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PHRP publishes original articles, review articles, guidelines, data profiles (including cohort profiles), special articles, short communications, viewpoints, editorials, commentaries, and correspondence, and book reviews, with a focus on the following areas of expertise: emerging infectious diseases, vaccinology, zoonotic diseases, non-communicable diseases, intractable and rare diseases, and human genomics.

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Editorial

Public health, research, and procedural justice

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With the launch of a new administration in June 2025, the Republic of Korea's health governance once again enters a period of reflection. "Fairness" has been identified as the first virtue of social justice in the new government's policy vision [1], and this emphasis has reignited long-standing debates, not only about policy conflicts between the medical profession and the government but also about the fundamental values and operational principles of the health system itself. Discussions regarding physician workforce distribution, reimbursement mechanisms, regional disparities, and the efficiency of the healthcare delivery system all highlight enduring structural challenges—specifically, how to balance professional autonomy, citizens' rights, and the state's stewardship.

Many Korean physicians recognize that medical professionalism is, by nature, a public good. Yet they also share a growing sense of exclusion from key decision-making processes in health policy. This accumulated sense of exclusion has contributed to a widening perception that government-led health reforms lack transparency and fairness. At this critical juncture, any reform agenda must therefore begin with a commitment to procedural justice—that is, ensuring fairness, transparency, inclusiveness, and the possibility of revision in both policymaking and implementation.

In particular, because stakeholders' perspectives have historically been excluded from decisions on health insurance budget allocation and national research funding, many professionals remain skeptical of reforms driven solely from the top down. Following the principles advanced by Norman Daniels, who extended John Rawls's theory of justice, accountability for reasonableness defines procedural justice not as equality of outcomes, but as a system of open deliberation and fair process through which diverse stakeholders can reach legitimate agreement [2]. In public health, this entails setting national goals collaboratively between citizens and experts. In research, it means treating data and evidence not as instruments of control but as shared public goods. As an open-access journal, Osong Public Health and Research Perspectives embodies precisely these values.

This issue revisits the meaning of research and policy from that perspective. The studies presented here underscore the importance of evidence-based policy and equity-centered protection for vulnerable populations. The Korean time-series analysis of scrub typhus and climate variability highlights the limitations of relying solely on mean temperature and humidity as indicators and calls for more dynamic and adaptive surveillance models. Meanwhile, the community-based infectious disease surveillance study from Malaysia

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exemplifies procedural fairness at the local level, showing how early-warning systems for high-risk regions and populations can empower communities and strengthen trust in public health systems. The study on tuberculosis (TB) adherence in Morocco reminds us that while directly observed treatment, short-course remains a cornerstone of TB control, adherence challenges persist. Its findings suggest that digital tools and telehealth interventions can provide practical solutions for patient-centered follow-up.

The comparative analysis of coronavirus disease 2019 (COVID-19) vaccine innovation in Brazil, Cuba, India, and Iran demonstrates that scientific capacity alone does not guarantee vaccine sovereignty. Instead, institutional coherence, public R&D, and effective policy coordination form the true foundations of self-reliance. The study highlights that low- and middle-income countries must strengthen pandemic preparedness through South–South collaboration and regional manufacturing networks, supported by sustained public investment, adaptive regulation, and strategic intellectual property rights to ensure both sovereignty and equitable access. The accompanying Korean COVID-19 Vaccine Injury Compensation Program experiment offers an important complement to this global discussion. It provides empirical evidence that when a compensation program is communicated as a symbol of fairness and solidarity, public trust and vaccine acceptance both increase. This finding provides a direct, evidence-based rationale for designing public health communication strategies that emphasize shared social values rather than administrative procedures.

In the field of chronic disease, the Turkish study on diabetes medication self-efficacy demonstrates that empowering individuals in self-management improves both health outcomes and system efficiency. Among older adults, higher self-efficacy is strongly associated with better quality of life, underscoring the need for education and psychosocial support systems that reinforce autonomy and adherence. Similarly, the Korean national study on digital literacy among older adults identifies digital competence as a new determinant of health equity and life satisfaction. Digital inclusion must therefore be regarded not merely as a technical issue but as a social responsibility linked to the right of access to information and health. The findings highlight the need for tailored interventions, particularly for vulnerable groups such as the less educated, low-income, and socially isolated older adults.

The Vietnamese longitudinal cohort study linking intimate partner violence during pregnancy with postpartum depression and child development demonstrates that gender-based violence lies at the intersection of public health and social justice. By establishing this connection in a low- and middle-income country context, the study expands the global evidence base and reinforces the principle that preventing and addressing such violence is not only a matter of women's health but also an essential intergenerational equity strategy—protecting maternal and child mental health across generations.

Collectively, the articles in this issue emphasize public health systems, governance transitions, and implementation science. While this composition reflects the growing maturity of policy-relevant research, it also reveals a relative lack of contributions from basic or mechanistic science, which remains a point of regret. In the long term, sustainable innovation in public health will require stronger integration between basic science and applied research, ensuring that discovery and implementation inform each other in a continuous cycle.

Notes

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Not applicable.

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

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Review Article

Bridging innovation and policy: comparative pathways of national vaccine development in low- and middle-income countries

Vahid Marandi

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ABSTRACT

Objectives: To examine how national innovation and policy configurations enabled vaccine development in Brazil, Cuba, India, and Iran, and to distil lessons for low- and middle-income country (LMIC) vaccine sovereignty.
Methods: Narrative review of peer-reviewed and grey literature (2020–2023), guided by a structured search and screening approach; synthesis mapped to national and sectoral innovation system perspectives and technology readiness levels.
Results: Cuba and Iran leveraged mission-oriented public research and development (R&D) and domestic platforms; India combined indigenous R&D with large-scale licensed manufacturing; Brazil's scientific capacity was constrained by fragmented governance and supply-chain dependence. Adaptive regulation (e.g., emergency use authorization/conditional approvals), targeted technology transfer, and South–South partnerships accelerated progress but raised longer-term questions about intellectual property (IP) control and economic sustainability.
Conclusion: Institutional coherence, strategic IP management, and regional manufacturing alliances are as critical as scientific capacity for LMIC vaccine self-reliance. Policy priorities include pre-negotiated tech-transfer frameworks, regulatory preparedness, and investment in public R&D linked to distributed manufacturing.

Keywords: Developing countries; Technology transfer; Vaccines

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic exposed severe inequities in global vaccine access, particularly for low- and middle-income countries (LMICs), which received vaccines later and in smaller quantities compared to high-income countries [1,2]. This disparity reflected structural weaknesses in global health governance and demonstrated how innovation capacities remain unevenly distributed across health systems [3]. Despite being

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largely excluded from early vaccine technology transfer, a subset of LMICs—including Brazil, Cuba, India, and Iran—displayed varying levels of self-reliance through state-led or hybrid vaccine development strategies. These cases illustrate how LMICs can overcome institutional, regulatory, and manufacturing constraints to advance public health innovation in emergencies. Although global initiatives such as the COVID-19 Technology Access Pool (C-TAP), COVID-19 Vaccines Global Access (COVAX), and the mRNA Technology Transfer Hub in South Africa sought to promote equitable access, national strategies often complemented or substituted for these multilateral efforts, especially when geopolitical or market barriers limited entry to proprietary platforms.

This paper investigates the technology management and commercialization challenges faced during COVID-19 vaccine development in Brazil, Cuba, India, and Iran. Drawing on these experiences, it identifies policy lessons for future pandemic preparedness, with a focus on strengthening vaccine innovation ecosystems, navigating intellectual property (IP) regimes, and developing sustainable research and development (R&D) capacity. The comparative analysis is framed around both country-specific dynamics and broader implications for South–South collaboration and multilateral reform. To guide this inquiry, the following research questions are posed: (1) How did Brazil, Cuba, India, and Iran mobilize distinct national innovation strategies to develop COVID-19 vaccines?; (2) What institutional, regulatory, and technological mechanisms were employed to overcome geopolitical and structural barriers?; (3) What policy insights from these national experiences can support vaccine sovereignty in LMICs during future global health crises?

Materials and Methods

This review utilized a qualitative, narrative-based design tailored to explore national policy environments, innovation systems, and commercialization strategies for vaccine development in 4 LMICs. Although the study draws on a broad range of peer-reviewed and gray literature, a systematic review methodology was not applied. This decision reflects both the heterogeneity of source types (e.g., policy documents, regulatory data, and institutional reports) and the conceptual emphasis on institutional arrangements and policy frameworks rather than clinical or epidemiological outcomes. A systematic review was not feasible due to the diversity of document types and the policy-focused scope of inquiry. Instead, a structured, replicable 4-step framework was implemented to ensure methodological rigor and transparency.

HIGHLIGHTS

- This review examined how Brazil, Cuba, India, and Iran developed coronavirus disease 2019 vaccines through national innovation systems under resource constraints.
- The study mapped policy instruments, regulatory frameworks, and commercialization pathways using a structured narrative approach.
- A comparative analysis identified critical enablers, including institutional maturity, flexible regulation, and geopolitical resilience.
- Findings inform actionable policy recommendations for low- and middle-income countries, such as strengthening South–South collaboration and establishing regional vaccine hubs.
- Lessons from this study support global pandemic preparedness and technology transfer mechanisms aimed at ensuring equitable vaccine access in low-resource settings.

Literature Selection

A comprehensive search of academic databases—including PubMed, Scopus, and Web of Science—was conducted to identify scholarly publications on vaccine innovation, technology management, and commercialization in LMICs. Special emphasis was placed on Brazil, Cuba, India, and Iran, given their documented efforts to develop and manufacture COVID-19 vaccines domestically. Parallel searches of gray literature were performed, focusing on reports issued by ministries of health, regulatory authorities, multilateral agencies, and national pharmaceutical institutions. These materials offered contextual and institutional insights not captured in academic sources [4–9].

A structured narrative approach was used, combining targeted searches in PubMed, Scopus, Google Scholar, and World Health Organization (WHO) repositories with official country sources published between 2020 and 2023. While systematic reviews offer broader generalizability, such an approach was unsuitable due to documentation heterogeneity, incomplete peer-reviewed coverage, and the highly context-specific nature of innovation pathways. Instead, a curated narrative synthesis was better aligned with the objective of identifying policy and implementation differences across cases.

In total, 123 peer-reviewed records were initially identified, along with 23 additional sources from institutional and

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governmental repositories. After removing duplicates and screening abstracts, 63 records underwent full-text review, of which 48 met the eligibility criteria for detailed synthesis. An overview of the selection process is presented in Figure S1.

To minimize selection bias in the gray literature, only documents issued by official institutions (e.g., ministries of health, regulatory agencies, or WHO-affiliated bodies) were included, and these were triangulated against academic sources or public datasets when feasible. The inclusion of diverse literature types was intended to capture under-documented institutional mechanisms while maintaining credibility.

Framework Design

A conceptual framework was constructed to structure the comparative analysis, drawing on established models that examine the relationship between innovation systems, technology progression, and institutional mechanisms.

The national innovation system (NIS) theory, which evaluates how formal institutions, public agencies, and policy networks interact to generate and diffuse innovation across national boundaries [10,11].

The sectoral innovation system (SIS) perspective, which emphasizes the specific actors, technologies, and institutional arrangements within the vaccine sector, offering a sector-focused lens for cross-country comparison.

The technology readiness level (TRL) model, which provides a structured means of mapping the progression of technologies from basic research through clinical development to large-scale deployment [12–14]. In the context of vaccine development, TRL stages can be summarized as follows: (1) TRL 1–3: Fundamental research—antigen discovery, mechanism studies; (2) TRL 4–5: Preclinical studies and early translational steps, such as formulation and initial human safety testing (e.g., phase I trials); (3) TRL 6–7: Expansion into phase II and early phase III trials, refining good manufacturing practices (GMP) processes and immunogenicity profiling; (4) TRL 7–8: Regulatory interaction, dossier submission, and conditional approvals; (5) TRL 8–9: Large-scale manufacturing, full licensure, and deployment.

Together, these perspectives support a comparative analysis across technical, institutional, and regulatory dimensions, with particular emphasis on how sectoral structures shape national innovation performance. Figure 1 illustrates this integration by aligning vaccine development stages with TRL

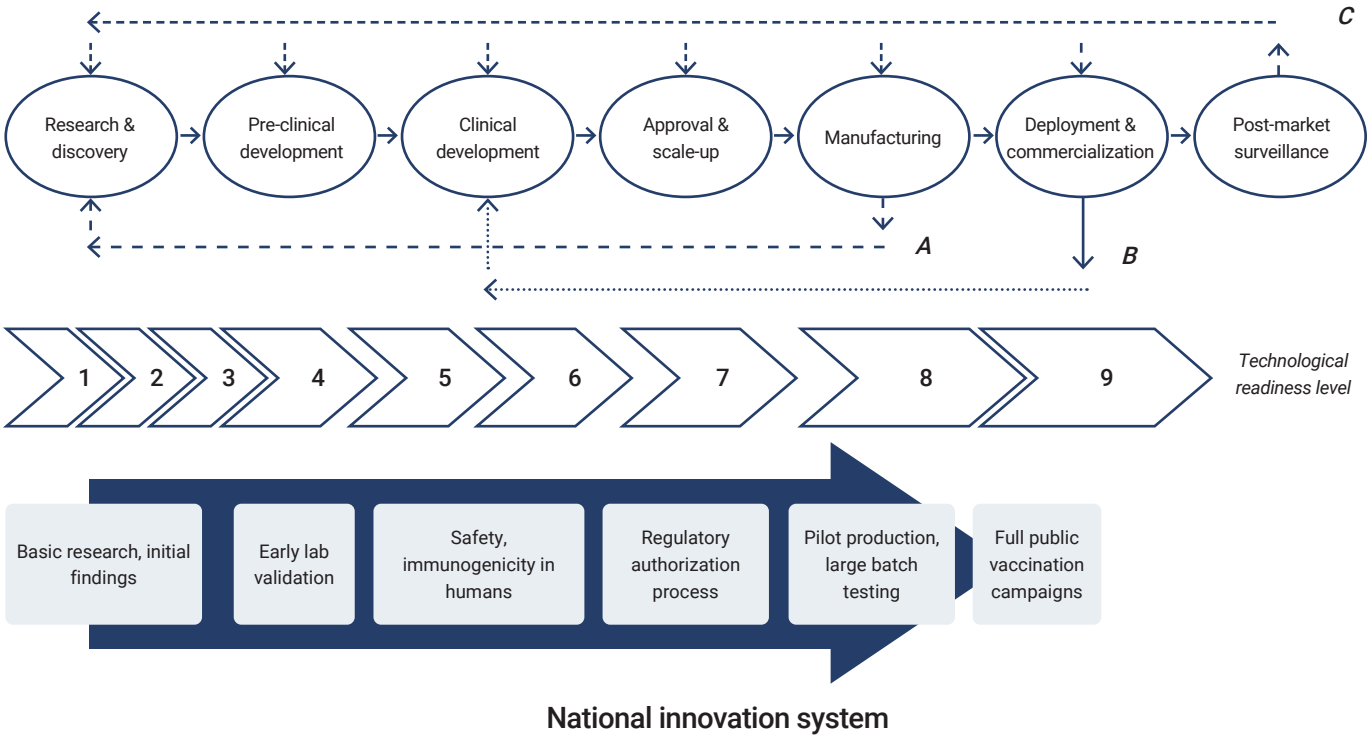


Figure 1. Integrated vaccine innovation system with feedback loops. Key feedback loops: (A) Challenges encountered during scaled production can yield insights into the need for modifications in vaccine design or formulation, prompting further research. (B) Real-world data on vaccine uptake and distribution logistics can inform adjustments in development strategies to enhance accessibility and efficacy. (C) Ongoing monitoring of vaccine performance and safety in the population provides critical insights that can influence every stage.

milestones and the institutional interactions most relevant to LMIC contexts.

While the SIS framework highlights industry-specific dynamics, this study prioritizes the NIS perspective to capture the broader institutional, regulatory, and public health interactions underpinning national vaccine responses during a global emergency. The NIS approach enables cross-country comparisons that account for policy-driven innovation capacities beyond the pharmaceutical sector alone—an essential consideration for LMICs navigating complex political and economic constraints.

Country Selection Criteria

Four countries—Brazil, Cuba, India, and Iran—were selected for comparative analysis based on the following criteria: (1) LMIC classification by the World Bank; (2) geographic and geopolitical diversity, representing Latin America, South Asia, and the Middle East; (3) active national vaccine development initiatives during the COVID-19 pandemic, including domestic R&D, production, and regulatory oversight; (4) variation in innovation governance models, including state-centric (e.g., Cuba, Iran), hybrid (e.g., India), and public–private arrangements (e.g., Brazil).

This sampling strategy enables balanced assessment of diverse policy and innovation ecosystems in LMICs. It also provides insight into how different institutional configurations and resource constraints influence trajectories toward vaccine sovereignty in lower-resource settings.

Comparative Data Synthesis

A structured matrix was developed to compare national vaccine strategies across 6 dimensions: institutional leadership, platform type, technology transfer, IP ownership, regulatory adaptation, and commercialization models (Table 1). Visual integration of chronological and institutional dynamics is presented in Figure 1, which maps vaccine development stages against TRL milestones and associated policy mechanisms. A complementary timeline was also compiled to track country-specific milestones in vaccine development, approval, and deployment (Table 2).

These tools facilitated cross-case comparison and thematic synthesis by aligning national experiences with innovation and governance benchmarks. Although this is not a systematic review, the literature selection and inclusion process was conducted with a high degree of transparency and rigor. To ensure reproducibility, a PRISMA-style flow diagram is included to summarize the identification, screening, and inclusion process, following PRISMA 2020 principles (Figure S1) [15].

Results

The following sections present the key comparative findings across the 4 country cases, beginning with innovation policy frameworks and continuing through implementation and geopolitical dimensions.

Policy Frameworks for Vaccine Innovation

A country's capacity to respond rapidly to public health emergencies depends not only on scientific capability but also on coherent innovation policies, mission-driven governance, and strategic procurement frameworks that guide both research and deployment.

Table 1. Comparative matrix of national vaccine development and commercialization strategies [9,17,21,23,25,27,32,46–53]

Country	Key vaccines	Institutional lead	Platform type	Technology transfer[a)]	Local ownership[b)]	Regulatory speed
Brazil	CoronaVac, ButanVac, AstraZeneca	Butantan Institute, Fiocruz	Inactivated virus, adenovirus	Yes (China, UK)	Partial	Moderate
Cuba	Soberana-01/02/Plus, Abdala	BioCubaFarma, Finlay Institute	Protein subunit, conjugate	No	Full	Fast
India	Covaxin, Covishield, ZyCoV-D	Bharat Biotech, SII, Zydus Cadila	Inactivated virus, viral vector, DNA	Yes (UK, US)	High	Fast
Iran	COVIran Barekat, SpikoGen, PastoCovac, COVOPars	Shifa Pharmed, CinnaGen, Pasteur Institute, Razi Institute	Inactivated, protein subunit, VLP	No (except PastoCovac)	Full	Adaptive/moderate

UK, United Kingdom; SII, Serum Institute of India; US, United States.
[a)]Technology transfer refers to the formal acquisition of vaccine-related know-how, processes, or production rights from an external entity, typically via licensing or collaborative agreements. "Yes" indicates that such agreements were executed and operationalized; "No" indicates that no such formal transfer occurred. [b)]Local ownership refers to the proportion of intellectual property (IP) and production capacity controlled within the country: "Partial" = minority IP or production rights held domestically; "Full" = all IP or production rights held domestically but dependent on imported critical inputs; "High" = full domestic IP and production capability, including all critical inputs, with minimal foreign reliance.

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Table 2. Timeline of major coronavirus disease 2019 vaccine developments in Brazil, Cuba, India, and Iran (2020–2022)

Country	Vaccine name	Key developers	Development start	Clinical trials	Emergency use approval	Mass rollout
Brazil	Oxford-AstraZeneca (Fiocruz)	Fiocruz, AstraZeneca	Mid-2020	Phase 3 (August 2020)	January 2021	January–February 2021
	CoronaVac (Butantan)	Instituto Butantan, Sinovac	Mid-2020	Phase 3 (July–November 2020)	January 2021	January 2021
Cuba	Soberana 01/02, Soberana Plus	Finlay Institute	May 2020	Phase 1/2 (October 2020–March 2021)	June 2021	July 2021
	Abdala	CIGB	July 2020	Phase 3 (March–May 2021)	June 2021	July–August 2021
India	Covishield	Serum Institute of India	May 2020	Phase 3 (August–November 2020)	January 2021	January 2021
	Covaxin	Bharat Biotech+ICMR	June 2020	Phase 1–3 (July–December 2020)	January 2021	January–February 2021
Iran	COVIran Barekat	Shifa Pharmed Industrial Co.	December 2020	Phase 1 (December 2020)–phase 3 (April–July 2021)	June 2021	July–August 2021
	PastoCovac (with Cuba)	Pasteur Institute+Finlay Institute	Late 2020	Phase 3 (April–June 2021)	July 2021	August–September 2021
	SpikoGen	CinnaGen (licensed from Australia)	2021	Phase 3 (July–September 2021)	October 2021	October–November 2021
	COVOPars	Razi Vaccine and Serum Research Inst.	2021	Phase 2/3 (August–November 2021)	December 2021	January 2022

CIGB, Center for Genetic Engineering and Biotechnology; ICMR, Indian Council of Medical Research.

NISs and vaccine development

The NIS model posits that innovation arises through interactions among public institutions, industry, academia, and regulatory agencies rather than in isolation [10,11]. During the COVID-19 pandemic, countries that had already integrated biotechnology into national innovation strategies—such as India and Cuba—were better able to mobilize institutional networks to support vaccine development [16,17].

Cuba's BioCubaFarma and India's Department of Biotechnology coordinated vaccine development through mission-oriented initiatives that linked scientific R&D with targeted policy incentives. Brazil's NIS, although institutionally mature, was hindered by bureaucratic bottlenecks and uneven public–private alignment, slowing the adoption of new technologies [18]. Iran, operating under international sanctions, relied on a centralized model driven by public research institutions and quasi-private biotech firms to preserve vaccine autonomy [19,20].

Public-private partnerships and strategic procurement

Public–private partnerships emerged as decisive enablers of vaccine development in all 4 countries. India's Serum Institute scaled up manufacturing through advance purchase agreements with the Indian government and international organizations such as Gavi [21]. Brazil's Fiocruz and Butantan Institute secured international technology transfers but faced delays from procedural and logistical challenges [22].

Cuba maintained a vertically integrated state model, in which BioCubaFarma managed R&D, production, and procurement—ensuring close coordination between science and policy [23]. Iran's strategy incorporated private-sector engagement through firms such as Shifa Pharmed (COVIran Barekat) and CinnaGen (SpikoGen), supported by regulatory fast-tracking under emergency authorization frameworks [24,25].

Technology Management Challenges

Managing vaccine R&D during a pandemic requires overcoming specific technical and institutional barriers that extend from early-stage formulation to mass production. These challenges are amplified in LMICs with limited infrastructure or fragile supply chains.

Scientific and technical barriers

High-stakes vaccine development demands expertise in multiple domains, including antigen design, adjuvant formulation, cold chain stability, and quality control systems. Without access to mRNA platforms or proprietary technologies, Cuba and Iran turned to protein subunit and conjugate vaccines, drawing on existing recombinant biotechnology capacities [26,27].

India's Covaxin project, developed by Bharat Biotech in

collaboration with the Indian Council of Medical Research (ICMR), faced significant scrutiny during phase II/III trials but advanced through agile iteration and extensive data-sharing partnerships [28]. Brazil's Butantan Institute, however, struggled with formulation bottlenecks and fill-and-finish limitations, which complicated scale-up of CoronaVac production [29].

Regulatory and clinical trials management

Regulatory flexibility was a critical differentiator. India and Iran implemented adaptive licensing mechanisms and rolling reviews to accelerate clinical trials while maintaining safety standards [21,27,28]. Brazil's multilayered ethics and regulatory procedures, although rigorous, introduced delays in trial approval [30]. In contrast, Cuba benefited from centralized oversight by national health institutes, which facilitated rapid recruitment and trial progression [31].

Prototyping and the TRL perspective

In LMIC settings, TRL stages often overlap due to the urgency of vaccine development under resource constraints. For instance, India and Iran progressed to TRL 7 (clinical-grade manufacturing) while still conducting TRL 5–6 clinical trials, reflecting adaptive regulatory practices. Feedback from downstream processes, such as manufacturing scalability and distribution logistics, frequently informed upstream refinements, including dosage adjustments and delivery optimization.

Iran's SpikoGen and COVOPars vaccines were developed in collaboration with Tehran University of Medical Sciences and the Razi Institute, respectively. These partnerships accelerated the transition from prototype to industrial scale by utilizing established bioreactor systems and GMP-certified facilities [32,33]. India's vaccine pipeline advanced quickly through strong linkages between private manufacturers and international clinical trial networks [34]. In contrast, Brazil's ButanVac initiative faced design and regulatory hurdles in early development, exemplifying TRL bottlenecks in contexts where innovation and regulatory ecosystems were misaligned.

These cases illustrate how institutional experience, infrastructure readiness, and adaptive regulation are essential for navigating TRL transitions in resource-constrained environments—elements conceptually mapped in Figure 1.

Global Coordination, South–South Collaboration, and Public Health Outcomes

The drive for vaccine self-sufficiency in LMICs during the COVID-19 pandemic intersected with global initiatives promoting equitable access, collaborative development, and regional capacity-building. While NISs shaped domestic responses, global mechanisms, such as the WHO C-TAP, the mRNA Technology Transfer Hub in South Africa, and broader South–South collaboration frameworks, provided important benchmarks and opportunities for countries facing structural constraints [35–37].

The WHO mRNA Hub, launched with Afrigen Biologics and the Medicines Patent Pool, aimed to disseminate mRNA technologies to LMICs, including Brazil and India, by providing platform training and regulatory support [35]. Although none of the vaccines studied here directly used mRNA technology from the hub, the initiative exemplifies horizontal collaboration and technology democratization. Similar principles were visible in co-development ventures such as the PastoCovac alliance between Cuba's Finlay Institute and Iran's Pasteur Institute [38]. These partnerships highlighted deeper South–South knowledge exchange beyond licensing—emphasizing joint R&D, distributed manufacturing, and regulatory co-approval.

Brazil and India also leveraged their positions in global vaccine manufacturing to expand bilateral and multilateral knowledge-sharing. India's Vaccine Maitri program exported more than 66 million doses of domestically produced vaccines to over 90 countries during the pandemic, reflecting not only large-scale industrial capacity but also the strategic use of soft power and regional diplomacy [39]. Brazil's Butantan Institute, although constrained in its attempt to indigenize ButanVac, continued to operate as a WHO-designated National Regulatory Authority and served as a training hub for regional vaccine developers, including collaborations within the Pan American Health Organization (PAHO) framework [40].

From a public health perspective, these innovation trajectories produced significant yet variable outcomes. Iran achieved rapid emergency use authorization for multiple domestic vaccines by mid-2021, vaccinating a substantial proportion of its population despite international sanctions [41]. India's dual-track strategy simultaneously pursuing domestic mass vaccination and global engagement positioned it as both a manufacturing hub and a diplomatic actor during the pandemic, underscoring the strategic value of combining innovation with global health solidarity [42]. Cuba, through strong state-led coordination, vaccinated more than 90% of its population with homegrown vaccines (Soberana and Abdala) by early 2022, achieving one of the highest global coverage rates [43]. These cases illustrate how institutional preparedness, global engagement, and adaptive capacity shaped LMIC vaccine ecosystems.

Despite uneven access to global IP and platform technologies, the pandemic demonstrated that LMICs could align with or replicate multilateral initiatives to build domestic capacities.

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South–South cooperation, underpinned by aligned governance structures and shared scientific missions, emerged as a pragmatic strategy to reduce dependency on Northern suppliers. These experiences highlight the strategic importance of shared innovation platforms for advancing health sovereignty, particularly in contexts where access to global supply chains remains constrained.

Geopolitical pressures, including sanctions, IP restrictions, and limited access to multilateral funding, further shaped innovation pathways. In particular, Iran and Cuba adapted to these barriers by fostering indigenous solutions and forging South–South alliances. These cases highlight how geopolitical constraints can serve both as obstacles and as drivers, pushing LMICs toward more autonomous vaccine development strategies with long-term implications for future pandemic preparedness.

Commercialization Pathways and Strategic Scaling

Translating vaccine candidates into widely distributed products requires strategic commercialization mechanisms, including licensing agreements, IP management, contract manufacturing, and regulatory harmonization. For LMICs, these processes must also contend with systemic barriers such as supply chain limitations, market access challenges, and geopolitical pressures.

Technology transfer and licensing

India and Brazil pursued international partnerships to acquire technological expertise. The Serum Institute of India secured non-exclusive licenses from AstraZeneca and Novavax to manufacture Covishield and Covovax, respectively [44]. Brazil's Fiocruz entered a technology transfer agreement with AstraZeneca to locally produce Vaxzevria. However, delays in process transfer and scale-up generated late-stage production bottlenecks [45].

In contrast, Cuba and Iran—confronted with geopolitical restrictions and IP barriers—relied largely on indigenous platforms. Development and internal commercialization of Cuba's Soberana and Abdala vaccines were supported through centralized IP governance under BioCubaFarma [46]. Iran's Pasteur Institute co-developed Soberana-02 with Cuba, while COVIran Barekat, SpikoGen, and COVOPars were advanced by domestic biopharmaceutical firms managing their own IP portfolios [47–49].

While bilateral licensing arrangements accelerated vaccine output in India and Brazil, they frequently depended on proprietary platforms that limited local control over upstream technologies such as cell lines and adjuvants. This dependency raises concerns about long-term self-reliance, particularly when IP restrictions constrain access to updated variants or platform know-how.

Supply chain and manufacturing scale-up

Scaling vaccine production requires reliable access to active pharmaceutical ingredients (APIs), fill-and-finish facilities, cold chain logistics, and robust quality assurance systems. In India, Covaxin production was supported by a consortium including Bharat Biotech and Indian Immunologicals Ltd., underpinned by the government's Mission COVID-19 Suraksha [50]. Brazil, however, experienced delays in its early rollout due to reliance on imported APIs [51].

Iran addressed supply constraints by expanding biosafety-level-2 facilities and scaling bioreactor capacity through firms such as Shifa Pharmed and CinnaGen [52]. Cuba mitigated cold chain challenges by deploying thermostable formulations and lyophilized products, facilitating smoother domestic distribution [53].

Despite these achievements, the sustainability of large-scale production remains uncertain in the post-pandemic era. Brazil and India face fiscal pressures in maintaining manufacturing capacity without sustained global procurement, while Iran and Cuba continue to depend on strong state support for operational and regulatory continuity. Achieving long-term vaccine sovereignty in LMICs will require not only innovation but also durable industrial financing.

Comparative Case Studies: Brazil, Cuba, India, and Iran

To contextualize the interplay between innovation and policy in vaccine development, a comparative analysis was undertaken across 4 countries representing diverse governance models, industrial maturity, and geopolitical conditions (Table 1) [9,17,21,23,25,27,32,46–53].

The analysis shows that countries with centralized governance and vertically integrated biotech sectors—such as Cuba and Iran—were more successful in retaining local ownership of R&D and ensuring end-to-end commercialization. India's hybrid public–private model enabled rapid international collaboration and licensing, while Brazil's dependence on foreign IP and procedural inefficiencies limited early scalability. Regulatory agility, institutional alignment, and domestic production autonomy emerged as central enablers of timely vaccine rollout [54].

Table 2 maps vaccine R&D milestones, partnerships, and licensing decisions across 2020–2022, highlighting temporal patterns of innovation, collaboration, and deployment.

Cuba and Iran initiated indigenous vaccine projects as early as mid-2020, while India and Brazil initially relied on technology access from external sources. This progression underscores not only technical timelines but also the

policy choices that determined when and how countries launched mass vaccination programs. It further highlights the strategic role of pre-existing biotech ecosystems in enabling rapid and autonomous responses.

Building on this chronological overview, Table 3 provides a comparative analysis of the organizational structures, R&D models, and primary challenges encountered by Brazil, Cuba, India, and Iran in their COVID-19 vaccine development efforts.

This comparative lens highlights the diverse approaches and constraints each country faced, shaped by distinct political, economic, and infrastructural contexts. Understanding these factors offers deeper insight into the structural complexity of global vaccine development and distribution.

The impact of these innovation strategies is evident in national outcomes. By late 2021, India had exported more than 66 million doses of Covishield to over 90 countries under COVAX and bilateral agreements. Cuba vaccinated over 90% of its population with domestically developed vaccines and supplied doses to Venezuela, Nicaragua, and Vietnam. Iran achieved full-cycle production capacity for at least 3 vaccine types despite the burden of international sanctions. Brazil, through Fiocruz, scaled fill-and-finish capacity to produce more than 100 million doses of AstraZeneca's vaccine. Collectively, these achievements underscore how the integration of innovation and policy directly shaped real-world access, resilience, and autonomy [27,46,55].

Geopolitical barriers—particularly the United States-led sanctions on Iran and Cuba—posed major obstacles to technology transfer, raw material imports, and participation in multilateral procurement mechanisms such as COVAX. Despite these challenges, both countries advanced public-sector-driven vaccine R&D. Nevertheless, limited access to international IP and funding mechanisms restricted their ability to scale production. The long-term sustainability of such domestically centered programs remains uncertain, particularly in the absence of integration into global supply chains or reliable financing beyond the emergency phase.

Discussion

The preceding results highlight the diverse institutional models, innovation pathways, and commercialization strategies adopted by Brazil, Cuba, India, and Iran. In this section, these case-specific insights are considered collectively to identify broader patterns in vaccine development within LMICs. The discussion emphasizes shared challenges, enabling factors, and implications for both national and international health policy, followed by actionable recommendations for strengthening vaccine innovation ecosystems in resource-constrained contexts.

Broader Findings and Thematic Insights

Across the 4 case studies, several cross-cutting themes emerge that provide lessons for policymakers and vaccine developers. While sector-specific factors, such as regulatory design and manufacturing pathways, were important, the broader institutional and governance context, framed by the NIS approach, was equally critical in shaping vaccine outcomes: (1) Strategic sovereignty in health technologies: Countries with prior investments in state-led bioscience and pharmaceutical sectors, notably Cuba and Iran, achieved vaccine autonomy despite geopolitical restrictions. Control over IP and production facilities was pivotal in ensuring independence; (2) Maturity of innovation ecosystems: India successfully leveraged both public and private sector strengths, combining in-house R&D with licensed foreign IP. By contrast, Brazil—despite its strong scientific capacity—was constrained by fragmented governance and weak institutional coordination; (3) Regulatory co-evolution: Adaptive regulatory mechanisms, such as India's Emergency Use Authorization and Iran's conditional approval processes, expedited vaccine rollout while upholding safety standards. Brazil's more rigid, multilayered ethics clearance processes introduced delays; (4) South-south scientific collaboration: The Iran–Cuba co-development of PastoCovac illustrates how Global South partnerships can overcome access barriers, facilitating shared technology platforms and joint clinical trials; (5) Distributed manufacturing models: Countries that mobilized both state and private sector manufacturers,

Table 3. National vaccine development overview

Country	Major developers	Vaccine	R&D model	Primary challenges
Brazil	Fiocruz, Butantan	AstraZeneca, CoronaVac	Public-private	Supply delays, coordination gaps
Cuba	Finlay, BioCubaFarma	Soberana, Abdala	Public-state biotech	Sanctions, international validation
India	SII, Bharat Biotech	Covishield, Covaxin	Private+state R&D	Export bans, regulatory controversy
Iran	Shifa, Pasteur, Razi	Barekat, PastoCovac, COVOPars	State-semi private	Sanctions, clinical trial access barriers

R&D, research and development; SII, Serum Institute of India.

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particularly India and Iran, demonstrated greater resilience to supply chain shocks and achieved more flexible production scale-up.

Policy Implications and Recommendations

Drawing from the comparative analysis, this section outlines key policy recommendations for LMICs seeking to strengthen their vaccine innovation systems:

Institutional capacity and public R&D support

National innovation strategies should prioritize consistent financing for public research institutions and long-term workforce development. Evidence from Cuba and Iran confirms that such investments generate resilience during crises.

Strategic IP management

Balancing local innovation with licensed production is essential. India's hybrid approach—blending domestic R&D with foreign IP—offers a model for enhancing sovereignty while maintaining global integration.

Regulatory preparedness

Developing fast-track, adaptable regulatory pathways in advance of emergencies is crucial. Institutionalizing foresight practices within regulatory systems can ensure timely approvals during future crises.

Regional vaccine hubs and south-south alliances

Cross-border collaboration among LMICs in vaccine R&D, clinical trials, and API production—exemplified by the Cuba–Iran alliance—can foster collective self-sufficiency and diversify global vaccine sources. These national experiences also resonate with WHO-led mechanisms such as the C-TAP and the mRNA Technology Transfer Hub in South Africa. The Iran–Cuba collaboration on PastoCovac, along with India's vaccine diplomacy through Covishield exports, reflects shared objectives of equitable technology exchange and distributed manufacturing. Strengthening such South–South collaborations could provide parallel or complementary pathways to WHO's multilateral platforms in addressing inequitable vaccine access during future pandemics [56,57].

Open access to technology

LMICs should actively engage in initiatives such as the WHO C-TAP to encourage equitable knowledge-sharing and reduce dependence on restrictive IP regimes.

Implications for multilateral health governance

The vaccine innovation and policy trajectories of Brazil, Cuba, India, and Iran carry significant implications for multilateral pandemic preparedness. Their experiences underscore the importance of flexible IP frameworks, diversified manufacturing, and public–private integration—factors that could guide reforms to COVAX governance, WHO Pandemic Accord negotiations, and regional regulatory harmonization efforts [58]. For example, decentralized innovation models in India and Iran align with the African Union and Association of Southeast Asian Nations calls for local manufacturing ecosystems [59]. Similarly, Cuba's and Iran's reliance on self-developed platforms underscores the necessity of national R&D investment in contexts where geopolitical barriers restrict access to multilateral resources.

To strengthen LMIC vaccine sovereignty, international organizations such as WHO can play a catalytic role by building pooled R&D platforms, pre-negotiating IP licenses during non-crisis periods, and ensuring equitable access to critical inputs. Initiatives such as the WHO mRNA Technology Transfer Hub and C-TAP should be reinforced with dedicated financing, sustained political support, and regional implementation mechanisms to ensure LMIC participation is substantive rather than symbolic. A WHO-led coordination framework could further enhance resilience by supporting regulatory alignment, pooled raw material procurement, and global clinical trial data-sharing.

Synthesis for LMIC policy pathways

Collectively, the cases of Brazil, Cuba, India, and Iran demonstrate that LMICs can pursue diverse yet effective innovation trajectories when public health goals are embedded in broader science and technology strategies. While no single model applies universally, transferable lessons include the strategic value of sustained investment in public research capacity, the establishment of adaptable regulatory systems, and the strengthening of South–South knowledge networks. LMICs can also leverage global platforms such as the WHO mRNA Hub and C-TAP without undermining national sovereignty, particularly when aligned with regional regulatory harmonization initiatives (e.g., through the African Medicines Agency or PAHO). Ultimately, equitable vaccine access depends not only on technology availability but also on reinforcing LMIC agency in governance, manufacturing, and innovation leadership.

In addition, the long-term economic sustainability of domestic vaccine programs remains a critical issue, particularly for LMICs confronting fiscal constraints in the post-emergency phase. Institutional frameworks must also anticipate barriers posed by sanctions and trade restrictions, which limit technology access and R&D financing.

Conclusion

The experiences of Brazil, Cuba, India, and Iran during the COVID-19 pandemic demonstrate that institutional coherence, flexible policy environments, and sustained investment in public R&D are as critical as scientific expertise for successful vaccine development. Countries that fostered strong NISs and adopted adaptive regulatory pathways proved resilient in both innovation and deployment. For LMICs, these insights underscore the importance of coordinated governance, preparedness for technology transfer, and strengthened South–South collaboration in advancing pandemic readiness. Building robust domestic ecosystems through inclusive innovation, regional partnerships, and global knowledge-sharing platforms remains essential for ensuring equitable access to life-saving technologies.

