illness were strongly associated with postpartum depression.
- Social determinants, including younger maternal age, divorce or separation, unemployment, and lack of social support, were significantly associated with postpartum depression.

Setting

The data were derived from the 2023 Indonesia Health Survey (SKI), which was conducted across 38 provinces and 514 districts/cities in Indonesia.

Participants

The analysis included postpartum mothers aged 15 years or older who had given birth within the previous 24 months and whose children were alive at the time of the survey interview. Mothers with insufficient responses for the study variables were excluded to ensure data completeness and analytical validity. Mothers experiencing severe pain at the time of the interview were also excluded because severe physical discomfort may interfere with cognitive functioning and the ability to provide accurate and reliable responses, potentially introducing response bias. After these criteria were applied, 26,656 mothers were included.

Variables and Measurement

PPD was assessed using the Mini International Neuropsychiatric Interview (MINI). The MINI is a structured interview comprising 10 questions developed by psychiatrists and physicians in the United States and Europe to evaluate psychiatric disorders listed in the Diagnostic and Statistical Manual of Mental Disorders,

https://doi.org/10.24171/j.phrp.2026.0223

Fourth Edition, and the International Classification of Diseases, 10th Revision [11]. The instrument assessed depressive symptoms during the 2 weeks preceding survey participation. In Indonesia, the MINI has been reported to have a sensitivity of 60%–80%, a positive predictive value of 30%–60%, and a negative predictive value of approximately 90% for diagnosing depression [1,12]. Participants were classified as having PPD if they met the following criteria: at least 2 "yes" responses to questions 1–3 and at least 2 "yes" responses to questions 4–10. The outcome variable was dichotomized as either not depressed or depressed.

Bias

This study may be subject to several sources of bias. Depressive symptoms were assessed using survey-based MINI responses rather than full clinical diagnostic interviews, which may have introduced reporting bias and limited diagnostic precision. In addition, stigma surrounding mental health in low- and middle-income country settings may have contributed to social desirability bias and potential underreporting of depressive symptoms. These potential biases were minimized through the use of standardized survey instruments, systematic enumerator training, and structured data collection procedures implemented in the national survey. Finally, the cross-sectional design precludes causal inference; therefore, the findings should be interpreted as associations rather than causal relationships.

Study Size

The 2023 Indonesia Health Survey (SKI) used a nationally representative sampling design covering 34,500 census blocks and approximately 345,000 households across Indonesia. Households were selected through a multistage sampling procedure designed to represent the population at national and subnational levels. After applying the study eligibility criteria described in the Participants subsection, a total of 26,656 postpartum mothers were included in the final analysis.

Quantitative Variables

The independent variables included maternal social determinants and child health indicators. Maternal social determinants included marital status, education level, occupational status, having a housekeeper, living with the participant's biological mother, and social support. Child health indicators included child age, child sex, low birth weight (LBW), unplanned pregnancy, and child chronic illness. For all categorical variables, the reference category, coded as 0, was intentionally selected to represent the more favorable or lower-risk condition, whereas higher codes represented less favorable conditions potentially associated with a higher risk of PPD. This coding approach ensured consistent interpretation of the adjusted odds ratios (aORs) across all variables in the regression analysis.

For marital status, a code of 0 indicated married and living with the husband, a code of 1 indicated married but not living with the husband, and a code of 2 indicated divorced. Living with the husband was defined as the husband typically residing and sleeping with his wife. For maternal education level, a code of 0 indicated university or diploma completion, a code of 1 indicated middle school or high school completion, and a code of 2 indicated less than primary school education. Occupational status was classified as formal employment, coded as 0; informal employment, coded as 1; and not working, coded as 2. Having a housekeeper was coded as 0 for yes and 1 for no. Living with the participant's biological mother was coded as 0 for yes and 1 for no. The participant's biological mother was defined as the participant's birth mother. Social support was defined as having someone available to help the participant in an emergency and was coded as 0 for yes and 1 for no.

Children aged 0–12 months were coded as 0, and children aged 13–24 months were coded as 1. Child sex was coded as 0 for male and 1 for female. LBW was coded as 0 for no and 1 for yes; LBW was defined as birth weight less than 2,500 g. The unplanned pregnancy variable was derived from the question, "Did the mother want this child?" The response "Yes, I wanted it" was categorized as planned, coded as 0, whereas the responses "I wanted it but later" and "I did not want it" were categorized as unplanned, coded as 1. Child chronic illness was defined as a physician diagnosis of cancer, diabetes mellitus, coronary heart disease, asthma, or a congenital abnormality present at birth, including clubfoot, hydrocephalus, conjoined twins, imperforate anus, congenital heart disease, and thalassemia. Child chronic illness was coded as 0 for no and 1 for yes. Higher codes for all variables were interpreted as indicating a higher risk of PPD than lower codes. This study investigated the associations of maternal social determinants and child health risk factors with PPD.

Statistical Methods

Before analysis, cases with missing data for any study variable were excluded, resulting in a complete-case dataset. Multiple logistic regression was used to analyze the data. All independent variables were first examined using univariate analysis and were grouped as social determinants (Table 1) and child health indicators (Table 2). Associations between the independent variables and PPD were then assessed using bivariate analysis with cross-tabulation and the chi-square test. A chi-square p-value of less than 0.05 was considered to indicate a statistically

Table 1. Frequency distribution based on social determinants and depression status of postpartum mothers in Indonesia

Variable	Total	Depression		*p*[a]
		Not depressed	Depressed	
Overall	26,656 (100.0)	25,856 (97.0)	800 (3.0)	
Marital status				< 0.001
Married, living with husband	18,846 (70.7)	18,299 (97.1)	547 (2.9)	
Married, not living with husband	7,490 (28.1)	7,251 (96.8)	240 (3.2)	
Divorced	320 (1.2)	306 (95.6)	13 (4.4)	
Education level				0.004
University/diploma	5,544 (20.8)	5,400 (97.4)	144 (2.6)	
Middle–high school	15,567 (58.4)	15,085 (96.9)	483 (3.1)	
Primary school	5,544 (20.8)	5,371 (96.9)	173 (3.1)	
Occupational status				< 0.001
Formally employed	3,385 (12.7)	3,300 (97.5)	85 (2.5)	
Informally employed	7,410 (27.8)	7,203 (97.2)	207 (2.8)	
Not working	15,860 (59.5)	15,353 (96.8)	508 (3.2)	
Housekeeper				0.997
Yes	80 (0.3)	78 (97.1)	3 (2.9)	
No	26,576 (99.7)	25,779 (97.0)	797 (3.0)	
Living with biological mother				0.065
Yes	4,345 (16.3)	4,193 (96.5)	152 (3.5)	
No	22,311 (83.7)	21,663 (97.1)	648 (2.9)	
Social support				< 0.001
Yes	13,221 (49.6)	12,864 (97.3)	357 (2.7)	
No	13,435 (50.4)	12,992 (96.7)	443 (3.3)	

Data are presented as number (%).
[a]By chi-square test.

Table 2. Frequency distribution based on child health and depression status of postpartum mothers in Indonesia

Child health	Total	Depression		*p*[a]
		Not depressed	Depressed	
Child age (mo)				0.764
0–12	13,168 (49.4)	12,799 (97.2)	369 (2.8)	
13–24	13,488 (50.6)	13,057 (96.8)	431 (3.2)	
Child sex				0.789
Male	13,754 (51.6)	13,356 (97.1)	400 (2.9)	
Female	12,902 (48.4)	12,500 (96.9)	400 (3.0)	
Low birth weight				0.980
No	25,057 (94.0)	24,305 (97.0)	752 (3.0)	
Yes	1,599 (6.0)	1,551 (97.0)	48 (3.0)	
Pregnancy intendedness				< 0.001
Planned	24,790 (93.0)	24,096 (97.2)	694 (2.8)	
Unplanned	1,866 (7.0)	1,760 (94.3)	106 (5.7)	
Child chronic illness				0.033
No	26,263 (98.5)	25,501 (97.1)	735 (2.9)	
Yes	363 (1.5)	298 (82.1)	65 (17.9)	

Data are presented as number (%).
[a]By chi-square test.

https://doi.org/10.24171/j.phrp.2026.0223

significant association between each independent variable and PPD.

To evaluate determinants of PPD, variables with $p < 0.25$ in the bivariate analysis (Tables 1, 2) were subsequently included in the multivariate logistic regression model (Table 3). Backward elimination was then applied to obtain the most parsimonious model by sequentially removing the least significant variable until all remaining variables met the statistical significance threshold of $p < 0.05$. aORs and 95% confidence intervals (CIs) were calculated to quantify the strength of association between each independent variable and PPD.

The analysis was conducted using IBM SPSS ver. 22.0 (IBM Corp.), accounting for the relevant SKI weights, strata, and primary sampling units in accordance with the SKI survey design. Assumptions underlying logistic regression were assessed before model estimation. Because all independent variables were categorical, the linearity assumption in the logit was not applicable. Multicollinearity diagnostics indicated no substantial correlation among predictors.

Ethics Statement

This study used secondary data from SKI 2023, which are publicly available. Respondent identities were not disclosed or analyzed. Ethical approval for SKI 2023 was obtained from the Ethics Committee of the Indonesian Ministry of Health (No: LB.02.01/I/KE/L/287/2023).

Results

Participants

A total of 70,851 mothers who had given birth within the previous 5 years were initially identified from the 2023 Indonesia Health Survey dataset. Participants were excluded if the child had died ($n = 232$), the mother was younger than 15 years ($n = 91$), or the respondent was not the biological mother ($n = 162$). Mothers whose children were older than 24 months at the time of the survey were also excluded ($n = 43,710$), because PPD in this study was defined within the first 24 months after childbirth. After these criteria were applied, 26,656 postpartum mothers with children aged 24 months or younger were included in the final analysis. The participant selection process is presented in Figure 1.

Descriptive Data

The frequency distribution of mothers who were 0–24 months postpartum in Indonesia is presented in Table 1. Among the 26,656 respondents, 18,846 (70.7%) were married and living with their husbands, 15,567 (58.4%) had middle

Table 3. Associations of child health and social factors with depression among postpartum mothers in Indonesia

Variable	aOR (95% CI)	p[a)]
Age (y)		
35–54	1	
25–34	1.169 (0.863–1.583)	0.313
15–24	2.063 (1.446–2.945)	<0.001
Marital status		
Married, living with husband	1	
Married, not living with husband	1.551 (1.199–2.007)	<0.001
Divorced	2.878 (1.428–5.800)	0.003
Occupational status		
Formally employed	1	
Informally employed	1.207 (0.706–2.063)	0.492
Not working	1.747 (1.069–2.854)	0.026
Pregnancy intendedness		
Planned	1	
Unplanned	3.903 (2.900–5.254)	<0.001
Child chronic illness		
No	1	
Yes	2.300 (1.007–5.256)	0.048
Social support		
Yes	1	
No	1.669 (1.288–2.164)	<0.001

aOR, adjusted odds ratio; CI, confidence interval.
[a)]By multiple logistic regression test.

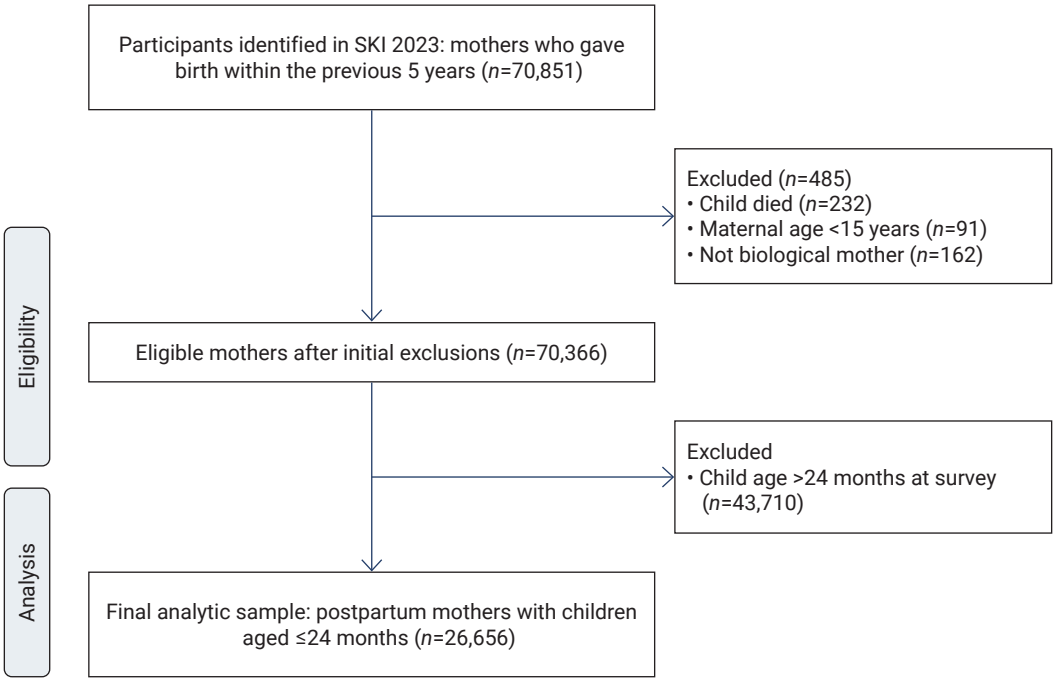


Figure 1. Participant selection. SKI, *Survei Kesehatan Indonesia*.

school or high school education, 15,860 (59.5%) were not working, 26,576 (99.7%) did not have a housekeeper, 22,311 (83.7%) did not live with their biological mothers, and 13,435 (50.4%) did not have social support (Table 1).

Outcome Data

Of the 26,656 mothers included in the analysis, 800 (3.0%) experienced PPD. In the bivariate analysis, the proportion of mothers with PPD was higher among those who were divorced, not working, and lacked social support. Marital status, maternal education level, maternal occupational status, and social support were associated with PPD among Indonesian mothers in the bivariate analysis (Table 1).

Table 2 presents the frequency distribution of mothers according to child health indicators and PPD depression status. The distribution of mothers was nearly even across child age groups and child sex. Overall, 25,057 mothers (94.0%) had children with normal birth weight, 24,790 (93.0%) had planned pregnancies, and 26,263 (98.5%) had children without chronic illness (Table 2). The prevalence of PPD was higher among mothers with an unplanned pregnancy than among those with a planned pregnancy (5.7% vs. 2.8%, $p < 0.001$) and was also higher among mothers whose child had a chronic illness than among those whose child did not (17.9% vs. 2.9%, $p = 0.033$). No significant differences in PPD prevalence were observed according to child age, child sex, or LBW status (Table 2).

Main Results

Table 3 presents the results of the multivariate analysis of the associations of child health and social factors with depression among mothers who were 0–24 months postpartum in Indonesia. Maternal age, marital status, maternal occupational status, unplanned pregnancy, child chronic illness, and lack of social support were associated with PPD among mothers in Indonesia. Younger maternal age was associated with higher odds of PPD: mothers aged 15–24 years were approximately 2.1 times more likely to experience PPD (aOR, 2.06; 95% CI, 1.45–2.96; $p < 0.001$) than mothers aged 35–54 years. Mothers who were married but not living with their husbands had higher odds of PPD (aOR, 1.55; 95% CI, 1.20–2.01; $p < 0.001$) than mothers who were married and living with their husbands. Divorced mothers also had higher odds of PPD (aOR, 2.88; 95% CI, 1.43–5.80; $p = 0.003$). Mothers who were not working had higher odds of PPD (aOR, 1.75; 95% CI, 1.07–2.85; $p = 0.026$), as did mothers who lacked social support (aOR, 1.67; 95% CI, 1.29–2.16; $p < 0.001$). Child factors associated with higher odds of PPD among postpartum mothers in Indonesia included having had an unplanned pregnancy (aOR, 3.90; 95% CI, 2.90–5.25; $p < 0.001$) and having a child with chronic illness (aOR, 2.30; 95% CI, 1.01–5.26; $p = 0.048$).

Discussion

Key Results

This study provides nationally representative evidence that PPD

https://doi.org/10.24171/j.phrp.2026.0223

among mothers in Indonesia is strongly associated with social variables and child health problems. The main findings indicate that PPD was significantly associated with younger maternal age, living separately from a partner while still married or being divorced, not working, having had an unplanned pregnancy, having a child with chronic illness, and lack of social support.