Future research should expand the sample of countries to include additional LMICs across Africa and Southeast Asia to assess the broader applicability of these findings. Longitudinal studies evaluating the economic viability of domestic vaccine programs, public trust in locally produced vaccines, and the durability of regulatory reforms post-pandemic would provide critical evidence on whether these strategies contribute to long-term strengthening of innovation systems. Furthermore, comparative analyses of emergency pandemic responses and routine immunization infrastructures may yield deeper insights into institutional resilience under pressure.

Supplementary Material

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses-style diagram illustrating the article screening and selection process. *n* refers to the number of records at each stage of the literature selection process. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0208.

Notes

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Not applicable.

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

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All data supporting the findings of this study are available within the manuscript and referenced sources.

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Original Article

Scrub typhus in the era of climate change: exploring lagged and cumulative effects of meteorological factors in the Republic of Korea, 2001–2024, a nationwide time-series study

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ABSTRACT

Objectives: Scrub typhus, caused by *Orientia tsutsugamushi*, is a climate-sensitive vector-borne disease with high incidence in the Republic of Korea. This study examined long-term epidemiological trends and changing meteorological influences in the context of climate change.
Methods: A retrospective time-series study was conducted using national surveillance data on 149,289 scrub typhus cases (2001–2024) across 4 surveillance phases. Temporal trends in age-standardized incidence rates were evaluated using Joinpoint regression. Associations between monthly meteorological variables and incidence were assessed with Spearman correlation analysis and time-series regression analysis using distributed lag non-linear models.
Results: The national incidence increased until 2017 and has decreased since 2018, whereas the AAPC rebound to 4.32% during phase IV (2019–2024). The proportion of female cases decreased, while that of adults ≥70 years increased significantly. In phase IV, the average annual percent change increased in central and urban regions. The lag effect of meteorological factors lengthened from 4 to 6 months, with mean temperature (Tmean) and relative humidity (RH) representing the primary predictors. Phase III (2013–2018) displayed the highest cumulative relative risk (RR) for Tmean at 25.2 °C (RR, 5.86; 95% confidence interval [CI], 2.56–13.42), whereas in phase IV, only moderate RH (58%) remained significantly associated with incidence (RR, 1.68; 95% CI, 1.29–2.20).
Conclusion: Over the past 2 decades, the influence of meteorological factors on scrub typhus has shifted, with recent years marked by greater uncertainty under increasing climate variability and instability. For timely risk prediction and targeted prevention, adaptive surveillance systems that integrate dynamic climate indicators—capturing the intensity, frequency, and variability of extreme weather events—are needed.

Keywords: Climate change; Meteorological factors; Scrub typhus; Time series analysis

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Introduction

Scrub typhus, also known as tsutsugamushi disease, is a naturally occurring febrile illness caused by the gram-negative bacterium *Orientia tsutsugamushi* [1]. The disease is transmitted to humans through the bite of the larval (chigger) stage of *Leptotrombidium* mites (Acari: Trombiculidae) [2], which act as vectors when infected with the pathogen. Wild rodents serve as both the natural and reservoir hosts of *O. tsutsugamushi*, while humans are considered accidental hosts [3]. The incubation period for scrub typhus is generally 10 to 12 days, although it can range from 6 to 21 days [4]. Clinical manifestations often include fever, headache, myalgia, rash, eschar formation, generalized lymphadenopathy, and transient hearing loss; however, severe complications such as acute encephalitis syndrome and multiorgan failure can occur [5]. To date, no effective vaccine is commercially available to prevent or control scrub typhus [6]. Prompt diagnosis and treatment (most commonly doxycycline) are crucial to reducing complications and mortality [7].

Scrub typhus is widely prevalent within the "Tsutsugamushi Triangle," extending north to northern Japan and eastern Russia, south to northern Australia, and west to Pakistan and Afghanistan [6]. Recent reports indicate spread beyond its traditional geographic boundaries, with evidence of wider distribution in Africa, the Middle East, and South America than previously recognized [8,9], highlighting the potential for global expansion. Among the 5 countries that classify scrub typhus as a notifiable infectious disease (Japan, mainland China, the Republic of Korea, Taiwan, and Thailand), the Republic of Korea reported the highest incidence rate (IR) as of 2016 [10]. Eight species of *Leptotrombidium* mites known to carry *O. tsutsugamushi* are found in the Republic of Korea [11]. Among them, *Leptotrombidium scutellare* is the dominant species, accounting for 37.7% of all identified mites, and is primarily distributed in the southern regions, including Gyeongnam, Jeonnam, and Jeonbuk [12,13]. *Leptotrombidium pallidum*, the second most prevalent species, accounts for 11.5% and is more commonly found in the central regions, such as Gyeonggi, Gangwon, and Chungbuk [12,13]. However, recent surveillance data from the Korea Disease Control and Prevention Agency (KDCA) indicate a northward expansion of *L. scutellare* [12,13], suggesting emerging risk in regions previously considered low-incidence areas.

As poikilothermic organisms, chigger mites are highly sensitive to climatic factors, which influence their ecology, reproductive capacity, and population dynamics [14,15]. A spatial regression study conducted in tropical India reported that a 1 °C increase in mean temperature (Tmean) was associated with an 18.8% decrease in monthly scrub typhus cases, whereas a 1% increase in mean relative humidity (RH) corresponded to a 7.6% increase [16]. Similarly, in a study from subtropical China applying a spatial lag model, Tmean and mean wind speed were identified as the most influential weather factors determining the risk of scrub typhus [1]. A study conducted in the Republic of Korea reported peak cumulative risks at 18.7 °C for temperature (relative risk [RR], 9.73; 95% confidence interval [CI], 5.54–17.10) and 162.0 mm for precipitation (RR, 1.87; 95% CI, 1.02–3.83), relative to baselines of 9.7 °C and 2.8 mm, respectively [2]. However, these studies did not incorporate more recent data and relied on analyses aggregated across the entire study period, limiting their capacity to capture how the impact of climate on scrub typhus incidence may have changed over time, particularly in the context of ongoing climate change.

Therefore, this study aimed to comprehensively describe the epidemiological trends of scrub typhus in the Republic of Korea using data from 2001 to 2024 and to evaluate the relationship between meteorological factors and disease occurrence using a distributed lag non-linear model (DLNM). In doing so, we sought to explore how climatic changes may be influencing the transmission dynamics of scrub typhus in the Republic of Korea.

HIGHLIGHTS

- This represents the largest study to date (n=149,289) assessing long-term, phase-specific climate–disease associations for scrub typhus in the Republic of Korea (2001–2024).
- Mean temperature and relative humidity (RH) were the most consistent predictors, with the greatest risk observed at 25.2 °C and 84% in phase III (2013–2018).
- In phase IV (2019–2024), only moderate RH (58%) remained significantly associated with incidence, reflecting shifting climate–disease dynamics amid increasing climate variability and instability.
- These findings highlight the need for adaptive, climate-responsive surveillance and early warning systems that account for lagged effects, evolving exposure–risk relationships, and extreme weather patterns.

Materials and Methods

National Surveillance

In the Republic of Korea, scrub typhus is classified as a third-grade notifiable infectious disease and must be

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reported within 24 hours. This disease has been included in the National Notifiable Disease Surveillance System since 2001. The KDCA established a centralized electronic reporting system, the Integrated Disease Health Management System (IS) in 2005; by 2007, all case notifications had transitioned to a web-based platform. Since 2015, an automated infectious disease reporting support system has been disseminated by integrating electronic medical record systems in healthcare institutions with the IS. In 2024, the KDCA reorganized the IS into the Integrated Disease Prevention Information System to support faster and more efficient quarantine operations; however, the fundamental structure of the existing infectious disease system remained unchanged.

Case Definition

The KDCA revised the reporting and diagnostic criteria for scrub typhus on April 30, 2019. First, clinically suspected cases without laboratory test results were excluded from the reporting requirements [17]. Second, whereas a single antibody titer of immunoglobulin (Ig) G ≥1:256 or IgM ≥1:16 had been considered positive, the diagnostic criterion was revised to a fourfold or greater increase in antibody titers [18]. This change was designed to improve diagnostic accuracy by distinguishing between past and recent infections [18]. Lastly, the previous non-confirmatory criterion, "detection of specific antibodies," was revised to "detection of specific antibodies in a blood specimen" [17]. Therefore, a confirmed case was defined as a patient presenting with compatible clinical symptoms and either (1) isolation and identification of *O. tsutsugamushi* from specimens (e.g., blood, tissue, or eschar), (2) a fourfold or greater increase in antibody titer between acute and convalescent sera, or (3) detection of *O. tsutsugamushi* DNA by polymerase chain reaction from specimens (e.g., blood, tissue, or eschar). A probable case was defined as a patient presenting with compatible clinical symptoms and epidemiological exposure (e.g., outdoor activity or chigger exposure within the 10 days before symptom onset), along with a positive result from either an immunochromatographic assay or a single immunofluorescence assay [13].

Study Design, Period, and Population

We conducted a retrospective time-series study of monthly scrub typhus incidence and meteorological factors in the Republic of Korea from 2001 to 2024. Of a total of 149,303 reported cases, 149,289 were included in the final study population, consisting of 87,995 probable cases and 61,294 confirmed cases. Fourteen suspected cases were excluded to ensure data quality and representativeness. Mortality data related to scrub typhus have been available since 2011, with a cumulative total of 174 deaths reported as of 2024. To reduce variability and ensure data homogeneity, the study period was divided into 4 phases based on major changes in surveillance systems, climate patterns, and case definitions: phase I (2001–2006), phase II (2007–2012), phase III (2013–2018), and phase IV (2019–2024).

Data Sources and Collection

To examine the incidence of scrub typhus in the Republic of Korea, we used monthly scrub typhus case counts from 2001 to 2024 and mortality data from 2011 to 2024 for 17 administrative regions, as published by the KDCA Infectious Disease Portal (https://dportal.kdca.go.kr). Because the portal data do not clearly distinguish between suspected and probable cases, we additionally reviewed records through the KDCA IS. Cases without a recorded diagnosis date were classified as suspected cases. Cumulative IR and annual age-standardized incidence rates (ASIR) for each region were calculated using mid-year population estimates obtained from the Korean Statistical Information Service of Statistics Korea (https://kosis.kr). For spatial analysis of the geographic distribution of scrub typhus, administrative boundary shapefiles were obtained from the Statistical Geographic Information Service of Statistics Korea (https://sgis.kostat.go.kr). To explore the lagged and cumulative effects of meteorological factors on scrub typhus incidence, meteorological data were acquired from the Korea Meteorological Administration's Open Data Portal (https://data.kma.go.kr). We used multisite statistics from at least 2 automated synoptic or disaster weather observation stations per region. The monthly meteorological variables included Tmean, cumulative precipitation, mean RH, mean wind velocity (WV), and total sunshine hours (SH).

Data Analysis

A descriptive analysis of scrub typhus cases and meteorological factors was performed using Microsoft Excel 2019 (Microsoft Corp.). Temporal trends were analyzed with Joinpoint Regression Software (ver. 5.3.0.0; National Cancer Institute). Spearman correlation analysis and time-series regression analysis with DLNM were conducted using R ver. 4.4.3 in RStudio (R Studio Inc.). All statistical tests were 2-sided, and p-values of less than 0.05 were considered to indicate statistical significance.

Descriptive analysis

Annual national incidence and mortality trends for scrub typhus were visualized using frequency analyses. Demographic characteristics of cases were summarized as percentages.

Monthly meteorological data from the 17 administrative

regions were aggregated by phase, and descriptive statistics—including mean, standard deviation, percentiles (P10, P25, P50, P75, and P90), minimum, and maximum—were calculated for each climatic variable to characterize the nationwide distribution during each phase.

Joinpoint regression analysis

To identify changes and parallel trends, Joinpoint analysis was conducted using ASIR per 100,000 population, calculated by the direct standardization method using the World Health Organization World Standard Population for 2000–2025. Because the analysis yielded zero joinpoints, the average annual percent change (AAPC) can be interpreted in the same way as the annual percent change. An upward trend was indicated by a positive AAPC with the lower bound of its 95% CI greater than zero.

Correlation analysis

To examine the relationship between meteorological variables and scrub typhus incidence, Spearman correlation analysis was used due to the non-normal distribution of the data and the presence of non-linear relationships. Multicollinearity among meteorological variables was assessed using variance inflation factors, all of which were below 5, indicating no significant multicollinearity [19]. Given that scrub typhus cases in the Republic of Korea typically peak in autumn (October–November), seasonality was addressed by pairing observations by calendar month, and Spearman's rank correlation coefficients were calculated.

Time-series regression analysis

To evaluate the lagged and cumulative effects of meteorological exposure on scrub typhus incidence, we implemented a DLNM framework using the "dlnm" package in R, built on a generalized linear model. DLNM is a flexible approach that captures both non-linear and delayed effects of predictors on an outcome over time [20]. In this study, meteorological factors (e.g., Tmean) were treated as independent variables, and monthly scrub typhus incidence represented the dependent variable. Both single-variable and multi-variable DLNM models were employed to assess the effects of individual meteorological variables. The single-variable models incorporated seasonal and temporal trends, incidence quantile groups, and 1-month lagged incidence to adjust for potential confounders [21]. In the multi-variable models, all meteorological variables and covariates—including time trends, seasonality, incidence quantiles, and prior-month incidence—were adjusted simultaneously [21]. The median value of each meteorological variable was set as the reference exposure. Low- and high-risk exposure levels were defined by P10 and P90, respectively, which also served as thresholds for estimating both lagged and cumulative RR.

Prior to model fitting, we defined a 2-dimensional function space using a cross-basis function. Overdispersion was evaluated by phase for each meteorological variable; where dispersion exceeded 1, the quasi-Poisson distribution was adopted. Precipitation was excluded due to skewed distribution, zero inflation, and failure to meet model convergence criteria within the P10–P90 range.

We tested lag periods ranging from 3 to 7 months and selected, for each phase, the lag duration that yielded the lowest quasi-Bayesian information criterion in the single-variable and multi-variable DLNM models. DLNM model [21], ensuring optimal model fit and capturing phase-specific temporal dynamics. While the overall model (2001–2024) adopted a 5-month lag, the optimal lags for the phase-specific models were 4, 7, 5, and 6 months for phases I–IV, respectively. Natural cubic splines of time with 7 degrees of freedom (df) per year were used to control for confounders by capturing long-term trends and seasonality [22]. The optimal df for the natural spline functions of the meteorological variables and their lag-response relationships was determined by comparing quasi-Akaike information criterion (QAIC) values across models with df from 3 to 5; a lower QAIC indicates a better fit [22]. In the final model, the lag dimension was set to 4 df for phase I and 3 df for phases II–IV. The B-spline function for the exposure dimension was fixed at 3 df, based on previous research [23].

Knots for the lag dimension were placed at equally spaced values on a logarithmic scale using the logknots() function. Lagged and cumulative RR values at the P10 and P90 exposure levels were estimated and visualized using contour plots and exposure-response curves to illustrate both the temporal patterns of delayed effects and the magnitude of cumulative effects.

IRB/IACUC Approval

This study was reviewed and approved by the Institutional Review Board of the KDCA (No: KDCA-2025-04-04-PE-01) and was performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because the study retrospectively collected de-identified data.

Results

Overall National Incidence and Case Fatality Trends

A total of 149,289 scrub typhus cases were reported in the Republic of Korea from 2001 to 2024, with an average annual IR of 12.4 per 100,000 population. From 2001 to 2017, the annual

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number of cases and the IR displayed a gradual increase, with intermittent stepwise changes. Since 2018, the total number of cases has declined, with a particularly sharp decrease in confirmed cases observed in 2019 (Figure 1A). From 2011 to 2024, a total of 174 deaths were reported, corresponding to a case fatality rate of 2.5%. Despite declining incidence in phase IV, both the number of deaths and the case fatality rate reached their highest levels in 2022 and 2023, with case fatality exceeding 0.3% (Figure 1B). The AAPC of ASIR decreased from 26.79% per year (95% CI, −2.46% to 63.84%; $p = 0.079$) in phase I to −6.72% (95% CI, −25.32% to 16.36%; $p = 0.439$) in phase III, representing a gradual slowdown in growth. However, the AAPC in phase IV was 4.32% (95% CI, −1.83% to 10.68%; $p = 0.174$), indicating a transition to a rising trend (Figure 2).

Demographic and Regional Features

The total number of scrub typhus cases was 149,289, including 23,915, 36,500, 56,309, and 32,565 in phase I, phase II, phase III, and phase IV, respectively. Overall, a higher proportion of cases was reported among female individuals (61.8%), although this proportion decreased over time. By age, the proportion of cases among those in their 70s increased from 20.5% in phase I to 28.6% in phase IV, whereas those aged ≥80 years showed a marked increase from 5.2% in phase I to 20.5% in phase IV. Regionally, the highest proportion was observed in Gyeongnam (16.1%), which increased from 12.1% in phase I to 20.6% in phase IV (Table 1).

Geographical and Temporal Trends

The geographical distribution of scrub typhus in the Republic of Korea showed that IRs per 100,000 population were largely concentrated in the southern, southeastern,

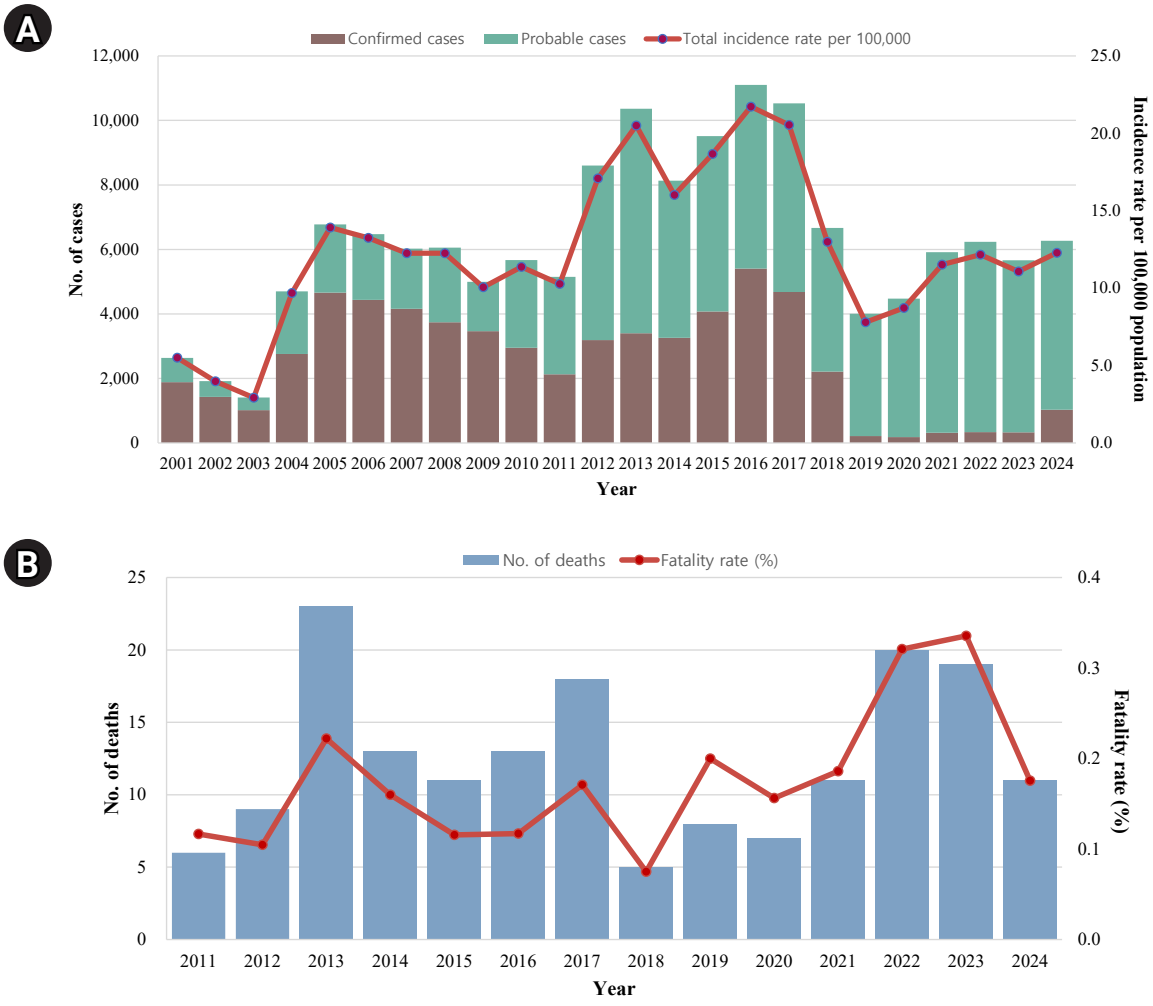


Figure 1. (A) Annual number of cases and incidence rate (per 100,000 population) for scrub typhus in the Republic of Korea, 2001–2024. (B) Annual number of deaths and case fatality rate (per 100 cases) for scrub typhus in the Republic of Korea, 2011–2024.

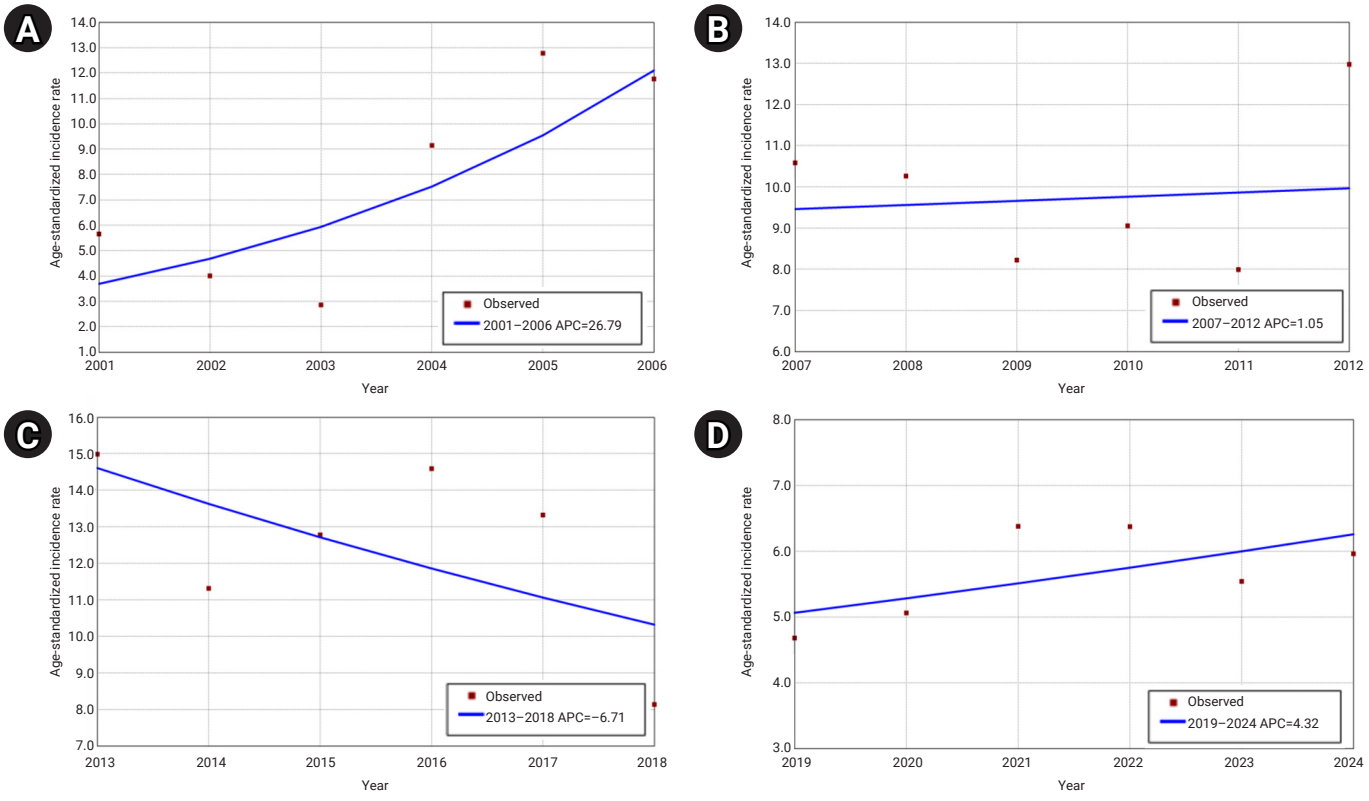


Figure 2. Trends in age-standardized incidence rate (per 100,000 population) of scrub typhus and Joinpoint regression analysis in the Republic of Korea, 2001–2024. (A) Phase I (2001–2006). (B) Phase II (2007–2012). (C) Phase III (2013–2018). (D) Phase IV (2019–2024). APC, annual percent change.

and southwestern regions. Jeonnam recorded the highest incidence, with 78.7 cases per 100,000 population in phase III and 52.2 in phase IV (Figure 3). Based on ASIR, which adjusts for differences in regional age structure, significant increases in AAPC were observed in specific regions across each phase. In phase I, Gyeonggi showed a substantial increase of 43.96% (95% CI, 14.06%–81.21%; $p < 0.001$). In phases I and II, Jeju experienced significant increases of 36.86% (95% CI, 13.02%–66.19%; $p = 0.002$) and 30.95% (95% CI, 3.82%–64.26%; $p = 0.014$), respectively. In phase IV, increases were observed in Gwangju (14.83%; 95% CI, 1.76%–29.58%; $p = 0.028$), Chungnam (11.95%; 95% CI, 4.4%–20.1%; $p < 0.001$) and Seoul (5.33%; 95% CI, 0.37%–10.52%; $p = 0.031$) (Tables S1, S2).

Distribution of Meteorological Factors

Based on mean values across the entire study period, Tmean increased from 13.1 to 14.0 °C, RH increased from 69.7% to 72.9%, and WV decreased from 2.3 to 2.0 m/s. In phase III, precipitation was the lowest of all phases, with a monthly mean of 98.5 mm and a maximum of 676.2 mm [24] (Table S3). These temporal trends in nationwide meteorological factors were similarly observed across all administrative regions (Tables S4, S5).

Correlation Analysis

Spearman correlation analysis revealed that the incidence of scrub typhus per 100,000 population was significantly positively correlated with Tmean, RH, and SH and negatively correlated with WV. In phase IV, unlike in previous phases, no notable correlations were observed with other climatic variables, except for Tmean ($r_s = 0.146$, $p < 0.001$) and RH ($r_s = 0.191$, $p < 0.001$). Among all climatic variables, RH displayed the strongest significant correlation across all phases, particularly in phase III ($r_s = 0.339$, $p < 0.001$) (Table 2).

Time-series Regression Analyses

Lag-specific risks of meteorological variables

Using DLNM, we observed significant non-linear exposure-response relationships between scrub typhus incidence and meteorological factors, with lag periods varying by phase: 4 months in phase I, 7 months in phase II, 5 months in phase III, and 6 months in phase IV.

Using the median value of each meteorological variable as the reference, the single-variable models showed that RH exhibited the highest RR in phases I and III, whereas Tmean displayed the maximum RR in phases II and IV. In phase I, RH of 54.1% was associated with increased risk with a 4-month

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Table 1. General characteristics of annual scrub typhus cases by phase in the Republic of Korea, 2001–2024

Characteristics	Total	Phase I	Phase II	Phase III	Phase IV	p[a]
Total	149,289 (100.0)	23,915 (100.0)	36,500 (100.0)	56,309 (100.0)	32,565 (100.0)	
Sex						
Male	56,991 (38.2)	8,496 (35.5)	13,746 (37.7)	22,010 (39.1)	12,739 (39.1)	<0.001
Female	92,298 (61.8)	15,419 (64.5)	22,754 (62.3)	34,299 (60.9)	19,826 (60.9)	<0.001
Age group (y)						
0–9	1,212 (0.8)	286 (1.2)	356 (1.0)	418 (0.7)	152 (0.5)	<0.001
10–19	1,432 (1.0)	264 (1.1)	481 (1.3)	522 (0.9)	165 (0.5)	<0.001
20–29	3,089 (2.1)	547 (2.3)	818 (2.2)	1,240 (2.2)	484 (1.5)	<0.001
30–39	5,641 (3.8)	1,357 (5.7)	1,693 (4.6)	1,923 (3.4)	668 (2.1)	<0.001
40–49	13,349 (8.9)	3,327 (13.9)	4,234 (11.6)	4,454 (7.9)	1,334 (4.1)	<0.001
50–59	29,330 (19.6)	4,897 (20.5)	8,137 (22.3)	11,895 (21.1)	4,401 (13.5)	<0.001
60–69	40,981 (27.5)	7,085 (29.6)	9,623 (26.4)	14,888 (26.4)	9,385 (28.8)	0.247
70–79	37,670 (25.2)	4,899 (20.5)	8,683 (23.8)	14,784 (26.3)	9,304 (28.6)	<0.001
≥80	16,585 (11.1)	1,253 (5.2)	2,475 (6.8)	6,185 (11.0)	6,672 (20.5)	<0.001
Region						
Seoul	4,630 (3.1)	878 (3.7)	1,284 (3.5)	1,688 (3.0)	780 (2.4)	<0.001
Busan	10,588 (7.1)	1,490 (6.2)	2,992 (8.2)	3,876 (6.9)	2,230 (6.8)	0.472
Daegu	4,598 (3.1)	1,191 (5.0)	1,258 (3.4)	1,419 (2.5)	730 (2.2)	<0.001
Incheon	1,608 (1.1)	237 (1.0)	496 (1.4)	538 (1.0)	337 (1.0)	0.056
Gwangju	5,071 (3.4)	928 (3.9)	1,235 (3.4)	1,990 (3.5)	918 (2.8)	<0.001
Daejeon	5,488 (3.7)	963 (4.0)	1,778 (4.9)	1,887 (3.4)	860 (2.6)	<0.001
Ulsan	6,621 (4.4)	781 (3.3)	1,648 (4.5)	2,810 (5.0)	1,382 (4.2)	<0.001
Sejong[b]	616 (0.4)	–	88 (0.2)	341 (0.6)	187 (0.6)	<0.001
Gyeonggi	12,415 (8.3)	2,159 (9.0)	3,567 (9.8)	4,628 (8.2)	2,061 (6.3)	<0.001
Gangwon	1,274 (0.9)	295 (1.2)	324 (0.9)	509 (0.9)	146 (0.4)	<0.001
Chungbuk	5,214 (3.5)	1,261 (5.3)	1,712 (4.7)	1,558 (2.8)	683 (2.1)	<0.001
Chungnam	16,789 (11.2)	2,869 (12.0)	4,448 (12.2)	5,850 (10.4)	3,622 (11.1)	<0.001
Jeonbuk	18,126 (12.1)	3,244 (13.6)	4,983 (13.7)	6,251 (11.1)	3,648 (11.2)	<0.001
Jeonnam	20,759 (13.9)	2,646 (11.1)	3,464 (9.5)	8,925 (15.9)	5,724 (17.6)	<0.001
Gyeongbuk	10,287 (6.9)	1,992 (8.3)	2,635 (7.2)	3,508 (6.2)	2,152 (6.6)	<0.001
Gyeongnam	23,978 (16.1)	2,901 (12.1)	4,368 (12.0)	9,994 (17.7)	6,715 (20.6)	<0.001
Jeju	1,227 (0.8)	80 (0.3)	220 (0.6)	537 (1.0)	390 (1.2)	<0.001

Data are presented as *n* (%).
Phase I, 2001–2006; phase II, 2007–2012; phase III, 2013–2018; phase IV, 2019–2024.
[a]$p<0.05$ was considered to indicate statistical significance. [b]Sejong was established in April 2012 and is included in regional analyses only from phase II onward.

lag (RR, 1.37; 95% CI, 1.20–1.56), whereas in phase III, RH of 87% showed a stronger association with no lag (RR, 1.95; 95% CI, 1.73–2.21). Tmean exhibited the highest RR values in phases II and IV with no lag. Specifically, Tmean of 6.4 °C was associated with increased risk in phase II (RR, 1.62; 95% CI, 1.29–2.03) and phase IV (RR, 1.98; 95% CI, 1.53–2.58) (Figures S1A–S4A, Tables S6, S7).

In the multi-variable models, Tmean consistently demonstrated the highest RR with notable lag effects from phases II to III; for example, in phase III, the highest RR was 1.79 (95% CI, 1.25–2.57) at 25.2 °C with a 3-month lag. RH and WV remained significant predictors with elevated RR across all phases. RH increased from 83.1% to 87% over time, peaking in phase III with an RR of 1.46 (95% CI, 1.25–1.71). Moreover, RH-associated risk tended to manifest immediately, with no observable lag. In contrast, WV gradually declined from 3.4 to 1.3 m/s over the study period, accompanied by a decreasing RR trend; however, a consistent lag effect of approximately 3 to 5 months for WV was observed in all phases. Regarding SH, in phase II, the 10th percentile (130.3 hours) was associated with a maximum RR of 1.19 (95% CI, 1.05–1.34) with a 7-month lag. In comparison, phase III showed an immediate increase in RR to 1.15 (95% CI, 1.06–1.25) from the 75th to 90th percentiles (256 hours) (Figures 4A–7A, Tables 3, 4).

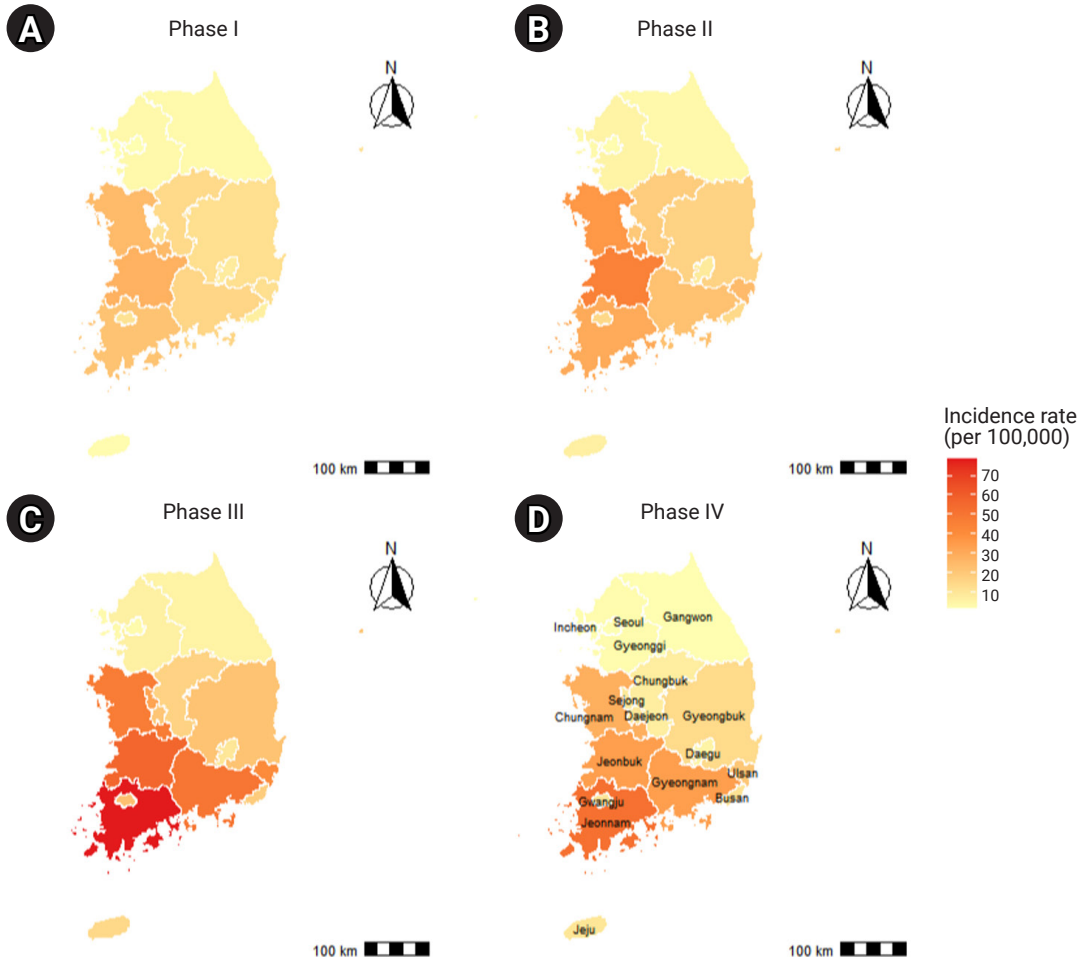


Figure 3. Geographical and temporal trends of scrub typhus in the Republic of Korea by phase. (A) Phase I (2001–2006). (B) Phase II (2007–2012). (C) Phase III (2013–2018). (D) Phase IV (2019–2024). The maps show the cumulative incidence of scrub typhus (per 100,000 population) across 17 administrative regions.

Table 2. Spearman correlation between monthly scrub typhus incidence and meteorological variables by phase in the Republic of Korea (phases I–IV)

Period	Tmean (°C)		Pr (mm)		RH (%)		WV(m/s)		SH (h)	
	r_s	p[a)]	r_s	p[a)]	r_s	p[a)]	r_s	p[a)]	r_s	p[a)]
Phase I	0.034	0.244	−0.022	0.454	0.152	<0.001	−0.136	<0.001	0.086	0.003
Phase II	0.041	0.169	−0.026	0.378	0.216	<0.001	−0.108	<0.001	0.132	<0.001
Phase III	0.143	<0.001	0.108	<0.001	0.339	<0.001	−0.118	<0.001	0.038	0.194
Phase IV	0.146	<0.001	0.038	0.183	0.191	<0.001	−0.044	0.121	0.052	0.068

Phase I, 2001–2006; phase II, 2007–2012; phase III, 2013–2018; phase IV, 2019–2024; Tmean, mean temperature; Pr, precipitation; RH, relative humidity; WV, wind velocity; SH, sunshine hours; r_s, Spearman's rank correlation coefficients.
[a)] $p < 0.05$ was considered to indicate statistical significance.

Cumulative RRs of meteorological variables

We present cumulative exposure-response relationships between meteorological variables and scrub typhus incidence, showing non-linear patterns across phases.

In the single-variable models, certain meteorological factors were associated with increased risk in phases I–III, whereas no significant weather factors were identified in phase IV (Figures S1B–S4B, Table S8).

In the multi-variable models, phase II showed significant risks for 3 variables, excluding Tmean, with RH at 84%

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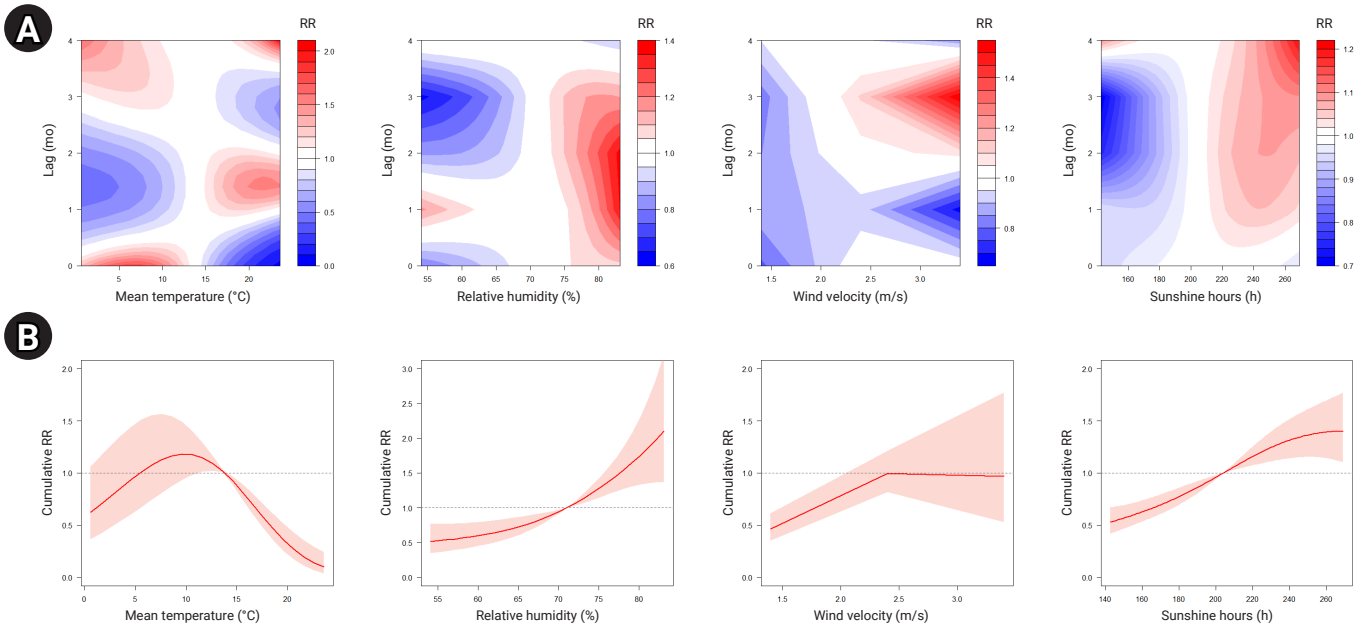


Figure 4. Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the multi-variable model for phase I. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 4 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals.

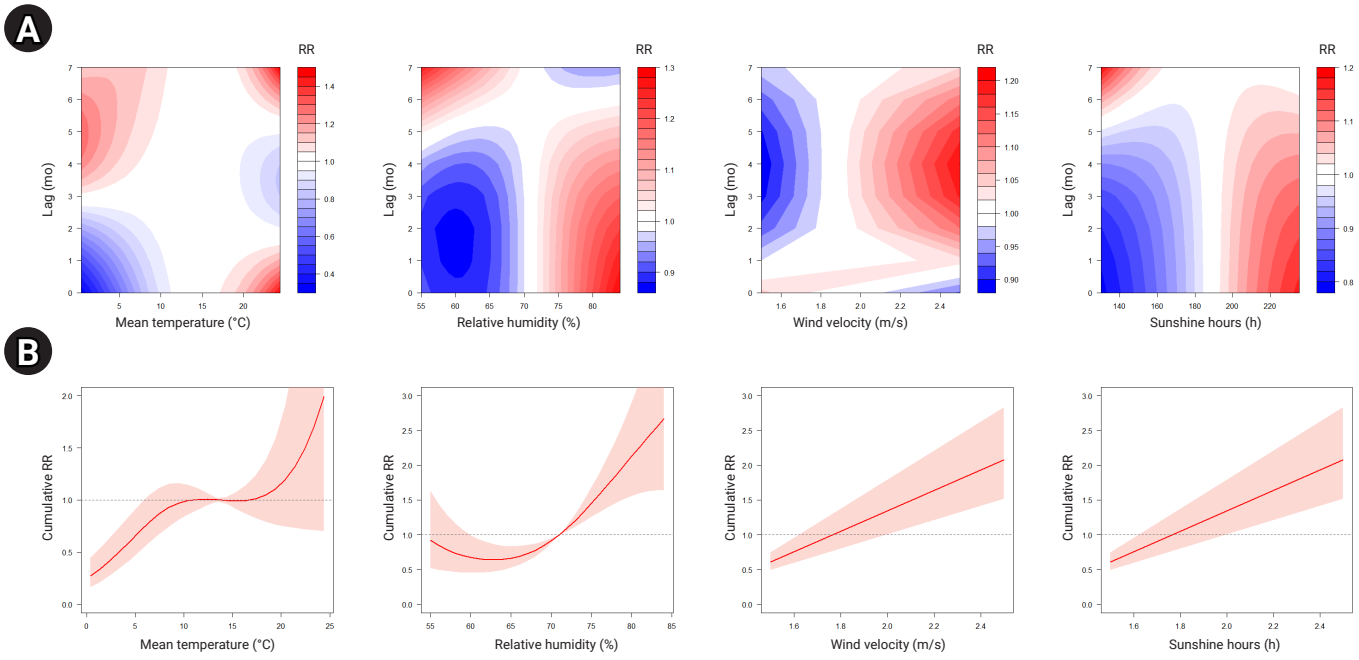


Figure 5. Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the multi-variable model for phase II. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 7 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals.

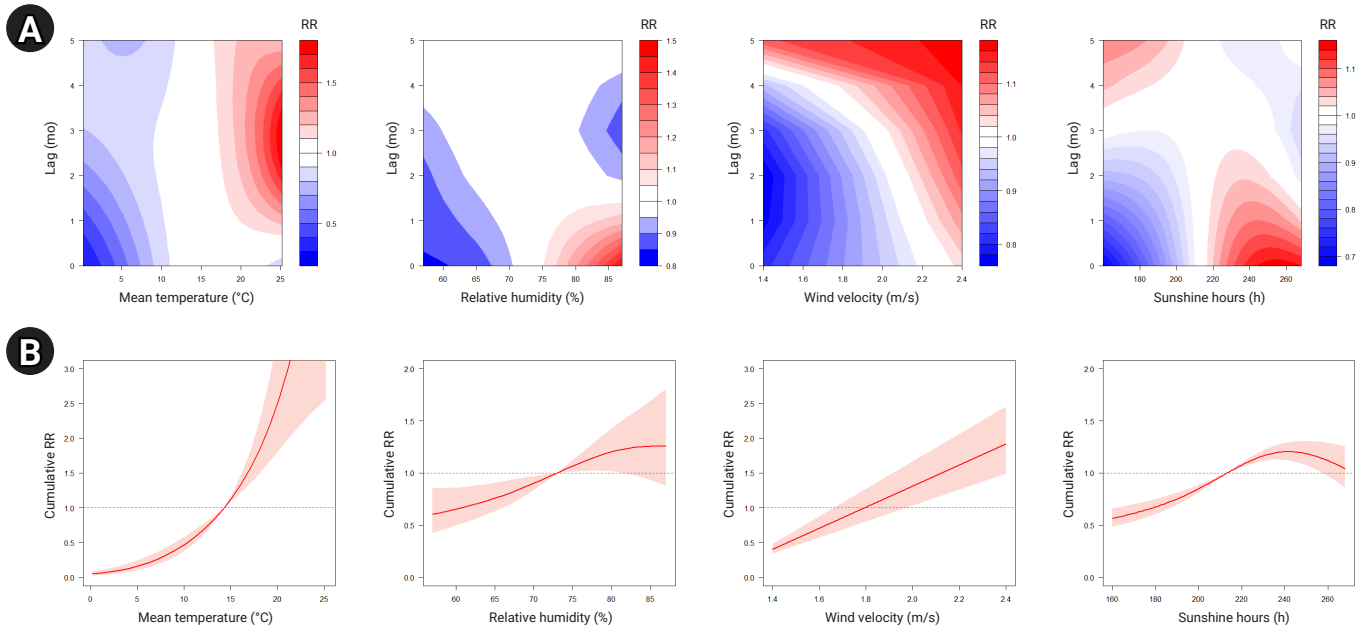


Figure 6. Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the multi-variable model for phase III. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 5 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals.

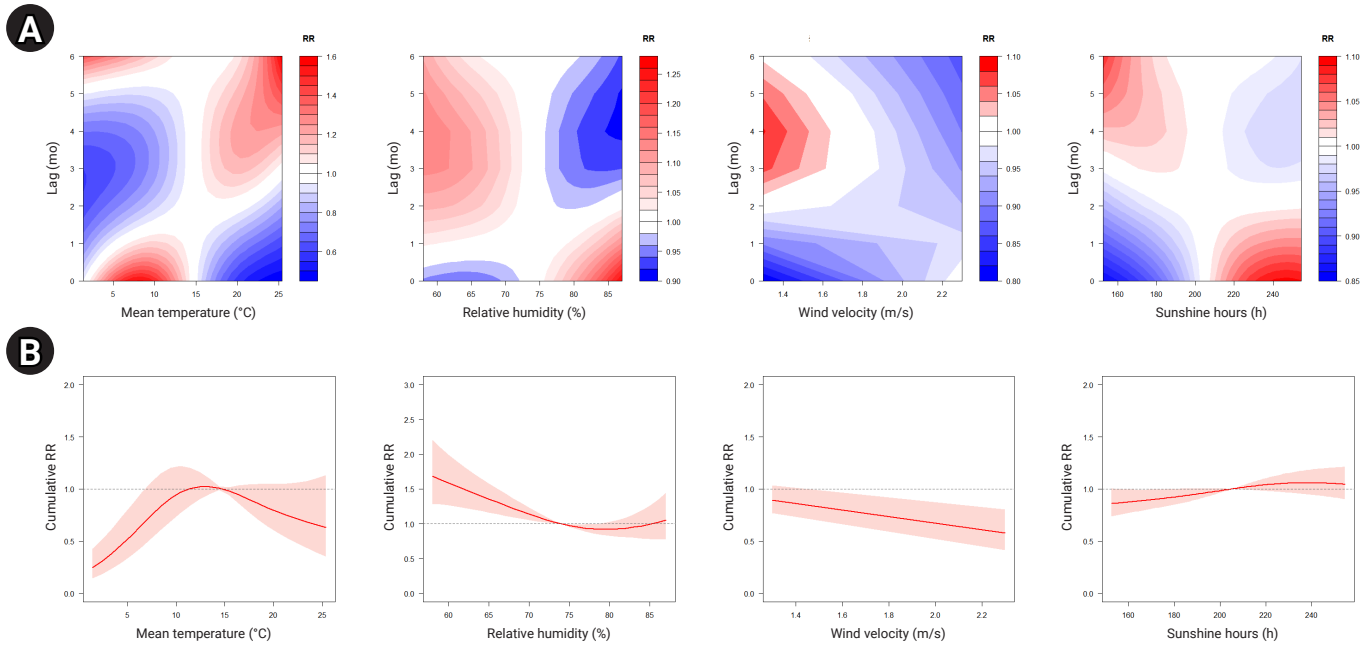


Figure 7. Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the multi-variable model for phase IV. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 6 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals.

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Table 3. RRs of meteorological parameters under different lag months by phase: multi-variable model, phases I–II (2001–2012)

Period	Lag months	Tmean (°C)	aRR (95% CI)	RH (%)	aRR (95% CI)	WV (m/s)	aRR (95% CI)	SH (h)	aRR (95% CI)
Phase I									
	0	6.6	1.76 (0.97–3.19)	83.1	1.08 (0.82–1.43)	3.4	0.99 (0.79–1.25)	221.9	1.01 (0.95–1.06)
	1	18.6	1.22 (0.86–1.74)	83.1	1.35 (1.11–1.66)	2.4	0.92 (0.84–1.01)	243.9	1.06 (0.97–1.16)
	2	19.6	1.17 (0.79–1.73)	83.1	1.37 (1.16–1.61)	3.4	1.07 (0.88–1.30)	247.9	1.08 (1.00–1.17)
	3	6.6	1.18 (0.79–1.76)	80.1	1.16 (1.00–1.34)	3.4	1.55 (1.18–2.03)	268.9	1.1 (0.92–1.32)
	4	23.6	2.04 (0.83–5.01)	60.1	1.05 (0.88–1.25)	2.4	0.96 (0.87–1.05)	268.9	1.2 (0.99–1.46)
Phase II									
	0	24.4	1.47 (0.74–2.92)	84	1.28 (1.09–1.51)	1.5	1.05 (0.95–1.15)	235.3	1.17 (1.06–1.29)
	1	24.4	1.16 (0.8–1.69)	84	1.25 (1.13–1.39)	2.5	1.03 (0.98–1.09)	235.3	1.15 (1.09–1.22)
	2	15.4	1.00 (0.98–1.03)	84	1.22 (1.12–1.33)	2.5	1.12 (1.06–1.18)	235.3	1.14 (1.09–1.18)
	3	0.4	1.03 (0.81–1.31)	84	1.18 (1.06–1.31)	2.5	1.18 (1.11–1.27)	235.3	1.11 (1.05–1.18)
	4	0.4	1.23 (0.96–1.57)	84	1.13 (1.01–1.26)	2.5	1.2 (1.12–1.28)	235.3	1.09 (1.03–1.15)
	5	0.4	1.28 (1.08–1.53)	84	1.07 (0.97–1.18)	2.5	1.17 (1.11–1.24)	231.3	1.06 (1.02–1.10)
	6	0.4	1.22 (1.02–1.47)	55	1.13 (1.01–1.27)	2.5	1.11 (1.05–1.17)	130.3	1.07 (1.00–1.15)
	7	24.4	1.49 (1.01–2.22)	55	1.26 (1.05–1.51)	2.5	1.04 (0.96–1.13)	130.3	1.19 (1.05–1.34)

RR, relative risk; phase I, 2001–2006; phase II, 2007–2012; Tmean, mean temperature; aRR, adjusted RR; CI, confidence interval; RH, relative humidity; WV, wind velocity; SH, sunshine hours.

Table 4. RRs of meteorological parameters under different lag months by phase: multi-variable model, phases III–IV (2013–2024)

Period	Lag months	Tmean (°C)	aRR (95% CI)	RH (%)	aRR (95% CI)	WV (m/s)	aRR (95% CI)	SH (h)	aRR (95% CI)
Phase III									
	0	16.2	1.02 (0.94–1.11)	87	1.46 (1.25–1.71)	2.4	1.03 (0.94–1.12)	256	1.15 (1.06–1.25)
	1	25.2	1.24 (0.92–1.68)	87	1.13 (1.03–1.23)	2.4	1.07 (1.02–1.13)	244	1.08 (1.05–1.11)
	2	25.2	1.66 (1.19–2.31)	74	1.00 (0.99–1.01)	2.4	1.11 (1.04–1.19)	236	1.04 (1.01–1.07)
	3	25.2	1.79 (1.25–2.57)	70	1.00 (0.98–1.03)	2.4	1.14 (1.07–1.22)	229	1.01 (0.99–1.03)
	4	25.2	1.56 (1.24–1.97)	71	1.00 (0.99–1.01)	2.4	1.16 (1.10–1.23)	160	1.05 (1.00–1.10)
	5	22.2	1.24 (0.96–1.60)	57	1.04 (0.9–1.21)	2.4	1.17 (1.07–1.28)	160	1.08 (0.98–1.18)
Phase IV									
	0	8.4	1.56 (1.23–1.99)	87	1.27 (1.09–1.47)	2.3	1.00 (0.91–1.09)	246.6	1.09 (1.00–1.19)
	1	10.4	1.12 (1.03–1.21)	87	1.12 (1.03–1.22)	2.3	0.97 (0.91–1.03)	249.6	1.05 (1.00–1.10)
	2	17.4	1.02 (0.98–1.07)	58	1.09 (1.00–1.18)	1.3	1.00 (0.95–1.05)	254.6	1.01 (0.95–1.06)
	3	20.4	1.17 (1.03–1.33)	58	1.13 (1.02–1.25)	1.3	1.07 (1.00–1.14)	181.6	1.01 (0.98–1.04)
	4	22.4	1.25 (1.08–1.44)	58	1.14 (1.04–1.24)	1.3	1.08 (1.03–1.14)	161.6	1.01 (0.98–1.04)
	5	25.4	1.41 (1.24–1.60)	58	1.12 (1.03–1.22)	1.3	1.06 (1.01–1.10)	152.6	1.05 (1.01–1.11)
	6	25.4	1.59 (1.18–2.15)	58	1.10 (0.95–1.27)	1.3	1.01 (0.93–1.11)	152.6	1.08 (0.99–1.18)

RR, relative risk; phase III, 2013–2018; phase IV, 2019–2024; Tmean, mean temperature; aRR, adjusted RR; CI, confidence interval; RH, relative humidity; WV, wind velocity; SH, sunshine hours.

(reference, 71%) exhibiting the highest risk (RR, 2.67; 95% CI, 1.64–4.36). In phase III, all variables except RH were significantly associated with increased risk, and Tmean at 25.2 °C (reference, 14.3 °C) displayed the highest RR (RR, 5.86; 95% CI, 2.56–13.42). In contrast, during phase IV, only RH at 58% (reference, 74%) was significantly associated with disease risk (RR, 1.68; 95% CI, 1.29–2.20) (Figures 4B–7B, Table 5).

Risk-enhancing exposure ranges

To identify specific meteorological conditions associated with increased disease incidence, we analyzed risk-enhancing exposure ranges. In the single-variable models, several meteorological variables were associated with increased risk (Table S9); however, in the multi-variable models, a clear difference emerged between phases I–III and phase IV. Specifically, during phase III, significant associations were observed for Tmean ranging from 15.2 to 25.2 °C (reference,

Table 5. Maximum cumulative RRs and corresponding meteorological variables by phase: multi-variable model, phases I–IV (2001–2024)

Period	Tmean (°C)	aRR (95% CI)	RH (%)	aRR (95% CI)	WV (m/s)	aRR (95% CI)	SH (h)	aRR (95% CI)
Phase I	-	-	83.1	2.1 (1.38–3.22)	-	-	267.9	1.4 (1.11–1.76)
Phase II	-	-	84	2.67 (1.64–4.36)	2.5	2.08 (1.52–2.84)	235.3	1.99 (1.76–2.25)
Phase III	25.2	5.86 (2.56–13.42)	-	-	2.4	1.92 (1.49–2.46)	242	1.2 (1.12–1.29)
Phase IV	-	-	58	1.68 (1.29–2.20)	-	-	-	-

RR, relative risk; phase I, 2001–2006; phase II, 2007–2012; phase III, 2013–2018; phase IV, 2019–2024; Tmean, mean temperature; aRR, adjusted RR; CI, confidence interval; RH, relative humidity; WV, wind velocity; SH, sunshine hours; -, no significant cumulative effect observed.

Table 6. Risk-associated exposure intervals for meteorological variables by phase: multi-variable model, phases I–IV (2001–2024)

Period	Tmean (°C)		RH (%)		WV (m/s)		SH (h)	
	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
Phase I	11.6	13.6	71.1	83.1	-	-	203.91	268.91
Phase II	-	-	72	84	2.5		189.3	235.3
Phase III	15.2	25.2	74	81	2.4		214.02	257.02
Phase IV	-	-	58	73	-	-	-	-

Phase I, 2001–2006; phase II, 2007–2012; phase III, 2013–2018; phase IV, 2019–2024; Tmean, mean temperature; RH, relative humidity; WV, wind velocity; SH, sunshine hours; -, no significant cumulative effect observed.

14.3 °C), RH between 74% and 81% (reference, 73%), WV at 2.4 m/s (reference, 2.0 m/s), and SH between 214.0 and 257.0 hours (reference, 213.2 hours). In phase IV, by contrast, increased incidence was significantly associated only with RH levels between 58% and 73% (reference, 74%) (Table 6).

Discussion

This study is the most comprehensive to date to evaluate the non-linear, delayed, and cumulative associations between meteorological variables and scrub typhus incidence in the Republic of Korea, spanning more than 2 decades in the context of accelerating climate change.

From 2001 to 2017, national incidence steadily increased, with a turning point in 2018, just before the 2019 revisions to case definitions. Historically, scrub typhus was concentrated in southern rural areas and predominantly affected older women. However, our findings highlight a shift; incidence has increased among older adults (≥70 years) and in central and urban regions, while the proportion of female cases has declined. These changes may reflect the combined effects of climatic, ecological, and sociodemographic factors on disease dynamics [25].

These temporal and demographic changes were paralleled by shifts in meteorological influences, with Tmean and RH emerging as key contributors to disease risk, although correlation strengths were modest—likely due to lagged effects [26]. In some tropical species of *Leptotrombidium*, the entire life cycle can be completed within 2–3 months, yielding at least 2 generations per year [27]. By contrast, in temperate regions, only a single generation per year is typically possible due to climatic constraints, consistent with previous research [28]. Our findings demonstrated an overall lagged effect of approximately 5 months (ranging from 4 to 7 months across phases) between meteorological exposure and scrub typhus incidence during 2001–2024. Given the sharp increase in cases between October and November, this pattern suggests a stronger association with climatic conditions occurring in spring to early summer. This contrasts with previous studies emphasizing summer conditions [29].

In the multi-variable models, phase III showed a peak RR of 1.79 at 25.2 °C with a 3 month lag, and the cumulative risk increased to 5.86. Incidence rose significantly within the 15.2–25.2 °C range. This period followed the "warming hiatus" and was characterized by a rapid rise in temperature [30,31], possibly promoting mite survival and reproduction and accelerating their life cycle [32]. In contrast, phase IV exhibited weaker associations and longer lag periods, with only RH at 58% showing a significant cumulative effect. The loss of statistical significance for Tmean in phase IV suggests that this pattern may reflect a new equilibrium in vector–host–climate interactions, potentially after exceeding critical thermal thresholds [33]. However, this attenuation does not preclude indirect or interacting effects with other climatic

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variables and non-climatic drivers. Non-climatic factors may include delayed ecological adaptation of vector populations, changes in agricultural practices that alter human–vector contact patterns, and modifications in surveillance systems. Meanwhile, the renewed positive trend observed in phase IV may have been influenced by mite adaptations to climatic extremes, potentially enabling habitat expansion and improved fitness [34–36], as well as anthropogenic factors such as land-use change, urbanization, and shifts in human mobility and behavior [37].

Environmental factors may affect the transmission of scrub typhus through 3 primary mechanisms: the development of vector populations, changes in host ecology, and patterns of human exposure [38].

Temperature plays a critical role in both the life cycle of *Leptotrombidium* mites and outdoor human behavior, making it a key determinant of the transmission dynamics of mite-borne diseases [39]. Mite activity is highly temperature-dependent: adult mites resume activity in spring when temperatures exceed 10 °C [25], and oviposition increases in early summer as temperatures reach 20–30 °C [40]. A temperature of approximately 23 ±1 °C has been reported to provide optimal hatching conditions for chigger mite eggs [41]. Consistent with previous studies, increased scrub typhus incidence was observed at temperatures below 25.2 °C during phases I–III in both single-variable and multi-variable models. However, in phase IV, no temperature range was significantly associated with increased incidence. The relationship between temperature and scrub typhus incidence generally follows a rise-then-decline pattern [42]. Compared with phase I, the average Tmean in phase IV was approximately 1 °C higher, possibly reflecting the accelerating effects of global warming. Once temperatures exceed certain thresholds, egg hatchability may decrease [27,41]. Moreover, extremely high temperatures may reduce outdoor human activity, thereby lowering the risk of exposure to infected chigger mites [42]. Collectively, these factors could suggest an attenuation of temperature effects in recent years.

Environmental humidity may be an important factor influencing the prevalence and geographic distribution of chigger mites and may also affect the reproduction of rodent reservoir hosts [43,44]. A study in Chile reported that chigger mites tend to thrive when RH exceeds 50%, while their activity appears to decrease markedly when humidity rises above 75%–80% or falls below 50% [44]. In our study, although the RR associated with humidity generally declined over time, consistent lagged and cumulative effects were observed through phase III, particularly under high-humidity conditions (P90). However, in phase IV, a statistically significant increase in scrub typhus incidence was observed only within the moderate humidity range of 58% to 73%. These findings suggest that RH continues to impact disease risk, with the peak-risk range potentially shifting toward more moderate levels. From a behavioral perspective, higher humidity conditions could influence human activities, such as agricultural work, which in turn might increase the likelihood of exposure to infected chigger mites.

WV influences scrub typhus transmission through effects on both vector–host interactions and environmental dispersal. Strong winds may disrupt larval attachment [45] and reduce outdoor human activity, lowering transmission risk [46]. Conversely, moderate winds associated with forested areas can aid the passive spread of chiggers, potentially increasing exposure [1]. Although most previous studies have reported positive correlations between wind speed and scrub typhus incidence [47–51], with a Korean study noting a significant association with a 5–6-month lag [50], our findings differ. In this study, WV showed a negative correlation with incidence, with lag effects ranging from 3 to 5 months. The single-variable models revealed elevated RR at low to moderate WV in earlier phases (e.g., 1.5 m/s in phase II and 2.4 m/s in phase III). However, in phase IV, no significant cumulative effect or specific risk-enhancing range was identified. This weakening association may reflect changing ecological dynamics or behavioral adaptations, indicating a need for further investigation into the evolving role of wind in disease ecology.

Chigger mites have a thin cuticle and a low capacity for water retention, making them prone to dehydration when exposed to direct sunlight for extended periods [27]. Consequently, they prefer humid, shaded environments and tend to be more active in the early morning and late afternoon. With climate change contributing to longer sunshine duration and more frequent heat waves, sunlight exposure may become increasingly important for mite survival. In our study, SH was associated with both lagged and cumulative risks in phases I–III, but no statistically significant effect was observed in phase IV. Although this suggests that light conditions may influence the ecological activity cycles of vectors and hosts, further studies are needed, as variations in seasonality and increasingly unpredictable weather linked to climate change may have obscured these effects.

When considered alongside the results for temperature, humidity, wind, and sunshine, these findings indicate that the climatic drivers of scrub typhus risk have become more variable and phase-dependent in recent years. These shifts support the need for dynamic, climate-responsive risk assessment frameworks capable of adapting to changes in the relative importance and timing of different

meteorological factors.

This study has several limitations. First, infectious diseases such as scrub typhus should be understood from a macro-level perspective. The sustained increase in case fatality from 2020 to 2023 is presumed to be partly attributable to coronavirus disease 2019, which may have influenced scrub typhus incidence through reduced healthcare utilization, altered healthcare-seeking behavior, and restricted community mobility. These observations highlight the need for long-term assessments of the burden of scrub typhus and underscore the importance of public health campaigns aimed at improving awareness and prevention among older and high-risk populations. Second, because climate change is a gradual and continuous process, robust analysis of meteorological trends generally requires at least 10 years of data. In this study, however, the observation period was divided into 6-year phases to explore temporal dynamics; therefore, our findings should be re-evaluated using longer observation windows to more accurately capture long-term effects. Lastly, although scrub typhus incidence may be influenced by both geographic and socioeconomic factors, this study considered only meteorological variables. Future research should incorporate additional covariates—such as land-use change, the Normalized Difference Vegetation Index, population density, and income levels—to better adjust for potential confounding.

Conclusion

This study suggests that the influence of meteorological factors on scrub typhus has evolved over time. In earlier years, relatively stable climate conditions produced more predictable disease–weather patterns, whereas in recent years increasing climate variability and instability have introduced greater uncertainty into risk prediction. The climate–scrub typhus relationship appears dynamic and non-linear and is likely to continue changing under ongoing climate change.

To address these challenges, future surveillance and early warning systems should move beyond reliance on traditional climate averages and adopt composite indices that capture the intensity, frequency, and variability of extreme weather events. Such adaptive, climate-responsive strategies may improve the timing and targeting of public health interventions, particularly in high-risk regions where both climate and demographic profiles are shifting rapidly.

Supplementary Material

Figure S1. Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the single-variable model for phase I. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 4 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals; **Figure S2.** Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and three meteorological conditions in the single-variable model for phase II. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 7 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals; **Figure S3.** Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the single-variable model for phase III. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 5 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals; **Figure S4.** Contour plots and cumulative exposure-response curves of exposure-response relationships between scrub typhus incidence and 4 meteorological variables in the single-variable model for phase IV. (A) Contour plots. The x-axis represents the range of observations for each meteorological variable and the y-axis indicates lag periods from 0 to 6 months. The color gradient represents relative risk (RR). Red represents RR >1, blue represents RR <1, and white represents no difference when RR=1. (B) Cumulative exposure-response curves. The x-axis represents the range of observations for each variable and the y-axis represents the cumulative RR, while the shaded areas denote the corresponding 95% confidence intervals; **Table S1.** AAPC in scrub typhus cases by region in Republic of Korea, phases I–II (2001–2012); **Table S2.** AAPC in scrub

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typhus cases by region in Republic of Korea, phase III–IV (2013–2024); **Table S3.** Descriptive statistics of meteorological variables by phase in Republic of Korea, 2001–2024; **Table S4.** Monthly mean meteorological variables by region in Republic of Korea, phases I–II (2001–2012); **Table S5.** Monthly mean meteorological variables by region in Republic of Korea, phase III–IV (2013–2024); **Table S6.** RRs of meteorological parameters under different lag months by phase: single-variable model, phases I–II (2001–2012); **Table S7.** RRs of meteorological parameters under different lag months by phase: single-variable model, phase III–IV (2013–2024); **Table S8.** Maximum cumulative RRs and corresponding meteorological variables by phase: single-variable model, phase I–IV (2001–2024); **Table S9.** Risk-associated exposure intervals for meteorological variables by phase: single-variable model, phase I–IV (2001–2024). Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0177.

Notes

Ethics Approval

This study was approved by the Korea Disease Control and Prevention Agency Institutional Review Board (No. KDCA-2025-04-04-PE-01) and was performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because the study retrospectively collected de-identified data.

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. Additional data may be requested from the corresponding author.

Authors' Contributions

Conceptualization: YK, HYL; Data curation: HYL; Formal analysis: HYL; Investigation: HYL; Methodology: HYL; Project administration: YK, JRK; Software: HYL; Supervision: YK, Validation: HYL, YK, JRK; Visualization: HYL; Writing–original draft: HYL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Impact of intimate partner violence during pregnancy on maternal mental health and child development: a birth cohort study in central Vietnam

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ABSTRACT

Objectives: This study measured the impact of prenatal intimate partner violence (p-IPV) on maternal mental health and suspected developmental delays (SDDs) in children at 6 months of age in central Vietnam.

Methods: Data were drawn from a community-based birth cohort of 285 mother–child dyads in Hue, central Vietnam. The exposure factor was p-IPV, assessed using the revised conflict tactics scale (CTS2). Maternal mental health was measured with the patient health questionnaire-9. Child development at 6 months was screened using the Vietnamese version of the Ages and Stages Questionnaire, 3rd Edition (ASQ-3). Robust Poisson regression was used to estimate associations of p-IPV with maternal mental health and SDDs.

Results: Among the women, 18.9% reported experiencing p-IPV. SDDs were identified in 13% of the children, with communication delays being the most prevalent (10.9%). The association between p-IPV and SDDs remained significant after adjustment for confounders in multilevel models, with the highest relative risk (RR) observed in the fully adjusted model (RR, 2.43; 95% confidence interval [CI], 1.08–5.48). p-IPV exposure was significantly associated with postpartum depression in the crude and partially adjusted models, but this association became non-significant after full adjustment—most notably after accounting for prenatal depression, which remained a predictor of postpartum depression (RR, 1.15; 95% CI, 1.06–1.25).

Conclusion: p-IPV is significantly associated with increased risk of postpartum depression and developmental delays in early infancy. Integrating IPV screening and targeted interventions into prenatal care may contribute to improved developmental outcomes in children and better maternal health.

Keywords: Child development; Intimate partner violence; Longitudinal studies; Pregnancy

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Introduction

Background

Prenatal intimate partner violence (p-IPV) is defined as any physical, sexual, or psychological harm perpetrated by a current or former partner during pregnancy [1]. The impact of p-IPV on pregnancy outcomes is complex and far-reaching. It is associated with adverse birth outcomes, including low birth weight, preterm delivery, and neonatal intensive care unit admission [2]. These early-life adversities can have long-lasting effects on children's health, cognitive development, and socio-emotional well-being [3–5]. Several studies have shown that exposure to p-IPV is linked to cognitive deficits, behavioral problems, and emotional difficulties in children, as well as increased risks of internalizing and externalizing problems in later childhood and adolescence [6–8]. A comprehensive review of IPV during pregnancy found that women who experience IPV may also be at risk of developmental delays in their offspring, including impairments in socializing, self-care abilities, and gross and fine motor skills [1]. Research in 11 low- and middle-income countries (LMICs) likewise found that p-IPV negatively impacts early child development [9]. This is consistent with findings from other prospective cohorts, including a 2025 study by Jiang et al. [10], which highlighted the detrimental effects of IPV during pregnancy on early child development. Furthermore, a 2025 systematic review by Tsunga et al. [11] synthesized evidence linking exposure to violence with adverse cognitive outcomes among children in LMICs.

Research on the impact of p-IPV on child development is critically important, as it clarifies how early exposure to violence can influence children's neurodevelopment, cognition, and behavior. These complex biopsychosocial mechanisms must be understood to design effective, developmentally appropriate interventions. However, most existing studies in LMICs rely on cross-sectional designs or retrospective reporting, limiting the ability to establish causality and to track developmental trajectories over time [12].

In Vietnam, a recent analysis of 15 studies indicated that p-IPV is a significant issue, affecting approximately 32% of pregnant women [13]. Several Vietnamese studies have documented the detrimental effects of IPV on maternal and child health outcomes. A qualitative survey by Nhi et al. [14] in 2018 found that emotional violence, such as controlling behaviors, verbal humiliation, and isolation, was prevalent among women in northern Vietnam and significantly impacted their psychological well-being, contributing to anxiety, depression, and feelings of powerlessness. In a longitudinal study, Tho Nhi et al. [15] demonstrated that exposure to IPV during pregnancy, particularly emotional and physical violence, was strongly associated with an increased risk of postpartum depression, with a clear dose–response relationship. Similarly, Vo et al. [16] reported that IPV was significantly associated with adverse birth outcomes, including preterm birth and low birth weight, highlighting the urgent need for IPV screening and intervention during antenatal care to protect both maternal and infant health.

Another prospective cohort study of 1,276 pregnant women in Dong Anh district found that those exposed to physical violence had 5 times the risk of preterm birth and nearly 6 times the risk of low birth weight compared with those not exposed [17]. Across 42 demographic and health surveys in 29 resource-poor countries from 1998 to 2012, analyses also found a negative association between child wasting and IPV of all forms [18].

While existing Vietnamese studies have established important links between IPV and adverse birth outcomes or postpartum depression, a critical gap remains concerning the longitudinal impact of p-IPV on specific multidomain early child development outcomes. To our knowledge, no prospective birth cohort study in Vietnam has used a validated developmental screening tool such as the Ages and Stages Questionnaire, 3rd Edition (ASQ-3), to track the consequences of p-IPV from pregnancy through the first 6 months of life. Our study was designed to fill this evidence

HIGHLIGHTS

- This birth cohort study examined the impact of prenatal intimate partner violence (p-IPV) on birth outcomes, maternal mental health, and child development at 6 months in Vietnam. It addressed gaps in the literature with a prospective design, moving beyond common cross-sectional approaches.
- Among participants, 18.9% reported experiencing at least 1 form of p-IPV (psychological, physical, or sexual violence).
- p-IPV was associated with a 1.76-fold increased risk of postpartum depression and a 2.05-fold increased risk of suspected developmental delays in children at 6 months.
- Routine antenatal care must incorporate IPV and mental health screening to improve maternal and child health trajectories.

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gap by providing robust, prospective data from central Vietnam.

Objectives

This study aims to measure the impact of p-IPV on birth outcomes, maternal mental health, and suspected developmental delays (SDDs) in children at 6 months of age in central Vietnam.

Materials and Methods

Study Design and Participants

From July 2023 to July 2024, a birth cohort study was conducted in Hue, Thua Thien-Hue province, central Vietnam. The target population comprised pregnant women in their third trimester who lived in the city at the time of recruitment. A stratified 2-stage cluster sampling method was employed. In the first stage, 8 wards/communes were randomly selected from the 36 in Hue, with equal representation from both sides of the Perfume River: 4 from the northern area and 4 from the southern area. In the second stage, all women in their third trimester within the selected wards/communes were identified from official pregnancy lists maintained by local commune health centers. According to the Thua Thien-Hue Provincial Population and Family Planning Division, these areas included approximately 1,334 pregnant women in 2023, of whom 446 were in their third trimester. A total population sampling approach was applied to this subgroup. Eligible participants were contacted by trained research staff in collaboration with local health workers, either in person or by phone.

Women were provided with information about the study's objectives, procedures, and confidentiality protections. Those who expressed interest were formally invited to participate. At baseline, data were collected either at the commune health station or at the participant's home, according to the woman's preference and convenience. In both settings, interviews were conducted privately and confidentially to ensure participant safety and comfort, particularly when discussing sensitive topics such as IPV.

For follow-up, trained investigators visited participants at home at predetermined time points after delivery. These visits included structured interviews and developmental assessments of the child. All study procedures were carried out in accordance with ethical guidelines to ensure voluntary participation and data privacy. Women with known severe medical or psychiatric conditions, or those planning to relocate outside the study area within the following year, were excluded.

Measures

Maternal characteristics

Measures for pregnant women included demographic factors, socioeconomic status, prenatal health and reproductive history, adverse childhood experiences (ACEs), community and social support, and prenatal depression (phase 1). Participants also retrospectively reported experiences before age 18 across multiple domains.

ACEs

We used an adapted version of the ACE-International Questionnaire, incorporating 9 of 13 domains, and the pregnant women retrospectively reported adverse experiences before age 18 years [19]. The 9 domains included in this study were emotional abuse; physical abuse; contact sexual abuse; an alcohol and/or drug abuser in the household; an incarcerated household member; a household member who was chronically depressed, mentally ill, institutionalized, or suicidal; a household member treated violently; one or no parents, parental separation, or divorce; and physical neglect. ACEs were scored using a binary method. For each domain, if a participant reported experiencing an event at any frequency (i.e., once, a few times, or many times), a score of "1" was assigned (indicating the presence of an ACE). If the participant reported never experiencing that event, it was scored as "0." The binary ACE score was then calculated by summing the scores across all 9 domains, yielding a total score ranging from 0 to 9 [20].

Community and social support

The multidimensional scale of perceived social support was used to evaluate community and social support [21]. The scale includes 12 items assessing support from family, friends, and a significant other. Each item was rated on a 5-point Likert scale ranging from 1 (very strongly disagree) to 5 (very strongly agree). Higher scores reflect greater perceived social support.

Prenatal depression

The patient health questionnaire-9 (PHQ-9) was used to assess the severity of depressive symptoms experienced over the past 2 weeks [22]. This tool evaluates the 9 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for depression, including anhedonia, dysphoria, sleep disturbances, fatigue, changes in appetite, low self-esteem, concentration difficulties, psychomotor retardation or agitation, and thoughts of suicide or homicide. Each item was rated on a 4-point Likert scale: 0, not at all; 1, several days; 2, more than half the days; or 3, nearly every day. The total score ranged from 0 to 27. A PHQ-9 score of

5 or higher was used as the cut-off for identifying possible depressive disorder, consistent with its widespread use in global mental health research [22,23].

Prior pregnancy risk

Prior pregnancy risk was defined as having experienced at least 1 of the following in a previous pregnancy: stillbirth, miscarriage, abortion, or preterm birth.

Neighborhood characteristics

We used an instrument developed by the Evidence for Better Lives Consortium to measure neighborhood characteristics in 8 LMICs, including Vietnam [24]. This 18-item questionnaire assesses aspects including neighborhood cohesion, intergenerational closure, neighborhood disorder, and social disorder. Each item is rated on a 4-point scale ranging from 1 (not a problem) to 4 (a large problem). A composite score was calculated, with higher scores indicating less favorable neighborhood conditions.

Exposure

p-IPV

The revised conflict tactics scale (CTS2) was employed to assess experiences of partner violence during pregnancy [25,26]. The CTS2 uses a 4-point Likert scale (0, never; 1, once; 2, 2–5 times; and 3, more than 5 times) that allows participants to report the frequency of exposure both over their lifetime and in the past 6 months. This widely used quantitative measure is a modification of the original conflict tactics scale (CTS, 1996) [25]. Although the CTS2 can be applied to various populations, including perpetrators, victims, and witnesses of domestic violence, our study focused on victims. We utilized 21 relevant items to evaluate 3 types of IPV: physical, psychological, and sexual violence. Participants with a total score ≥1 were considered to have experienced at least 1 form of p-IPV. The CTS2 was administered at the third-trimester baseline visit, and women were asked to report violent acts experienced during the current pregnancy. Pregnant women who experienced at least 1 type of IPV were considered IPV-exposed during the current pregnancy (phase 1).