The association between younger maternal age (15–24 years) and higher odds of PPD (aOR, 2.08) warrants particular attention in the Indonesian context. Mothers in this age group may still be undergoing psychological and emotional development, making the transition to motherhood especially challenging. Younger mothers are often less prepared to manage the emotional and psychological changes associated with motherhood, which may increase their vulnerability to parenting-related psychosocial problems [13]. This vulnerability is compounded by the Indonesian social context, where child marriage remains prevalent. Nationally representative longitudinal data from Indonesia have shown that early marriage, particularly by age 18, has adverse effects on women's mental health; women who marry early are significantly more likely to experience depression, and each 1-year delay in marriage is associated with an approximately 4% reduction in the likelihood of depression [14]. Furthermore, young mothers who marry early are often separated from their families and friends and may be required to live with their husband's family, increasing their risk of social isolation. At the same time, childbearing and child-rearing impose substantial physical and emotional demands on adolescents and young adults who are still undergoing developmental transitions [9]. These findings underscore the urgent need for targeted mental health screening and psychosocial support programs for young postpartum mothers in Indonesia, particularly those who married at an early age.

Mothers who lived apart from their husbands or were divorced had higher odds of PPD symptoms. Research conducted in Indonesian cities has shown that women who live apart from their husbands are 3.82 times more likely to develop PPD than women who live with their husbands [9]. The presence of a partner during the postpartum period may support financial stability, provide practical assistance with childcare, and offer emotional support, all of which may reduce psychological stress [15,16]. In contrast, divorce was significantly associated with higher odds of PPD. In Indonesia, divorced women often experience social stigma, which may intensify the psychological pressure experienced by single mothers who face marginalization and negative stereotypes [17]. Single mothers may also experience a complex cycle of emotional strain related to the dual burden of single parenthood and financial responsibility as the head of the household [18].

Mothers who were not working had higher odds of PPD. Employment after childbirth may benefit postpartum mothers by increasing self-esteem, social engagement, life satisfaction, and financial independence [19,20]. The mechanism underlying this association is likely multifaceted. Socioeconomic status may affect PPD through multiple mediating pathways, including satisfaction with material needs, access to health care, and postpartum social support; lower socioeconomic status has consistently been associated with higher levels of depression among postpartum mothers [21]. This economic vulnerability may be further compounded by prevailing social norms in Indonesia that position women primarily as caregivers and homemakers, thereby limiting their economic participation and autonomy. When unemployed mothers internalize these norms, they may experience heightened role entrapment, feeling obligated to fulfill domestic responsibilities without adequate emotional or financial support, which may increase psychological distress. Reinforcing this pattern, Indonesian women are expected to care for their families and often bear a disproportionate burden of unpaid domestic work, which exacerbates gender inequality and may further marginalize their mental health needs [22,23].

However, the relationship between employment and PPD is not straightforward, and the literature includes contradictory findings. Women who continue working after childbirth may experience tension between family and work demands. Despite changes in traditional role models, a gendered imbalance in household responsibilities persists, with employed women continuing to shoulder many childcare and domestic tasks [24]. Furthermore, work–privacy conflict, low reward at work, and precarious working conditions have been shown to significantly predict symptoms of PPD among employed mothers, even after adjustment for depression history, anxiety, education, parity, and age [25]. These findings suggest that the protective effect of employment on PPD may depend on work quality and working conditions rather than employment status alone. Future studies in Indonesia should therefore examine not only whether mothers are employed but also the nature of their employment, working conditions, and the availability of workplace support systems to better clarify the complex interplay among work, social norms, and maternal mental health.

This study indicates that the lack of social support was significantly associated with higher odds of PPD among postpartum mothers. In many Asian societies, including among Bengali women in India, women often live temporarily with their birth mothers during the postpartum period, a practice that provides encouragement, care, and protection [26]. Support from husbands, such as accompanying wives to prenatal care and listening to their concerns, has also been

shown to reduce emotional stress during the postpartum period [27]. Assistance from neighbors or close family members with childcare and domestic tasks, whether paid or unpaid, may help mothers adjust to the postpartum period and has been shown to reduce depressive symptoms [28].

With respect to child-related factors, mothers with an unplanned pregnancy had substantially higher odds of PPD; this was the strongest risk factor identified in the present study. Unplanned pregnancy is associated with a higher risk of depression and lower social support, reflecting emotional instability and reduced control over life circumstances [29]. Unplanned pregnancy has also been associated with poorer mother–infant bonding after birth [30]. In addition, caring for a child with chronic illness was significantly associated with higher odds of PPD in mothers. Mothers of children with chronic illness are significantly more likely to experience despair, anxiety, and serious mental disorders [31,32]. Children with chronic illness often require long-term care, frequent medical appointments, high expenses, and ongoing psychological concern about their prognosis [33]. Together, these factors may increase maternal stress and impair coping capacity.

The burden of caring for a child with chronic illness is unlikely to operate in isolation; rather, it may interact with other social risk factors identified in this study and produce compounding effects on maternal mental health. Health spillovers from child illness to maternal mental health have been found to be strongly related to illness severity, with larger associations observed for more severe child conditions, suggesting that the psychological burden on mothers escalates as caregiving demands intensify [25]. For example, a mother who is both unemployed and caring for a child with chronic illness may face the dual burden of financial strain and intensive caregiving demands, with limited resources for professional help or respite care. Among caregivers of children with chronic illness, those who are unemployed are more likely to depend on family support networks, highlighting the critical role of social support in buffering the psychological burden of caregiving, particularly among those without financial independence [14]. Similarly, mothers who lack social support while caring for a child with chronic illness may experience heightened isolation and helplessness as they navigate complex medical needs without adequate assistance. Poor social support, marital dissatisfaction, and low socioeconomic status have been identified as co-occurring risk factors that collectively amplify the likelihood of PPD, underscoring the importance of considering the cumulative burden of multiple risk factors rather than examining each factor in isolation [34]. Marital instability may further compound this burden, as divorced or separated mothers caring for a child with chronic illness often must manage both the emotional and practical demands of single parenthood alongside the challenges of chronic disease management. These compounding effects suggest that the association between child chronic illness and PPD may be moderated by the social context in which caregiving occurs. Mothers with multiple co-occurring risk factors, such as unemployment, lack of social support, and marital instability, may therefore represent a particularly vulnerable subgroup requiring prioritized screening and targeted psychosocial intervention.

The possibility of a bidirectional relationship between maternal mental health and child health outcomes should also be acknowledged. Although this study examined child health indicators as predictors of PPD, emerging evidence suggests that the relationship may also operate in the reverse direction. Mothers experiencing PPD may have difficulty recognizing and appropriately responding to their infant's needs, leading to delays or inconsistencies in comfort, feeding, and interaction. These difficulties can contribute to disconnection between the mother and infant and may affect the infant's emotional and social development [35]. Maternal depression also impairs infant and young child care practices related to breastfeeding, health care, safety, and development and may contribute to inadequate nutrition during infancy and childhood, resulting in suboptimal brain development and growth [36]. From a perceptual standpoint, mothers with depression may also overestimate or misattribute their child's health problems, creating a cycle in which perceived child illness amplifies maternal distress, which in turn, distorts health perceptions. If PPD persists after childbirth, it may affect the quality of parenting and care, as well as the mother's perception of the newborn; inconsistent caregiving may undermine the relational foundations that support the development of self-regulation and higher-order cognitive skills in the child [37]. This bidirectional dynamic underscores the importance of early identification and treatment of PPD not only for maternal well-being but also as a strategy to protect child health outcomes. Future longitudinal studies are needed to disentangle the temporal and causal pathways between maternal mental health and child health indicators in the Indonesian context.