Outcomes

The follow-up measures (phases 2–3) collected data on mothers' mental health, birth outcomes, and child developmental outcomes, as follows.

Birth outcomes

Two key variables were extracted from health records: maternal delivery mode (cesarean section or vaginal birth) and infant birth weight.

Assessment of developmental performance in children

The ASQ-3 was used to screen and assess children's developmental performance in communication, gross motor skills, fine motor skills, problem-solving, and personal–social skills between the ages of 1 month and 5½ years [27]. For the 6-month questionnaire, the sensitivity of the ASQ-3 has been reported as 75% and the specificity as 92% [28]. The ASQ-3 is versatile and available in multiple languages, making it suitable for various settings, including homes, clinics, preschools, and early intervention programs [29]. In Vietnam, the ASQ-3 was adapted by the Pediatric Rehabilitation Department to fit local conditions and was approved by the Ministry of Health [30]. The ASQ-3 comprises 20 questionnaires designed to assess developmental performance across the domains above. Each question has 2 response options: yes or no. Based on the responses, a final evaluation determines whether a child is suspected of having a developmental disorder. A child is considered at risk based on an answer of "no" to 2 of 3 skills in 5 areas, or "yes" to any one of the 5 additional abnormal signs [30].

Postpartum depression

The PHQ-9 was also used to assess postpartum depressive symptoms, using the same scoring approach as for prenatal depression [22]. The total score ranged from 0 to 27.

Data Collection

At baseline, data were collected through face-to-face interviews conducted in private rooms within community health centers (CHCs) to ensure privacy and confidentiality. During follow-up, health workers conducted interviews and children's developmental assessments during home visits under the supervision of research team members. Eight CHC health workers were recruited as interviewers. Both data collectors and supervisors completed a 2-day training session covering interviewing techniques, the study's purpose, the importance of privacy, the sensitivity of the topics, and the need for confidentiality and a respectful approach toward respondents.

Statistical Methods

Participant characteristics were summarized using frequencies and percentages for categorical variables, means with standard deviations for normally distributed continuous variables, and medians with interquartile ranges (Q1, Q3) for non-normally distributed continuous variables. Depending on distribution, group comparisons were performed using independent t-tests for normally distributed variables or Mann-Whitney U-tests for non-

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normally distributed variables. The association between p-IPV, maternal mental health, and SDDs was assessed using robust Poisson regression, which provides more accurate estimates of relative risk (RR), particularly when variance is underestimated by standard Poisson regression applied to binary outcomes [31,32]. Covariates were selected based on the prior literature, subject-matter expertise, and theoretical relevance as potential confounders [12,33,34]. All statistical tests were 2-sided, and results were considered statistically significant at a p-value of less than 0.05. Data were analyzed using IBM SPSS ver. 26.0 (IBM Corp.).

Ethics Approval

This study was approved by the Ethical Review Committee of University of Medicine and Pharmacy, Hue University (No: H2023/146, dated May 22, 2023). Informed consent was confirmed by the institutional review board.

Results

At baseline, 312 pregnant women aged 18 years or older were recruited. Participants were followed up at 1 and 6 months postpartum, with response rates of 98% and 91%, respectively. The primary reason for loss to follow-up was the inability to contact women who had moved to a new residence (Figure 1).

Table 1 provides a detailed comparison of participant characteristics stratified by p-IPV exposure among the sample of 285 individuals. Overall, 18.9% of participants experienced p-IPV, with psychological IPV the most prevalent (15.1%); physical and sexual IPV were reported in 2.5% and 8.1%, respectively. Maternal age was similar across groups, averaging approximately 29.6 years (p=0.667). Maternal employment status varied, with a higher proportion of government officials in the group without p-IPV exposure, but a higher proportion of freelancers among those exposed to p-IPV. Maternal education levels showed no significant association with p-IPV exposure (p=0.525), with higher education being the most common overall (40.7%). Pregnancy-related factors, including prior pregnancy risk and current pregnancy illness, were not significantly associated with p-IPV exposure. However, psychosocial factors such as ACE score (median score, 12.0 vs. 1.0; p<0.001) and prenatal depression (median score, 4.0 vs. 2.0; p<0.001) displayed notable differences between groups. Perceived social support (median score, 3.8 vs. 4.0; p<0.001), and neighborhood characteristics (mean score, 33.6 vs. 26.5; p<0.001) were significantly worse for the p-IPV group. Most mothers had no previous pregnancies (38.6%), or only one (36.8%). A large proportion reported no history of stillbirths or miscarriages, preterm births, and abortions (Table S1).

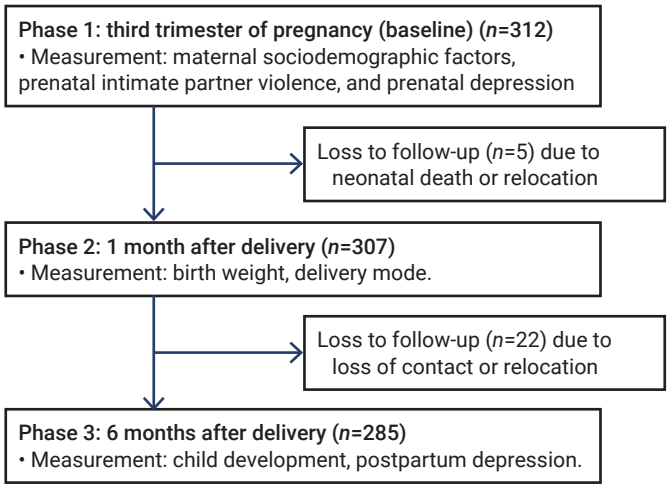


Figure 1. Diagram of the study.

Table 2 presents the prevalence of SDDs across the 5 domains. Communication delays were the most prevalent, affecting 31 children (10.9%). In contrast, gross motor and fine motor delays were identified in only 1 child each (0.4%). Problem-solving delays were observed in 4 children (1.4%), while social–personal delays were noted in 2 children (0.7%). Overall, 37 children (13%) exhibited suspected delays in at least 1 domain, with communication being the most frequently affected area.

Table 3 presents a multilevel analysis examining the association between p-IPV exposure and SDDs in 6-month-old children. The analysis includes crude estimates and 3 adjusted models that incorporate maternal sociodemographic, pregnancy- and birth-related, psychosocial, and environmental factors. The crude analysis indicates that p-IPV exposure is significantly associated with SDDs. This association remained significant across all adjusted models, with model 3 displaying the highest RR (2.43; 95% CI, 1.08–5.48; p=0.033). In model 3, the absence of prior pregnancy risk demonstrated a protective effect (RR, 0.42; 95% CI, 0.19–0.91; p=0.028).

Regarding the prevalence of postpartum depression, among 285 participants, 55 women (19.3%) were identified as having at least minimal depressive symptoms, while 230 (80.7%) did not show signs of depression. Table 4 presents a multilevel analysis of the association between p-IPV and postpartum depression at 6 months, showing that p-IPV exposure was significantly associated with increased risk in the crude model (RR, 1.76; 95% CI, 1.06–2.90; p=0.028), model 1 (adjusted for maternal sociodemographic factors; RR, 1.70; 95% CI, 1.05–2.78; p=0.033), and model 2 (further adjusted for pregnancy- and birth-related factors; RR, 1.66; 95% CI, 1.01–2.74; p=0.047). However, this association became non-

Table 1. Participant characteristics of the total sample, stratified by p-IPV

Characteristic	Category	Total (*n* = 285)	p-IPV exposure (*n* = 54)	No p-IPV (*n* = 231)	*p*
p-IPV	Overall p-IPV	54 (18.9)			
	Psychological p-IPV	43 (15.1)			
	Physical p-IPV	7 (2.5)			
	Sexual p-IPV	23 (8.1)			
Maternal sociodemographic factors	Maternal age (y)	29.6 ± 5.3	29.9 ± 5.1	29.5 ± 5.4	0.667
	Maternal employment status				0.093
	Business/trading	49 (17.2)	9 (16.7)	40 (17.3)	
	Government official	60 (21.1)	11 (20.3)	49 (21.2)	
	Freelance	99 (34.7)	21 (38.9)	78 (33.8)	
	Not working	77 (27.0)	13 (24.1)	64 (27.7)	
	Maternal education				0.525
	Elementary school	25 (8.8)	2 (3.7)	23 (9.9)	
	Middle school	66 (23.2)	14 (25.9)	52 (22.5)	
	High school	78 (27.4)	15 (27.8)	63 (27.3)	
	Higher education	116 (40.7)	23 (42.6)	93 (40.3)	
	Subjective social status		5.3 ± 1.3	5.5 ± 1.3	0.503
Paternal sociodemographic factors	Paternal age (y)	32.5 ± 5.9	33.1 ± 5.4	33.3 ± 6.0	0.298
	Paternal education				0.595
	Elementary school	25 (8.8)	3 (5.6)	22 (9.5)	
	Middle school	81 (28.4)	14 (25.9)	67 (29.0)	
	High school	82 (28.8)	19 (35.2)	63 (27.3)	
	Higher education	97 (34.0)	18 (33.3)	79 (34.2)	
	Paid work in the past 12 mo				
	Yes	274 (96.1)	52 (96.3)	222 (96.1)	0.947
	No	11 (3.9)	2 (3.7)	9 (3.9)	
Pregnancy and birth-related factors	Prior pregnancy risk				0.509
	No	261 (91.6)	50 (92.6)	211 (91.3)	
	Yes	24 (8.4)	4 (7.4)	20 (8.7)	
	Current pregnancy illness				0.558
	No	235 (82.50)	46 (85.2)	189 (81.8)	
	Yes	50 (17.50)	8 (14.8)	42 (18.2)	
	Delivery mode				0.429
	Vaginal delivery	151 (53.0)	26 (48.1)	125 (54.1)	
	Cesarean delivery	134 (47.0)	28 (51.9)	106 (45.9)	
	Birth weight (g)	3.200 (3.000, 3.400)	3.200 (2.975, 3.400)	3.200 (3.000, 3.400)	0.678[a]
Psychosocial and environmental factors	Adverse childhood experiences[b]	1.0 (0.0, 2.0)	2.0 (1.0, 2.0)	1.0 (0.0, 1.0)	< 0.001[a]
	Prenatal depression	2.0 (0.0, 4.0)	4.0 (2.0, 5.0)	2.0 (0.0, 3.0)	< 0.001[a]
	Perceived social support[c]	4.0 (3.8, 4.4)	3.8 (3.6, 4.0)	4.0 (3.8, 4.4)	< 0.001[a]
	Neighborhood characteristics[d]	26.0 (20.0, 32.0)	32.0 (25.0, 42.0)	25.0 (19.0, 29.0)	< 0.001[a]

Data are presented as *n* (%), mean ± standard deviation, or median (Q1, Q3).
p-IPV, prenatal intimate partner violence.
[a]Mann-Whitney U-test. [b]Adverse childhood experiences (ACEs) were measured with an adapted version of the ACE-International Questionnaire, which ranged from 0–9; one point was assigned for each experience reported, regardless of frequency. [c]Perceived social support was measured with the multidimensional scale of perceived social support, which ranged from 1–7; higher scores reflect greater perceived social support. [d]Neighborhood characteristics were measured with the 18-item Evidence for Better Lives Consortium questionnaire, which ranged from 18–72; higher scores indicate less favorable neighborhood conditions.

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Table 2. Prevalence of SDDs by ASQ-3 domain

ASQ-3 domain	No. of children with SDDs	Prevalence (%)
Communication	31	10.9
Gross motor	1	0.4
Fine motor	1	0.4
Problem solving	4	1.4
Social–personal	2	0.7
At least 1 domain	37	13.0

SDD, suspected developmental delay; ASQ-3, Ages and Stages Questionnaire, 3rd Edition.

significant in model 3, which also adjusted for psychosocial and environmental factors. Notably, prenatal depression was a significant predictor of postpartum depression in the fully adjusted model (RR, 1.15; 95% CI, 1.06–1.25; $p = 0.001$), while other factors such as maternal age, education, delivery mode, and social support did not show significant associations in the final model.

Discussion

Key Findings

Our community-based longitudinal study identified significant associations of p-IPV with SDDs in children at 6 months of age and postpartum depression among mothers. Specifically, exposure to p-IPV was associated with a 2.5-fold increased risk of developmental delays. Using a prospective cohort design, our study builds on the existing literature, which in this region has often relied on cross-sectional data, thereby strengthening temporal evidence regarding the effects of p-IPV. These findings underscore the need for routine screening for IPV during antenatal care and the implementation of timely interventions to support maternal mental health, promote early child development, and ensure maternal well-being.

Our results align with prior research indicating that p-IPV negatively affects early childhood development. A cross-sectional analysis by Jeong et al. [9] found that children of mothers who experienced p-IPV had significantly lower developmental scores (β = −0.11; 95% CI, −0.15 to −0.07) in LMICs. Similarly, a systematic review by Toso et al. [35] concluded that nearly 75% of observational studies found a significant association between maternal exposure to violence and impaired neurodevelopment in children.

In Vietnam, research on the impact of IPV on child development is limited in the public health literature, especially longitudinal studies with a birth cohort design [17,18]. In a 2021 study, Do et al. [33] examined the impact of p-IPV on birth outcomes. The findings indicate that p-IPV is significantly associated with adverse neonatal outcomes, including low birth weight, preterm birth, and admission to neonatal intensive care.

p-IPV can negatively affect child development through both psychosocial and biological pathways. It disrupts maternal attachment and parenting behaviors, leading to insecure attachment and an increased risk of emotional and behavioral problems in children [36–42]. Biologically, p-IPV activates maternal stress responses, especially the hypothalamic–pituitary–adrenal axis, resulting in elevated cortisol levels that cross the placenta and interfere with fetal brain development [43–45]. These changes are associated with altered brain structures and disrupted neural connectivity, particularly in regions involved in emotional regulation and cognitive function [46]. Moreover, the developmental delays identified at 6 months may not be solely attributable to the prenatal environment. The presence of p-IPV is a strong predictor of postnatal IPV, meaning that the violent and stressful household environment may have continued after birth [47]. Furthermore, maternal stress and depression resulting from IPV can impair parenting capacity, potentially increasing the risk of direct child neglect or insensitive parenting during the first 6 months of life [48–50]. These postnatal factors could mediate the effects of prenatal exposure or act as independent contributors to the observed developmental delays.

Association between p-IPV and postpartum depression

Our findings highlight the complex interplay between violence exposure, mental health, and social factors in maternal health outcomes. First, the results indicate that p-IPV is associated with postpartum depression. This association appears geographically consistent across settings: studies from Vietnam, Bangladesh, and Latin America have reported that p-IPV approximately doubles the risk of postpartum depression [51–53]. Furthermore, a systematic review including 131,131 participants across 33 studies worldwide confirmed a strong and consistent association between p-IPV and increased risk of postpartum depression [54]. Second, our results indicate that while p-IPV was initially associated with postpartum depression, this relationship may operate through pathways involving pre-existing depression and other psychosocial factors. Our finding that the association between p-IPV and postpartum depression was attenuated to non-significance after adjusting for prenatal depression suggests a strong mediating pathway. It is plausible that p-IPV primarily exerts an indirect influence on postpartum mental health—that is, as a potent risk factor for the onset or exacerbation of depressive symptoms during pregnancy. This prenatal

Table 3. Multilevel analysis of the association between p-IPV and suspected developmental delays in children at 6 months

Characteristic	Category	Crudwe		Model 1[a]		Model 2[b]		Model 3[c]	
		RR (95% CI)	*p*	RR (95% CI)	*p*	RR (95% CI)	*p*	RR (95% CI)	*p*
p-IPV	p-IPV exposure	2.05 (1.10–3.82)	0.023[d]	2.42 (1.28–4.57)	0.006[d]	2.36 (1.26–4.43)	0.007[d]	2.43 (1.08–5.48)	0.033[d]
	No p-IPV	1		1		1			
Maternal sociodemographic factors	Maternal age			0.97 (0.91–1.04)	0.385	0.93 (0.85–1.02)	0.113	0.92 (0.83–1.02)	0.101
	Maternal employment status								
	Business/trading			0.54 (0.20–1.45)	0.221	0.65 (0.22–1.86)	0.419	0.64 (0.22–1.8)	0.394
	Government official			0.52 (0.19–1.40)	0.195	0.68 (0.23–1.96)	0.472	0.74 (0.25–2.22)	0.592
	Freelance			0.76 (0.37–1.16)	0.457	0.84 (0.38–1.84)	0.665	0.87 (0.39–1.93)	0.728
	Not working			1		1		1	
	Maternal education								
	Elementary school			2.51 (1.14–5.50)	0.022[d]	2.27 (0.84–6.11)	0.106	2.4 (0.88–6.53)	0.086
	Middle school			0.85 (0.34–2.10)	0.717	0.75 (0.29–1.97)	0.561	0.77 (0.29–2.01)	0.588
	High school			0.61 (0.25–1.50)	0.281	0.55 (0.19–1.65)	0.290	0.57 (0.18–1.75)	0.323
	Higher education			1		1		1	
	Subjective social status			1.25 (1.00–1.57)	0.553	1.06 (0.82–1.38)	0.646	1.07 (0.82–1.4)	0.613
Paternal sociodemographic factors	Paternal age					1.03 (0.95–1.13)	0.424	1.04 (0.95–1.14)	0.377
	Paternal education								
	Elementary school					0.25 (0.03–1.87)	0.176	0.23 (0.04–1.45)	0.117
	Middle school					1.34 (0.48–3.72)	0.570	1.31 (0.47–3.66)	0.608
	High school					1.42 (0.53–3.80)	0.486	1.38 (0.51–3.74)	0.527
	Higher education					1			
	Paid work in the past 12 mo								
	Yes					1.5 (0.28–8.12)	0.641	1.52 (0.27–8.42)	0.633
	No					1		1	
Pregnancy and birth-related factors	Prior pregnancy risk								
	No					0.41 (0.19–0.9)	0.026[d]	0.42 (0.19–0.91)	0.028[d]
	Yes					1		1	
	Current pregnancy illness								
	No					0.65 (0.3–1.39)	0.269	0.58 (0.27–1.24)	0.160
	Yes					1		1	
	Delivery mode								
	Vaginal delivery					1.06 (0.56–2.00)	0.855	1.11 (0.57–2.16)	0.757
	Cesarean delivery					1		1	
	Birth weight					1.84 (0.65–5.23)	0.250	2.11 (0.7–6.35)	0.184
Psychosocial and environmental factors	Adverse childhood experiences							1.02 (0.74–1.42)	0.885
	Prenatal depression							0.99 (0.91–1.07)	0.809
	Perceived social support							0.76 (0.58–0.98)	0.037[d]
	Neighborhood characteristics							0.99 (0.96–1.02)	0.470

p-IPV, prenatal intimate partner violence; RR, relative risk; CI, confidence interval.
[a]Crude+maternal sociodemographic factors (age, employment status, education, and subjective social status). [b]Model 1+paternal sociodemographic factors+pregnancy and birth-related factors (prior pregnancy risk, current pregnancy illness, delivery mode, birth weight). [c]Model 2+psychosocial and environmental factors (adverse childhood experiences, antenatal depression, perceived social support, neighborhood characteristics). [d]Statistical significance.

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Table 4. Multilevel analysis of the association between p-IPV and postpartum depression at 6 months

Characteristic	Category	Crude		Model 1[a]		Model 2[b]		Model 3[c]	
		RR (95% CI)	*p*	RR (95% CI)	*p*	RR (95% CI)	*p*	RR (95% CI)	*p*
p-IPV	p-IPV exposure	1.76 (1.06–2.90)	0.028[d]	1.70 (1.05–2.78)	0.033[d]	1.66 (1.01–2.74)	0.047[d]	1.17 (0.63–2.19)	0.619
	No p-IPV	1		1		1		1	
Maternal sociodemographic factors	Maternal age			0.98 (0.94–1.03)	0.982	1.04 (0.97–1.11)	0.311	1.03 (0.96–1.11)	0.380
	Maternal employment status								
	Business/trading			0.87 (0.36–2.11)	0.765	0.94 (0.4–2.18)	0.877	1.04 (0.45–2.38)	0.928
	Government official			1.54 (0.62–3.86)	0.353	1.43 (0.59–3.48)	0.434	1.56 (0.6–4.05)	0.357
	Freelance			1.75 (0.98–3.14)	0.060	1.78 (1.01–3.16)	0.047[d]	1.93 (1.04–3.6)	0.038[d]
	Not working			1		1		1	
	Maternal education								
	Elementary school			1.05 (0.35–3.20)	0.930	1.36 (0.5–3.71)	0.553	1.49 (0.58–3.83)	0.403
	Middle school			1.57 (0.75–3.29)	0.230	1.86 (0.85–4.08)	0.119	2.43 (1.04–5.7)	0.041
	High school			1.24 (0.62–2.48)	0.539	1.25 (0.6–2.6)	0.547	1.61 (0.73–3.55)	0.235
	Higher education			1		1		1	
	Subjective social status			1.00 (0.82–1.23)	0.990	1.01 (0.82–1.25)	0.932	1.04 (0.84–1.29)	0.728
Paternal sociodemographic factors	Paternal age					0.94 (0.88–1)	0.067	0.95 (0.89–1.02)	0.130
	Paternal education								
	Elementary school					0.84 (0.3–2.32)	0.733	0.75 (0.27–2.06)	0.570
	Middle school					0.74 (0.33–1.65)	0.460	0.62 (0.26–1.47)	0.278
	High school					0.9 (0.44–1.84)	0.764	0.88 (0.43–1.82)	0.740
	Higher education					1		1	
	Paid work in the past 12 mo								
	Yes					2.8 (0.39–20.21)	0.308	2.23 (0.38–13.26)	0.376
	No					1		1	
Pregnancy and birth-related factors	Prior pregnancy risk					2.12 (0.54–8.31)	0.281	2.77 (0.82–9.3)	0.100
	No					1		1	
	Yes								
	Current pregnancy illness								
	No					1.7 (0.71–4.07)	0.235	1.79 (0.77–4.18)	0.178
	Yes					1		1	
	Delivery mode								
	Vaginal delivery					1.04 (0.64–1.69)	0.880	1.06 (0.65–1.73)	0.811
	Cesarean delivery					1		1	
	Birth weight					0.91 (0.42–1.98)	0.814	0.78 (0.37–1.65)	0.507
Psychosocial and environmental factors	Adverse childhood experiences							0.89 (0.71–1.12)	0.321
	Prenatal depression							1.15 (1.06–1.25)	0.001[d]
	Perceived social support							1.02 (0.71–1.47)	0.925
	Neighborhood characteristics							1.01 (0.98–1.03)	0.575

p-IPV, prenatal intimate partner violence; RR, relative risk; CI, confidence interval.

[a]Crude+maternal sociodemographic factors (age, employment status, education, subjective social status). [b]Model 1+paternal sociodemographic factors+pregnancy and birth-related factors (prior pregnancy risk, current pregnancy illness, delivery mode, birth weight). [c]Model 2+psychosocial and environmental factors (adverse childhood experiences, antenatal depression, perceived social support, neighborhood characteristics). [d]Statistical significance.

depression then serves as the more proximate and powerful predictor of continued depression in the postpartum period. This has important implications for intervention strategies, suggesting that addressing prenatal depression might be particularly important for preventing postpartum depression, especially in women with a history of IPV [55]. p-IPV, including emotional and physical violence, was associated with an increased risk of postpartum depression.

Strengths and Limitations

Our study represents the first longitudinal survey in Vietnam to examine the effect of p-IPV on child development at 6 months of age. The cohort design enables observation of temporal relationships between p-IPV and developmental outcomes, reducing potential recall and selection biases. This design strengthens the evidence base by providing a longitudinal perspective on early childhood development. Additionally, we utilized the ASQ-3, a validated tool for assessing early childhood development, administered by well-trained health staff to ensure accuracy and reliability. The Vietnamese version of the ASQ-3—translated by the Ministry of Health of Vietnam and authorized for use in screening for developmental delays—was employed in this study [56]. The ASQ-3 enables efficient large-scale screening while minimizing reporting bias through careful administration. Given the paucity of cohort studies in this area, our study fills a critical gap in the literature [12] and contributes valuable prospective data to understanding the long-term effects of p-IPV on child development. Furthermore, the association between p-IPV, maternal mental health, and SDDs was assessed using robust Poisson regression, which yields more accurate RR estimates compared with traditional logistic regression, increasing the validity of our findings [31,32].

However, this study has certain limitations. First, studies of this type may face under-reporting of IPV due to denial, fear of stigma, or embarrassment. Although we trained female interviewers and ensured privacy during data collection to encourage disclosure, social desirability bias may have led to underestimation of IPV prevalence. Second, the inability to assess whether IPV exposure was ongoing throughout the study limited our ability to evaluate its cumulative or changing effects on maternal and child health. Third, potential differences in outcomes by IPV type could not be explored due to sample size limitations. Fourth, this study did not collect data on several potentially influential variables, including the child's sex, gestational age (weeks), low birth weight relative to gestational age, neonatal hospitalization, breastfeeding practices, and maternal substance use. Their omission may limit our ability to fully account for alternative explanations or to explore effect modification. Lastly, the study did not find a significant association between p-IPV and birth outcomes (delivery mode and birth weight; data not shown). This may be attributable to the limited sample size, which could have reduced the ability to detect differences reported in previous research.

Conclusion

Our findings contribute to the growing evidence that p-IPV has lasting adverse effects on early child development and maternal mental health. By employing a prospective birth cohort design, this research provides robust evidence on how early exposure to violence affects early childhood development and maternal health, informing public health strategies and policy efforts aimed at prevention and early intervention. Our findings support evidence-based programs and policies to reduce violence during pregnancy and to improve maternal-child health through comprehensive screening and interventions; such efforts could play a critical role in promoting optimal child development and maternal well-being. Future research should explore long-term developmental outcomes beyond infancy to provide a more complete picture of these impacts.

Supplementary Material

Table S1. Mother's obstetric history at baseline (n=285). Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0178.

Notes

Ethics Approval

This study was approved by the Ethical Review Committee of Hue University of Medicine and Pharmacy (No: H2023/146, dated May 22, 2023). Informed consent was confirmed by the institutional review board.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets are not publicly available; however, they can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: TVV, HDTT, CVT; Data curation: all authors; Formal analysis: TVV, HDTT, CVT; Investigation: HDTH, CTV, HTLN, DNHV, TVV; Methodology: TVV, HDTT, CVT; Project administration: TVV; Writing–original draft: TVV, HDTT, CVT, BYLT; Writing–review & editing: all

authors. All authors read and approved the final manuscript.

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Original Article

The impact of digital literacy on older adults' self-rated health, depression, and life satisfaction: a cross-sectional study using 2023 National Survey of Older Koreans

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ABSTRACT

Objectives: This study examined the associations between digital literacy and self-rated health (SRH), depression, and life satisfaction among older adults in the Republic of Korea.
Methods: Data were obtained from the 2023 National Survey of Older Koreans (n=9,951). Digital literacy was evaluated based on participants' ability to use 8 smartphone functions and their perceived difficulty adapting to a digital society. Dependent variables included SRH, depression (measured using the short form of Geriatric Depression Scale), and life satisfaction (assessed through a composite score across 7 domains). Multiple logistic regression was applied for SRH and depression, while linear regression was conducted for life satisfaction, adjusting for sociodemographic and health-related covariates.
Results: Higher digital literacy was significantly associated with better SRH and greater life satisfaction. Compared to participants with no digital skills, those with moderate or high digital literacy had higher odds of reporting good SRH and significantly higher life satisfaction scores. Older adults who reported difficulty adapting to a digital society demonstrated significantly lower SRH and life satisfaction. However, after adjusting for covariates, the association between digital literacy and depression was not statistically significant.
Conclusion: Higher digital literacy is linked to better SRH and greater life satisfaction. Moreover, digital literacy reduced the explanatory power of socioeconomic variables, suggesting that it serves as an important behavioral determinant. These findings underscore the importance of promoting digital literacy as a means of improving health equity and well-being in aging populations.

Keywords: Depression; Digital literacy; Life satisfaction; Older adults; Self-rated health

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Introduction

The rapid digital transformation of modern society is occurring alongside accelerated population aging, raising increasing interest in how digital literacy relates to quality of life among older adults. Smartphones have become a primary tool for information access and social interaction across all age groups, including older adults. According to the National Information Society Agency [1], the digital access rate among Korean adults aged 65 years or older was 95.3%, while the digital utilization rate was 75.0%. Although 94.0% of this population owned a smartphone, many used it for activities beyond basic communication, such as searching for information, watching videos, and performing financial transactions.

These technological changes affect older adults' daily lives directly and indirectly and are increasingly linked to psychological and health-related outcomes such as self-rated health, depression, and life satisfaction. Previous studies have suggested that digital literacy can mitigate social isolation and strengthen self-efficacy in older adults, thereby reducing depression and improving life satisfaction [2,3]. Digital literacy refers not only to the ability to operate digital devices but also to the skills required to access, evaluate, and apply digital information effectively [4]. As the digital divide expands from access to competency, concerns have emerged that disparities in digital literacy may exacerbate health inequalities [5]. Limited access to digital information can lead to exclusion from health-related services and resources, impeding individuals' ability to manage their health and negatively affecting both perceived and actual health status.

Smartphones have been reported to support social connections, facilitate access to information, and encourage personal development in older adults, thereby improving overall quality of life [6]. Digital competencies such as information searching, video calling, and social media use can strengthen older adults' social networks, reduce feelings of isolation, and enhance life satisfaction [7]. Kim et al. [8] noted that, given older adults' strong interest in health, many actively seek health-related information while learning to use smartphones. Furthermore, higher digital literacy levels have been linked to greater self-efficacy, autonomy, and sense of control [9]. Such digital engagement has been shown to promote social participation and increase subjective well-being in older adults [3]. Korean studies similarly report that older adults who regularly use smartphones experience higher life satisfaction and more positive health perceptions compared with non-users [8].

Numerous studies have found that higher digital literacy is associated with fewer depressive symptoms and better self-rated health in older adults [2]. Conversely, limited use of social media has been associated with increased feelings of emotional loneliness [10]. Video calls and social media engagement may therefore provide important emotional support and contribute to psychological well-being.

Life satisfaction is a key indicator of subjective well-being in later life and is shaped by multiple factors, including health, emotional stability, social connections, and financial security [11]. Recent studies identify digital literacy as a significant predictor of life satisfaction, suggesting that digital engagement enhances quality of life by fostering self-expression, social connectedness, and access to information [12]. In contrast, digital exclusion may result in emotional withdrawal, psychological vulnerability, and reduced life satisfaction [6,13]. Older adults with stronger digital skills typically access a wider range of social and cultural resources, which contributes to higher life satisfaction [14,15]. For example, an earlier study using data from the 2020 National Survey of Older Koreans found that life satisfaction was higher among women, individuals with higher education or household income, better SRH, and more frequent and longer smartphone or tablet use, as well as among those who reported fewer difficulties using digital devices [16].

Therefore, this study aimed to assess the impact of digital literacy on self-rated health, depression, and life satisfaction among older adults, drawing on data from the 2023 National Survey of Older Koreans. By adjusting for relevant sociodemographic and health-related covariates, this study provides evidence to guide digital inclusion strategies and information and communication technology education initiatives for older adults.

HIGHLIGHTS

- Digital literacy is positively associated with self-rated health and life satisfaction in older adults.
- Difficulty adapting to digital society is associated with poorer health outcomes.
- Promoting digital literacy may reduce health disparities in aging populations.

Materials and Methods

Research Design

This study employed a cross-sectional observational design to examine associations between digital literacy and 3 key health-related outcomes—self-rated health, depression, and life satisfaction—among older adults in the Republic

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of Korea. The analysis was based on secondary data from the 2023 National Survey of Older Koreans, which provides nationally representative information on the health status and social circumstances of the country's aging population. Given the cross-sectional design, the purpose was to identify associations and patterns rather than infer causality. Digital literacy was conceptualized as a potential behavioral determinant of well-being in later life, and multiple regression models were applied to estimate adjusted associations while controlling for sociodemographic and health-related covariates.

Data Source and Study Population

Data were obtained from the 2023 National Survey of Older Koreans, conducted by the Korea Institute for Health and Social Affairs. This survey targets community-dwelling adults aged 65 years and older and is administered every 3 years to track their health status, socioeconomic conditions, and overall quality of life. A stratified multistage probability sampling method was employed to ensure national representativeness, taking into account factors such as geographic region, urban–rural distribution, and housing type. Trained interviewers collected data through structured, face-to-face interviews.

The total sample included 10,078 respondents, of whom approximately 1.2% provided proxy responses through family members due to physical or cognitive limitations. For the analytic dataset, cases with missing values on key variables were excluded (Figure 1). Accordingly, all proxy responses were also removed. The final analytic sample consisted of 9,951 older adults.

Variables

The study aimed to examine associations between digital literacy and health outcomes among older adults. The dependent variables were self-rated health, depression, and life satisfaction. Self-rated health was dichotomized as "good health" if respondents reported "very good" or "good." Depression was measured with the short form of Geriatric Depression Scale [17], with scores ≥8 indicating the presence of depressive symptoms. Life satisfaction was evaluated across 7 domains: (1) health status, (2) financial situation, (3) relationship with spouse, (4) relationship with children, (5) participation in social activities, (6) social relationships, and (7) overall life satisfaction. Each item was rated on a 5-point Likert scale (1=very dissatisfied to 5=very satisfied). A mean score was calculated using the items for which the respondent provided valid responses, and this score was used as a continuous variable in the analysis. In line with the survey design, respondents without a living spouse or children were not asked items (3) and/or (4); these were excluded from the mean calculation for those individuals. Specifically, 40.9% of respondents had no living spouse, and 5.5% had no living children. The remaining 5 items were answered by all participants.

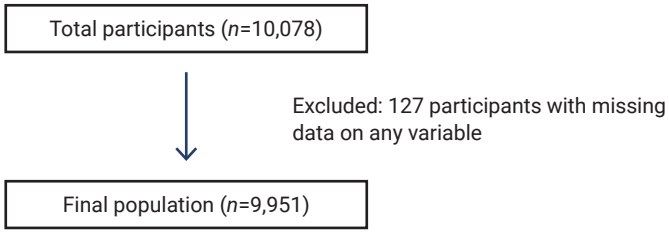


Figure 1. Flow chart of study population selection.

The key independent variable was digital literacy, measured through respondents' ability to use smartphone functions and their perceived difficulty adapting to a digital society. Digital literacy was assessed with the question: "Without assistance, can you use a PC, smartphone, tablet PC, or kiosk to perform the following activities?" Respondents answered "yes" or "no" for each of 8 functions: (1) sending messages, (2) video calling, (3) searching for information, (4) taking photos or videos, (5) using social networking services (SNS), (6) engaging in e-commerce, (7) conducting online banking transactions, and (8) searching for and installing applications. Each "yes" response was coded as 1 and each "no" as 0. The composite digital literacy score ranged from 0 to 8 and was categorized as 0, 1–2, 3–4, or 5 or more. Additionally, respondents were asked whether they experienced difficulties using digital devices in their daily lives.

Covariates included sociodemographic characteristics such as sex, age, educational attainment, income level, employment status, household composition, and residential area, as well as health-related variables including the number of chronic diseases, history of falls, disability status, physical and cognitive impairment, and frailty. These variables were selected based on prior research demonstrating significant associations with self-rated health, depression, and life satisfaction among older adults [3,18–20].

Physical impairment was defined as requiring assistance with activities of daily living or instrumental activities of daily living, both of which have been associated with functional decline and lower life satisfaction in older populations [21]. Cognitive function was assessed using the standardized Korean Mini-Mental State Examination, 2nd Edition (K-MMSE-2) [22]. The K-MMSE-2 provides raw scores ranging from 0 to 30, and cognitive impairment was determined using T-scores adjusted for age and educational level. Respondents with scores below the established threshold

were classified as having suspected cognitive impairment.

Frailty was assessed using the Korean version of the fatigue, resistance, ambulation, illnesses, & loss of weight (FRAIL) scale, adapted from the original tool developed by Morley et al. [23]. Its clinical reliability and validity in older Korean adults have been confirmed by Jung et al. [24]. The scale comprises 5 items: (1) Have you felt fatigued in the past month? (2) Do you have difficulty climbing 10 stairs without assistance or rest? (3) Do you have difficulty walking 300 meters without assistance? (4) Have you been diagnosed by a physician with 5 or more of the following 11 chronic conditions: hypertension, diabetes, cancer, chronic lung disease, myocardial infarction, heart failure, angina, asthma, arthritis, stroke, or kidney disease? (5) Have you lost more than 5% of your body weight in the past year? Respondents scoring 3 or more were classified as frail, those scoring 1–2 as pre-frail, and those scoring 0 as non-frail.

Detailed definitions of all variables, including the questionnaire items and response categories used in their construction, are provided in Table S1 for transparency and reproducibility [17,22–24].

Statistical Analysis

Descriptive statistics were used to summarize the sociodemographic characteristics, health status, and digital literacy of the study population. Univariate analyses were conducted to assess group differences in self-rated health, depression, and life satisfaction according to digital literacy levels. Specifically, the chi-square test was used for categorical dependent variables (self-rated health and depression), while the independent-sample t-test and 1-way analysis of variance (ANOVA) were employed to compare mean scores of the continuous variable (life satisfaction). The independent t-test was used for comparisons based on binary indicators of digital literacy, and ANOVA was applied for comparisons across the categorized digital literacy scores.

To investigate associations between digital literacy and health outcomes, multiple logistic regression analyses were performed for binary outcomes (self-rated health and depression), and multiple linear regression analysis was conducted for the continuous outcome (life satisfaction), adjusting for all covariates. Three separate regression models were constructed to evaluate the independent associations of digital literacy with self-rated health, depression, and life satisfaction. Covariates were consistent across models; however, self-rated health and depression were also included as covariates in the life satisfaction model. This decision was supported by extensive empirical evidence indicating that both self-rated health and depression are strong predictors of life satisfaction in older adults. Including them in the life satisfaction model allowed us to better isolate the specific contribution of digital literacy to subjective well-being. In contrast, life satisfaction was not included as a covariate in the models for self-rated health and depression to avoid overadjustment, which could obscure the direct effects of digital literacy on these outcomes. Supplementary analyses, not shown in the main manuscript, additionally included all 3 psychosocial variables as covariates in each model and produced results largely consistent with the primary findings, suggesting that the observed associations were robust to model specification. All analyses were performed using SAS version 9.4 (SAS Institute Inc.).

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of Hanyang Cyber University (IRB No: HYCU-IRB-2025-004) and conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because the study used de-identified, publicly available secondary data.

Results

General Characteristics of the Study Population

Among the 9,951 respondents, 3,824 (38.4%) were men and 6,127 (61.6%) were women. The largest age group was 65 to 74 years (57.4%), followed by those aged 75 to 84 years (34.6%) and those aged 85 years or older (8.0%). In terms of educational attainment, 35.0% had completed high school or higher, 29.3% were elementary school graduates, 21.2% were middle school graduates, and 14.4% had no formal education. A total of 39.6% were currently employed, and 70.1% resided in urban areas. With respect to household composition, the most common arrangement was living with a spouse aged 65 years or older (54.5%), followed by living alone (34.4%) and living with children or other cohabitants (11.1%). Additionally, 50.3% reported participating in social activities, such as hobby groups, social gatherings, religious services, or political events, at least once per month (Table 1).

Digital Literacy of the Study Population

Among older adults aged 65 and over, an assessment of digital competency across 8 smartphone functions revealed substantial variation in ability. The highest proportion of respondents (70.6%) reported being able to send text messages, whereas fewer were able to make video calls (41.8%), search for information (46.5%), or take photos or videos (49.2%). Utilization rates were lower for SNS (8.0%), e-commerce (10.8%), online banking (17.9%), and searching for or installing applications

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Table 1. General characteristics of the study population (*n* = 9,951)

Variable	Value
Sociodemographic factors	
Sex	
Male	3,824 (38.4)
Female	6,127 (61.6)
Age (y)	
65–74	5,710 (57.4)
75–84	3,442 (34.6)
≥85	799 (8.0)
Education	
None	1,435 (14.4)
Elementary school	2,920 (29.3)
Middle school	2,114 (21.2)
≥High school	3,482 (35.0)
Income quartile	
1st	2,484 (25.0)
2nd	2,481 (24.9)
3rd	2,474 (24.9)
4th	2,512 (25.2)
Employment status	
Not working	6,009 (60.4)
Working	3,942 (39.6)
Household	
Living alone	3,423 (34.4)
Living with spouse	5,419 (54.5)
Others	1,109 (11.1)
Residence area	
Urban	6,977 (70.1)
Rural	2,974 (29.9)
Social activities	
<Once a month	4,946 (49.7)
≥Once a month	5,005 (50.3)
Health status	
Comorbidities	
0	1,363 (13.7)
1–2	4,907 (49.3)
≥3	3,681 (37.0)
Fall history	
No	9,339 (93.8)
Yes	612 (6.2)
Disability	
Non-disabled	9,547 (95.9)
Disabled	404 (4.1)
Cognitive impairments	
No	7,503 (75.4)
Yes	2,448 (24.6)
Functional impairments	
No	8,303 (83.4)
Yes	1,648 (16.6)
Frailty	
Non-frail	6,251 (62.8)
Pre-frail	3,214 (32.3)
Frail	486 (4.9)
Total	9,951 (100.0)

Data are presented as *n* (%).

(11.9%).

Based on the number of functions respondents could perform, digital literacy scores were categorized. Notably, 26.5% of older adults were unable to use any of the 8 functions (score = 0). Meanwhile, 26.4% could use 1–2 functions, 27.8% could use 3–4 functions, and 19.3% could use 5 or more functions. Furthermore, 93.0% of respondents reported experiencing difficulties in coping with the demands of an increasingly digital society (Table 2).

Health Status and Life Satisfaction according to Digital Literacy Levels

Univariate analyses revealed significant differences in self-rated health, depression, and life satisfaction according to the level of digital literacy among older adults.

Table 2. Digital literacy of the study population (*n* = 9,951)

Variable	Value
Sending messages	
No	2,930 (29.4)
Yes	7,021 (70.6)
Video calling	
No	5,793 (58.2)
Yes	4,158 (41.8)
Information searching	
No	5,325 (53.5)
Yes	4,626 (46.5)
Taking photos or videos	
No	5,056 (50.8)
Yes	4,895 (49.2)
Using social networking services	
No	9,150 (92.0)
Yes	801 (8.0)
Engaging in e-commerce	
No	8,877 (89.2)
Yes	1,074 (10.8)
Conducting online banking transactions	
No	8,169 (82.1)
Yes	1,782 (17.9)
Searching for and installing applications	
No	8,769 (88.1)
Yes	1,182 (11.9)
Digital literacy levels (0–8)	
0	2,633 (26.5)
1–2	2,623 (26.4)
3–4	2,770 (27.8)
≥5	1,925 (19.3)
Perceived difficulties in coping with a digitalized society	
No	701 (7.0)
Yes	9,250 (93.0)

Data are presented as *n* (%).

Respondents who reported being able to perform functions such as sending messages, making video calls, searching for information, taking photos or videos, using SNS, conducting e-commerce or online banking, and installing applications were more likely to report better self-rated health, fewer depressive symptoms, and greater life satisfaction ($p < 0.001$). Higher composite digital literacy scores were likewise significantly associated with better self-rated health, fewer depressive symptoms, and higher life satisfaction ($p < 0.001$).

In contrast, respondents who reported difficulties adapting to a digital society exhibited significantly lower self-rated health and life satisfaction than those without such difficulties ($p < 0.001$) (Table 3).

Effects of Digital Literacy on Older Adults' Health Status and Life Satisfaction

After adjusting for sociodemographic characteristics and health-related variables, multiple regression analyses were conducted to assess the effects of digital literacy on self-rated health, depression, and life satisfaction. While sociodemographic and health-related factors showed strong and consistent associations with both self-rated health and life satisfaction, digital literacy remained a significant predictor even after adjustment for covariates.

Table 3. Health status and life satisfaction according to digital literacy levels

Variable	Self-rated health		Depression		Life satisfaction (1–5)	
	n (%)	χ^2 (*p*)	*n* (%)	χ^2 (*p*)	Mean ± SD	t/F (*p*)
Sending messages		673.48 (< 0.001)		211.54 (< 0.001)		−27.09 (< 0.001)
No	630 (21.5)		532 (18.2)		3.12 ± 0.54	
Yes	3,483 (49.6)		570 (8.1)		3.43 ± 0.53	
Video calling		659.96 (< 0.001)		168.59 (< 0.001)		−31.20 (< 0.001)
No	1,772 (30.6)		842 (14.5)		3.20 ± 0.55	
Yes	2,341 (56.3)		260 (6.3)		3.53 ± 0.50	
Information searching		1,055.44 (< 0.001)		188.38 (< 0.001)		−33.89 (< 0.001)
No	1,405 (26.4)		804 (15.1)		3.17 ± 0.54	
Yes	2,708 (58.5)		298 (6.4)		3.53 ± 0.51	
Taking photos or videos		844.77 (< 0.001)		175.09 (< 0.001)		−31.93 (< 0.001)
No	1,376 (27.2)		767 (15.2)		3.17 ± 0.55	
Yes	2,737 (55.9)		335 (6.8)		3.51 ± 0.50	
Using social networking services		349.74 (< 0.001)		36.86 (< 0.001)		−18.50 (< 0.001)
No	3,532 (38.6)		1,065 (11.6)		3.31 ± 0.55	
Yes	581 (72.5)		37 (4.6)		3.64 ± 0.47	
Engaging in e-commerce		432.78 (< 0.001)		85.73 (< 0.001)		−23.73 (< 0.001)
No	3,352 (37.8)		1,073 (12.1)		3.30 ± 0.55	
Yes	761 (70.9)		29 (2.7)		3.66 ± 0.45	
Conducting online banking transactions		689.21 (< 0.001)		129.04 (< 0.001)		−29.24 (< 0.001)
No	2,882 (35.3)		1,041 (12.7)		3.27 ± 0.55	
Yes	1,231 (69.1)		61 (3.4)		3.64 ± 0.46	
Searching for and installing applications		461.60 (< 0.001)		73.62 (< 0.001)		−23.76 (< 0.001)
No	3,283 (37.4)		1,058 (12.1)		3.30 ± 0.55	
Yes	830 (70.2)		44 (3.7)		3.65 ± 0.47	
Digital literacy level (0–8)		1,284.53 (< 0.001)		291.07 (< 0.001)		508.59 (< 0.001)
0	555 (21.1)		485 (18.4)		3.10 ± 0.55	
1–2	830 (31.6)		338 (12.9)		3.23 ± 0.53	
3–4	1,379 (49.8)		202 (7.3)		3.46 ± 0.50	
≥ 5	1,349 (70.1)		77 (4.0)		3.65 ± 0.46	
Perceived difficulties in coping with a digitalized society		321.13 (< 0.001)		27.01 (< 0.001)		19.84 (< 0.001)
No	515 (73.5)		36 (5.1)		3.70 ± 0.49	
Yes	3,598 (38.9)		1,066 (11.5)		3.31 ± 0.55	
Total	4,113 (41.3)		1,102 (11.1)		3.34 ± 0.55	

SD, standard deviation.

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Older adults with digital literacy scores corresponding to the ability to use 3–4 functions had significantly higher odds of reporting good self-rated health (odds ratio [OR], 1.530; 95% confidence interval [CI], 1.309–1.788), as did those with scores reflecting the ability to use 5 or more functions (OR, 2.316; 95% CI, 1.922–2.792), compared to those with a score of 0. By contrast, respondents who reported difficulties coping with the digital society were significantly less likely to report good self-rated health (OR, 0.499; 95% CI, 0.411–0.606).

Regarding life satisfaction, respondents with digital literacy scores of 3–4 and 5 or more functions reported significantly higher mean scores by 0.106 points ($p < 0.001$) and 0.163 points ($p < 0.001$), respectively, compared to those with a score of 0. Conversely, those reporting digital difficulties had significantly lower mean life satisfaction scores by 0.117 points ($p < 0.001$).

Although differences in depression across digital literacy levels were statistically significant in univariate analyses, the association became non-significant after adjusting for sociodemographic and health-related covariates (Table 4).

Discussion

We are living in an era where the rapid transition to a digital society coincides with the demographic shift toward super-aged populations. In this context, the quality of life of older

Table 4. Effects of digital literacy on older adults' health status and life satisfaction

Variable	Category	Self-rated health	Depression	Life satisfaction		
		OR (95% CI)	OR (95% CI)	Coefficients	SE	*p*
Digital literacy						
Digital literacy levels (ref. none)	1–2	1.029 (0.888–1.191)	1.163 (0.964–1.402)	0.007	0.014	0.588
	3–4	1.530 (1.309–1.788)	1.016 (0.806–1.281)	0.106	0.015	<0.001
	≥5	2.316 (1.922–2.792)	0.833 (0.598–1.161)	0.163	0.019	<0.001
Perceived difficulties in coping with a digitalized society (ref. no)	Yes	0.499 (0.411–0.606)	0.935 (0.645–1.355)	−0.117	0.018	<0.001
Sociodemographic factors						
Sex (ref. male)	Female	0.930 (0.839–1.030)	0.724 (0.614–0.852)	0.028	0.010	0.005
Age (ref. 65–74 y)	75–84	0.931 (0.829–1.045)	0.720 (0.606–0.856)	0.080	0.011	<0.001
	≥85	1.006 (0.806–1.256)	0.763 (0.591–0.985)	0.083	0.020	<0.001
Education (ref. none)	Elementary school	1.174 (0.982–1.403)	0.866 (0.709–1.058)	0.048	0.015	0.002
	Middle school	1.380 (1.132–1.681)	0.838 (0.654–1.073)	0.005	0.018	0.764
	≥High school	1.623 (1.327–1.984)	0.735 (0.563–0.959)	0.038	0.019	0.041
Income quartile (ref. 1st quartile)	2nd	1.186 (1.029–1.366)	0.929 (0.774–1.115)	0.058	0.013	<0.001
	3rd	1.484 (1.281–1.720)	0.779 (0.626–0.969)	0.123	0.014	<0.001
	4th	1.514 (1.289–1.778)	0.634 (0.490–0.819)	0.152	0.016	<0.001
Employment status (ref. not working)	Working	1.304 (1.176–1.447)	0.544 (0.453–0.652)	0.014	0.010	0.175
Household (ref. others)	Living alone	0.931 (0.781–1.110)	1.014 (0.787–1.306)	0.020	0.017	0.237
	Living with spouse	0.960 (0.819–1.125)	0.693 (0.542–0.884)	0.091	0.015	<0.001
Residence area (ref. rural)	Urban	1.048 (0.939–1.171)	1.443 (1.221–1.704)	−0.062	0.011	<0.001
Social activities (ref. <once a month)	≥Once a month	1.236 (1.120–1.363)	0.635 (0.544–0.742)	0.109	0.010	<0.001
Health status						
Comorbidities (ref. none)	1–2	0.354 (0.306–0.409)	1.410 (1.015–1.960)	−0.037	0.014	0.009
	≥3	0.164 (0.140–0.192)	2.746 (1.978–3.811)	−0.110	0.016	<0.001
Fall history (ref. none)	Yes	0.683 (0.542–0.862)	1.884 (1.514–2.345)	0.001	0.019	0.972
Disability (ref. none)	Yes	0.471 (0.345–0.641)	1.834 (1.420–2.367)	−0.156	0.023	<0.001
Cognitive impairments (ref. none)	Yes	0.707 (0.631–0.793)	1.382 (1.189–1.606)	−0.089	0.011	<0.001
Function impairments (ref. none)	Yes	0.695 (0.594–0.813)	1.857 (1.572–2.194)	−0.096	0.014	<0.001
Frailty (ref. non-frail)	Pre-frail	0.670 (0.601–0.747)	2.377 (2.011–2.810)	−0.080	0.011	<0.001
	frail	0.252 (0.170–0.371)	6.867 (5.339–8.833)	−0.305	0.023	<0.001
Self-rated health (ref. poor)	Good			0.310	0.011	<0.001
Depression (ref. not depressed)	Depressed			−0.161	0.019	<0.001
Model fit		Nagelkerke $R^2 = 0.333$	Nagelkerke $R^2 = 0.274$	Adjusted $R^2 = 0.344$		

OR, odds ratio; CI, confidence interval; SE, standard error; Ref, reference.

adults has become a major determinant of overall population well-being, and the use of digital technology is expected to be a critical factor in everyday life. This study sought to empirically examine the impact of digital literacy on key mental and emotional health indicators, including self-rated health, depression, and life satisfaction. The 2023 National Survey of Older Koreans, which included responses from 10,078 participants, provided a nationally representative dataset with broad coverage of health indicators, living environments, social relationships, and life satisfaction, making it a highly appropriate source for this research.

Comparison with Previous Surveys and Age Cohorts

Compared with the 2020 wave of the same survey, the 2023 data reveal further aging of the older population, accompanied by notable improvements in education and income levels [25]. Smartphone ownership reached 94%, a dramatic increase compared with the early 2000s, when access to such technology was limited [1]. However, actual utilization remains modest, with only 48.3% reporting experience using health-related apps, highlighting a persistent gap between device ownership and effective use. The main functions used by older adults in 2023 were sending messages (70.6%), taking photos or videos (49.2%), searching for information (46.5%), and video calling (41.8%). In contrast, utilization of SNS (8.0%), e-commerce (10.8%), application installation (11.9%), and online banking (17.9%) remained notably lower. These patterns suggest that older adults still face barriers to meaningful social participation and information use. More importantly, such disparities extend beyond device access and are closely tied to quality of life. Compared with younger cohorts, older adults demonstrate the lowest digital engagement, especially in domains such as SNS use and financial transactions, where generational gaps are particularly pronounced. When compared internationally, older adults in the Republic of Korea report higher accessibility to e-government services but lower SNS usage than their counterparts in the United States, Japan, and Europe [9,15]. Such low utilization is not a mere technical issue; it is tied to reduced autonomy and unequal access to health resources. A holistic approach—incorporating user-friendly digital environments, tailored education, and social support—is therefore essential.

Adjusted Associations between Digital Literacy and Depression

Digital literacy encompasses more than technical skills; it involves the ability to access, evaluate, and apply digital information [4]. In this study, higher digital literacy, measured by the number of smartphone functions used, was initially associated with better self-rated health, higher life satisfaction, and fewer depressive symptoms. However, after adjusting for demographic and health-related covariates, the association with depression was no longer statistically significant.

This result indicates that while digital literacy may be related to psychological well-being descriptively, its independent effect on depressive symptoms is likely mediated or confounded by other factors such as physical health, social relationships, or economic resources. Depression in older adults is shaped by a complex interplay of vulnerabilities, including chronic disease, functional limitations, and social isolation [26,27]. Consequently, digital literacy alone may not be sufficient to buffer against depression unless it occurs within socially meaningful contexts.

Furthermore, the benefits of digital engagement for mental health arise less from the number of functions used and more from the purpose and context of use. For example, video calling may alleviate loneliness if it facilitates regular communication with family or friends, but offers little benefit if used sporadically or without emotional reciprocity. Park [28] found that the context and intent of digital use were more influential for emotional outcomes than frequency or technical proficiency alone.

These results collectively imply that digital literacy could serve as a potential enabler, but not a direct determinant, of mental health in older adults. Interventions should therefore go beyond technical training to emphasize socially and emotionally meaningful digital engagement.

Substitutive Effect of Digital Literacy on Socioeconomic Variables

Hierarchical regression analyses demonstrated that digital literacy attenuated or eliminated the explanatory power of several socioeconomic variables across all 3 health outcomes.

For self-rated health, older age (75–84 years: OR, 0.657; 95% CI, 0.539–0.728; ≥85 years: OR, 0.596; 95% CI, 0.489–0.727) and rural residence (urban: OR, 1.108; 95% CI, 1.000–1.227) were significantly associated with poorer subjective health in models without digital literacy. However, when digital literacy was included, these associations became statistically non-significant, suggesting a mediating or substitutive role.

For depression, higher educational attainment was significantly associated with fewer depressive symptoms (elementary school: OR, 0.678; 95% CI, 0.566–0.812; middle school: OR, 0.589; 95% CI, 0.472–0.736) in models without digital literacy. These effects disappeared once digital literacy was incorporated, again suggesting a substitutive effect.

For life satisfaction, higher education (middle school: $b = 0.142$, $p < 0.001$; high school: $b = 0.260$, $p < 0.001$) and current employment ($b = 0.098$, $p < 0.001$) were significantly associated with higher scores in models without digital literacy, but these

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associations were no longer significant after its inclusion.

These results highlight the potential of digital literacy as a behavioral determinant that can reduce disparities traditionally explained by education or income. Rather than functioning simply as an additional skill, digital literacy enables older adults to access resources, practice self-care, and maintain autonomy, thereby influencing well-being in ways comparable to, or substitutive of, structural socioeconomic advantages. This perspective aligns with emerging arguments that frame digital inclusion as a matter of equity, particularly in aging societies where participation and access to information are increasingly mediated by digital technologies [14,26,27].

Accordingly, digital literacy interventions should prioritize older adults most at risk of digital exclusion, including those with lower education, lower income, or those living alone. Training should emphasize core functions—such as information searching, video calling, and social networking—that are most strongly linked to health and life satisfaction. Incorporating peer mentoring and community resources can simultaneously enhance social interaction and amplify the positive effects on life satisfaction identified in this study.

Recent Research on Digital Literacy

Recent studies further emphasize the importance of digital literacy. Lee et al. [15] reported that older adults with higher digital competence scored, on average, 2.3 points higher in life satisfaction than those with lower competence. Jung et al. [29] found that digital engagement improved life quality through the mediating role of social capital. Xin et al. [30] reported that 74.5% of digitally active seniors underwent regular health checkups, compared with 52.7% of non-active seniors—a difference of more than 20%. Their analysis also revealed lower chronic disease prevalence and higher levels of both physical and social activity among digitally literate seniors. These findings underscore that digital literacy extends beyond technical proficiency, significantly influencing preventive health behaviors, emotional stability, and overall quality of life.

Policy Implications and Recommendations

This study highlights the persistently low digital literacy levels among older adults in the Republic of Korea. Despite high rates of device ownership, effective use remains limited, and many seniors report feelings of exclusion from the digital information society. Improving digital literacy is not merely a matter of teaching technology; it is fundamental to promoting autonomy in health management and ensuring the realization of health rights. In today's health environment, where telemedicine, mobile health apps, and online medication management are increasingly prevalent, digital usage disparities can rapidly translate into health disparities. Accordingly, comprehensive strategies are needed that extend beyond device distribution. These include designing age-friendly digital interfaces, developing sustainable community-based digital education programs, and fostering intergenerational mentoring systems. Furthermore, older adults with low digital literacy often have weaker social support networks, underscoring the need for integrated interventions targeting multi-vulnerable groups. In conclusion, digital literacy is a decisive factor in promoting both equity and quality of life for older adults. Sustainable aging policies should integrate policy design with community-level implementation. Bridging the digital divide must therefore be reframed as a social responsibility—encompassing not only technical training but also the rights to health, information, and dignified living.

Conclusion

Digital literacy is a critical determinant of health equity and quality of life among older adults. Promoting digital competence and encouraging active community engagement are essential for building a sustainable health care system in an aging society. In this context, digital accessibility and literacy should no longer be considered optional, but fundamental components of realizing the health rights of older populations. Stratified interventions are especially needed for vulnerable subgroups, such as those with limited education or weaker social support. Policies must address not only technological barriers but also psychological resistance and social exclusion.

This study has several limitations. Its cross-sectional design restricts causal inference, and the measurement of digital engagement emphasized functional use rather than qualitative or emotional dimensions. In addition, the reliance on self-reported data may have introduced response bias. While this study focused on overall digital literacy levels and perceived difficulty in adapting to a digital society, future research should investigate patterns and clusters of digital function use among older adults. Identifying which functions tend to co-occur could reveal distinct usage typologies and inform targeted digital inclusion strategies. Although this study was not designed to capture such behavioral patterns, future work could employ advanced analytical methods to examine the co-occurrence of digital behaviors and their contextual significance. Longitudinal research designs are also needed to track changes in digital engagement and health outcomes over time. Furthermore, qualitative approaches—such as in-depth interviews and participant observations—should be incorporated to capture

motivations, lived experiences, and barriers to digital engagement in greater depth.

Supplementary Material

Table S1. Definitions and original survey items of the variables. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0255.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Hanyang Cyber University (IRB No: HYCU-IRB-2025-004) and performed in accordance with the principles of the Declaration of Helsinki. Informed consent was waived because this study used secondary data from a nationally representative survey.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

The datasets generated and/or analyzed during the current study are available in the Korea Institute for Health and Social Affairs repository, https://www.kihasa.re.kr/dataportal/main.html.

Authors' Contributions

Conceptualization: all authors; Data curation: NHY; Formal analysis: NHY; Investigation: MGK, JH; Methodology: MGK, NHY; Project administration: JH; Supervision: MGK, JH; Validation: all authors; Writing–original draft: all authors; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Factors influencing adherence to anti-tuberculosis treatment in Morocco: a cross-sectional study from the Béni Mellal-Khénifra region

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ABSTRACT

Objectives: Adherence to anti-tuberculosis treatment is essential for achieving successful outcomes and preventing the emergence of drug-resistant strains. This study aimed to evaluate adherence levels and identify factors associated with non-adherence among tuberculosis patients in the Béni Mellal-Khénifra region of Morocco. We hypothesized that sociodemographic, clinical, and behavioral factors influence adherence.

Methods: A facility-based cross-sectional study was conducted from January 2023 to December 2024 in 2 Tuberculosis and Respiratory Disease Diagnostic Centers in the Béni Mellal-Khénifra region. A total of 481 patients who had been on treatment for at least 2 months were recruited using convenience sampling. Data were collected through structured, pre-tested questionnaires administered in face-to-face interviews and verified against treatment cards and medical records. Adherence was defined as taking ≥90% of prescribed doses. Multivariable logistic regression was used to identify independent predictors of non-adherence.

Results: Among the 481 participants, 8.1% were non-adherent. Significant predictors of non-adherence included forgetfulness (adjusted odds ratio [AOR], 38.84; 95% confidence interval [CI], 11.35–132.88), adverse effects (AOR, 14.26; 95% CI, 3.17–64.13), male sex (AOR, 6.77; 95% CI, 1.45–31.60), rural residence (AOR, 4.42; 95% CI, 1.37–14.25), self-adjusted dosing (AOR, 5.83; 95% CI, 1.20–28.34), stopping treatment after symptom improvement (AOR, 6.56; 95% CI, 1.34–32.14), and missed follow-up visits (AOR, 6.74; 95% CI, 1.56–29.19).

Conclusion: Although overall adherence was high, 8.1% of patients were non-adherent. Strategies to improve adherence should focus on addressing forgetfulness, managing side effects, enhancing access in rural areas, and reinforcing patient education and follow-up systems to improve treatment outcomes in this and similar settings.

Keywords: Anti-tuberculosis treatment; Morocco; Non-adherence; Risk factors; Treatment adherence

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Introduction

Adherence to anti-tuberculosis (TB) treatment refers to the extent to which patients follow the prescribed therapeutic regimen. This includes taking medications as directed, attending follow-up appointments, and adopting lifestyle modifications recommended by healthcare providers [1]. The World Health Organization (WHO) emphasizes that adherence is a critical determinant of treatment success, as poor adherence may lead to prolonged infectiousness, treatment failure, disease relapse, and the emergence of drug-resistant TB strains [1]. Given TB's communicable nature and the need for long-term, rigorous treatment regimens, adherence is crucial both for individual recovery and public health [1]. Osterberg and Blaschke highlight that medication adherence is a key driver of treatment outcomes, yet non-adherence remains widespread across chronic conditions, including TB [2]. Extending this framework, Vrijens et al. [3] classify adherence into 3 phases—initiation, implementation, and discontinuation—each of which plays an essential role in ensuring the effectiveness of long-term therapies.

Currently, no universally accepted standard exists for measuring adherence to anti-TB treatment [4]. The WHO notes the difficulty of defining adherence empirically, as there is no clear threshold that guarantees successful therapeutic outcomes. Instead, adherence is often inferred from practical indicators such as treatment success rates within the directly observed therapy, short-course (DOTS) strategy [1]. Research studies commonly measure adherence as the proportion of prescribed doses actually taken. While some studies define adequate adherence as taking at least 80% of prescribed doses [5], others apply more stringent thresholds of 90% or higher [6–10]. These differences reflect varying perspectives on the level of medication intake required to prevent treatment failure, relapse, or drug resistance. Despite the lack of a universal definition, the WHO consistently stresses the importance of maintaining high adherence levels to ensure therapeutic success and to curb the development of multidrug-resistant TB (MDR-TB) [1].

Medication adherence is influenced by a wide range of factors, which can be grouped into 5 key dimensions: the nature of the disease, characteristics of the treatment regimen, patient-related aspects, the demographic and socio-economic context, and the health care system [11,12].

In Morocco, the introduction of the DOTS strategy in 1991 [13], contributed to a significant decline in TB incidence and mortality. Nevertheless, TB remains a major public health concern. According to WHO estimates in 2023, approximately 35,000 individuals were affected by TB, corresponding to an incidence rate of 92 cases per 100,000 population. The disease accounted for 1,954 deaths, of which 1,900 occurred among human immunodeficiency virus (HIV)-negative individuals and 54 among those living with HIV. Furthermore, 590 patients developed MDR-TB or rifampicin-resistant TB [14]. In 2021, Morocco's National TB Program (NTP) reported 29,327 new TB cases (incidence rate, 80 per 100,000 population), including 295 MDR-TB cases [15].

In the Béni Mellal-Khénifra (BMK) region specifically, 1,353 TB cases were reported, corresponding to an incidence rate of 51 per 100,000 population [15], highlighting the continuing burden of TB in this region. Despite this, data on adherence to anti-TB treatment in Morocco remain limited. Previous studies have reported widely varying non-adherence prevalence, ranging from 20.5% [16] to 53.1% [17]. To address this knowledge gap, the present study aimed to assess adherence levels and identify determinants of non-adherence among TB patients in the BMK region of Morocco.

HIGHLIGHTS

- A cross-sectional study identified an 8.1% non-adherence rate among 481 tuberculosis (TB) patients in Morocco.
- Major risk factors included forgetfulness, adverse effects, male sex, and rural residence.
- Stopping treatment upon symptom improvement and missed follow-up visits also increased the risk of non-adherence.
- Tailored education, reminder systems, and rural service access are essential.
- The findings support patient-centered strategies to sustain TB control and reduce drug resistance.

Materials and Methods

Study Design and Setting

We conducted a facility-based cross-sectional study in the BMK region, located in central Morocco, from January 1, 2023, to December 31, 2024. The region consists of 5 prefectures with a total population of 2,525,801 [18].

All TB cases in the region are registered and treated under the DOTS strategy at 5 designated Tuberculosis and Respiratory Disease Diagnostic Centers (TRDDCs). These facilities provide comprehensive TB services, including diagnosis, treatment, and prevention, free of charge.

In Morocco, newly diagnosed TB patients undergo a

6-month standardized chemotherapy regimen consisting of 2 phases: a 2-month intensive phase with a fixed-dose combination of RHZE (Rifampicin, Isoniazid, Pyrazinamide, and Ethambutol), followed by a 4-month continuation phase with RH (Rifampicin and Isoniazid). Patients collect their medications from primary health centers every 2 weeks and are scheduled for follow-up visits at the TRDDCs every 2 months [16]. Routine provider-initiated HIV testing is also offered to all TB patients.

Of the 5 TRDDCs in the BMK region, 2 centers—Béni Mellal and Fqih Ben Salah—were purposively selected for this study due to their high TB burden and geographic representativeness. According to the Moroccan Ministry of Health and Social Protection, these 2 centers accounted for approximately 50% of the region's TB cases in the years prior to the study [15]. Their inclusion ensured a representative urban–rural mix, capturing patients from diverse socio-geographic contexts.

Participants

The study population comprised TB patients aged 15 years or older receiving treatment at the selected centers, regardless of disease site (pulmonary or extrapulmonary). Eligibility required patients to have completed at least 2 months of anti-TB therapy at the time of data collection, ensuring they had sufficient treatment experience for adherence assessment.

Sample Size and Sampling Method

Participants were recruited through convenience sampling from TB patients attending the selected TRDDCs during the study period (January 2023–December 2024). Eligible patients present during the researchers' scheduled visits and who provided consent were enrolled.

A total of 555 patients were initially screened. Of these, 39 were excluded because they were younger than 15 years, and 35 were excluded for having received less than 2 months of anti-TB treatment. The final sample size (n=481) reflected the available eligible patients during the study period, which was adequate for performing multivariable analysis on adherence outcomes.

Variables and Data Sources

Data were collected using a structured, interviewer-administered questionnaire designed to capture factors influencing adherence. These included sociodemographic variables (e.g., age, household income), clinical characteristics (e.g., type of TB, comorbidities), behavioral risk factors (e.g., smoking, alcohol use), treatment-related aspects (e.g., side effects, follow-up), and TB-related knowledge.

Knowledge of TB was assessed using 5 questions addressing etiology, transmission, symptoms, treatment duration, and side effects. Each correct answer was awarded 1 point. Participants scoring ≥60% (at least 3 of 5 correct answers) were classified as knowledgeable, while those scoring <60% were considered non-knowledgeable.

The questionnaire underwent rigorous translation (French to Arabic and back-translation) and pretesting to ensure linguistic validity and cultural appropriateness.

Two trained investigators (M.D. and S.B.) conducted face-to-face exit interviews with eligible participants. Informed consent was obtained after explaining study objectives, confidentiality procedures, and the voluntary nature of participation. All questionnaires were completed anonymously to preserve confidentiality.

Adherence was assessed using a triangulated approach combining patient self-reports, treatment card verification, and medical record review. In cases of discrepancy, adherence classification was determined through clinician-led review of patients' full medical records. Participants were considered adherent if they had taken ≥90% of prescribed doses during the treatment period. This threshold was selected based on WHO operational guidance [19] and is consistent with guidelines from Morocco's NTP [20], which emphasize near-complete adherence to prevent relapse, treatment failure, and drug resistance. The ≥90% cut-off has also been adopted in previous studies in high-burden settings [6–9,21], supporting its validity as a rigorous standard for assessing TB treatment adherence.

Bias Control

Measures were taken to minimize recall and social desirability bias by triangulating adherence data and conducting interviews privately using behaviorally neutral language. Interviewers received standardized training to avoid suggestive phrasing, and participants were assured of strict confidentiality. Selection bias is acknowledged as a limitation due to the use of non-probability sampling, which was required by logistical constraints.

Statistical Methods

Data were analyzed using IBM SPSS Statistics ver. 25.0 (IBM Corp.). Descriptive statistics, including frequencies and percentages, were used to summarize participant characteristics and adherence patterns. To identify factors associated with adherence, bivariate binary logistic regression analyses were performed. Variables with a p-value ≤0.05 were included in the multivariable logistic regression model to adjust for confounding.

Prior to multivariable analysis, collinearity among independent variables was assessed using variance inflation

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factors (VIF) from a linear regression model. All VIF values were below 3.5, indicating no evidence of problematic multicollinearity.

Multivariable logistic regression was then conducted to identify independent predictors of treatment adherence. Statistical significance was defined as $p \leq 0.05$ in the final model. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test, while model performance was assessed using Nagelkerke's R^2, overall classification accuracy, sensitivity, and specificity. The model demonstrated acceptable fit.

Results of the bivariate analysis were reported as crude odds ratios (CORs), whereas the multivariable analysis provided adjusted odds ratios (AORs) with corresponding 95% confidence intervals (CIs). No missing data were identified for the variables included in the final analysis.

Ethical Considerations

The study received ethical approval from the Ethics Committee for Biomedical Research at Mohammed Premier University's Faculty of Medicine and Pharmacy, Oujda (approval number: 2022-08), and administrative authorization from the BMK Regional Directorate of Health and Social Protection.

All participants provided informed consent after receiving detailed explanations of study objectives, potential risks, and benefits. For adults (≥18 years), verbal consent was obtained, while minors (<18 years) gave verbal assent accompanied by parental permission. Participation was entirely voluntary, and participants retained the right to withdraw at any stage without consequences.

Results

Participants

A total of 555 patients were screened for eligibility. Of these, 39 were excluded for being under 15 years of age, and 35 were excluded for having received less than 2 months of treatment. The final sample included 481 participants.

Descriptive Characteristics of Study Participants

The study population comprised 481 TB patients, with a nearly equal sex distribution (51.1% male, 48.9% female). Most participants were adults aged 35–59 years (41.3%) or 15–34 years (38.9%), with the majority residing in urban areas (57.4% vs. 42.6% rural). Nearly half were married (49.2%), while 36.4% reported being single (Table 1). Clinically, extrapulmonary TB (54.3%) was more common than pulmonary TB (45.7%), with new diagnoses predominating (91.1%). Reported comorbidities included diabetes mellitus (13.7%) and HIV co-infection (1.2%). Behavioral risk factors included smoking (31.2%), alcohol use (15.8%), and illicit drug use (20.2%) (Table 2).

Several patient-related factors were identified as potential barriers to treatment adherence (Table 3). Adverse effects during treatment were reported by 58.2% of participants. Forgetfulness in taking medication was reported by 12.7%; 5.2% admitted to reducing their doses without medical advice, and 4.2% discontinued treatment once symptoms improved. Although the majority of participants (84.2%) could access healthcare facilities within 30 minutes, 15.8% reported longer travel times. In total, 90 participants (18.7%) were classified as knowledgeable about TB, correctly answering at least 3 of the 5 knowledge questions (≥60%). The remaining 81.3% were categorized as non-knowledgeable, highlighting substantial educational gaps within the study population. Despite these challenges, almost all patients (99.4%) expressed satisfaction with their healthcare providers, suggesting that non-adherence was primarily driven by patient-level and systemic factors rather than provider-related issues.

Prevalence of Non-Adherence

The overall prevalence of non-adherence was 8.1% (39/481),

Table 1. Sociodemographic characteristics of tuberculosis patients ($n = 481$)

Variable	Category	Frequency (%)
Sex	Male	246 (51.1)
	Female	235 (48.9)
Age (y)	15–34	187 (38.9)
	35–59	199 (41.3)
	>60	95 (19.8)
Residence	Urban	276 (57.4)
	Rural	205 (42.6)
Marital status	Single	175 (36.4)
	Married	237 (49.2)
	Divorced	33 (6.9)
	Widowed	36 (7.5)
Body mass index (kg/m^2)	≥18.5	344 (71.5)
	<18.5	137 (28.5)
Education status	No formal education	192 (39.9)
	At least primary school	289 (60.1)
Employment	Employed	210 (43.7)
	Unemployed	271 (56.3)
Family income (MAD)	≤3,000	399 (83.0)
	>3,000	82 (17.0)
Health insurance	Yes	344 (71.5)
	No	137 (28.5)
Family size	≥4	335 (69.6)
	<4	146 (30.4)

MAD, Moroccan dirham.

Table 2. Clinical and behavioral characteristics of TB patients ($n = 481$)

Variable	Category	Frequency (%)
Form of TB	PTB	220 (45.7)
	EPTB	261 (54.3)
Treatment history	New cases	438 (91.1)
	Re-treatment cases	43 (8.9)
HIV status	Sero-negative	475 (98.8)
	Sero-positive	6 (1.2)
Diabetes mellitus	Yes	66 (13.7)
	No	415 (86.3)
Alcohol use	Yes	76 (15.8)
	No	405 (84.2)
Smoking	Yes	150 (31.2)
	No	331 (68.8)
Illicit drug use (primarily cannabis or hashish)	Yes	97 (20.2)
	No	384 (79.8)

TB, tuberculosis; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus.

Table 3. Treatment-related and behavioral characteristics of TB patients ($n = 481$)

Variable	Category	Frequency (%)
Adverse effects during treatment	Yes	280 (58.2)
	No	201 (41.8)
Time to reach to the health facility (min)	≤30	405 (84.2)
	>30	76 (15.8)
Satisfied with health service provider's behavior	Yes	478 (99.4)
	No	3 (0.6)
Forgetfulness	Yes	61 (12.7)
	No	420 (87.3)
Taking a lower dose without informing the physician	Yes	25 (5.2)
	No	456 (94.8)
Stopping medication when symptoms improve	Yes	20 (4.2)
	No	461 (95.8)
Missing 1 or more follow-up visits during treatment	Yes	30 (6.2)
	No	451 (93.8)
Knowledge of TB	Knowledgeable	90 (18.7)
	Non-knowledgeable	391 (81.3)

TB, tuberculosis.

defined as taking less than 90% of prescribed doses, while 91.9% (442/481) adhered to their treatment regimen.

Factors Associated with Non-Adherence

Bivariate analysis identified several statistically significant predictors of treatment non-adherence ($p \leq 0.05$) across sociodemographic, clinical, and behavioral domains (Table 4). Among sociodemographic factors, male sex ($p = 0.004$) and rural residence ($p = 0.034$) were both significantly associated with non-adherence. Clinically, adverse treatment effects ($p = 0.001$) and pulmonary TB ($p = 0.009$) were significant predictors. Behavioral factors strongly associated with non-adherence included medication forgetfulness ($p < 0.001$), self-adjusted dosing ($p < 0.001$), premature treatment cessation ($p < 0.001$), and missed follow-up visits ($p < 0.001$). These 8 variables were retained in the final multivariable logistic regression model to ensure stability and interpretability.

Multivariable logistic regression revealed several independent predictors of non-adherence (Table 5). Forgetfulness remained the strongest behavioral factor (AOR, 38.84; 95% CI, 11.35–132.88; $p < 0.001$), followed by adverse effects (AOR, 14.26; 95% CI, 3.17–64.13; $p < 0.001$). Male sex (AOR, 6.77; 95% CI, 1.45–31.60; $p = 0.015$) and rural residence (AOR, 4.42; 95% CI, 1.37–14.25; $p = 0.013$) were also significant predictors. Pulmonary TB showed elevated odds (AOR, 2.60; 95% CI, 0.84–8.02) but did not reach statistical significance ($p = 0.096$). Other significant behavioral predictors included self-adjusted dosing (AOR, 5.83; 95% CI, 1.20–28.34; $p = 0.029$), premature cessation of treatment (AOR, 6.56; 95% CI, 1.34–32.14; $p = 0.020$), and missed follow-up visits (AOR, 6.74; 95% CI, 1.56–29.19; $p = 0.011$). These findings underscore the multifactorial nature of TB treatment non-adherence and highlight the need for multidimensional, patient-centered strategies to improve adherence outcomes.

Discussion

Key Results

This study assessed adherence to anti-TB treatment and its determinants among patients in the BMK region of Morocco. We found a non-adherence rate of 8.1%, defined as taking less than 90% of prescribed doses. This rate is comparable to findings from Ethiopia (8.4%) [22] and China (9.4%) [9], which used similar definitions, and aligns with reports of approximately 10% non-adherence in studies employing monthly dose-count methods [23]. However, our rate is notably lower than those reported in India (15.5%) [24], China (12.2%) [8], and Ethiopia (24.5%[7]; 21.2% [10]). These differences may reflect variations in study methodology, the evolution of NTPs, or differences in patient characteristics.

Interpretation

Sociodemographic factors

Multivariable analysis identified several independent predictors of non-adherence. Male patients had significantly higher odds of non-adherence, consistent with results from Argentina [25] and India [24,26].