The findings of this study have important practical implications for maternal and child health services in Indonesia. Because child health indicators, particularly chronic illness and unplanned pregnancy, were identified as significant predictors of PPD, these factors should be incorporated into existing primary health care platforms. The Maternal and Child Health (Kesehatan Ibu dan Anak,

https://doi.org/10.24171/j.phrp.2026.0223

KIA) handbook, which is routinely used during antenatal and postnatal visits, provides an accessible and feasible entry point for integrating a simple PPD risk screening checklist. Specifically, questions regarding pregnancy intendedness and the presence of chronic illness or congenital abnormalities in the child could be added to existing KIA documentation without requiring substantial additional resources. Similarly, the *Posyandu* (integrated health post) program, which reaches communities at the village level and is staffed by trained community health workers (Kader), represents a strategic platform for early detection of PPD among postpartum mothers. Community health workers could be trained to identify mothers with key risk indicators identified in this study, including younger maternal age, marital instability, unemployment, lack of social support, having had an unplanned pregnancy, and having a child with chronic illness, and to refer them promptly to the nearest primary health care facility (*Puskesmas*) for further assessment and management. To strengthen early detection, adoption of a validated and standardized screening instrument, such as the Edinburgh Postnatal Depression Scale (EPDS), is strongly recommended at all primary health care levels, including *Posyandu* and *Puskesmas*. The EPDS is a brief, widely validated, and culturally adaptable tool that has demonstrated good sensitivity and specificity for identifying mothers at risk of PPD in various low- and middle-income country settings, including Indonesia.

Beyond screening, the findings of this study underscore the importance of family-based support programs as a complementary strategy. Because marital instability, lack of social support, and unemployment were identified as significant risk factors, interventions that actively engage husbands, extended family members, and community networks in supporting postpartum mothers are particularly warranted. Existing programs such as *Kelas Ibu Hamil* (Pregnant Mothers' Class) could be expanded to include sessions on paternal involvement, recognition of PPD symptoms, and provision of emotional and instrumental support during the postpartum period. Home visit programs conducted by midwives or community health workers could also be strengthened to provide psychosocial support to mothers identified as high risk.

At the broader policy level, the findings of this study support the formal integration of perinatal mental health into Indonesia's national maternal and child health policy framework. PPD screening and management are not yet systematically embedded in national guidelines for maternal health services. Policymakers should consider mandating routine PPD screening as part of the standard postnatal care package, allocating dedicated resources for training frontline health workers in perinatal mental health, and establishing clear referral pathways from community-level services to higher-level mental health facilities. Strengthening the integration of perinatal mental health screening into existing programs would be a cost-effective and culturally appropriate strategy to improve early detection and management of PPD across Indonesia.

Limitations

A major strength of this study is its use of nationally representative SKI 2023 data, which provide generalizable insights into postpartum mental health in Indonesia. However, several limitations should be acknowledged. First, the cross-sectional design precludes causal inference because the temporal sequence between the identified risk factors and PPD cannot be established. Future studies should use longitudinal designs to investigate causal pathways and evaluate the long-term effects of changing child health trajectories on maternal mental health. Second, because PPD was assessed using self-reported measures, recall and reporting bias cannot be ruled out. Mothers may underreport depressive symptoms because of social stigma, fear of judgment, or cultural norms that discourage open disclosure of mental health difficulties, particularly in the Indonesian context. This may have led to an underestimation of the true prevalence of PPD in this study. Third, the social support measure used in this study was limited to emergency situations and did not capture support with daily activities. Future studies should use more comprehensive instruments that assess both daily emotional and instrumental support to obtain a more accurate and nuanced understanding of the maternal caregiving burden and its relationship to PPD. However, emergency social support was assessed during the same period as maternal mental health, which may have minimized recall bias. Fourth, as with any observational study, the possibility of unmeasured confounding cannot be excluded. Important variables, such as domestic violence, intimate partner violence, household socioeconomic status, and history of prior mental health disorders, were not captured in this study, and their omission may have influenced the observed associations between the identified risk factors and PPD. Future studies should incorporate these variables to provide a more comprehensive understanding of the determinants of PPD in Indonesia.

Interpretation

Overall, the findings suggest that child health problems and adverse social conditions are important correlates of PPD among mothers in Indonesia. In particular, having had an unplanned pregnancy and caring for a child with chronic

illness showed strong associations with maternal depressive symptoms, highlighting the potential psychological burden associated with childcare challenges during the postpartum period. Social vulnerabilities, including divorce or separation, unemployment, and limited social support, were also associated with a higher likelihood of PPD, consistent with previous studies showing that socioeconomic stressors and insufficient support systems contribute to maternal mental health problems. However, these findings should be interpreted cautiously. The cross-sectional design precludes causal inference, and the observed associations may reflect complex bidirectional or contextual relationships. In addition, the use of self-reported measures and the limited scope of the social support variables may have influenced the estimates. Despite these limitations, the large nationally representative dataset provides valuable population-level insights into postpartum mental health in Indonesia and supports the need for integrated maternal and child health services that consider both child health conditions and maternal social environments when identifying mothers at risk of PPD.

Generalizability

The generalizability of these findings is strengthened by the use of data from the 2023 Indonesia Health Survey (SKI), a nationally representative survey covering 38 provinces and 514 districts/cities across Indonesia. The large sample size and probability-based sampling approach increase the likelihood that the study population reflects the broader population of postpartum mothers in Indonesia, thereby supporting the external validity of the findings at the national level. However, caution is warranted when extending these results to other countries or contexts because cultural norms, health system structures, and social support mechanisms may differ across settings. In particular, the experience of PPD and the roles of child health problems and social determinants may vary in countries with different socioeconomic conditions or maternal health services. Therefore, although the findings are broadly applicable to the Indonesian context and potentially to similar low- and middle-income settings, further studies in other populations are needed to confirm these associations.

Conclusion

Social conditions and child health problems were significantly associated with PPD. PPD was more common among younger mothers, mothers who were unemployed, mothers who were divorced or geographically separated from their husbands, and mothers who lacked social support. A higher mental health burden was also observed among mothers with an unplanned pregnancy and those caring for a child with a chronic illness.

Notes

Ethics Approval

This study was approved by the Ethics Committee of the Indonesian Ministry of Health (No: LB.02.01/I/KE/L/287/2023). The requirement for informed consent was waived due to the retrospective nature of this study.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The datasets are available from the Indonesian Ministry of Health upon reasonable request.

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phrp
OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2026.0153
Osong Public Health Res Perspect 2026;17(4):362-370

Original Article

Association between lifestyle inflammation score and quality of life according to depressive symptom status: a cross-sectional study in the Republic of Korea

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ABSTRACT

Objectives: This study examined the association between lifestyle inflammation score (LIS) and health-related quality of life, assessed using the EuroQol-5 Dimensions (EQ-5D) index, among adults in the Republic of Korea. It also evaluated whether depressive symptoms moderated this association.

Methods: Data from the 2024 Community Health Survey were analyzed, and 231,386 adults were included. LIS was calculated by integrating smoking, alcohol consumption, physical activity, and body mass index. The dependent variable, quality of life, was assessed using the EQ-5D index. Depressive symptoms, the moderator variable, were assessed using the Patient Health Questionnaire-9, with a score of ≥10 indicating depressive symptoms. Data were analyzed using complex-sample multivariable linear regression to examine interaction effects according to depressive symptom status, followed by simple-slope analyses.

Results: After adjustment for demographic and health-related variables, LIS was significantly and negatively associated with the EQ-5D index ($\beta = -0.0069$, $p < 0.001$), indicating that higher levels of inflammation-related lifestyle behaviors were associated with poorer quality of life. Depressive symptoms significantly moderated the association between LIS and the EQ-5D index ($\beta = -0.01727$, $p < 0.001$). Simple-slope analyses showed that the adverse association between LIS and quality of life was stronger among individuals with depressive symptoms ($\beta = -0.02349$) than among those without depressive symptoms ($\beta = -0.00621$).

Conclusion: Inflammation-related lifestyle behaviors were associated with reduced quality of life, and this negative association was stronger among individuals with depressive symptoms. These findings suggest that considering both lifestyle-related inflammatory burden and depressive symptoms may help explain population-level differences in quality of life.

Keywords: Depression; Health surveys; Inflammation; Life style; Quality of life

Received: February 10, 2026
Revised: April 28, 2026
Accepted: May 5, 2026

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Introduction

Chronic low-grade inflammation disrupts homeostasis and is closely associated with the development of various chronic diseases, including cardiovascular disease, diabetes, hypertension, and stroke [1,2]. Emerging evidence indicates that chronic inflammatory states are associated not only with poorer overall health but also with reduced quality of life. For example, studies of patients with metabolic syndrome have shown that higher concentrations of high-sensitivity C-reactive protein (CRP) are significantly associated with lower health-related quality of life, as measured using the EuroQol-5 Dimensions (EQ-5D) index [3,4]. These findings suggest that individuals with elevated inflammatory burden tend to perceive their physical and mental health more negatively. However, routine measurement of hematological indicators, such as CRP or interleukins (ILs), which are needed to assess systemic inflammation more directly, is challenging in the general population.

The lifestyle inflammation score (LIS) was developed to address these limitations. This score integrates lifestyle factors associated with systemic inflammation, including smoking, alcohol consumption, physical activity, and body mass index (BMI), using a weighted approach [5]. The LIS provides a comprehensive estimate of the inflammatory potential of an individual's lifestyle behaviors, with higher scores indicating a greater tendency toward pro-inflammatory behaviors [5]. By estimating inflammation-related risk without requiring blood testing, the LIS serves as a practical tool for population-level health assessment [6,7].

Depression is associated with alterations in neuroendocrine and immune function, including hyperactivation of the stress response, elevated cortisol secretion, and autonomic nervous system imbalance. These changes may contribute to elevated inflammatory cytokine levels and enhanced systemic inflammatory responses [8,9]. Individuals with high levels of depressive symptoms tend to have elevated levels of inflammatory markers, such as CRP and IL-6 [10,11]. These physiological changes have also been associated with cardiovascular disease, metabolic abnormalities, chronic pain, and reduced quality of life [8,10].

Quality of life is a multidimensional indicator that encompasses an individual's perceived physical, mental, and social well-being. The EQ-5D assesses quality of life across 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [12]. Previous studies have indicated that individuals with chronic inflammatory diseases or unhealthy lifestyle behaviors tend to have a lower quality of life, with consistent associations reported between inflammatory physiological responses and reduced quality of life [3,13].

HIGHLIGHTS

- The lifestyle inflammation score (LIS) was inversely associated with health-related quality of life, as measured using the EuroQol-5 Dimensions.
- Depressive symptoms were associated with a stronger negative relationship between LIS and health-related quality of life.
- LIS may serve as a practical tool for identifying populations at risk of reduced well-being.

Based on this evidence, this study hypothesized that higher LIS scores would be associated with a lower EQ-5D index. The study also hypothesized that depressive symptoms, measured using the Patient Health Questionnaire-9 (PHQ-9), would moderate this relationship [14]. Specifically, individuals with both higher LIS scores and depressive symptoms were expected to show a stronger negative association between LIS and the EQ-5D index, potentially reflecting overlapping physiological and psychological burdens.

This study used data from the 2024 Korea Community Health Survey (KCHS) to investigate the association between LIS and the EQ-5D index. First, the main association between LIS and the EQ-5D index was assessed to examine the relationship between inflammation-related lifestyle behaviors and quality of life. Second, the association between depressive symptoms, assessed using the PHQ-9, and the EQ-5D index was examined. Third, the interaction between LIS and PHQ-9 was analyzed to determine whether depressive symptoms moderated the association between LIS and quality of life.

Through this stepwise analysis, the study examined whether depressive symptoms were associated with a stronger negative LIS–EQ-5D association and sought to provide evidence that may inform future population health research addressing both mental health and lifestyle behaviors.

Materials and Methods

Data Sources

This study used raw data from the 2024 KCHS, conducted by the Korea Disease Control and Prevention Agency (KDCA). The 2024 KCHS was a cross-sectional survey that used a complex sampling design to represent the adult population of the Republic of Korea across all cities, counties, and districts. Data were collected by trained interviewers using computer-assisted personal interviewing from May 16 to July 31, 2024 [15].

Among 231,728 respondents, 342 individuals with missing data on LIS, stress, diabetes, or hypertension were excluded by listwise deletion, yielding a final analytic sample of 231,386 participants. Survey weights and design variables provided by the KCHS were applied to produce estimates representative of the national adult population.

The study protocol was approved by the relevant institutional review board, which waived the requirement for additional informed consent because only de-identified secondary data were used. All methods adhered to the Declaration of Helsinki and relevant guidelines and regulations.

Variables

Dependent variable

The EQ-5D index was calculated using KDCA-specific quality weights [16]. The instrument assesses 5 domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents who reported "some problems" (level 2) or "severe problems" (level 3) in any domain were assigned the corresponding domain- and level-specific penalty coefficients: M2, M3, SC2, SC3, UA2, UA3, PD2, PD3, AD2, and AD3. If any domain was rated as "severe problems" (level 3), an additional penalty corresponding to the N3 term was applied. The final EQ-5D index was calculated as 1 minus the sum of penalties, with values closer to 1 indicating better overall health-related quality of life [12].

The EQ-5D index was calculated using the following formula:

$$EQ-5D = 1-(0.05+0.096M_2+0.418M_3+0.046C_2+0.136C_3+0.051A_2+0.208A_3+0.037PD_2+0.151PD_3+0.043AD_2+0.158AD_3+0.05N_3)$$

Independent variables

The primary independent variable was the LIS, which integrates 4 lifestyle factors: alcohol consumption, physical activity, smoking, and BMI. The LIS quantifies the overall extent to which an individual's lifestyle behaviors may contribute to systemic inflammatory responses. Each component was scored so that behaviors that induce or exacerbate inflammation received higher scores. The final LIS was calculated by applying weights to these component scores and summing them [5]. Each lifestyle factor was dummy-coded, with "1" assigned to the exposed or high-risk category and "0" assigned to the unexposed or reference category.

Heavy alcohol consumption, defined as more than 8 drinks per week for men and more than 4 drinks per week for women, induces oxidative stress during the metabolism of ethanol to acetaldehyde, thereby triggering inflammatory responses [17]. In contrast, moderate alcohol intake, defined as 8 or fewer drinks per week for men and 4 or fewer drinks per week for women, may reduce pro-inflammatory free fatty acids through acetate, a byproduct of ethanol metabolism. Moderate intake has also been reported to increase adiponectin levels while suppressing IL-6 signaling pathways, thereby exerting anti-inflammatory effects [18].

Physical activity, assessed using International Physical Activity Questionnaire criteria [19], enhances antioxidant defense, increases anti-inflammatory cytokine levels, and reduces vascular inflammation [20]. Because the weekly frequency of physical activity could not be directly derived for the LIS calculation, metabolic equivalents per week were categorized into quantiles to construct dummy variables and apply the corresponding weights. This approach was used as a proxy for relative activity level because the original LIS definition based on weekly frequency could not be directly derived from the KCHS variables.

Current smokers, including users of cigarettes, heated tobacco products, and e-cigarettes, are exposed to toxins that damage tissues and upregulate cytokines and acute-phase reactants. These processes contribute directly to increased systemic inflammatory responses [21].

Obesity status, defined according to Korean criteria as overweight (BMI, 23–24.9 kg/m^2) or obesity (BMI ≥25 kg/m^2), promotes adipose tissue production of pro-inflammatory adipokines, such as plasminogen activator inhibitor-1 and tumor necrosis factor-α. Adipokine production is a key driver of chronic low-grade inflammation [22].

The LIS component criteria were partially converted and classified according to Korean standards. One standard drink contains 14 g of alcohol, corresponding to 350 mL of draft beer, 300 mL (1 bowl) of rice wine, 150 mL of wine, 94 mL (1/4 bottle) of 19% soju, or 45 mL (1 shot) of whisky [23]. Because this study targeted adults in the Republic of Korea, Korean BMI criteria were applied.