Although prior studies have suggested that employment responsibilities and time constraints may hinder men's

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Table 4. Bivariate logistic regression analysis of factors associated with treatment non-adherence among TB patients (*n* = 481)

Variable	Category	Adherents (*n*, %)	Non-adherents (*n*, %)	COR (95% CI)	*p*
Sex	Male	217 (88.2)	29 (11.8)	3.01 (1.43–6.31)	0.004
	Female	225 (95.7)	10 (4.3)	1	
Residence	Rural	182 (88.8)	23 (11.2)	2.05 (1.05–3.99)	0.034
	Urban	260 (94.2)	16 (5.8)	1	
Marital status	Single	158 (90.3)	17 (9.7)	1.18 (0.27–8.15)	0.646
	Married	219 (92.4)	18 (7.6)	0.90 (0.07–71.34)	0.635
	Divorced	32 (97.0)	1 (3.0)	0.34 (0.29–24.24)	0.388
	Widowed	33 (91.7)	3 (8.3)	1	
Family size	< 4 Members	129 (88.4)	17 (11.6)	1.87 (0.39–5.62)	0.559
	≥ 4 Members	313 (93.4)	22 (6.6)	1	
Body mass index (kg/m^2)	< 18.5	123 (89.8)	14 (10.2)	1.45 (0.33–5.29)	0.696
	≥ 18.5	319 (92.7)	25 (7.3)	1	
Age (y)	15–34	79 (90.9)	17 (9.1)	1.48 (0.28–16.34)	0.461
	35–59	183 (92.0)	16 (8.0)	1.29 (0.21–5.95)	0.901
	> 60	89 (93.7)	6 (6.3)	1	
Health insurance	No	121 (88.3)	16 (11.7)	1.85 (0.44–5.89)	0.475
	Yes	321 (93.3)	23 (6.7)	1	
Employment	Employed	188 (89.5)	22 (10.5)	1.75 (0.29–10.37)	0.548
	Unemployed	254 (93.7)	17 (6.3)	1	
Education status	At least primary school	265 (91.7)	24 (8.3)	1.07 (0.31–8.34)	0.567
	No formal education	177 (92.2)	15 (7.8)	1	
Family income (MAD)	≤ 3,000	366 (91.7)	33 (8.3)	1.14 (0.89–27.16)	0.068
	> 3,000	76 (92.7)	6 (7.3)	1	
Adverse effects during treatment	Yes	246 (87.9)	34 (12.1)	5.42 (2.08–14.11)	0.001
	No	196 (97.5)	5 (2.5)	1	
Treatment history	Re-treatment cases	29 (67.4)	14 (32.6)	7.97 (0.75–28.69)	0.100
	New cases	413 (94.3)	25 (5.7)	1	
Time to health facility (min)	> 30	63 (82.9)	13 (17.1)	3.00 (0.24–5.96)	0.838
	≤ 30	379 (93.6)	26 (6.4)	1	
HIV status	Sero-positive	5 (83.3)	1 (16.7)	2.30 (0.001–1371.39)	0.919
	Sero-negative	437 (92.0)	38 (8.0)	1	
Smoking	Yes	129 (86.0)	21 (14.0)	2.83 (0.11–21.58)	0.765
	No	313 (94.6)	18 (5.4)	1	
Illicit drug use	Yes	80 (82.5)	17 (17.5)	3.50 (0.59–92.80)	0.120
	No	362 (94.3)	22 (5.7)	1	
Alcohol use	Yes	64 (84.2)	12 (15.8)	2.62 (0.46–32.82)	0.214
	No	378 (93.3)	27 (6.7)	1	
Diabetes mellitus	No	380 (91.6)	35 (8.4)	1.43 (0.32–17.68)	0.403
	Yes	62 (93.9)	4 (6.1)	1	
Form of TB	PTB	198 (90.0)	22 (10.0)	1.59 (1.20–39.82)	0.009
	EPTB	244 (93.5)	17 (6.5)	1	
Forgetfulness	Yes	32 (52.5)	29 (47.5)	37.16 (16.63–83.00)	< 0.001
	No	410 (97.6)	10 (2.4)	1	
Taking a lower dose without informing the physician	Yes	10 (40.0)	15 (60.0)	27.00 (10.98–66.38)	< 0.001
	No	432 (94.7)	24 (5.3)	1	
Stopping medication when symptoms improve	Yes	5 (25.0)	15 (75.0)	54.62 (18.32–162.85)	< 0.001
	No	437 (94.8)	24 (5.2)	1	
Missing 1 or more follow-up visits during treatment	Yes	22 (73.3)	8 (26.7)	4.93 (2.03–11.97)	< 0.001
	No	420 (93.1)	31 (6.9)	1	
Knowledge of TB	Knowledgeable	86 (95.6)	4 (4.4)	2.11 (0.45–52.15)	0.193
	Non-knowledgeable	356 (91.0)	35 (9.0)	1	

TB, tuberculosis; COR, crude odds ratio; CI, confidence interval; MAD, Moroccan dirham; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis.

Table 5. Multivariable logistic regression model to identify independent predictors of treatment non-adherence of TB patients ($n = 481$)

Variable	Category	Adherents (*n*, %)	Non-adherents (*n*, %)	COR (95% CI)	AOR (95% CI)	*p*
Sex	Male	217 (88.2)	29 (11.8)	3.01 (1.43–6.31)	6.77 (1.45–31.60)	0.015
	Female	225 (95.7)	10 (4.3)	1	1	
Residence	Rural	182 (88.8)	23 (11.2)	2.05 (1.05–3.99)	4.42 (1.37–14.25)	0.013
	Urban	260 (94.2)	16 (5.8)	1	1	
Adverse effects during treatment	Yes	246 (87.9)	34 (12.1)	5.42 (2.08–14.11)	14.26 (3.17–64.13)	< 0.001
	No	196 (97.5)	5 (2.5)	1	1	
Form of TB	PTB	198 (90.0)	22 (10.0)	1.59 (1.20–39.82)	2.60 (0.84–8.02)	0.096
	EPTB	244 (93.5)	17 (6.5)	1	1	
Forgetfulness	Yes	32 (52.5)	29 (47.5)	37.16 (16.63–83.00)	38.84 (11.35–132.88)	< 0.001
	No	410 (97.6)	10 (2.4)	1	1	
Taking a lower dose without informing the physician	Yes	10 (40.0)	15 (60.0)	27.00 (10.98–66.38)	5.83 (1.20–28.34)	0.029
	No	432 (94.7)	24 (5.3)	1	1	
Stopping medication when symptoms improve	Yes	5 (25.0)	15 (75.0)	54.62 (18.32–162.85)	6.56 (1.34–32.14)	0.020
	No	437 (94.8)	24 (5.2)	1	1	
Missing 1 or more follow-up visits during treatment	Yes	22 (73.3)	8 (26.7)	4.93 (2.03–11.97)	6.74 (1.56–29.19)	0.011
	No	420 (93.1)	31 (6.9)	1	1	

TB, tuberculosis; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval; PTB, pulmonary tuberculosis; EPTB, extrapulmonary tuberculosis.

ability to adhere to treatment schedules, our data did not identify employment status as a significant predictor, nor did we observe interaction effects between sex and employment. Thus, this explanation should be interpreted cautiously. Nonetheless, the observed sex disparity highlights the importance of developing sex-sensitive adherence strategies. Interventions should consider men's social roles and potential structural barriers by incorporating workplace-based programs or mobile adherence support.

Rural residence was also strongly associated with non-adherence, consistent with findings from Ethiopia [21], where geographic distance and limited transportation were major barriers. Decentralizing services through mobile clinics or community health worker programs could improve access and continuity of care for rural populations.

Behavioral and Treatment-Related Factors

Treatment-related side effects were another major determinant of non-adherence. In line with findings from Ethiopia [22,27], Somalia [28], and China [8,9,29], our results suggest that adverse events such as gastrointestinal or dermatologic reactions contribute to treatment discontinuation. Providing comprehensive pre-treatment counseling and timely management of side effects may help mitigate this barrier and improve adherence.

Missed follow-up visits were also strongly associated with non-adherence, likely reflecting broader socioeconomic constraints, including transportation costs and logistical challenges, especially in rural areas. Similar barriers have been reported in Brazil [30]. Providing transportation support or financial incentives may help mitigate these obstacles and reduce missed appointments. In parallel, expanding access to telemedicine follow-ups—via phone or video—offers a practical and increasingly viable solution. Morocco has made substantial progress in this regard, with a national telemedicine program launched in 2018 and integrated into the Ministry of Health and Social Protection's "Plan Santé 2025" [31]. This initiative aims to equip 160 rural sites by 2025, serving more than 2 million people in medically underserved areas [32]. These efforts, supported by national legislation and high mobile phone penetration, reflect the country's readiness to implement digital health solutions [31]. A recent scoping review by Olowoyo et al. [33] confirmed that telemedicine interventions can effectively improve treatment adherence and outcomes among TB patients, making it a promising area for continued investment and locally tailored implementation in Morocco.

Forgetfulness emerged as the strongest predictor of non-adherence, corroborating prior evidence from Zegeye et al. [34] and Adane et al. [23]. This highlights the need for simple, cost-effective strategies such as SMS reminders, pillboxes, and family involvement in medication routines. Routine clinical assessments that include screening for forgetfulness could help identify at-risk patients early and enable timely interventions.

Behavioral misconceptions, such as self-adjusting doses or discontinuing treatment when symptoms improve, were also important contributors to non-adherence. These

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behaviors reflect an inadequate understanding of TB treatment requirements, consistent with findings from India [24] and Eritrea [35]. Targeted health education, particularly through community health workers, can help correct these misconceptions and reinforce the importance of completing the full course of therapy.

Strengths and Limitations

This study provides robust evidence on TB treatment adherence in the BMK region by using methodological triangulation and a comprehensive analysis of clinical, behavioral, and structural factors. Adherence was evaluated using a validated threshold aligned with WHO recommendations, strengthening both reliability and comparability across studies. While the cross-sectional design limits causal inference and the use of convenience sampling may have introduced selection bias, the study nonetheless identifies critical and actionable barriers to adherence that are highly relevant for public health planning and TB control programming.

Generalizability

In Morocco, TB treatment is provided exclusively through public health facilities known as TRDDCs, where medications are dispensed free of charge. The 2 TRDDCs included in this study were purposively selected for their high TB burden and their representation of both urban and rural populations, accounting for nearly half of the region's TB cases. Therefore, the findings are likely generalizable to similar semi-urban and rural populations within Morocco and to countries with comparable public-sector TB programs. However, caution should be exercised when applying these results to settings with different healthcare delivery structures or greater private-sector involvement.

Based on these findings—and consistent with the review by Volmink and Garner [36], which suggests that addressing social and systemic barriers is more effective than restrictive approaches that compromise patient autonomy—we recommend 3 key policy actions: (1) the NTP should integrate digital reminder tools and structured side-effect management into routine care; (2) the Ministry of Health and Social Protection should prioritize sex-sensitive strategies and decentralize TB services in rural areas by strengthening community health worker networks; and (3) policymakers should implement transportation subsidies to improve access for vulnerable populations. Additionally, motivating healthcare personnel involved in TB control through targeted incentives could enhance service delivery. To reinforce these efforts, we also advocate for patient-centered education initiatives and future longitudinal mixed-methods research to further examine and address persistent adherence challenges in Morocco and other high-burden contexts.

Conclusion

This study demonstrates a high overall adherence rate to anti-TB treatment among patients in the BMK region. Nonetheless, a subset of patients continues to experience significant barriers to adherence, including forgetfulness, adverse drug effects, male sex, rural residence, and missed follow-up visits. These results highlight the multifactorial and context-specific nature of non-adherence, shaped by clinical, behavioral, and structural determinants.

To overcome these challenges, targeted interventions are required. These include enhanced patient education, proactive side-effect management, digital reminder tools, and expanded healthcare access in rural areas. Incorporating community-based support and integrating psychosocial care into TB programs may further strengthen adherence. Sustained improvements in adherence are critical not only for optimizing individual outcomes but also for advancing Morocco's national TB control strategy and preventing the emergence and spread of drug-resistant TB.

Notes

Ethics Approval

The study received ethical approval from the Ethics Committee for Biomedical Research at Mohammed Premier University's Faculty of Medicine and Pharmacy, Oujda (approval number: 2022-08) and performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: MD, SB; Data curation: MD; Formal analysis: MD, SB; YA; Investigation: DM, SB; Methodology: MD, SB, YA, KH; Project administration: SB, KH; Software: DM; Supervision: KH; Writing–original draft: DM, SB; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Comparative effectiveness of construal-level messaging in the COVID-19 Vaccine Injury Compensation Program in the Republic of Korea: a randomized controlled trial

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ABSTRACT

Objectives: This study aimed to assess the impact of high-level versus low-level construal messages about the coronavirus disease 2019 (COVID-19) Vaccine Injury Compensation Program (CVICP) on public attitudes toward the program and COVID-19 vaccination.
Methods: A randomized controlled experimental design was employed. Adults aged 18 to 64 residing in the Republic of Korea were randomly assigned to either an experimental group (high-level construal message) or a control group (low-level construal message). Both groups viewed a 2-minute video about the CVICP, with construal level as the sole variable. Pre- and post-intervention questionnaires evaluated attitudes toward the CVICP and COVID-19 vaccination, including satisfaction, perceived necessity, and perceived effectiveness in enhancing vaccine acceptance. Data were analyzed using the paired t-test, repeated measures 2-way analysis of variance, and multiple linear regression.
Results: The experimental group showed statistically significant improvements across all 6 attitude measures following exposure to the high-level construal message. By contrast, the control group demonstrated significant improvement in only 3 attitudes: satisfaction with the CVICP, willingness to recommend vaccination, and willingness for future vaccination. A significant difference between groups was observed for perceived effectiveness of the CVICP in enhancing vaccine acceptance ($p = 0.01$), with high-level construal messaging being more impactful.
Conclusion: High-level construal messages are more effective than low-level messages in shaping public perceptions and addressing vaccine hesitancy. Policymakers and health authorities should incorporate high-level construal elements into communication strategies to build trust and support for vaccination programs.

Keywords: Compensation and redress; COVID-19; Health communication; Psychological distance; Vaccine hesitancy

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Introduction

Since its emergence in December 2019, the coronavirus disease 2019 (COVID-19) pandemic has posed a global challenge, prompting a wide array of policy responses to manage and mitigate its impact. In the Republic of Korea, COVID-19 vaccine approval began in February 2021, launching a nationwide vaccination campaign. Despite these efforts, vaccine hesitancy has remained a substantial barrier, fueled by concerns over rapid vaccine development, accelerated authorization, and perceived insufficiency of long-term safety data. Such hesitancy has impeded both individual vaccination and the broader attainment of community or national herd immunity [1].

To address these issues, the Republic of Korea implemented the COVID-19 Vaccine Injury Compensation Program (CVICP) in 2021, subsequently enhancing it by relaxing compensation criteria, expanding coverage, and streamlining claims processes [2]. Nevertheless, a 2023 survey found that most adults remained unaware of the CVICP, perceived it as the least effective COVID-19-related policy, and viewed it as unreliable [3]. Although the government expanded the CVICP in July 2023, public skepticism persisted into 2024. Given the substantial investment and its implications for vaccine hesitancy, effective communication strategies are urgently needed.

According to the theory of planned behavior, individuals' attitudes are predictive of their behavioral intentions [4]. Similarly, population attitudes toward policy are critical determinants of program participation in democratic societies. Positive attitudes enhance compliance and, consequently, policy effectiveness. Cognitive Appraisal Theory further suggests that individuals assess policies based on their perceived impact, controllability, and relevance, a framework used by Li's team to evaluate perceived severity, controllability, and knowledge of disease [5,6]. In the Republic of Korea, Choi et al. [7] measured 'perceived value' and 'patient satisfaction' to gauge attitudes toward healthcare interventions. Drawing from these theories and studies, public attitudes can be conceptualized in terms of perceived severity, value (explained by perceived necessity and effectiveness), and satisfaction. Knowledge is also an important determinant of attitude. However, in this study, all participants received the same program information before attitudes were measured. Thus, attitudes toward the CVICP were operationally defined as a composite of satisfaction, perceived necessity, and perceived effectiveness.

Recognizing the need for strategies to foster favorable attitudes towards the CVICP—especially in light of increased funding and expansion efforts— the importance of strategic communication is clear. Effective communication strategies are crucial for building public support for policies, particularly given current deficits in awareness and trust surrounding the CVICP. Construal level theory (CLT) offers a valuable framework for designing such public communication messages [8].

CLT posits that people mentally represent events differently depending on their psychological distance: events perceived as close are construed concretely, while distant events are construed more abstractly [9]. This framework suggests that both perceived distance and construal level are mutually influential. Prior studies have shown that varying the construal level in health-related messages can significantly affect persuasiveness and behavioral outcomes [10,11]. Thus, adjusting the construal level of CVICP messages may effectively alter public attitudes toward the program.

Currently, the Korea Disease Control and Prevention Agency (KDCA) communicates information about the CVICP primarily through its website, detailing administrative procedures, eligibility requirements, documentation, and compensation timelines [12]. However, these communications predominantly use concrete, procedural language, lacking higher-level framing that highlights the program's rationale and social benefits. Framing the CVICP in more abstract terms—emphasizing social solidarity—may resonate more strongly in the Republic of Korea, where collective responsibility is a key element of the 5C model of vaccine hesitancy (confidence, complacency, constraints, calculation of risk, and collective responsibility) [3]. Given the KDCA's current focus on concrete, procedural messaging, this low-construal style was selected as the control condition to reflect real-world public communication.

This study aimed to examine how different message

HIGHLIGHTS

- High-level construal messages, emphasizing abstract values and collective benefits, significantly improved perceptions of the COVID-19 Vaccine Injury Compensation Program's effectiveness in promoting vaccine acceptance, outperforming low-level construal messages.
- The findings suggest that integrating high-level construal elements into public health messaging can enhance vaccine acceptance by fostering trust, highlighting social solidarity, and promoting the broader societal benefits of vaccination policies.
- This study provides actionable recommendations for policymakers and public health authorities to improve communication strategies, thereby ensuring more effective engagement with the public regarding vaccination programs.

framings (specifically, high-level versus low-level construal messages) affect attitudes toward the CVICP. In particular, it investigates how these messages influence public perceptions of the CVICP and their willingness to accept COVID-19 vaccination.

Construal Level Theory

CLT, developed by Trope and Liberman [9], provides a framework for understanding how individuals mentally represent events according to their psychological distance. The theory differentiates between high-level construals, which are abstract, generalized, and goal-oriented, and low-level construals, which are concrete, detailed, and context-dependent. Psychological distance may arise from temporal, spatial, social, or hypothetical sources, thereby shaping whether individuals focus on the "why" (high-level) or the "how" (low-level) aspects of an issue.

In public policy settings, including health programs, CLT offers valuable insight into variations in public engagement and the formation of attitudes. When a program such as the CVICP is presented using high-level construals—emphasizing concepts like fairness, collective responsibility, or public health equity—it may better align with the broader values of society. Conversely, low-level construals present specific operational or procedural details, such as compensation steps or eligibility requirements, which may be more immediately relevant for individuals directly affected.

Prior research supports the utility of CLT in designing public information campaigns. Park et al. [8] demonstrated that construal-level fit between message framing and an individual's cognitive orientation significantly enhances the effectiveness of health-related messaging. Similarly, studies in behavioral medicine and nutrition have demonstrated that high-level construals increase the perceived importance of preventive behaviors, while low-level construals may facilitate clarity and promote immediate action [6,7].

Applying CLT to the CVICP is especially pertinent given the abstract and complex nature of compensation policies, as well as the generally low public awareness of their existence and function. The CVICP operates within socio-political and legal frameworks that often appear remote to ordinary citizens, potentially reducing trust and perceived relevance. Utilizing high-level construal messages may elevate the program's perceived legitimacy and moral rationale. This strategy is particularly compatible with values central to Korean public health culture, such as social solidarity and institutional trust, which have been identified as key antecedents of vaccine acceptance in the 5C model [9].

In summary, CLT provides a scientifically grounded foundation for tailoring message strategies related to the CVICP. Its application in this study offers empirical evidence regarding how abstract versus concrete messaging can alter public attitudes and help mitigate vaccine hesitancy (Figure 1).

Materials and Methods

Participants

An online survey was conducted by Hankook Research Co. Ltd., which managed both data collection and the de-identification of respondents. The survey commenced on April 12, 2024. Eligible participants were adults aged 18 to 64 years residing in the Republic of Korea who could read and understand Korean. Individuals were excluded if they declined to participate or had conditions likely to affect study outcomes. The sample size was determined to be 520 adults, providing 90% power to detect a 30% difference in attitude ratings between the experimental and control groups, with an alpha level of 0.05.

Intervention

The study was designed to evaluate the effects of different construal levels in messaging about the CVICP on attitudes toward both the program and COVID-19 vaccination. A professional communication company was contracted to produce 2 short videos, with construal level as the sole manipulated variable. All other video components—including background music, color scheme, and voice tone—were held constant to minimize confounding. Across multiple planning sessions, the research team clarified the study's aims, detailed desired content, and suggested visual elements for inclusion. Narrative scripts were developed collaboratively

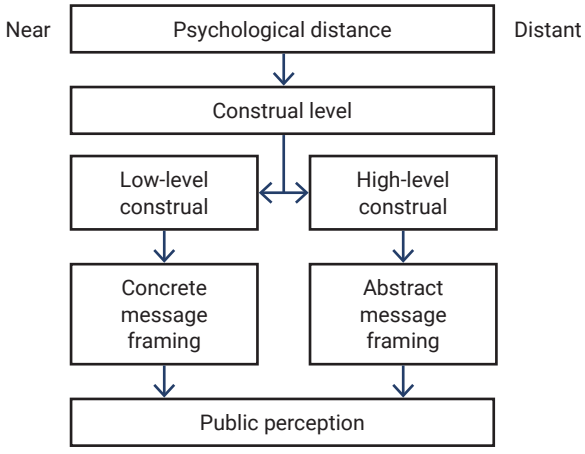


Figure 1. Conceptual diagram of construal level theory as applied to message framing for the COVID-19 Vaccine Injury Compensation Program.

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by the research team and the communication company, ensuring alignment with both research objectives and communication best practices. The company produced initial video drafts, which were revised in consultation with the research team through several iterations until final approval. Throughout the process, oversight by a communication expert and the research team ensured consistency and quality. A pilot test was conducted with 12 participants recruited from the survey company's panel to assess the clarity and feasibility of the intervention. Participants were asked whether the survey content was understandable, whether the videos were clear, and if they experienced any confusion or difficulty completing the survey. All participants completed the survey in full, and there were no dropouts. Feedback confirmed that both the survey and video content were clear and appropriate, validating the suitability of the intervention materials for the target audience.

The experimental group received a video framed at a high construal level, emphasizing the CVICP's fundamental values, abstract principles, and overarching messages (Figure S1). Key points included (1) The Korean government operates the vaccine injury compensation program (VICP) as part of its responsibility to ensure public safety, particularly concerning unavoidable adverse effects from COVID-19 vaccination; (2) Despite the clear public health benefits of vaccination, some individuals inevitably experience adverse effects; (3) Vaccination is not only a personal health decision but also a contribution to herd immunity and societal well-being. On the principle of social solidarity, the government compensates individuals who suffer harm from vaccines administered for public purposes; (4) The government distributes the risk of adverse events, ensuring the burden does not fall solely on the individual, but is shared collectively by society.

In contrast, the control group viewed a video at a low construal level, focusing on detailed, specific information and procedural content (Figure S2). Key messages included (1) Submission of required documents is mandatory when applying for compensation, including a medical certificate, death certificate (if applicable), or a physician-issued diagnosis; (2) The compensation process begins when a healthcare institution, the vaccinated individual, or a guardian reports an adverse event, either through the institution or online. A claim is submitted to the local public health center, forwarded for preliminary review by the city or provincial governor, and finally sent to the KDCA for a final decision; (3) If the claimed medical expense is under 300,000 Korean won (KRW), the city or province manages the review independently; (4) Claims must be filed within 5 years from the date of injury, and the entire review process must be completed within 120 days of application submission; (5) Since 2021 and 2022, the scope of the compensation system has expanded. Previously, only cases involving out-of-pocket medical expenses exceeding 300,000 KRW were eligible. This threshold has now been removed, broadening access to compensation; (6) Additionally, to increase convenience for applicants, the application procedure has been made more flexible.

Procedure

A randomized controlled experimental design was employed. Participants accessed the study via a provided URL, gave informed consent, and completed questionnaires between April 12 and April 18, 2024. The intervention consisted of exposure to information about the CVICP. Participants randomly assigned to the experimental arm viewed a 2-minute video emphasizing the establishment of the CVICP using higher-level construal. In contrast, those in the control arm were shown a 2-minute video presenting information currently available on the KDCA website, representing lower-level construal. After viewing the assigned video, participants completed follow-up questionnaires designed to assess changes in their perceptions of the CVICP and vaccine-related attitudes. The overall study procedure is depicted in Figure 2.

Recruitment was conducted via email or text invitation

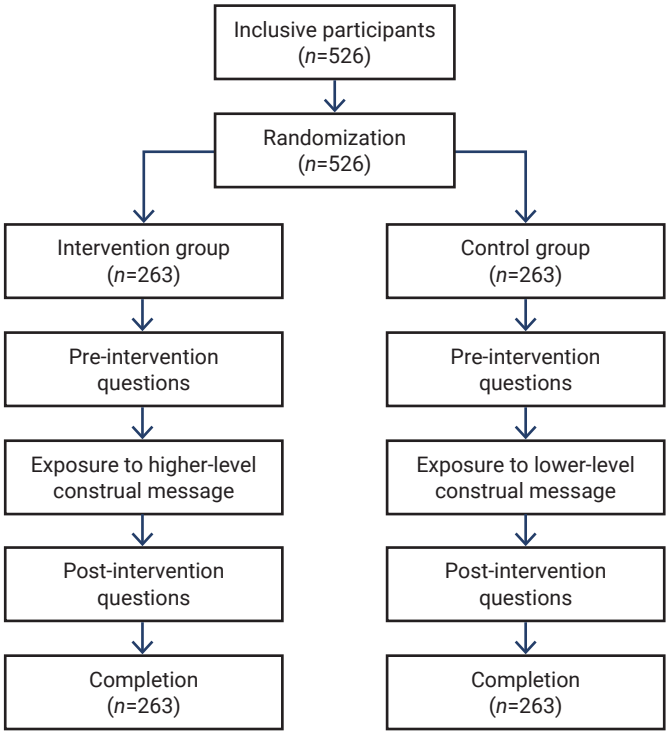


Figure 2. Procedure of the randomized controlled experiment.

from the contracted research firm. Upon clicking the URL, participants were directed to an online platform where they first reviewed and agreed to an informed consent form. Following consent, they completed a baseline (pre-intervention) questionnaire that included demographic information, COVID-19 vaccination history, and baseline perceptions of the CVICP and COVID-19 vaccination.

After completing the baseline survey, participants were automatically and randomly allocated by the platform's algorithm to 1 of 2 groups: the experimental group (high construal-level message) or the control group (low construal-level message). Participants then watched a 2-minute video, embedded directly within the survey platform. To ensure full exposure to the intervention, participants were required to view the entire video before proceeding. Immediately after viewing the video, participants completed a post-intervention questionnaire, which repeated the assessment of attitudes toward the CVICP and vaccination.

The survey was self-administered and designed to be completed in a single session, requiring approximately 10 minutes in total. The survey platform enforced data completeness by requiring responses to all questions before submission. No personally identifiable information was collected, thus ensuring participant anonymity.

Measures

The research team developed a questionnaire to collect demographic information, COVID-19 vaccination history and experiences, experience with adverse events following vaccination, knowledge and experience with the CVICP, and evaluations of the CVICP and COVID-19 vaccination (Table 1). A pilot test was conducted to refine the questionnaire and ensure the clarity of its items.

Demographic data included socioeconomic status, age, gender, education level, occupation, household size, residential area, and perceived general health status. Additional items assessed experiences related to COVID-19, vaccination status, adverse effects following vaccination (either personally experienced or observed in acquaintances), and awareness and perceptions of the CVICP. Attitudes toward the CVICP—comprising satisfaction, perceived necessity, and perceived effectiveness in promoting vaccine acceptance—were measured, alongside perceived necessity of COVID-19 vaccination, willingness for future vaccination, and willingness to recommend vaccination [13]. All attitude-related items were assessed using a 7-point Likert scale, ranging from "not at all" (1) to "strongly agree" (7).

Data Analysis

Data analysis was conducted using RStudio software ver. 2023.12.1+402 (Posit Software, PBC). Descriptive statistics were calculated for all variables. To test the hypothesis that attitudes toward the CVICP would differ between the experimental and control groups, paired t-tests were performed. Subsequently, repeated measures 2-way analysis of variance (ANOVA) was used to assess whether changes in the dependent variables differed between the groups over time. This ANOVA examined the effects of group (between-subjects), time (within-subjects), and their interaction. Multiple linear regression analyses were then conducted to determine whether significant differences in the dependent variables persisted between groups after controlling for demographic characteristics, COVID-19 infection history, vaccine uptake, prior adverse events, and CVICP awareness and experience, all of which might influence perceptions of the compensation system and COVID-19 vaccination [14–17]. We used a tiered approach: the paired t-test for within-group changes, ANOVA for group × time interaction, and regression to control for covariates and explore predictors of attitude change. This strengthened internal validity and interpretability.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of Korea University Anam Hospital (IRB No: 2024 AN 0065). All procedures adhered to ethical standards for human experimentation and conformed to the principles outlined in the Helsinki Declaration of 1975, as revised in 2000.

Results

Participant Characteristics

Although the target sample size was 520, the final number of participants reached 526 due to simultaneous access to the study URL. Table 2 summarizes the socio-demographic characteristics of the participants.

The sample was stratified by gender, age, and region. Office workers comprised the largest occupational group (36.5%), and 63.7% of respondents resided in large cities. In terms of health status, 49.0% reported their health as average. Households with 3 or more members accounted for 62.0% of the sample. There were no significant differences between the experimental and control groups in most socio-demographic variables, except for political tendency ($p = 0.003$) and residential area ($p = 0.006$). To address these differences, political ideology and residential area were included as covariates in the multiple linear regression analyses. This ensured that any observed effects of the intervention were independent of these socio-demographic

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Table 1. Measurement items of the questionnaire

Category	Variable	Item description	Response format/scale
Demographics	Gender	What is your gender?	1 = Male, 2 = female
	Age	What is your birth year?	Open numeric
	Education level	What is your highest level of education completed?	1 = Middle school or less, 2 = high school, 3 = college, 4 = graduate school
	Self-rated health	How would you rate your overall health?	1 = Very poor, 5 = very good
	Household size	How many people live in your household (including yourself)?	1 = One, 2 = two, 3 = three or more
	Monthly household income	What is your household's average monthly income?	1 = < 1 M KRW, 2 = 1–3 M, 3 = 3–5 M, 4 = > 5 M
	Occupation	What is your current occupation?	1 = Production, 2 = office, 3 = sales/service, 4 = health/medical, 5 = homemaker, 6 = other (e.g., student, military)
	Region	Where do you currently live?	1 = Large city, 2 = small/medium city, 3 = rural
	Political orientation	What is your political ideological tendency?	1 = Liberal, 2 = moderate, 3 = conservative, 4 = no comment
COVID-19 experience	COVID-19 infection	Have you ever been infected with COVID-19?	1 = No, 2 = yes
	Vaccination status	What is your COVID-19 vaccination status?	1 = None, 2 = partial primary series, 3 = completed primary, 4 = 1st booster, 5 = 2nd booster, 6 = 3rd or more boosters
	Adverse events after vaccination	What adverse events did you experience after COVID-19 vaccination? (multiple responses allowed)	1 = None, 2 = injection site pain/swelling/bruising, 3 = fever/chills, 4 = fatigue/drowsiness, 5 = headache/dizziness, 6 = muscle pain/cramps, 7 = menstrual irregularities, 8 = nausea/vomiting, 9 = loss of appetite, 10 = diarrhea, 11 = other (free text)
CVICP awareness & experience	Awareness of CVICP	Are you aware of the CVICP?	1 = No, 2 = yes
	Experience with CVICP	Have you or someone you know applied for the compensation program?	1 = no, 2 = yes (from methods; inferred)
Attitudes toward the CVICP	Satisfaction	I am satisfied with the government's compensation program.	7-Point Likert scale (1 = not at all, 7 = strongly agree)
	Perceived necessity	The compensation program is necessary for our society.	7-Point Likert scale
	Perceived effectiveness	The program helps improve vaccine acceptance.	7-Point Likert scale
Attitudes toward COVID-19 vaccination	Perceived necessity	COVID-19 vaccination is necessary for our society.	7-Point Likert scale
	Willingness to recommend	I would recommend COVID-19 vaccination to others.	7-Point Likert scale
	Willingness to receive	I am willing to receive COVID-19 vaccination in the future.	7-Point Likert scale

KRW, Korean won; COVID-19, coronavirus disease 2019; CVICP, COVID-19 Vaccine Injury Compensation Program.

factors. Additionally, sensitivity analyses were performed to confirm the robustness of the findings by excluding participants with extreme or outlier values in these variables.

Experience with COVID-19, the CVICP, and Attitudes Toward the CVICP and Vaccination

Table 3 provides details on participants' experiences with COVID-19 vaccination and the CVICP. Overall, 78.1% of respondents reported a history of COVID-19 infection, and 94.3% had received at least 1 dose of a COVID-19 vaccine. The largest subgroup (35.9%) consisted of participants who had received 3 or more booster doses. The most frequently reported side effects following vaccination were fever and chills (34.5%), followed by localized pain, redness, or swelling at the injection site (28.8%). About a quarter of respondents reported no side effects. No significant differences were found between the experimental and control groups in terms of vaccine or CVICP experience. Awareness of the CVICP was reported by 52.1% of the experimental group and 49.8% of the control group, with no significant difference between groups ($p = 0.601$).

Table 3 also presents participants' baseline attitudes

Table 2. Characteristics of the survey respondents

Socio-demographic characteristic	Experimental group (n = 263)	Control group (n = 263)	x^2 (p)
Sex			0.37 (0.541)
Male	131 (49.8)	138 (52.5)	
Female	132 (50.2)	125 (47.5)	
Age (y)			6.71 (0.152)
18–29	49 (18.6)	61 (23.2)	
30–39	59 (22.4)	39 (14.8)	
40–49	66 (25.2)	61 (23.2)	
50–59	59 (22.4)	71 (27.0)	
60–64	30 (11.4)	31 (11.8)	
Education			0.25 (0.969)
Middle school or lower education	1 (0.4)	1 (0.4)	
High school or equivalent	53 (20.2)	55 (20.9)	
Undergraduate education	179 (68.1)	174 (66.2)	
Postgraduate education	30 (11.4)	33 (12.5)	
Political ideological tendency			13.93 (0.003**)
Liberal	75 (28.5)	78 (29.7)	
Middle	117 (44.5)	121 (46.0)	
Conservative	47 (17.9)	59 (22.4)	
No comment	24 (9.1)	5 (1.9)	
Perceived general health status			1.08 (0.898)
Very bad	2 (0.8)	2 (0.8)	
Bad	28 (10.6)	24 (9.1)	
Not good, not bad	131 (49.8)	127 (48.3)	
Good	90 (34.2)	100 (38.0)	
Very good	12 (4.6)	10 (3.8)	
No. of household members			0.28 (0.87)
1	42 (16.0)	43 (16.3)	
2	60 (22.8)	55 (20.9)	
≥3	161 (61.2)	165 (62.7)	
Household income (million KRW)			3.27 (0.352)
1 or below	9 (3.4)	12 (4.6)	
1–3	52 (19.8)	67 (25.4)	
3–5	89 (33.8)	78 (29.7)	
≥5	113 (43.0)	106 (40.3)	
Occupation			2.63 (0.756)
Production worker	15 (5.7)	14 (5.3)	
Office worker	102 (38.8)	90 (34.2)	
Service and sales worker	47 (17.9)	53 (20.2)	
Healthcare worker	12 (4.6)	8 (3.0)	
Housewife	34 (12.9)	37 (14.1)	
Other	53 (20.2)	61 (23.2)	
Residential area			10.19 (0.006**)
Metropolitan city	174 (66.2)	161 (61.2)	
Small and medium sized city	81 (30.8)	76 (28.9)	
Rural area	8 (3.0)	26 (9.9)	

Data are presented as n (%).
KRW, Korean won.
**p < 0.01.

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Table 3. Experiences and attitudes regarding COVID-19, CVICP, and vaccination

	Experimental group (n = 263)	Control group (n = 263)	x^2 (p)[a]/t-value (p)[b]
Experiences of COVID-19			
Have been affected by COVID-19			0.01 (0.916)[a]
No	57 (21.7)	58 (22.1)	
Yes	206 (78.3)	205 (77.9)	
COVID-19 vaccination			6.23 (0.284)[a]
Never	14 (5.3)	16 (6.1)	
Part of basic vaccination	6 (2.3)	12 (4.6)	
Basic vaccination	49 (18.6)	43 (16.3)	
First booster	25 (9.5)	15 (5.7)	
Second booster	72 (27.4)	85 (32.3)	
Third booster or more	97 (36.9)	92 (35.0)	
Adverse events following COVID-19 vaccination			4.63 (0.796)[a]
None	71 (27.0)	59 (22.4)	
Pain, redness, swelling, or bruising at the injection site	70 (26.6)	73 (27.8)	
Fever and chills	58 (22.1)	57 (21.7)	
Fatigue and drowsiness	23 (8.7)	21 (8.0)	
Headache and dizziness	6 (2.3)	9 (3.4)	
Muscle pain and muscle cramps	15 (5.7)	15 (5.7)	
Abnormal uterine bleeding and menstrual irregularities	2 (0.8)	5 (1.9)	
Nausea and vomiting	2 (0.8)	3 (1.1)	
Loss of appetite	2 (0.8)	5 (1.9)	
Diarrhea	71 (27.0)	59 (22.4)	
Others	70 (26.6)	73 (27.8)	
Aware of CVICP			0.27 (0.601)[a]
No	126 (47.9)	132 (50.2)	
Yes	137 (52.1)	131 (49.8)	
Attitudes toward the CVICP and COVID-19 vaccination			
CVICP: satisfaction levels	3.63 ± 1.38	3.61 ± 1.53	−0.15 (0.88)[b]
CVICP: perceived necessity	5.33 ± 1.32	5.33 ± 1.33	0.03 (0.97)[b]
CVICP: enhancing vaccine acceptance	4.99 ± 1.40	5.08 ± 1.47	0.76 (0.45)[b]
COVID-19 vaccination: perceived necessity	5.10 ± 1.45	5.12 ± 1.49	0.21 (0.84)[b]
COVID-19 vaccination: willingness to recommend	4.74 ± 1.65	4.72 ± 1.67	−0.11 (0.92)[b]
COVID-19 vaccination: willingness for future vaccination	4.58 ± 1.79	4.59 ± 1.81	0.05(0.96)[b]

Data are presented as n (%) or mean ± standard deviation.
COVID-19, coronavirus disease 2019; CVICP, COVID-19 Vaccine Injury Compensation Program.
[a]By chi-square test. [b]By Student t-test.

toward the CVICP and COVID-19 vaccination. No significant differences were observed between the experimental and control groups for any of the measured attitudes, including satisfaction with the CVICP, perceived necessity of the CVICP, perceived effectiveness in enhancing vaccine acceptance, perceived necessity of COVID-19 vaccination, willingness to recommend COVID-19 vaccination, and willingness for future vaccination (all $p > 0.05$). These findings confirm that both groups had comparable baseline attitudes before the intervention, allowing for a fair assessment of the effects of the message frames.

Changes in Attitudes Toward the CVICP and COVID-19 Vaccination

In the experimental group, statistically significant improvements were observed across all 6 measured attitudes after exposure to the high-level construal message. For instance, satisfaction with the CVICP increased from mean (M) ± standard deviation (SD) = 3.63 ± 1.38 to 4.27 ± 1.30, $t(262) = -8.18$, $p < 0.001$; and perceived effectiveness of the CVICP in enhancing vaccine acceptance increased from 4.99 ± 1.40 to 5.26 ± 1.23, $t(262) = -3.64$, $p < 0.001$. Similarly, willingness to recommend vaccination rose from 4.74 ± 1.65 to 4.91 ± 1.64, $t(262) = -2.74$, $p = 0.01$.