The LIS was calculated as follows:

$$\mathrm{LIS} = \left(\beta_{\mathrm{Drinker}} \times \mathrm{W}_{\substack{\mathrm{Heavy}(0.30)\\ \mathrm{Moderate}(-0.66)}}\right) + \left(\beta_{\mathrm{Physical\ activity}} \times \mathrm{W}_{\substack{\mathrm{Heavy}(-0.41)\\ \mathrm{Moderate}(-0.18)}}\right) + \left(\beta_{\mathrm{Smoker}} \times \mathrm{W}_{0.50}\right) + \left(\beta_{\mathrm{BMI}} \times \mathrm{W}_{\substack{\mathrm{Overweight}(0.89)\\ \mathrm{Obese}(1.57)}}\right)$$

Moderator variables

Depressive symptoms were measured using the PHQ-9 items included in the KCHS. The PHQ-9 assesses depression-related symptoms experienced during the previous 2 weeks. It comprises 9 items: loss of interest or pleasure, depressed mood, sleep problems, fatigue, appetite changes, feelings of worthlessness or guilt, difficulty concentrating, psychomotor

https://doi.org/10.24171/j.phrp.2026.0153

agitation or retardation, and suicidal thoughts. Although the EQ-5D includes a single anxiety/depression domain, the PHQ-9 was included as a moderator to capture depressive symptom severity across multiple domains. Each item is rated on a 4-point scale ranging from "not at all true" (1 point) to "nearly every day" (4 points). In this study, 1 point was subtracted from each original item score to convert the scale to 0–3, and the 9 item scores were summed to calculate the total PHQ-9 score. Total scores therefore ranged from 0 to 27 points, with higher scores indicating more severe depressive symptoms [24].

Depressive symptom status was classified according to criteria established in prior studies: a total PHQ-9 score of ≥10 indicated depressive symptoms, whereas scores of 0–9 indicated no depressive symptoms. The PHQ-9 cutoff of ≥10 has been validated in Korean adults and has demonstrated acceptable sensitivity and specificity for identifying depression [25].

Control variables

Control variables included demographic, economic, and health-related factors. Demographic factors comprised sex and age, with age categorized into 4 KCHS-defined groups: 19–44, 45–64, 65–74, and ≥75 years. Economic factors included monthly household income, which was categorized into <1 million Korean won (KRW), 1–2.99 million KRW, and ≥3 million KRW.

Health-related factors comprised chronic diseases (diabetes and hypertension), mental health factors (perceived stress), sleep health factors (Pittsburgh sleep quality index [PSQI]), and healthcare accessibility (unmet medical needs). Stress was classified as present if respondents answered "I feel a lot of stress" or "I feel a great deal of stress" to the question, "How much stress do you generally feel in your daily life?" Sleep quality was assessed using the PSQI. The total PSQI score ranged from 0 to 21, with higher scores indicating poorer sleep quality. For analysis, total PSQI scores were categorized as "good" (0–5 points) or "poor" (≥6 points) [26]. A PSQI cutoff of >5 has been validated in Korean adults and has demonstrated acceptable sensitivity and specificity for identifying poor sleepers [27].

Statistical Analysis

The KCHS data were collected using a complex sampling design. Therefore, all analyses incorporated the KCHS survey design variables, including primary sampling units, sampling weights, and strata, to ensure national representativeness. Descriptive statistics for the general characteristics of the study participants were calculated using frequency analyses. To examine the association between LIS and the EQ-5D index, complex-sample multivariable linear regression analysis was performed, with depressive symptoms (assessed using the PHQ-9) included as a moderator to evaluate interaction effects. In addition, simple-slope marginal analyses were conducted according to depressive symptom status to compare the magnitude of the association between LIS and the EQ-5D index between groups. Binary variables were entered as dummy variables, whereas ordinal variables (e.g., age group and monthly household income) were treated as ordinal variables. Continuous variables were analyzed as continuous variables. Statistical analyses were performed using Stata/MP 18 software (StataCorp.), with the significance level set at 5% for 2-tailed tests.

Ethics Approval

The 2024 Korea Community Health Survey was conducted by the KDCA. The present study protocol was approved by the Yonsei University Mirae Institutional Review Board (IRB No: 1041849-202510-SB-225-01), which waived the requirement for additional informed consent because only de-identified secondary data were used. All methods followed the Declaration of Helsinki and relevant guidelines and regulations.

Results

General Characteristics of Participants

A total of 231,386 respondents were included in the analysis. The mean LIS was 0.35, and the mean EQ-5D index was 0.95 (Table 1). According to the PHQ-9 criterion, 4.1% of participants were classified as having depressive symptoms. The distribution by sex was nearly equal, and the 45- to 64-year age group accounted for the largest proportion of participants. Participants with a monthly household income of ≥3 million KRW accounted for 71.0% of the sample. The prevalence of unmet medical needs was 4.6%, and the prevalence of perceived stress was 22.3%. The prevalence rates of hypertension and diabetes were 24.4% and 10.7%, respectively.

Association Between LIS and the EQ-5D Index

LIS was significantly and negatively associated with the EQ-5D index ($\beta = -0.0069$, $p < 0.001$); that is, higher LIS scores were associated with a lower EQ-5D index (Table 2). Depressive symptoms were also significantly and negatively associated with the EQ-5D index ($\beta = -0.1273$, $p < 0.001$), indicating that participants with depressive symptoms had lower EQ-5D index scores than those without depressive symptoms.

Among demographic and health-related factors, the EQ-5D index was significantly lower among female participants, older adults, participants with unmet medical needs, those with perceived stress or poor sleep quality, and those with hypertension or diabetes. Monthly household income was positively associated with the EQ-5D index.

Table 1. General characteristics of participants (n = 231,386)

Characteristic	Category	Value
LIS		0.35 ± 0.003
EQ-5D		0.95 ± 0.0003
PHQ-9	No	221,634 (95.9)
	Yes	9,752 (4.1)
Sex	Male	106,005 (49.5)
	Female	125,381 (50.5)
Age (y)	19–44	61,228 (39.0)
	45–64	86,603 (37.7)
	65–74	45,619 (13.6)
	≥ 75	37,936 (9.7)
Monthly household income	< 1 million KRW	29,240 (7.7)
	1–2.99 million KRW	63,700 (21.3)
	≥ 3 million KRW	138,446 (71.0)
Unmet medical needs	No	220,581 (95.4)
	Yes	10,805 (4.6)
Stress	No	184,488 (77.7)
	Yes	46,898 (22.3)
PSQI	Good	166,618 (73.0)
	Poor	64,768 (27.0)
Hypertension	No	157,073 (75.6)
	Yes	74,313 (24.4)
Diabetes	No	198,697 (89.3)
	Yes	32,689 (10.7)

Data are presented as mean ± standard error or number (weighted %). All analyses incorporated complex survey weights and stratification using the 2024 Korea Community Health Survey design.
LIS, lifestyle inflammation score; EQ-5D, EuroQol-5 Dimensions; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh sleep quality index; KRW, Korean won.

Multivariable Linear Regression of Factors Associated with the EQ-5D Index

In the multivariable linear regression model that included the interaction term, LIS remained significantly and negatively associated with the EQ-5D index (β = −0.00621, p < 0.001) (Table 3). Depressive symptoms, defined as a PHQ-9 score ≥ 10, were also significantly and negatively associated with the EQ-5D index (β = −0.11834, p < 0.001). The LIS×PHQ-9 interaction term was statistically significant (β = −0.01727, p < 0.001), indicating that the association between LIS and the EQ-5D index was stronger among participants with depressive symptoms. When PHQ-9 was treated as a continuous variable, the interaction between LIS and PHQ-9 remained statistically significant and was consistent in direction, supporting the robustness of the moderation effect (Table S1).

Among demographic and health-related factors, the EQ-5D index was significantly lower among female participants, older adults, participants with unmet medical needs, those with perceived stress or poor sleep quality, and those with hypertension or diabetes. Monthly household income showed a significant positive association with the EQ-5D index.

Comparison of LIS–EQ-5D Association Slopes by Depressive Symptom Status

Simple-slope analysis indicated that the estimated slope for the association between LIS and the EQ-5D index was −0.02349 (p < 0.001) among participants with depressive

Table 2. Associations between LIS and the EQ-5D index

Variable	B	SE	p	95% CI
LIS	−0.0069	0.00026	< 0.001	−0.00741 to −0.00639
PHQ-9 (yes)	−0.1273	0.00247	< 0.001	−0.13217 to −0.12249
Sex	−0.0170	0.00047	< 0.001	−0.01800 to −0.01615
Age	−0.0289	0.00036	< 0.001	−0.02960 to −0.02820
Monthly household income	0.0229	0.00049	< 0.001	0.02196 to 0.02389
Unmet medical needs	−0.0338	0.00151	< 0.001	−0.0368 to −0.03084
Stress	−0.0244	0.00064	< 0.001	−0.0257 to −0.02319
PSQI	−0.0321	0.00059	< 0.001	−0.03331 to −0.03099
Hypertension	−0.0071	0.00067	< 0.001	−0.00847 to −0.00581
Diabetes	−0.0121	0.00098	< 0.001	−0.0140 to −0.01017

Reference categories for binary variables were as follows: PHQ-9 (No), Sex (Male), Unmet medical needs (No), Stress (No), PSQI (Good), Hypertension (No), and Diabetes (No). Age and Monthly household income were modeled as ordinal variables.
LIS, lifestyle inflammation score; EQ-5D, EuroQol-5 Dimensions; SE, standard error; CI, confidence interval; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh sleep quality index.

https://doi.org/10.24171/j.phrp.2026.0153

symptoms and −0.00621 ($p < 0.001$) among participants without depressive symptoms (Table 4). Thus, the negative association between LIS and the EQ-5D index was stronger among participants with depressive symptoms than among those without depressive symptoms, as illustrated in Figure 1.

Discussion

This large community-based study found that LIS was significantly associated with a lower EQ-5D index and that this association differed according to depressive symptom status. The LIS, which integrates smoking, alcohol consumption, physical activity, and BMI, showed a consistent negative association with the EQ-5D index. This finding is consistent with previous evidence indicating that chronic inflammation adversely affects perceived physical and mental health and daily functioning [3,4], as well as recent population-based evidence showing that adverse lifestyle factors, such as poor sleep health, are associated with higher LIS levels [28]. Notably, depressive symptoms emerged as a key factor moderating the relationship between LIS and the EQ-5D index [8,29,30]. Among participants without depressive symptoms, the decrease in the EQ-5D index associated with higher LIS was relatively small, whereas among participants with depressive symptoms, this decrease was more pronounced. These results suggest that depressive symptoms are associated with a stronger relationship between inflammation-related lifestyle factors and health-related quality of life.

The moderating effect of depressive symptoms may be explained by both physiological and behavioral mechanisms. Although the EQ-5D includes an anxiety/depression dimension, this dimension is assessed using a single item within an overall quality-of-life measure, whereas the PHQ-9 provides a more comprehensive assessment of depressive symptom severity across multiple domains. Therefore, using the PHQ-9 as a moderator allowed a more detailed evaluation of how depressive symptom burden influenced the association between LIS and quality of life. Depression has been associated with hyperactivation of the hypothalamic–pituitary–adrenal axis, increased cortisol secretion, and disruption of autonomic nervous system balance, which may collectively promote systemic inflammatory responses [31]. This physiological stress response is associated with elevated levels of inflammatory cytokines, such as CRP and IL-6, potentially increasing overall inflammatory burden [32,33]. The potential interplay between depressive symptom–related physiological changes and health behaviors may help explain why the negative association between inflammation-related lifestyle behaviors and quality of life was more pronounced among individuals with depressive symptoms, consistent

Table 3. Multivariable linear regression of factors associated with the EQ-5D index

Variable	B	SE	*p*	95% CI
LIS	−0.00621	0.00025	<0.001	−0.00669 to −0.00573
PHQ-9 (yes)	−0.11834	0.00261	<0.001	−0.12347 to −0.11323
LIS × PHQ-9 (yes)	−0.01727	0.00248	<0.001	−0.02214 to −0.01240
Sex	−0.01693	0.00047	<0.001	−0.01786 to −0.01601
Age	−0.02895	0.00036	<0.001	−0.02965 to −0.02825
Monthly household income	0.02287	0.00049	<0.001	0.02190 to 0.02383
Unmet medical needs	−0.0338	0.00151	<0.001	−0.03678 to −0.03087
Stress	−0.02446	0.00064	<0.001	−0.02571 to −0.02320
PSQI	−0.03219	0.00059	<0.001	−0.03335 to −0.03103
Hypertension	−0.00712	0.00067	<0.001	−0.00843 to −0.00579
Diabetes	−0.01192	0.00098	<0.001	−0.01384 to −0.01001

EQ-5D, EuroQol-5 Dimensions; SE, standard error; CI, confidence interval; LIS, lifestyle inflammation score; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh sleep quality index.
Reference categories for binary variables were as follows: PHQ-9 (No), Sex (Male), Unmet medical needs (No), Stress (No), PSQI (Good), Hypertension (No), and Diabetes (No). Age and Monthly household income were modeled as ordinal variables.

Table 4. Comparison of LIS–EQ-5D association slopes by depressive symptom status

Category	Slope for LIS (β)	SE	*p*	95% CI
PHQ-9 (yes)	−0.02349	0.00248	<0.001	−0.02834 to −0.01863
PHQ-9 (no)	−0.00621	0.00025	<0.001	−0.00669 to −0.00573

LIS, lifestyle inflammation score; EQ-5D, EuroQol-5 Dimensions; SE, standard error; CI, confidence interval; PHQ-9, Patient Health Questionnaire-9.

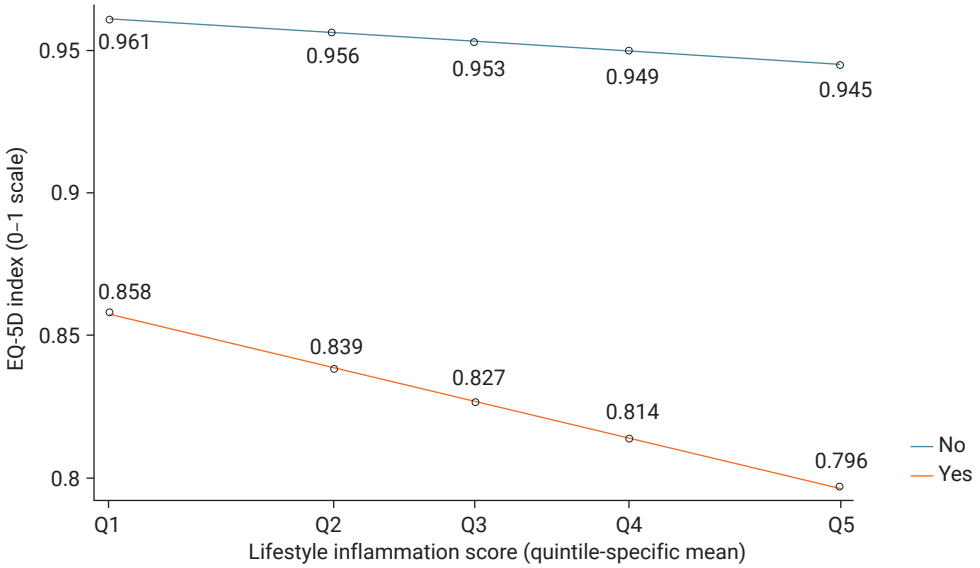


Figure 1. Predicted EuroQol-5 Dimensions (EQ-5D) index according to lifestyle inflammation score and depressive symptom status.

with the statistically significant interaction between LIS and depressive symptom status, defined using the PHQ-9 cutoff, observed in this study.

These findings may have implications for public health and clinical practice. First, the LIS serves as an integrated indicator of the cumulative relationship between health behaviors and quality of life, suggesting its potential utility for identifying high-risk groups and informing lifestyle-based approaches. Second, depressive symptoms are associated with quality of life; in particular, individuals with both a higher LIS and depressive symptoms may experience a greater reduction in quality of life, suggesting that mental health assessment may be relevant when evaluating lifestyle-related inflammatory burden. Although this cross-sectional study did not evaluate interventions, the findings suggest that future studies should examine whether mental health management strategies influence the relationship between lifestyle-related inflammatory burden and quality of life [34,35]. Thus, considering mental health and lifestyle factors together may help explain population-level differences in quality of life.

Moreover, LIS remained significantly associated with the EQ-5D index after adjustment for mental health factors, including perceived stress, and chronic diseases, including hypertension and diabetes. This finding suggests that the association between LIS and quality of life was not fully explained by the variables included in the model.

This study has several strengths. First, it used a nationally representative sample and a complex sampling design, enhancing the generalizability of the results. Second, quality of life and depressive symptoms were measured using validated instruments with established reliability, including the EQ-5D and PHQ-9. Third, key potential confounders, including mental health factors, chronic diseases, and socioeconomic factors, were included in the models, strengthening the robustness of the observed associations with LIS.