In the control group, improvements were limited to 3 areas:

satisfaction with the CVICP (M=3.61 to M=4.32, t(262)=–8.77, $p<0.001$), willingness to recommend COVID-19 vaccination (M=4.72 to M=4.83, t(262)=–1.98, $p=0.05$), and willingness for future vaccination (M=4.59 to M=4.89, t(262)=–4.80, $p<0.001$) (Table 4).

Results from repeated measures 2-way ANOVA revealed significant main effects for time (pre- vs. post-intervention) across all attitudes (e.g., satisfaction with the CVICP: F(1, 524)=143.75, $p<0.001$; willingness for future vaccination: F=48.71, $p<0.001$) (Table 5). However, interaction effects (group×pre–post) were significant only for "perceived effectiveness in enhancing vaccine acceptance" (F(1, 524)=7.29, $p=0.01$), indicating that the experimental group experienced a significantly greater improvement on this measure compared to the control group.

Socio-demographic variables associated with each attitude variable were explored using multiple regression analysis. Variables that increased the explained variance (F-value) were retained in the final model. Even after adjusting for demographic factors, the experimental group showed a significant positive effect on "perceived effectiveness in enhancing vaccine acceptance" (β=0.28, $p=0.01$). No other significant group effects were observed (Tables 6, 7).

These results indicate that high-level construal messages significantly enhanced perceptions of the CVICP's effectiveness in promoting vaccine acceptance compared to low-level construal messages. While both message types led to overall improvements in attitudes, high-level construal messaging had a more pronounced impact on perceptions of program effectiveness.

Discussion

The COVID-19 pandemic has necessitated rapid and effective policy responses worldwide. Although vaccines have been available in the Republic of Korea since early 2021, vaccine hesitancy continues to pose a significant barrier to achieving herd immunity. The CVICP was introduced to address these concerns by compensating for adverse events following vaccination. However, a 2023 survey revealed substantial gaps in public awareness and trust regarding the CVICP, highlighting the urgent need for strategic communication to

Table 4. Changes in attitudes toward the CVICP and COVID-19 vaccination in each group

Attitudes toward the CVICP and COVID-19 vaccination	Experimental group				Control group			
	Pre	Post	Change		Pre	Post	Change	
	Mean±SD	Mean±SD	t	*p*	Mean±SD	Mean±SD	t	*p*
CVICP: satisfaction levels	3.63±1.38	4.27±1.30	−8.18	0.00**	3.61±1.53	4.32±1.29	−8.77	0.00**
CVICP: perceived necessity	5.33±1.32	5.50±1.23	−2.27	0.02*	5.33±1.33	5.38±1.27	−0.65	0.52
CVICP: enhancing vaccine acceptance	4.99±1.40	5.26±1.23	−3.64	0.00**	5.08±1.47	5.08±1.36	0.11	0.92
COVID-19 vaccination: perceived necessity	5.10±1.45	5.30±1.36	−3.55	0.00**	5.12±1.49	5.20±1.41	−1.27	0.2
COVID-19 vaccination: willingness to recommend	4.74±1.65	4.91±1.64	−2.74	0.01**	4.72±1.67	4.83±1.56	−1.98	0.05*
COVID-19 vaccination: willingness for future vaccination	4.58±1.79	4.88±1.70	−5.09	0.00**	4.59±1.81	4.89±1.69	−4.80	0.00**

COVID-19, coronavirus disease 2019; CVICP, COVID-19 Vaccine Injury Compensation Program.
*$p<0.05$, **$p<0.01$.

Table 5. Changes in attitudes toward the CVICP and COVID-19 vaccination: repeated measures 2-way analysis of variance

Attitudes toward the CVICP and COVID-19 vaccination	Group		Pre–post		Group:pre–post	
	F	*p*	F	*p*	F	*p*
CVICP: satisfaction levels	0.02	0.90	143.75	0.00**	0.33	0.56
CVICP: perceived necessity	0.35	0.55	4.44	0.04*	1.49	0.22
CVICP: enhancing vaccine acceptance	0.17	0.68	6.52	0.01*	7.29	0.01*
COVID-19 vaccination: perceived necessity	0.11	0.75	11.26	0.00**	2.25	0.13
COVID-19 vaccination: willingness to recommend	0.11	0.74	11.33	0.00**	0.56	0.46
COVID-19 vaccination: willingness for future vaccination	0.00	0.95	48.71	0.00**	0.00	0.96

COVID-19, coronavirus disease 2019; CVICP, COVID-19 Vaccine Injury Compensation Program.
*$p<0.05$, **$p<0.01$.

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Table 6. Changes in attitudes toward the CVICP: multiple linear regression models

Variable	Attitude toward the CVICP											
	Satisfaction				Necessity				Enhancing acceptance			
	β	SE	t	*p*	β	SE	t	*p*	β	SE	t	*p*
(Intercept)	0.92	0.62	1.47	0.14	−0.41	0.58	−0.71	0.46	−1.39	0.58	−2.39	0.02*
Experimental group	−0.10	0.12	−0.84	0.40	0.10	0.11	0.90	0.37	0.28	0.11	2.60	0.01*
Gender												
Age					x							
Region												
Education	x											
Income					x							
Occupation												
Ideological tendency	x				x							
Residential area	x											

CVICP, COVID-19 Vaccine Injury Compensation Program; SE, standard error; x, variables included in the final model.
*$p < 0.05$.

Table 7. Changes in attitudes toward the COVID-19 vaccination: multiple linear regression models

Variable	Attitude toward COVID-19 vaccination											
	Necessity				Recommend				Future vaccination			
	β	SE	t	*p*	β	SE	t	*p*	β	SE	t	*p*
(Intercept)	0.43	0.48	0.89	0.37	0.18	0.46	0.38	0.70	1.01	0.47	2.13	0.03*
Experimental group	0.10	0.09	1.14	0.26	0.06	0.09	0.69	0.49	−0.03	0.09	−0.39	0.70
Gender	x								x			
Age	x											
Region												
Education	x				x				x			
Income	x								x			
Occupation												
Ideological tendency									x			
Residential area												

COVID-19, coronavirus disease 2019; SE, standard error; x, variables included in the final model.
*$p < 0.05$.

shape public perceptions and support vaccination policies.

CLT, as a theoretical framework for message framing, offers valuable insights into strategies that can influence attitudes and behaviors. The present study demonstrates that varying the construal level of CVICP messages leads to differing changes in policy attitudes toward both the CVICP and vaccination. High-level construal messages significantly improved participants' perceptions of the CVICP's effectiveness in enhancing vaccine acceptance and produced broader improvements across all measured attitudes. In contrast, low-level construal messages led to more limited gains, improving only satisfaction with the CVICP, willingness to recommend COVID-19 vaccination, and willingness to receive additional vaccination.

These findings partially contradict previous research on the general effects of CLT in health messaging, which suggested that messages framed to reduce psychological distance (low-level construal) are typically more persuasive [18]. Instead, this study highlights the potential for high-level construal messages to drive broader attitudinal shifts, particularly in contexts where abstract values such as social solidarity and institutional trust are central.

To our knowledge, this is the first empirical investigation of how different construal levels in messaging affect attitudes toward the CVICP and vaccination. While extensive research has explored the impact of various message frames on vaccine uptake, little is known about how messaging influences attitudes toward VICPs specifically. Schoch-Spana et al. [19] have indicated that raising awareness and understanding of the vaccine safety system can positively

influence public attitudes toward vaccination by addressing concerns about potential vaccine injuries. Transparent communication regarding eligibility criteria, processes, and benefits of compensation programs has been shown to foster trust and confidence in vaccination efforts [20]. When individuals understand that a reliable system exists to address vaccine injuries, their confidence in vaccines grows—an effect crucial for mitigating vaccine hesitancy and promoting vaccine acceptance. The present study extends this knowledge, showing that high-level construal messages emphasizing the broader purpose and societal benefits of compensation programs are particularly effective in improving attitudes toward the CVICP.

This study offers both theoretical and practical contributions. Theoretically, it extends the application of CLT to health policy communication. While CLT has been widely used to study health behaviors and patient decision-making, this research is among the first to apply it to public communication about compensatory health policies like VICPs. The findings illustrate how message abstraction can influence public perceptions of institutional responsibility and highlight the importance of tailoring communication strategies to enhance confidence in vaccination programs. Additionally, this study suggests that different components of attitudes, such as satisfaction, perceived necessity, and perceived effectiveness, may vary in their sensitivity to abstract framing, offering new insights for message targeting within the CLT framework. Practically, these findings provide evidence-based recommendations for governments on how to frame communication about vaccine injury compensation. Abstract, value-based messaging may better foster institutional trust and vaccine confidence than procedural, detail-heavy information. In the context of vaccine hesitancy, this study demonstrates that not only the content, but also the construal level of communication, can influence attitudes. These results have important implications for addressing vaccine hesitancy and strengthening trust in public health infrastructure, both during pandemics and in other health emergencies.

There are several limitations of the present study that warrant consideration. This study assessed immediate attitudinal changes following the intervention; thus, the long-term effects on attitudes toward the CVICP and vaccination remain unknown. This limits insight into the persistence of observed attitude changes. Furthermore, the study's generalizability may be constrained by cultural factors specific to the Republic of Korea, which could influence both the framing and reception of CVICP messages. Future research should assess whether these effects persist over time and replicate these findings in different cultural and policy contexts to determine the broader applicability of construal-level messaging strategies.

Despite these limitations, the study's findings provide valuable insights for public health communication aimed at reducing vaccine hesitancy and increasing vaccine acceptance. By adopting evidence-based message frames and supporting further research, policymakers and health authorities can improve public trust and confidence in vaccination programs, thereby contributing to the overall success of immunization efforts.

Conclusion

This study highlights the importance of strategic communication in shaping public attitudes toward vaccination policies, with a specific focus on the CVICP. In the present study, which applied CLT, we demonstrated that high-level construal messages are more effective than low-level messages in improving perceptions of the CVICP's effectiveness in enhancing vaccine acceptance. The results suggest that while both high-level and low-level construal messages can positively influence attitudes toward the CVICP and vaccination, high-level messages are particularly effective at highlighting the program's broader societal role in supporting vaccine acceptance.

Policymakers and health authorities should consider integrating high-level construal elements into communication strategies about VICPs to enhance public understanding and support. Such strategies should focus on conveying the fundamental values of these programs, such as equity and social solidarity, alongside clear procedural information about compensation processes.

Future research should examine the long-term impact of these messaging strategies on public attitudes and behaviors, as well as their applicability to other public health policies and contexts. By further refining and validating these communication approaches, we can more effectively address vaccine hesitancy and support the successful implementation of vaccination programs.

Supplementary Material

Figure S1. Images of the experimental group video (high construal level); **Figure S2.** Images of the control group video (low construal level). Supplementary data are available at Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0354.

Notes

Ethics Approval

The study protocol received approval from the Institutional Review

Board of Korea University Anam Hospital (IRB No: 2024 AN 0065). All procedures were conducted in accordance with ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

Conflicts of Interest

Jong-Koo Lee has been the editor-in-chief of *Osong Public Health and Research Perspectives* since October 2021. Young June Choe was not involved in the editorial process or review of this manuscript, despite being a member of the Editorial Board of the *Osong Public Health and Research Perspectives*. The other authors have no potential conflicts of interest to disclose.

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Availability of Data

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

Authors' Contributions

Conceptualization: JM, YJC, JKL; Data curation: JM, DK; Formal analysis: JM; Funding acquisition: JKL; Investigation: JM, YJC, CRK, JKL; Methodology: JM, SHJ; Project administration: TK; Supervision: JKL; Writing–original draft: JM, YJC; Writing–review & Editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

Hankook Research Co. Ltd. provided data collection services. Hapoom Studio produced the video messages used in the study.

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Original Article

Relationship between diabetes medication self-efficacy and quality of life in older adults with diabetes: a cross-sectional study in Turkey

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ABSTRACT

Objectives: The aim of this study was to investigate the relationship between diabetes medication self-efficacy and quality of life in older adults with diabetes.
Methods: The study included 192 older adults who attended the diabetes clinic of a public hospital in Istanbul. Data were collected between June and October 2024. Participants were informed about the study and provided both verbal and written consent. Data collection instruments comprised a sociodemographic questionnaire, the diabetes medication self-efficacy scale, and the quality of life scale for older adults.
Results: Of the participants, 98 (51.0%) were women and 105 (54.7%) were aged 65 to 74 years. The mean diabetes medication self-efficacy score was 38.95 ± 10.31, and the mean quality of life score was 18.24 ± 6.37. A weak but statistically significant positive correlation was observed between the autonomy and satisfaction subscale of quality of life and the necessity subscale of self-efficacy ($p < 0.05$).
Conclusion: This study, which examined the relationship between self-efficacy in diabetes management and quality of life in older adults, provides valuable guidance for clinical practice aimed at improving care for this population.

Keywords: Diabetes; Geriatrics; Medicine; Quality of life; Self efficacy

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Introduction

Diabetes mellitus has emerged as a major global public health issue. Although rates vary across regions, the overall trend in diabetes prevalence appears consistent across many populations [1]. The International Diabetes Federation Diabetes Atlas (2025) reports that 11.1% of adults aged 20 to 79—approximately 1 in 9 people—live with diabetes, and more than 4 in

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10 of these individuals are unaware of their condition [2]. Approximately 28.7% of individuals with diabetes in Turkey are older adults, and it was estimated that the age-adjusted diabetes prevalence in this age group would reach 35.1% by 2021. Current data indicate a 35.2% increase in diabetes prevalence in the general population, whereas the increase among older adults is 51.3%. The rise in diabetes prevalence among older adults is therefore about 1.5 times higher than that observed in the general population [3].

When managing diabetes in older adults, priority should be given to individualized care strategies. Approximately 90% of older adults with diabetes have type 2 diabetes. Treatment plans should be tailored to patient needs to prevent complications effectively and achieve optimal glycemic control in this population. Maintaining quality of life and preventing complications in older adults with diabetes largely depend on adequate self-care skills [4].

Regular monitoring of blood glucose levels is essential for achieving glycemic control [5]. However, comorbidities such as hypertension, cardiovascular disease, and osteoarthritis often lead to polypharmacy, which increases the risk of drug interactions and complicates treatment adherence [6].

Factors such as visual impairment, cognitive decline, and social isolation can further hinder medication adherence in older adults. Therefore, lifestyle interventions—including education, nutrition counselling, and physical activity—should be tailored to patients' ages, comorbid conditions, and functional status. The primary goal in managing the care of these individuals is to maintain quality of life and functional independence for as long as possible [4].

The aim of this study is to analyze the relationship between medication self-efficacy and quality of life in older adults with diabetes and to provide baseline data to improve treatment processes for older individuals with diabetes. By determining the effect of medication self-efficacy on quality of life, this research aims to support the self-management capacities of older adults, improve their overall well-being, and provide valuable information for healthcare providers and policymakers.

Few studies have directly examined the relationship between medication self-efficacy and quality of life in older adults with diabetes. Current research generally focuses on the broader diabetes population and does not sufficiently address the impact of factors such as cognitive decline, polypharmacy, and social isolation on medication management in older adults [4,7]. Furthermore, treatment adherence is closely related to an individual's medication management skills and self-confidence [8]. This study evaluates the relationship between self-efficacy and quality of life in older individuals in the Turkish context using validated scales, thereby demonstrating the impact of self-management skills on quality of life with concrete data. The findings may contribute to non-pharmacological interventions and self-efficacy–based care models.

HIGHLIGHTS

This study is among the few investigations examining the relationship between medication self-efficacy and quality of life in older adults with diabetes. The findings indicate that higher self-efficacy is associated with better treatment adherence and improved overall quality of life. The study underscores the need to integrate psychosocial components alongside physical health considerations in interventions for older adults. Emphasizing self-efficacy through structured education, particularly in medication management, can lead to significant improvements in quality of life. Additionally, by considering age-related cognitive and physical limitations, the study offers insights to inform comprehensive, evidence-based clinical strategies and public health policies.

Materials and Methods

Study Design and Setting

This study used a descriptive-analytical cross-sectional design to examine the relationship between diabetes medication self-efficacy and quality of life in older adults with diabetes. The research included 192 older adults who visited the diabetes clinic of a public hospital in Istanbul. Data were collected between June and October 2024. Participants were informed about the study.

Participants

This study targeted patients aged 65 years and older who had been diagnosed with diabetes and had no communication or cognitive difficulties that could hinder participation. Data were collected through face-to-face interviews with participants, who voluntarily provided written informed consent.

The sample comprised older adults who visited the diabetes clinic of a public hospital in Istanbul. The sample size was calculated using G*Power ver. 3.1.9.4 (University of Düsseldorf) for correlation analysis, with an effect size of 0.3, an alpha level of 0.05 (2-tailed), and statistical power (1–β error probability) of 0.95. At least 134 participants were required. To reduce the margin of error, increase statistical power, improve generalizability, and facilitate subgroup

analyses, 192 participants were included.

Measurements/Instruments

The questionnaire comprised a personal information form developed by the researchers, containing 17 items on sociodemographic, personal, and disease-specific characteristics. It also included 19 items from the diabetes medication self-efficacy scale, originally developed by Sleath et al. [9] in 2016 and adapted into Turkish by Kavuran and Turkoglu [10] in 2022 following validity and reliability testing. In addition, 13 items from the CASP-19 quality of life scale for older adults, originally developed by Hyde et al. [11] in 2003 and adapted into Turkish by Turkoglu and Adıbelli [12] in 2014 after validity and reliability studies, were used to assess quality of life.

Demographic information form

This form was used to collect participants' sociodemographic and diabetes-related information.

Diabetes medication self-efficacy scale

The self-efficacy scale was developed by Sleath et al. [9] in 2016. The Turkish version was adapted and validated by Kavuran and Turkoglu [10] with permission from the original authors. The scale comprises 19 items and is evaluated using a 3-point Likert scale (1, not at all confident; 2, confident; 3, very confident). Total scores range from 19 (low self-efficacy) to 57 (high self-efficacy), with higher scores indicating greater medication adherence self-efficacy. The Cronbach alpha coefficient for the original scale was 0.94. In this study, the reliability coefficients for the subscales were as follows: necessity, 0.70; busyness, 0.83; anxiety, 0.90; and overall scale, 0.93. These values indicate high internal consistency. Thus, the scale demonstrates high construct validity and internal consistency in both the original version and the Turkish adaptation.

CASP-19 Quality of Life Scale for Older Adults

CASP-19 was developed by Hyde et al. [11] in 2003. The Turkish version (CASP-13) was validated in 2014 by Turkoglu and Adıbelli [12] with the authors' permission. This version consists of 13 items across 2 factors. Each item is rated on a 4-point scale (0, never; 1, rarely; 2, sometimes; 3, often), yielding a total score ranging from 0 to 39. Higher scores indicate better perceived quality of life. In the original study, Cronbach alpha for the overall scale was 0.91; the subscales had values of 0.93 for autonomy and satisfaction and 0.75 for perceived limitations. In our study, these values were: autonomy and satisfaction, 0.86; perceived limitations, 0.76; and overall scale, 0.76, indicating high reliability. These findings demonstrate that the scale exhibits high levels of construct validity and internal consistency in both the original version and the Turkish adaptation.

Data Collection

Data were collected between June and October 2024. Participants were informed about the purpose of the study and provided both verbal and written consent prior to participation. Data collection utilized a demographic information form, a disease-specific characteristics form, the diabetes medication self-efficacy scale for older adults with diabetes, and the CASP quality of life scale for older adults. The inclusion criteria were as follows: individuals aged 65 and over, diagnosed with diabetes, receiving diabetes treatment, without visual or hearing impairments, able to communicate verbally, and willing to participate voluntarily. During data collection, the researchers distributed the questionnaires to participants, who were asked to complete them independently. For participants with literacy difficulties, researchers read the forms aloud and recorded the participants' verbal responses.

Data Analysis

Data were analyzed using IBM SPSS Statistics ver. 27.0 (IBM Corp.). Frequency tables and descriptive statistics were used to summarize the data. Non-parametric statistical tests were employed for variables that did not follow a normal distribution. The Mann-Whitney U-test (Z statistic) was used for comparisons between 2 independent groups, while the Kruskal-Wallis H test (χ^2 statistic) was used for comparisons between 3 or more groups. Relationships between non-normally distributed quantitative variables were analyzed using the Spearman rank correlation coefficient.

Ethical Considerations

The study was approved by the Ethics Committee of Istanbul Esenyurt University (approval number: E-12483425-604.01-45665, dated 02.05.2024, Meeting No: 2024-04) in accordance with the principles of the Declaration of Helsinki. Participants were informed about the objectives of the study, were assured of confidentiality, and provided both verbal and written informed consent prior to participation.

Results

General Characteristics of the Study Population

Sociodemographic characteristics of the participants are presented in Table 1, while clinical characteristics are presented in Table 2.

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Table 1. Descriptive characteristics of the study population (*n* = 192)

Variable	Value
Sex	
Female	98 (51.0)
Male	94 (49.0)
Age range (y)	
65–74 (young old)	105 (54.7)
75–84 (old-old)	63 (32.8)
≥85 (oldest old)	24 (12.5)
Marital status	
Married	132 (68.8)
Single	60 (31.3)
Profession	
Housewife	46 (24.0)
Worker	10 (5.2)
Pensioner	92 (47.9)
Civil servant	9 (4.7)
Other	35 (18.2)
Employment status	
Employed	21 (10.9)
Not employed	171 (89.1)
Education level	
Illiterate	22 (11.5)
Literate, below secondary school	50 (26.0)
Secondary school	52 (27.1)
High school	41 (21.4)
University	27 (14.1)
Receiving social security	
Yes	41 (21.4)
No	151 (78.6)
Income level	
Income less than expenditures	66 (34.4)
Income equal to expenditures	91 (47.4)
Income more than expenditures	35 (18.2)
Place of residence	
City	143 (74.5)
District	42 (21.9)
Village	7 (3.6)
Living situation	
With spouse	66 (34.4)
With spouse and children	50 (26.0)
With children	22 (11.5)
Alone	54 (28.1)

Data are presented as *n* (%).

Scale Scores

Table 3 presents descriptive statistics for participants' scores on the administered scales. The mean score on the diabetes medication self-efficacy scale was 38.95 ± 10.31, while the mean score on the CASP-19 quality of life scale was 18.24 ± 6.37.

Table 2. Disease characteristics of the study population (*n* = 192)

Variable	Value
Duration of diabetes diagnosis	
Less than 1 y	10 (5.2)
1–3 y	15 (7.8)
3–5 y	14 (7.3)
More than 5 y	153 (79.7)
Diabetes complications	
Retinopathy	47 (24.5)
Nephropathy	37 (19.3)
Neuropathy	60 (31.3)
Vasculopathy	13 (6.8)
Diabetic foot	35 (18.2)
Chronic disease in addition to diabetes	
No	75 (39.1)
Yes	117 (60.9)
Diabetes treatment	
OAD	76 (39.6)
OAD+insulin	47 (24.5)
Insulin	67 (34.9)
Monitoring	3 (1.6)
Diabetes nutrition education	
Not received	94 (49.0)
Received	98 (51.0)
Frequency of exercise	
Never	70 (36.5)
Sometimes	82 (42.7)
Frequently	40 (20.8)
Frequency of home blood glucose measurement	
Never	14 (7.3)
Sometimes	83 (43.2)
Frequently	95 (49.5)

Data are presented as *n* (%).
OAD, oral antidiabetic.

Relationship between Diabetes Medication Self-Efficacy and Quality of Life in Older Adults

Table 4 presents a comparison of diabetes medication self-efficacy and quality of life among older adults with diabetes, based on their demographic and clinical characteristics.

For overall CASP-19 scores, significantly higher quality of life levels were observed among male participants, individuals aged 65 to 74, those who were married, workers, individuals with a secondary school education, participants who reported equal income and expenses, those living with a spouse and children, individuals diagnosed with diabetes for less than 1 year, those without comorbid chronic diseases, individuals receiving oral antidiabetic treatment, and those who exercised regularly.

Regarding diabetes medication self-efficacy, significantly higher scores were noted among participants aged 65 to 74,

Table 3. Descriptive statistics regarding scale scores ($n = 192$)

Scale	Category	Average	Standard deviation	Median	Minimum	Maximum
DMSS	Necessity	7.88	2.26	8.0	4.0	12.0
	Busyness	10.35	2.99	10.0	5.0	15.0
	Anxiety	20.71	5.87	20.0	10.0	30.0
	DMSS (overall)	38.95	10.31	37.0	19.0	57.0
CASP-19	Autonomy and satisfaction	13.40	6.34	14.0	0.0	30.0
	Perception of disability	4.83	1.98	5.0	1.0	9.0
	CASP-19 (overall)	18.24	6.37	19.0	3.0	33.0

DMSS, diabetes medication self-efficacy scale; CASP-19, quality of life scale for older adults.

Table 4. Comparison of scale scores ($n = 192$)

Variable	*n*	DMSS (overall)			CASP-19 (overall)		
		Mean ± SD	Statistical analysis[a]/*p*	Median (IQR)	Mean ± SD	Statistical analysis[a]/*p*	Median (IQR)
Sex			$Z = -0.997/p = 0.319$			$Z = -2.738/p = 0.006$	
Female	98	38.46 ± 10.36		36.0 (12.0)	16.91 ± 6.06		18.0 (9.0)
Male	94	39.45 ± 10.38		37.0 (12.5)	19.61 ± 6.42		20.0 (7.0)
Age range (y)			$\chi^2 = 9.021/p = 0.011$ (1–3)			$\chi^2 = 6.430/p = 0.040$ (1–2)	
65–74	105	40.67 ± 10.40		38.0 (20.0)	19.28 ± 6.31		20.0 (7.0)
75–84	63	37.74 ± 10.49		37.0 (10.0)	16.53 ± 6.45		18.0 (11.0)
≥85	24	34.54 ± 7.59		34.0 (6.5)	18.13 ± 5.63		19.5 (9.3)
Income level			$\chi^2 = 4.081/p = 0.130$			$\chi^2 = 12.508/p = 0.002$ (1–2, 3)	
Income less than expenditures	66	40.11 ± 10.62		37.0 (19.3)	15.95 ± 6.70		16.0 (11.3)
Income equal to expenditures	91	39.53 ± 10.92		36.0 (17.0)	19.33 ± 5.95		20.0 (7.0)
Income more than expenditures	35	35.23 ± 6.89		35.0 (7.0)	19.71 ± 5.74		20.0 (4.0)
Living situation			$\chi^2 = 27.959/p < 0.001$ (1–2, 4) (3–2, 4)			$\chi^2 = 19.542/p < 0.001$ (1–3, 4) (2–3, 4)	
With spouse	66	42.63 ± 10.76		39.0 (21.0)	19.71 ± 6.41		21.0 (7.3)
With spouse and children	50	34.34 ± 6.64		34.0 (7.5)	20.14 ± 3.11		20.0 (4.0)
With children	22	45.36 ± 12.55		54.0 (21.5)	13.77 ± 7.18		11.0 (13.5)
Alone	54	36.09 ± 8.67		34.0 (10.3)	16.50 ± 6.99		16.0 (9.5)
Duration of diabetes diagnosis			$\chi^2 = 0.940/p = 0.816$			$\chi^2 = 11.957/p = 0.008$ (1,2–4)	
Less than 1 y	10	36.90 ± 11.93		34.0 (18.5)	24.10 ± 8.05		22.5 (13.3)
1–3 y	15	38.20 ± 8.42		38.0 (10.0)	21.47 ± 4.84		22.0 (3.0)
3–5 y	14	37.79 ± 8.59		37.0 (5.8)	19.07 ± 3.17		19.5 (5.0)
More than 5 y	153	39.26 ± 10.56		37.0 (14.0)	17.46 ± 6.34		18.0 (9.5)
Diabetes treatment			$\chi^2 = 0.645/p = 0.724$			$\chi^2 = 8.327/p = 0.016$ (1–2, 3)	
OAD	76	38.73 ± 10.32		36.0 (11.0)	19.96 ± 5.50		20.0 (5.0)
OAD+insulin	47	39.89 ± 10.01		37.0 (13.5)	16.84 ± 5.17		17.0 (9.5)
Insulin	67	38.66 ± 10.45		37.0 (14.0)	17.32 ± 7.02		17.0 (11.0)
Frequency of exercise			$\chi^2 = 12.180/p = 0.002$ (1–2, 3)			$\chi^2 = 22.210/p < 0.001$ (1–2, 3) (2–3)	
Never	70	43.14 ± 11.42		40.5 (21.0)	15.67 ± 7.33		16.0 (12.3)
Sometimes	82	36.50 ± 9.07		35.5 (8.0)	18.73 ± 5.47		18.0 (7.0)
Often	40	36.63 ± 8.31		35.0 (6.8)	21.72 ± 4.03		21.0 (4.0)

DMSS, diabetes medication self-efficacy scale; CASP-19, quality of life scale for older adults; SD, standard deviation; IQR, interquartile range; OAD, oral antidiabetic.
[a]The independent samples t-test (t statistic) was used to compare the measurement values of 2 independent groups for normally distributed data; analysis of variance (F statistic) was used to compare 3 or more independent groups. The Kruskal-Wallis H test (χ^2 statistic) was used to compare the measurement values of 3 or more independent groups when the data were not normally distributed.

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housewives, illiterate individuals, those residing in districts (rather than central urban areas), those living with their children, and those who did not engage in daily exercise (Table 4).

Comparison of the Relationship Between Diabetes Medication Self-Efficacy and Quality of Life in Older Adults

Very weak but statistically significant positive correlations were identified between the necessity subscale of self-efficacy and both the autonomy and satisfaction subscale and the CASP-19 total score ($p < 0.05$). As necessity scores increased, autonomy and satisfaction scores, as well as the overall CASP-19 score, tended to increase (Table 5).

Discussion

Summary of Findings

This study investigated the relationship between medication self-efficacy and quality of life in older adults with diabetes. Our findings indicate that as medication self-efficacy increases in this population, quality of life also improves. The results highlight the importance of strengthening medication self-efficacy within medication management, with the potential to enhance overall well-being and health outcomes in this vulnerable group.

CASP-19 Findings

The average score of participants on the CASP-19 quality of life scale was 18.24 ± 6.37, indicating moderate quality of life. Similar findings were reported by Yildirim et al. [13] (19.36 ± 7.00) and by Korkmaz [14] (18.1 ± 6.2). A moderate quality of life suggests that well-being is negatively affected by the difficulties encountered in managing health problems and chronic diseases; this underscores the need for multidisciplinary interventions to improve quality of life.

The study found that men, individuals aged 65 to 74, and married participants had significantly higher CASP-19 scores compared with other groups. These findings are consistent with those of Deger and Ordu [15], who reported higher quality of life scores among these demographic groups. Associated factors—such as stronger social support structures and maintained functional capacity—may positively influence quality of life. This highlights the importance of considering demographic factors in diabetes care for older adults.

Consistent with our findings, Yildirim et al. [13] observed that individuals with higher income levels and those living with their spouses or children had significantly higher quality of life scores. Strong social support systems and economic resources can facilitate access to healthcare services and positively influence psychosocial well-being. This underscores the critical role of social environment and economic status in interventions aimed at improving quality of life.

Participants diagnosed with diabetes for less than 1 year or for 1 to 3 years had significantly higher CASP-19 scores compared to those with a disease duration exceeding 5 years. Similar results have been reported by Em et al. [16]. Shorter disease duration, fewer adjustment difficulties, and higher treatment adherence in the early stages appear to represent key factors in maintaining quality of life.

The CASP-19 scores of individuals without additional chronic conditions were significantly higher than those of individuals with comorbid conditions. Rashidi et al. [17] similarly noted higher quality of life scores in individuals without chronic conditions, and other studies report comparable findings [18–23]. This may be interpreted as the absence of additional disease burden positively impacting physical functioning, treatment adherence, and psychosocial well-being, thereby

Table 5. Analysis of interrelationships among scale scores ($n = 192$)

Correlation[a]	Category	CASP-19		
		Autonomy and satisfaction	Perception of disability	CASP-19 (overall)
DMSS				
Necessity	*r*	0.176	0.076	0.172
	p	0.015	0.294	0.017
Busyness	*r*	0.115	0.081	0.125
	p	0.112	0.267	0.083
Anxiety	*r*	0.045	0.041	0.040
	p	0.533	0.569	0.585
DMSS (overall)	*r*	0.129	0.073	0.133
	p	0.073	0.317	0.067

CASP-19, quality of life scale for older adults; DMSS, diabetes medication self-efficacy scale.
[a]The Spearman correlation coefficient was used when at least 1 of the 2 quantitative variables did not follow a normal distribution.

improving quality of life. Moreover, complications and management difficulties arising from multiple chronic conditions likely contribute to a decline in quality of life.

Participants who engaged in regular exercise had significantly higher CASP-19 scores than those who exercised occasionally. This aligns with the existing literature indicating that exercise supports physiological well-being and confers psychosocial benefits that positively influence quality of life [15,24]. These findings suggest that exercise not only supports physiological well-being but also enhances quality of life through its psychosocial effects. In addition, the role of regular physical activity in improving treatment adherence and reducing the risk of complications in chronic disease management likely contributes to this difference.

In summary, while social environment and economic resources enhance quality of life, the burden of chronic disease and lack of physical activity have a negative impact. These findings underscore the need for multifaceted and individualized strategies to improve the quality of life of older adults with diabetes.

Diabetes Medication Self-Efficacy Findings

The average self-efficacy score for diabetes medications among older adults was 38.95 ± 10.31, indicating moderate self-efficacy. Similar scores were reported by Kaleli [25] in 2024 (35.02 ± 5.44) and by Genc and Uslu [26] in 2023(38.60 ± 6.00). Moderate medication management self-efficacy suggests that patients may have difficulty adhering to treatment consistently, highlighting the importance of individualized support and education-based interventions to improve treatment adherence and quality of life.

No significant difference was observed in diabetes medication self-efficacy scores between patients with and without additional chronic conditions. This finding is consistent with the existing literature, which suggests that comorbidities may not directly affect perceptions of self-efficacy regarding diabetes medication use [27,28]. It indicates that the presence of additional chronic conditions does not directly influence self-efficacy and highlights the importance of individual factors and support mechanisms in treatment management.

Male participants exhibited significantly higher self-efficacy scores for diabetes medication usage than female participants. Our results are consistent with findings indicating better medication adherence among men than women [14,29,30]. Gender differences may influence self-efficacy and treatment attitudes in chronic disease management. Therefore, gender-sensitive interventions that enhance self-efficacy in male patients may be an effective approach to improving treatment adherence and quality of life.

Older adults aged 65 to 74 had significantly higher self-efficacy regarding diabetes medications than other age groups. The data largely align with relevant studies in the literature [31,32]. Increasing self-efficacy in middle-aged and older adults positively affects treatment adherence and quality of life; therefore, age-specific interventions are critical for improving health outcomes.

Unmarried older adults had significantly higher diabetes medication self-efficacy scores than married individuals. Similar findings have been reported previously [33]. This underscores the importance of including married patients in support programs designed to increase self-efficacy in medication use.

Self-efficacy scores among participants who were housewives, workers, or retirees were significantly higher than those of participants in other occupations. Similar trends have been reported [31,33]. Occupational status may influence individuals' confidence and perceived competence in medication management.

Additionally, older adults without formal education demonstrated significantly higher self-efficacy in diabetes medication use than those with higher education levels. This finding aligns with studies reporting lower medication adherence among literate individuals [33]. Conversely, other research has reported lower medication adherence scores among non-literate participants [14]. The higher self-efficacy observed among non-literate individuals in our study may be related to personal experiences, social support mechanisms, and the quality of communication with healthcare professionals.

The self-efficacy scores for diabetes medications among participants residing in rural districts were significantly higher than those among participants living in urban areas. This finding is consistent with studies measuring self-efficacy in people with diabetes [34]. Perceptions of self-efficacy regarding medication management among patients in rural and semi-urban areas are influenced by factors such as access to healthcare services and social support. Therefore, this underscores the importance of developing health policies and education programs tailored to regional needs.

When it comes to exercise, individuals who did not exercise daily had significantly higher diabetes medication self-efficacy scores than those who exercised daily. Similar trends have been reported in the literature [28]. This counterintuitive finding, which indicates an unexpected relationship between physical activity levels and perceived self-efficacy in medication use, suggests that individuals who do not exercise regularly may exhibit more cautious and controlled attitudes and behaviors regarding medication

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adherence. Additionally, it points to complex interactions between lifestyle choices and treatment adherence among older adults with diabetes and warrants more comprehensive research.

According to the study results, the overall diabetes medication self-efficacy scores of individuals living with both their spouse and children were significantly higher than those of individuals living only with their children or alone. Other studies have not found a significant difference in diabetes self-efficacy based on living arrangement [34,35]. Our finding suggests that social support and family structure may positively affect perceptions of medication self-efficacy in older adults with diabetes.

Overall, these findings emphasize the importance of considering both individual and environmental factors in diabetes management and support the development of multidisciplinary and personalized approaches.

Self-Efficacy and Quality of Life Findings Regarding Diabetes Medications in Geriatric Patients with Diabetes

In this study, the measurements revealed a significant, positive relationship between self-efficacy in medication use and quality of life. This finding suggests that perceived self-efficacy in diabetes management plays a decisive role in the overall health status and quality of life of older individuals. Similarly, the literature reports that diabetes-related complications negatively affect quality of life [36,37], that treatment adherence improves quality of life [38,39], and that medication adherence is significantly related to quality of life [8]. Additionally, a study by Rosli et al. [31] showed that high self-efficacy regarding medication use positively affects an individual's quality of life. In this context, our findings are consistent with the existing literature and highlight that strengthening one's perception of self-efficacy in diabetes treatment is an important factor that not only increases treatment adherence but also supports quality of life. Especially in older adults, given that chronic disease management is closely associated with individual psychosocial resources, interventions aimed at increasing medication self-efficacy may provide meaningful benefits for both health outcomes and quality of life.

Conclusion and Recommendations

This study highlights the impact of self-efficacy in diabetes treatment on the quality of life of older individuals and presents findings that could contribute to both clinical practice and health policy in healthcare for older adults. The relationship between self-efficacy in the use of diabetes medications and quality of life in older adults was examined, with individuals with higher self-efficacy in medication use exhibiting significantly higher overall quality of life.

These findings indicate that patients' knowledge, skills, and confidence regarding the use of diabetes medications are key determinants of both metabolic control and overall health status. In this context, the importance of education and support programs aimed at promoting the regular and informed use of diabetes medications in older adults should be emphasized. Furthermore, this study highlights the value of interventions aimed at understanding the challenges older adults face in medication management and increasing their self-efficacy within nursing practice. Nurses play a critical role in monitoring medication adherence, promoting correct medication use, and developing solution-oriented approaches to address emerging challenges. In particular, raising awareness about medication use through patient education and counselling directly contributes to improving quality of life. Considering these findings, developing comprehensive care plans through multidisciplinary collaboration and providing support mechanisms tailored to individual needs are essential for improving health outcomes in older adults with diabetes.

Limitations

This study had several limitations. Cognitive differences among older participants may have affected their ability to fully understand and accurately answer the survey questions. The cross-sectional design also limited our capacity to establish causal relationships or track changes over time. In addition, factors such as multimorbidity, polypharmacy, and varying levels of social support may have influenced self-efficacy perceptions and quality of life. The voluntary nature of participation and characteristics of the sample may also limit the generalizability of the findings.

Notes

Ethics Approval

The study received ethical approval from the Ethics Committee of Istanbul Esenyurt University ((approval number: E-12483425-604.01-45665, dated 02.05.2024, Meeting No: 2024-04), in accordance with the principles of the Declaration of Helsinki. Participants were informed about the study's objectives, were assured of confidentiality, and provided both verbal and written informed consent prior to participation.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

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.