However, this study also has several limitations. The mean EQ-5D index was relatively high, at approximately 0.95, suggesting a potential ceiling effect that may partly explain the small magnitude of the observed associations. The magnitude of the LIS coefficient was small on the EQ-5D scale and should therefore be interpreted cautiously, particularly at the individual clinical level. Nevertheless, given the large nationally representative sample and the stronger negative LIS–EQ-5D association among participants with depressive symptoms, these modest differences may still be relevant from a population health perspective.

The potential ceiling effect may have influenced the estimation of associations using linear regression. The cross-sectional design precludes causal inference, and reverse causality cannot be ruled out because individuals with a lower quality of life may be less motivated to maintain healthy behaviors, resulting in higher LIS scores. Future research should use longitudinal designs to clarify temporal sequences and causal pathways. In addition, the LIS weights were estimated based on previous findings and may not fully reflect population-specific inflammatory risks; therefore, their applicability to the Korean population should be validated in future research. Some LIS components were adapted to fit the KCHS data structure, which may limit comparability with the original LIS. Furthermore, because the LIS is based

https://doi.org/10.24171/j.phrp.2026.0153

on self-reported health behavior data, underreporting of certain health-risk behaviors, such as smoking and alcohol consumption, is possible. Similarly, because the PHQ-9 is a self-report measure, future studies incorporating objective mental health assessments or biomarkers are warranted. Residual confounding may remain because information on other chronic conditions, detailed dietary factors, and broader psychosocial variables was not available in the KCHS. If these unmeasured factors are associated with both LIS and the EQ-5D index, the observed associations may have been overestimated or underestimated.

In addition, the modified LIS used in this study should be interpreted as a proxy measure of lifestyle-related inflammatory burden rather than as a direct biomarker-based measure of systemic inflammation. The construct validity of the modified LIS is conceptually supported by the inclusion of lifestyle components that represent distinct inflammation-related pathways, including smoking, alcohol consumption, physical activity, and BMI. The direction of the assigned weights was also consistent with prior biological evidence, with smoking and obesity contributing positive pro-inflammatory weights and physical activity contributing negative anti-inflammatory weights. Contextual relevance was further improved by using Korean-specific BMI cutoffs and standard drink definitions. Nevertheless, because inflammatory biomarkers such as CRP or IL-6 were not available in the KCHS, direct internal validation was not possible. Future studies should validate this modified LIS in populations in the Republic of Korea using biomarker-based data.

In conclusion, higher LIS scores were associated with lower quality of life, and this association was moderated by depressive symptoms. Addressing both lifestyle behaviors and mental health may be important, given their associations with overall well-being.

Supplementary Material

Table S1. Comparison of LIS–PHQ-9 interaction models using continuous and categorical PHQ-9 variables. LIS, lifestyle inflammation score; PHQ-9, Patient Health Questionnaire-9. Supplementary data are available at https://doi.org/10.24171/j.phrp.2026.0153.

Notes

Ethics Approval

The 2024 Korea Community Health Survey was conducted by the KDCA. The present study protocol was approved by the Yonsei University Mirae Institutional Review Board (IRB No: 1041849-202510-SB-225-01), which waived the requirement for additional informed consent because only de-identified secondary data were used. All methods followed the Declaration of Helsinki and relevant guidelines and regulations.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

The raw data from the 2024 Korea Community Health Survey are not publicly available due to participant privacy regulations but can be requested from the KDCA.

Authors' Contributions

Conceptualization: JC, YJW; Data curation: JC; Formal analysis: JC; Methodology: JC, EK; Investigation: JC; Project administration: YJW; Supervision: YJW; Writing–original draft: JC; writing–review & editing: all authors. All authors read and approved the final manuscript.

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https://doi.org/10.24171/j.phrp.2026.0153

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

pISSN 2210-9099 eISSN 2233-6052
https://doi.org/10.24171/j.phrp.2025.0594
Osong Public Health Res Perspect 2026;17(4):371-372

Commentary

Early circulation of influenza A(H3N2) subclade K: antigenic drift and vaccine effectiveness

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The 2025–2026 influenza season in the Northern Hemisphere started earlier than in recent seasons, with a marked increase in influenza A activity. A recent study from England by Kirsebom et al. [1] reported that influenza A(H3N2) subclade K (formerly J.2.4.1) dominated early-season circulation and was accompanied by increased hospitalizations and high test positivity rates, particularly among school-aged children [2]. Similar trends have been observed across the European Union (EU)/European Economic Area and Canada, where subclade K has contributed to rising influenza activity in recent weeks [3,4]. In the Western Pacific Region, subclade K accounts for 89% of reported H3N2 sequences [5].

Early antigenic evaluations indicate that circulating subclade K viruses show reduced reactivity to the Northern Hemisphere 2025–2026 vaccine reference strain. These findings are consistent with World Health Organization reports of ongoing antigenic drift among contemporary A(H3N2) viruses [1,6]. Nonetheless, vaccine effectiveness (VE) against medically attended influenza and hospitalization remained within expected ranges in England (children/adolescents, 72%–75%; adults, 32%–39%) during the early postvaccination period. Complementary data from the European Centre for Disease Prevention and Control's Vaccine Effectiveness, Burden and Impact Studies program showed an overall VE of 52% against outpatient H3N2 infection across nine EU countries [3]. Canadian data also reported a VE of 40% against medically attended A(H3N2) illness, with subclade K-specific VE estimated at 37% during November 2025–January 2026 [4,7]. This contrast underscores the importance of interpreting laboratory evidence of antigenic drift in the context of real-world VE. Although hemagglutination inhibition assays using ferret antisera are central to strain selection, they may not fully predict population-level clinical protection, particularly in atypical seasons [8].

Several limitations should be considered. First, these early VE estimates do not capture possible waning of effectiveness later in the season [1,3]. Second, the wide confidence intervals for A(H3N2)-specific VE in adults likely reflect limited viral subtyping in older age groups. In addition, antigenic characterization based on a relatively small subset of viruses may not capture the full diversity of circulating strains. Geographic representativeness is also limited by reliance on secondary care samples with batch referrals and variable site adherence [1].

Overall, early VE findings provide reassuring evidence of vaccine protection against severe influenza outcomes despite laboratory evidence of reduced reactivity in emerging A(H3N2) variants. These findings highlight the importance of ongoing genomic surveillance and

Received: December 22, 2025
Revised: April 4, 2026
Accepted: April 13, 2026

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The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the Korea Disease Control and Prevention Agency and Korea National Institute of Health.

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continued VE monitoring throughout the season during atypical influenza activity. Given the rapid circulation of this variant, coordinated international surveillance and response measures are particularly important. In addition, reinforced vaccination campaigns for high-risk populations and improved public communication strategies are essential to maintaining confidence in influenza vaccination. For healthcare systems, surge-capacity planning, including pediatric bed expansion and provision of post-exposure antiviral prophylaxis to frontline staff within 48 hours of exposure, are key measures for protecting healthcare workers [5]. At the community level, healthcare systems should strengthen communication with long-term care facilities and schools regarding early symptom recognition and isolation protocols, while maintaining adequate stockpiles of personal protective equipment and antiviral medications for sustained response periods.

HIGHLIGHTS

- The 2025–2026 influenza season began unusually early in the Northern Hemisphere, with dominance of influenza A(H3N2) subclade K.
- Early antigenic analyses show reduced reactivity between subclade K viruses and the 2025–2026 vaccine reference strain.
- Despite antigenic drift, vaccine effectiveness remains reassuring across multiple studies, and vaccination remains the most effective tool for protection.

Notes

Ethics Approval
Not applicable.

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

Funding
None.

Availability of Data
Not applicable.

Authors' Contributions
Conceptualization: MN, SFKJ; Writing–original draft: MN, SFKJ; Writing–review & editing: GG. All authors read and approved the final manuscript.

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https://doi.org/10.24171/j.phrp.2025.0594

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

Instruction for authors

Enacted: January 1, 2010
Last revision: June 1, 2024
Partial revision: October 21, 2025

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.

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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/)

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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.

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- 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.
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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.

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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).

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3 tables and figures combined is allowed. Authorship is generally limited to 1–2, and these articles are often commissioned by the Editorial Board.

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
Perspective	Not required	2,000	20	3

*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.
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- **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.

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  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.
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  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.
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