Authors' Contributions

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

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Original Article

A confirmatory analysis of the knowledge, attitudes, and perceptions questionnaire for community-based surveillance of infectious diseases: a cross-sectional study in Malaysia

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ABSTRACT

Objectives: This study aimed to validate the psychometric properties of the recently developed knowledge, attitudes, and perceptions questionnaire for community-based surveillance of infectious diseases (KAP-CBS-ID questionnaire), using confirmatory factor analysis (CFA) and item response theory (IRT).

Methods: A cross-sectional study using multistage sampling recruited 470 schoolteachers from Kelantan, Malaysia. The self-administered KAP-CBS-ID questionnaire consists of 3 domains: knowledge (31 items), attitudes (23 items), and perceptions (21-items). Two-parameter logistic (2-PL) IRT analysis and CFA were performed to validate the knowledge section. For attitudes and perceptions sections, CFA proceeded using a 4-factor model to evaluate both model fit and construct validity.

Results: Two-PL IRT analysis of the knowledge section resulted in elimination of 14 items due to inadequate discrimination or difficulty parameters. The 3-factor CFA model demonstrated good fit indices for knowledge (root mean square error of approximation [RMSEA], 0.028; comparative fit index [CFI], 0.945; Tucker-Lewis index [TLI], 0.941) without any modifications. The attitudes section required re-specification, ultimately yielding 21 items across 4 factors with acceptable fit indices (standardized root mean square residual [SRMR], 0.067; RMSEA, 0.055; CFI, 0.937; TLI, 0.927). Similarly, the perceptions section was refined to 17 items across 4 factors, showing good model fit (SRMR, 0.055; RMSEA, 0.059; CFI, 0.962; TLI, 0.954). Factor loadings ranged from 0.33 to 0.98, while Raykov's rho reliability estimates ranged from 0.71 to 0.93. Factor determinacy exceeded 80% for all factors.

Conclusion: The KAP-CBS-ID is a valid and reliable instrument for assessing community representatives' knowledge, attitudes, and perceptions regarding community-based surveillance of infectious diseases.

Keywords: Communicable diseases; Community-based surveillance; Factor analysis, statistical; Psychometrics; Surveys and questionnaires; Validation

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Introduction

Infectious disease outbreaks and epidemics typically begin within the community. Community members are often the first to observe changes in health patterns and identify health threats, yet delays in transmitting this information to health authorities can hinder timely interventions [1,2]. Community-based surveillance (CBS) leverages the capabilities of community members to perform surveillance activities within their own communities, thereby enhancing the early detection and response to disease outbreaks [3]. The World Health Organization defines CBS as the systematic detection and reporting of public health events or cases of specific diseases by community members to health authorities [4]. This approach can substantially expedite the detection and response to outbreaks [5–11].

Multiple studies have shown that CBS can facilitate more timely responses and improved containment of disease outbreaks [1,9,10,12]. However, evidence supporting the overall effectiveness of CBS remains limited [13]. Documented cases have shown that community health workers can effectively implement CBS programs, even in challenging contexts such as conflict zones [10,13–15] or during natural disasters [16,17]. The International Federation of the Red Cross and Red Crescent (IFRC) maintains a network of more than 15 million volunteers worldwide who are deeply embedded in their local communities [18]. These volunteers, who possess linguistic and cultural familiarity and are physically present within their communities, represent a critical resource for implementing preparedness activities, including CBS, in remote regions with limited access to health services [9,13]. This highlights the vital role of community members in the early identification and reporting of health threats.

Malaysia has implemented event-based surveillance, defined as the organized and rapid collection of information regarding events that may pose risks or concerns to public health. These events, which arise within the community, may have actual, suspected, or potential impacts on human health, thereby generating concern, fear, or alarm [19]. Information about such events may be collected from rumors or other ad hoc reports via both formal channels (such as routine reporting systems) and informal sources (including non-governmental organizations, community members, and social media).

However, as noted in the 2018 Event-Based Surveillance Protocol [19], the flow of information from the community to health authorities remains slow. An administrative directive from the Deputy Director-General of Health (Public Health) issued in January 2014 highlighted that these events were often reported in the media well before they reached Ministry of Health officials. This delay can be attributed to a lack of community awareness regarding the CBS process. Although the community is recognized as the primary source of initial signals in the CBS system, the Event-Based Surveillance Protocol [19] also notes a lack of empirical studies evaluating community members' knowledge, attitudes, and perceptions concerning this crucial surveillance mechanism.

Therefore, this study aims to confirm the structure of the knowledge, attitudes, and perceptions questionnaire for community-based surveillance of infectious diseases (KAP-CBS-ID questionnaire) [20] to assess these constructs among Malaysian community representatives. The selection of community representatives, rather than the general community, was intended to increase the signal-to-noise ratio and provide adequate specificity, ensuring that reporting does not overwhelm the surveillance system [21].

HIGHLIGHTS

- A psychometrically valid questionnaire on knowledge, attitudes, and perceptions regarding community-based surveillance of infectious diseases was previously developed.
- Item response theory and confirmatory factor analysis validated the 3-domain questionnaire among 470 schoolteachers in Malaysia.
- The final questionnaire retained 17 knowledge items, 21 attitude items, and 17 perception items that exhibited high reliability.
- This validated tool can effectively assess community leaders' preparedness for infectious disease surveillance.

Materials and Methods

Study Design and Setting

This study employed a cross-sectional design and was conducted among Malaysian community representatives residing in Kelantan from March 2024 to June 2024. It constitutes the third stage of a larger research project. The first stage involved the development and translation of the questionnaire [20], while the second stage focused on item response theory (IRT) analysis for the knowledge domain and exploratory factor analysis (EFA) for the attitudes and perception domains.

Setting

The study was conducted in primary and secondary schools across the state of Kelantan, Malaysia. Four districts—

Kota Bharu, Bachok, Pasir Puteh, and Kuala Krai—were selected, with schools within each district chosen randomly. The KAP-CBS-ID questionnaire comprises 3 main sections: knowledge, developed based on a comprehensive literature review; attitudes, constructed using the theory of reasoned action (TRA); and perceptions, grounded in the health belief model (HBM). The questionnaire underwent thorough EFA in a previous phase, utilizing principal component analysis with varimax rotation to identify the underlying factor structure. This process revealed distinct factors within each domain, which were then confirmed in the current confirmatory factor analysis (CFA) study. Each scale underwent a rigorous validation process, including content validation by 11 experts, face validation, and a pilot study involving 30 participants, followed by EFA. The knowledge section used a dichotomous response format, whereas the attitudes and perceptions sections were rated on 5-point Likert scales. The questionnaire's structure is as follows: the knowledge section contains 3 subdomains—knowledge of infectious diseases (18 items), knowledge of CBS of infectious diseases (3 items), and community-level case definition (10 items)—with responses of "yes," "no," and "I don't know." The attitudes section comprises 4 subdomains: negative attitudes (6 items), subjective norms (4 items), intention to participate in CBS (6 items), and behavioral likelihood to engage in CBS (7 items), each rated on a 5-point Likert scale ranging from "1-strongly disagree" to "5-strongly agree" or "1-never" to "5-always," depending on the item. The perceptions section also includes 4 subdomains: perceived susceptibility (5 items), perceived benefit (5 items), perceived barriers (3 items), and self-efficacy (4 items), rated on 5-point Likert scales from "1-never true" to "5-always true" and from "1-extremely unlikely" to "5-extremely likely," as appropriate [20]. Data collection commenced in May 2024 and concluded in June 2024, utilizing the KAP-CBS-ID questionnaire.

Participants

A total of 470 community representatives, including teachers from both public and Islamic schools, were recruited using a multistage sampling method. After obtaining informed consent, participants completed the self-administered questionnaires during school break times. To be eligible for inclusion, participants had to be at least 18 years old and proficient in both written and spoken Malay. Participants were encouraged to provide honest responses, and the estimated time to complete the questionnaire was approximately 20 to 25 minutes.

Bias

The researchers implemented several measures to minimize bias in the validation study of the KAP-CBS-ID questionnaire. The use of a multistage sampling technique ensured representative participation across varied geographic and demographic settings within Kelantan. Selection bias was reduced by applying clear inclusion criteria for schoolteachers. Comprehensive psychometric analyses, including 2-parameter logistic (2-PL) IRT and CFA, enabled the removal of items with poor performance. The self-administered questionnaire featured a balance of positively and negatively worded statements, and assurances of anonymity and confidentiality were provided to all participants. To further reduce cultural and linguistic biases, the questionnaire underwent a thorough translation and back-translation process with local experts, ensuring its suitability for the Malaysian context.

Study Size

Sample size determination for the CFA was performed using 2 approaches. First, the "rule of thumb" ratio of 5 participants per questionnaire item (N:P = 5:1) was applied, indicating a need for 375 participants for the 75-item questionnaire. This calculation incorporated a 20% anticipated dropout rate. Second, Arifin's web-based sample size calculator (2017) estimated a requirement of 463 participants [22]. Based on these calculations, a sample size of 470 participants was deemed adequate.

The sampling process comprised 3 stages. Initially, 4 districts in Kelantan were purposively selected: Kota Bharu and Bachok (urban), and Pasir Puteh and Kuala Krai (rural). While the rural-urban distinction was not directly analyzed in this validation study, it is considered relevant for future research, as some evidence suggests that CBS may be more effective in rural than in urban settings [3]. In the second stage, schools within each district were randomly selected. In the final stage, participants within each school were approached conveniently during their free periods. An overview of the study was provided, and verbal consent was obtained, with the process facilitated by a Malay-speaking research assistant.

Statistical Methods

To minimize data entry errors, all questionnaire items were compiled into a Google Form (Google LLC). Responses from the paper-based questionnaires were then manually entered into this Google Form. Subsequently, all responses were exported as an Excel spreadsheet for data cleaning and further analysis. After data cleaning and numerical coding, the dataset was transferred to RStudio ver. 4.4.1 (RStudio), for CFA and 2-PL IRT analysis.

Item response theory

The knowledge section of the questionnaire was analyzed

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using IRT due to its dichotomous response format. Specifically, a 2-PL IRT model was implemented using the ltm package, version 1.2-0. The 2-PL IRT model estimates 2 parameters for each item: difficulty (b) and discrimination (a). The difficulty parameter represents the ability level at which an individual has a 50% probability of answering the item correctly, with acceptable values typically ranging from −3 to +3. The discrimination parameter indicates how well an item distinguishes between individuals with varying ability levels; values above 0.25 are considered acceptable, and values above 1.0 are regarded as good. Unidimensionality was assessed using the modified parallel analysis method to ensure that items measured a single underlying construct. Cronbach's alpha was calculated to evaluate the internal consistency reliability of the knowledge domain, with values above 0.7 considered acceptable. Items with low discrimination ($a < 0.25$) or extreme difficulty ($|b| > 3$) were considered for revision.

Confirmatory factor analysis

CFA was conducted following the exploratory study to verify the factor structure of the questionnaire. The CFA utilized the lavaan package ver. 0.6–18 [23]. Model fit was evaluated using a range of indices: absolute fit indices, including chi-square (χ^2) and standardized root mean square residual (SRMR); parsimony-adjusted indices, such as the root mean square error of approximation (RMSEA); and comparative fit indices, including the comparative fit index (CFI) and the Tucker-Lewis index (TLI) [24].

Thresholds for model fit indices in this study were set as follows: a p-value for χ^2 greater than 0.05, RMSEA and SRMR less than or equal to 0.08, and CFI and TLI greater than or equal to 0.92, based on the model structure and sample size considerations [25]. Composite reliability (CR) was assessed using the semTools package ver. 0.5–6, within RStudio, with reliability indicated by Raykov's rho [24,26]. A Raykov's rho value exceeding 0.7 was considered acceptable for reliability [27]. Factor determinacy, representing the precision with which factor scores can be estimated from observed items, was evaluated, with values above 0.80 considered good. Average variance extracted (AVE), measuring the amount of variance captured by a construct relative to measurement error, was deemed acceptable at values above 0.50. CR, another measure of internal consistency, was also considered adequate if it was above 0.70.

For the knowledge section, CFA was conducted after IRT analysis. The combined use of IRT and CFA is generally recommended, as this approach enhances the quality of scale measurement and results in more robust assessments in applied research settings [28]. Due to the categorical nature of responses, the weighted root mean square residual (WRMR) was used in place of SRMR.

Ethics Statement

Ethical approval for this study was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (ref. no: USM/JEPeM/22050317). All participants were provided with information about the study, and informed consent was obtained from those who agreed to participate.

Results

Descriptive Data

As shown in Table 1, a total of 470 community representatives

Table 1. Demographic profile of the study participants ($n = 470$)

Variable	Frequency
Age (y)	43.3 ± 9.5
Sex	
Female	354 (75.3)
Male	116 (24.7)
Ethnicity	
Malay	467 (99.4)
Others	3 (0.6)
Marital status	
Single	73 (15.5)
Married	373 (79.4)
Divorced	6 (1.3)
Widowed	18 (3.8)
Occupation	
Government employee	402 (85.5)
Private sector	60 (12.8)
Pensioner	3 (0.6)
Others	5 (1.1)
Education level	
Primary school	3 (0.6)
Secondary school (PMR/SRP)	2 (0.4)
Secondary school (SPM)	16 (3.4)
Religious school (Pondok)	2 (0.4)
Diploma	37 (7.9)
University and higher	410 (87.2)
Role	
Public school teacher	412 (87.7)
Religious school teacher	58 (12.3)
Residency	
Urban	301 (64.0)
Rural	169 (36.0)
Received information about infectious diseases	
Yes	441 (93.8)
No	29 (6.2)

Data are presented as mean ± standard deviation or *n* (%).
PMR, Penilaian Menengah Rendah (lower secondary assessment); SRP, Sijil Rendah Pelajaran (lower education certificate); SPM, Sijil Pelajaran Malaysia (Malaysian certificate of education).

participated in this study. The demographic data show that the sample was predominantly female (75.3%) and Malay (99.4%), with a mean age of 43.3 years (standard deviation, 9.5). Most participants were married (79.4%) and employed as government servants (85.5%), while 87.2% held university degrees or higher qualifications. The majority worked as public schoolteachers (87.7%), resided in urban areas (64.0%), and reported having received information about infectious diseases (93.8%).

Figure 1 illustrates the sources from which community representatives most frequently obtained information. The internet was the most widely used source, with 85% of respondents reporting that they obtain information about infectious diseases online. In contrast, the animal health sector was the least utilized, with only 5% receiving information from this source.

Main Results

Knowledge section

The 2-PL IRT analysis indicated that the difficulty and discrimination parameters were generally acceptable for most items in the knowledge domain. This section includes 3 subdomains: information on infectious diseases (18 items), knowledge of CBS of infectious diseases (3 items), and community-level case definitions (10 items). Although a few items exhibited poor model fit, as indicated by a significant chi-square p-value, they were retained because their difficulty and discrimination parameters remained within acceptable ranges, as shown in Table 2. The proportion of information explained by the knowledge items was 93.57%, 89.35%, and 98.31% for the 3 subdomains, respectively. Both the knowledge of CBS and community-level case definitions subdomains met the unidimensionality assumption ($p = 0.53$ and $p = 0.81$, respectively). The internal consistency of the knowledge section was acceptable, with a Cronbach's alpha of 0.71 in IRT analysis.

Following the 2-PL IRT analysis, CFA was performed using the weighted least squares mean and variance adjusted (WLSMV) estimator to confirm the 3-factor structure of the knowledge section. The model demonstrated a good fit, with fit indices as follows: CFI = 0.945, TLI = 0.941, WRMR = 1.301, RMSEA = 0.028 (90% CI, 0.022–0.033), and an RMSEA p-value > 0.950.

Attitudes section

CFA was conducted on the attitudes section. Since multivariate normality was not achieved, the robust maximum likelihood estimator was employed. The initial CFA model did not meet criteria for adequate fit, with a CFI of 0.874 and TLI of 0.858. However, SRMR and RMSEA values were within acceptable thresholds at 0.073 and 0.072 (0.066–0.079), respectively. To

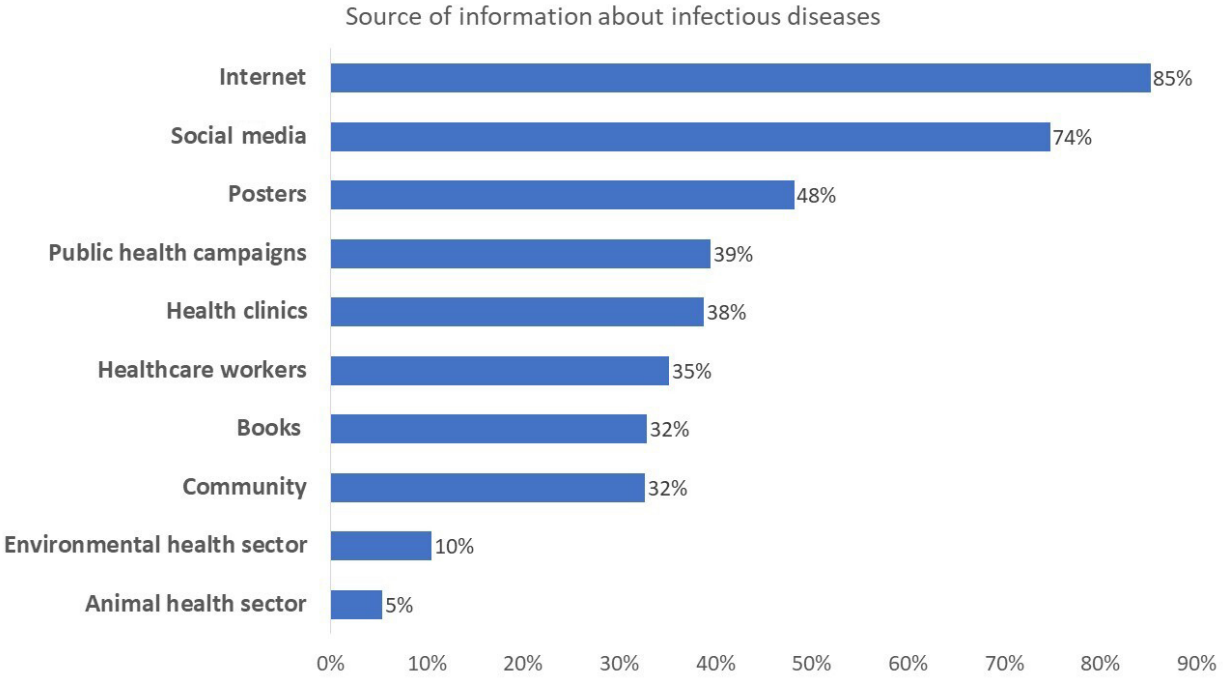


Figure 1. Primary sources of information on infectious diseases.

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Table 2. Results of the IRT analysis of the knowledge section ($n = 470$)

Factor/items in original questionnaire	IRT results				CFA results			
	b	a	x^2 ($df = 8$)	p	Recoded items	Standardized item loading	AVE	CR
Information on infectious diseases							0.45	0.92
Q1	−7.81	0.43	9.20	0.33	Q1	0.33		
Q3	−7.73	0.41	12.73	0.12	Q2	0.55		
Q4	−2.58	1.09	11.62	0.17	Q3	0.67		
Q7	−2.81	1.28	26.16	0.00	Q4	0.55		
Q8	−2.24	2.54	10.83	0.21	Q5	0.65		
Q9	−1.23	0.33	4.33	0.83	Q6	0.49		
Q10	−0.76	11.43	3.05	0.93	Q7	0.91		
Q11	−0.68	23.29	2.35	0.97	Q8	0.96		
Q12	−1.06	6.90	0.96	0.99	Q9	0.98		
Q14	−1.36	3.51	9.39	0.31	Q10	0.61		
Q15	−1.37	29.73	2.08	0.98	Q11	0.92		
Q16	−1.34	4.72	2.63	0.96	Q12	0.90		
Q17	−4.79	0.78	44.87	< 0.001	Q13	0.62		
Q18	−3.52	0.78	65.61	< 0.001	Q14	0.71		
Q22	−1.55	1.70	21.63	< 0.001	Q15	0.61		
Q23	−1.54	1.47	23.42	< 0.001	Q16	0.62		
Q24	−2.63	1.17	26.59	< 0.001	Q17	0.65		
Q25	−2.94	0.72	6.48	0.59	Q18	0.60		
Knowledge of CBS							0.58	0.78
Q33	−1.52	3.10	27.66	< 0.001	Q19	0.68		
Q34	−1.74	3.11	29.68	< 0.001	Q20	0.85		
Q35R	−1.19	2.07	51.82	< 0.001	Q21R	0.74		
Community-level case definition							0.50	0.93
Q36	−1.33	2.38	11.55	0.17	Q22	0.69		
Q37	−2.44	1.66	9.48	0.30	Q23	0.74		
Q38	−1.63	1.00	34.37	< 0.001	Q24	0.81		
Q39	−3.42	1.11	16.70	0.03	Q25	0.78		
Q40	−1.09	3.31	4.60	0.80	Q26	0.79		
Q41	−0.91	4.58	9.55	0.30	Q27	0.87		
Q42	−0.91	5.92	6.60	0.58	Q28	0.91		
Q43	−0.10	0.73	15.89	0.04	Q29	0.63		
Q44	−3.52	0.78	11.34	0.18	Q30	0.70		
Q45	−2.44	0.98	23.02	0.00	Q31	0.79		

Items Q2, Q5, Q6, Q13, Q19, Q20, Q21, Q26, Q27, Q28, Q29, Q30, Q31, and Q32 were removed during IRT analysis.
IRT, item response theory; CFA, confirmatory factor analysis; x^2, chi-square; b, difficulty; a, discrimination; df, degree of freedom; AVE, average variance extracted; CR, composite reliability; CBS, community-based surveillance.

enhance model fit, item Q48 was removed due to a low factor loading (0.14), followed by the exclusion of item Q47, which had a high standardized residual (5.157). An error correlation was also added between items Q45 and Q46. These modifications were carried out iteratively in consultation with research team experts. As a result, model fit indices improved, as detailed in Table 3.

The final model for attitudes comprised 21 items, organized into 4 distinct factors in alignment with the TRA: behavioral likelihood to be involved in CBS (7 items), subjective norms (4 items), intention to engage in CBS (6 items), and negative attitudes toward CBS (6 items). The CR coefficients (Raykov's rho) for these factors were 0.860, 0.895, 0.714, and 0.546, respectively. Although the fourth factor's reliability was relatively low, its factor determinacy value above 0.80 indicates good internal consistency reliability, as suggested by Wang and Wang [29].

Table 4 presents the initial and final CFA models for the attitude factors, including factor loadings, AVE, CR, and factor determinacy for all final model factors.

Table 3. CFA model re-specification for the attitudes section

Model	Modification	CFI	TLI	SRMR	RMSEA (90% CI)	RMSEA *p*
Initial model (model 0)	-	0.874	0.858	0.073	0.072 (0.066–0.079)	<0.000
Model 1	Item Q48 removed (factor loading = 0.140)	0.876	0.858	0.074	0.075 (0.069–0.082)	<0.000
Model 2	Item Q47 removed (SR = 5.157)	0.893	0.877	0.071	0.072 (0.064–0.079)	<0.000
Model 3	Correlated residual for item q45 with Q46 (MI = 159.4)	0.937	0.927	0.067	0.055 (0.048–0.063)	0.126

CFA, confirmatory factor analysis; CFI, comparative fit index; TLI, Tucker-Lewis index; SRMR, standardized root mean square residual; RMSEA, root mean square error of approximation; CI, confidence interval; SR, standardized residual; MI, modification index; -, no modification was made.

Table 4. CFA of the attitudes section

Factor/item	Initial CFA model (model 0)			Final CFA model (model 3)			Factor determinacy for model 3
	λ	AVE	CR	λ	AVE	CR	
Behavioral likelihood (BL)		0.54	0.859		0.58	0.860	0.85
Q45F1	0.484			0.441			
Q46F1	0.565			0.529			
Q47F1[a)]	0.530			-			
Q49F1	0.872			0.879			
Q50F1	0.830			0.835			
Q51F1	0.902			0.906			
Q52F1	0.865			0.870			
Subjective norms (SN)		0.69	0.895		0.69	0.895	0.83
Q39F2	0.728			0.728			
Q40F2	0.815			0.815			
Q41F2	0.905			0.905			
Q42F2	0.886			0.886			
Intention to engage in CBS (INT)		0.31	0.714		0.31	0.714	0.94
Q32F3	0.652			0.651			
Q33F3	0.627			0.628			
Q34F3	0.642			0.642			
Q36F3	0.334			0.332			
Q38F3	0.491			0.490			
Q43F3	0.388			0.387			
Negative attitudes (ATT)		0.17	0.504		0.20	0.546	0.86
Q35RF4	0.365			0.366			
Q37RF4	0.467			0.475			
Q44RF4	0.356			0.364			
Q48RF4[b)]	0.140			-			
Q53RF4	0.424			0.415			
Q54RF4	0.665			0.658			

CFA, confirmatory factor analysis; λ, factor loadings, AVE, average variance extracted; CR, composite reliability.
[a)]Item Q47 was excluded from the final model due to a high standardized residual; [b)]Item Q48 was excluded from the final model due to low factor loading; -, the item was removed.

Perceptions section

Initial CFA of the perceptions section, structured into 4 factors, did not produce satisfactory model fit. To improve the model, problematic items (Q55, Q66, Q69, and Q70) were removed based on both fit indices and theoretical rationale. Additional error correlations were introduced between items Q56 and Q57, as well as Q61 and Q62. Improved model fit indices are summarized in Table 5.

The 4 factors in this section align with the HBM framework: perceived susceptibility (5 items), perceived benefit (5 items), perceived barriers (3 items), and self-efficacy (4 items). Each factor exhibited strong internal consistency reliability, with CR values of 0.816, 0.904, 0.808, and 0.820, respectively.

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Table 5. CFA model re-specification for the perceptions section

Model	Modification	CFI	TLI	SRMR	RMSEA (90% CI)	RMSEA *p*
Initial model (model 0)	None	0.850	0.827	0.091	0.094 (0.087–0.102)	<0.000
Model 1	Q70RF3 removed low factor loading	0.866	0.845	0.089	0.093 (0.085– 0.101)	<0.000
Model 2[a)]	Q66RF3 removed low factor loading	0.880	0.860	0.085	0.092 (0.084–0.101)	<0.000
Model 3	Q69RF3 removed low factor loading	0.884	0.862	0.084	0.096 (0.087–0.106)	<0.000
Model 4	Q55RF3 removed low factor loading	0.905	0.886	0.065	0.069 (0.063–0.075)	<0.000
Model 5	Correlate item 56 with 57 (MI = 191.9)	0.952	0.941	0.068	0.066 (0.055–0.077)	0.011
Model 6	Correlate item 61with 62 (MI = 63.4)	0.962	0.954	0.055	0.059 (0.047–0.070)	0.111

CFA, confirmatory factor analysis; CFI, comparative fit index; TLI, Tucker-Lewis index; SRMR, standardized root mean square residual; RMSEA, root mean square error of approximation; CI, confidence interval; MI, modification index.
[a)]Model 2: items (Q55, Q66, Q69, Q70) were removed, and residuals of the following items were correlated (Q56–Q57) and (Q61–Q62).

Discussion

Studies evaluating CBS programs have traditionally focused on metrics such as reporting completeness, report frequency, and related indicators, primarily emphasizing healthcare workers and health facilities [7,30–32]. Although comprehensive tools exist to assess the need for CBS, such as the Community-Based Surveillance Assessment Tool by IFRC [33], these instruments do not specifically target community awareness, attitudes, or perceptions toward CBS. To address this gap, we developed and validated a new questionnaire and used CFA to provide robust evidence for the validity of its factor structure [34]. This study presents the psychometric properties and model fit of the newly developed instrument using CFA.

The 3 domains of the KAP-CBS-ID questionnaire (knowledge, attitudes, and perceptions) were analyzed separately to evaluate their respective psychometric properties and factor structures. This approach ensures that each domain preserves its theoretical integrity while improving the overall construct validity of CBS assessment. Such a design is especially useful for targeted interventions, allowing for the independent assessment of specific components of knowledge, attitudes, and perceptions as needed.

The cut-off values for model fit indices used in this study were guided by the recommendations of Hair [35]. For questionnaires with more than 30 items and sample sizes exceeding 300, the suggested thresholds are: CFI and TLI above 0.92, SRMR no greater than 0.08 when CFI exceeds 0.92, and RMSEA below 0.07 if CFI is at least 0.92. These criteria ensure an adequate model fit for large-scale instruments. The fit indices observed in our models met these cut-off values. Several studies from Malaysia further support the use of these indices as standard benchmarks [36–38], with some reporting slightly lower values than those obtained in our study.

The IRT analysis of the knowledge section led to the removal of 14 items due to inadequate discrimination or difficulty, mirroring the process described by Hung et al. [39]. This refinement resulted in 31 items in the knowledge section, which were subsequently confirmed through CFA [40]. The 3-factor CFA model for the knowledge section demonstrated a good fit without requiring modification. The WLSMV estimator was employed due to the categorical nature of the data. As SRMR is not appropriate for categorical responses, the WRMR was used, where lower values indicate better fit, with a cut-off of 1.0 generally considered acceptable [41]. Although the WRMR value in our study did not reach the ideal threshold, prior research, such as Shuan [42], suggests that a less-than-ideal WRMR is not problematic when other fit indices confirm model adequacy.

The CFA for the attitudes section initially produced unsatisfactory fit indices. The re-specification process involved iterative adjustments to improve fit (Table 4). The initial model (model 0) exhibited suboptimal indices (CFI, 0.874; TLI, 0.858; RMSEA, 0.072; SRMR, 0.073). Modifications included sequential removal of items with low factor loadings (such as Q48 and Q47) and the addition of residual correlations between selected item pairs, such as Q45 and Q46 (modification index [MI], 159.4), based on factor loadings and modification indices. These changes resulted in a final re-specified model with a CFI of 0.962, TLI of 0.954, SRMR of 0.055, and RMSEA of 0.059 (90% confidence interval, 0.047–0.070; $p = 0.111$), consistent with guidelines from Hair et al. [25], as summarized by Newsom [43], who recommend CFI and TLI > 0.90, RMSEA < 0.08, and SRMR < 0.08 as thresholds for adequate fit.

The CFA for the perceptions domain also revealed initial model misfit, prompting a sequential re-specification process to improve fit (Table 6). The original model yielded fit indices of CFI = 0.850, TLI = 0.827, SRMR = 0.091, and RMSEA = 0.094. Although these indices were not ideal, similar studies have deemed such values acceptable [26]. Incremental improvements were achieved by removing items with low factor loadings (Q70RF3, Q66RF3, Q69RF3,

Table 6. Results of CFA of the perceptions domain

Factor/item	Initial CFA model (model 0)			Final CFA model (model 6)			Factor determinacy for model 6
	λ	AVE	CR	λ	AVE	CR	
Perceived susceptibility (SUS)		0.58	0.862		0.545	0.816	0.83
Q56F1	0.629			0.621			
Q57F1	0.609			0.594			
Q61F1	0.841			0.787			
Q62F1	0.854			0.799			
Q63F1	0.842			0.873			
Perceived benefit (BEN)		0.65	0.904		0.65	0.904	0.85
Q71F2	0.702			0.702			
Q72F2	0.803			0.804			
Q73F2	0.889			0.889			
Q74F2	0.834			0.835			
Q75F2	0.811			0.810			
Perceived barriers (BARR)		0.23	0.504		0.58	0.808	0.82
Q58RF3	0.741			0.731			
Q59RF3	0.755			0.765			
Q60RF3	0.789			0.796			
Q55RF3[a]	0.274			-			
Q66RF3[a]	0.145			-			
Q69RF3[a]	0.160			-			
Q70RF3[a]	0.105			-			
Self-efficacy (SE)		0.53	0.819		0.53	0.820	0.85
Q64F4	0.794			0.791			
Q65F4	0.782			0.777			
Q67F4	0.627			0.630			
Q68F4	0.739			0.745			

CFA, confirmatory factor analysis; λ, factor loadings, AVE, average variance extracted; CR, composite reliability; -, the item was removed.
[a]Item Q55, Q66, Q69, and Q70 were excluded from the final model due to a high standardized residual.

and Q55RF3), with a significant improvement following the removal of Q55RF3 (CFI, 0.905; TLI, 0.886; SRMR, 0.065; RMSEA, 0.069). Further enhancement was accomplished by adding error correlations between Q56 and Q57, as well as Q61 and Q62. The final model (model 6) exhibited a CFI of 0.962, TLI of 0.954, SRMR of 0.055, and RMSEA of 0.059, indicating satisfactory fit. The justification for correlated errors was based on item similarity, with such method effects often arising from similarly or reversely worded items [34]. All factor loadings in the questionnaire exceeded the recommended threshold of 0.3 [25], with observed values ranging from 0.33 to 0.98. Internal consistency reliability across domains was satisfactory, with Raykov's rho values ranging from 0.71 to 0.93. The exception was the negative attitudes domain, which fell below the recommended threshold. However, because of its conceptual importance, determinacy—a supplementary measure of internal consistency—was evaluated and surpassed the recommended value of 0.80, indicating adequate reliability [29].

This study has a few limitations. First, the focus on schoolteachers as community representatives resulted in a relatively homogeneous and accessible sample; future validation should incorporate a broader range of community leaders, such as religious figures, local government officials, community health volunteers, and traditional healers, to enhance the tool's applicability. Second, the sample was predominantly Malay, limiting generalizability across other ethnic groups. Third, the sample size calculations did not account for the cluster effect inherent in the multistage sampling design, which could affect the precision of the estimates. Future research should address these limitations by including more racially diverse and heterogeneous samples.

Conclusion

The KAP-CBS-ID questionnaire demonstrated strong validity, reliability, and psychometric properties for assessing the knowledge, attitudes, and perceptions of Malaysian

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community leaders regarding CBS of infectious diseases. The finalized model consists of 69 items, with 31 assessing knowledge, 21 evaluating attitudes, and 17 measuring perceptions. Given the relative homogeneity of the current sample, further validation is recommended to ensure generalizability to broader target groups and individuals with different racial backgrounds.

Notes

Ethics Approval

This study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (ref. no: USM/JEPeM/22050317) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained for publication of this study and accompanying images.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

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

Authors' Contributions

Conceptualization: all authors; Data curation: AAH, NAMN, FS; Formal analysis: AAH, AKG; Methodology: AAH, AKG; Supervision: AKG, NMY, NSB, SMH; Validation: AAH, AKG, NMY, NSB; Writing–original draft: AAH, NAMN, FS; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Association of demographic and biochemical factors with hypercalciuria among Meitei adults in Manipur, Northeast India: a cross-sectional study

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ABSTRACT

Objectives: This study aimed to investigate the association of demographic variables and serum calcium with hypercalciuria among the Meitei adult population of Manipur, Northeast India.

Methods: A cross-sectional study was conducted involving 413 participants (272 females and 141 males) aged 19 to 60 years. Participants were selected through a multistage sampling method from 5 valley districts of Manipur. Demographic and biochemical parameters were collected, including serum calcium, creatinine, and spot urine calcium and creatinine levels. One-way analysis of variance, Tukey's post hoc test, chi-square test, multinomial logistic regression, and receiver operating characteristic (ROC) curve analysis were performed. The area under the ROC curve was calculated to determine the cut-off value of random urine calcium.

Results: The overall prevalence of hypercalciuria was 18.64%. The incidence of hypercalciuria increased with age; 41 to 60 age group were 3 times more likely to develop hypercalciuria than those in the 19 to 40 age group (95% confidence interval [CI], 1.86–5.47; $p < 0.001$). A significant association ($p < 0.05$) was also found between serum calcium and urine calcium levels. Hypocalcemic individuals were 3.5 times more likely to have hypercalciuria than normocalcemic individuals (95% CI, 1.33–9.31; $p = 0.01$). ROC analysis revealed a predictive cut-off value of 23.07 mg/dL for random urine calcium.

Conclusion: This study demonstrates a high prevalence of hypercalciuria exceeding the global average. Given that Manipur has also been reported to have a high prevalence of kidney stones, this finding indicates a considerable health risk. Early intervention could therefore improve public health outcomes related to calcium and mineral metabolism.

Keywords: Hypercalcemia; Hypercalciuria; Hypocalcemia; Kidney calculi

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Introduction

Calcium metabolism and excretion play a crucial role in human health. As a micromineral, calcium is essential for many physiological processes, and alterations in serum calcium levels (hypocalcemia or hypercalcemia) can have serious health consequences. Complex regulatory systems, including calcium-sensing receptors and hormones such as parathyroid hormone (PTH) and vitamin D [1], work together to maintain calcium balance [2]. This balance between absorbed calcium, secreted calcium, and serum calcium is achieved through interactions among calcitonin, 1,25-dihydroxycholecalciferol, PTH, and ionized calcium. Glomerular filtration of albumin-free plasma calcium, along with substantial calcium reabsorption along different tubular segments, produces urinary calcium. Urinary calcium excretion is influenced by multiple calciuric factors, including $1,25(OH)_2D$, PTH, sex hormones, and dietary intake [3]. Thus, excessive intestinal absorption or increased bone resorption may overload the glomerulus, while tubular dysfunction and reduced reabsorption can result in elevated urinary calcium excretion, or hypercalciuria.

Hypercalciuria, defined as excessive urinary calcium excretion, is a significant health concern most commonly linked to kidney stones and osteoporosis. Its occurrence worldwide is influenced by geographical location, diet, and heredity. Approximately 5% to 10% of the general population is estimated to have hypercalciuria, with idiopathic hypercalciuria being the most common type, particularly among individuals with calcium oxalate nephrolithiasis and osteoporosis [4]. Hypercalciuria is especially prevalent in developed countries, where dietary practices increase the risk of kidney stones and osteoporosis [5]. In India, the prevalence of hypercalciuria among children was reported at 6.5% [6]. However, its prevalence among the adult Indian population remains inadequately studied. While relatively few studies on hypercalciuria exist, several have reported no significant sex differences in urinary calcium excretion [6–8].

Numerous studies have explored the association of hypercalciuria with kidney stone formation [9] and osteoporosis [10]. However, the relationship between serum calcium status (hypocalcemia or hypercalcemia) and urinary calcium excretion (hypocalciuria or hypercalciuria) has received less attention. Moreover, the association of demographic variables with hypercalciuria has not been thoroughly examined in Northeast India, particularly in Manipur. Considering these gaps and the importance of the issue, this study sought to investigate the association of demographic variables and serum calcium with hypercalciuria among Meitei adults in Manipur, Northeast India.

HIGHLIGHTS

- A high prevalence of hypercalciuria was observed compared to the global occurrence of hypercalciuria.
- The incidence of hypercalciuria increases with age; older adults are more likely to develop hypercalciuria than younger individuals.
- A significant difference between serum calcium and urine calcium was identified, indicating that hypocalcemic individuals are more likely to have hypercalciuria than normocalcemic individuals.

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational research. Participants were recruited between June 2023 and December 2023 from Meitei communities residing in the 5 valley districts of Manipur: Imphal-East, Imphal-West, Bishnupur, Thoubal, and Kakching (Figure 1).

Study Population and Sampling

The study population comprised adults of Meitei ethnicity, aged 19 to 60 years, who were permanent residents of the 5 valley districts of Manipur (Imphal-East, Imphal-West, Bishnupur, Thoubal, and Kakching). Pregnant women were excluded to avoid confounding from pregnancy-related changes and calcium supplementation. Other individuals reporting current use of calcium supplements were also excluded, as supplementation could alter serum and urinary calcium levels.

The required sample size was estimated using Epi Info software, assuming a 95% confidence level, 50% expected frequency, and a 5% margin of error, yielding a target of 663 participants. Eligible individuals were identified through a multistage random sampling process involving the selection of constituencies, polling stations, and households. In the first stage, 19 constituencies were randomly selected across the 5 districts. In the second stage, 20 polling stations were chosen to represent specific localities. In the final stage, households within the selected polling stations were surveyed, and eligible individuals were identified according to the inclusion criteria (Figure 2).

A total of 663 individuals were approached through

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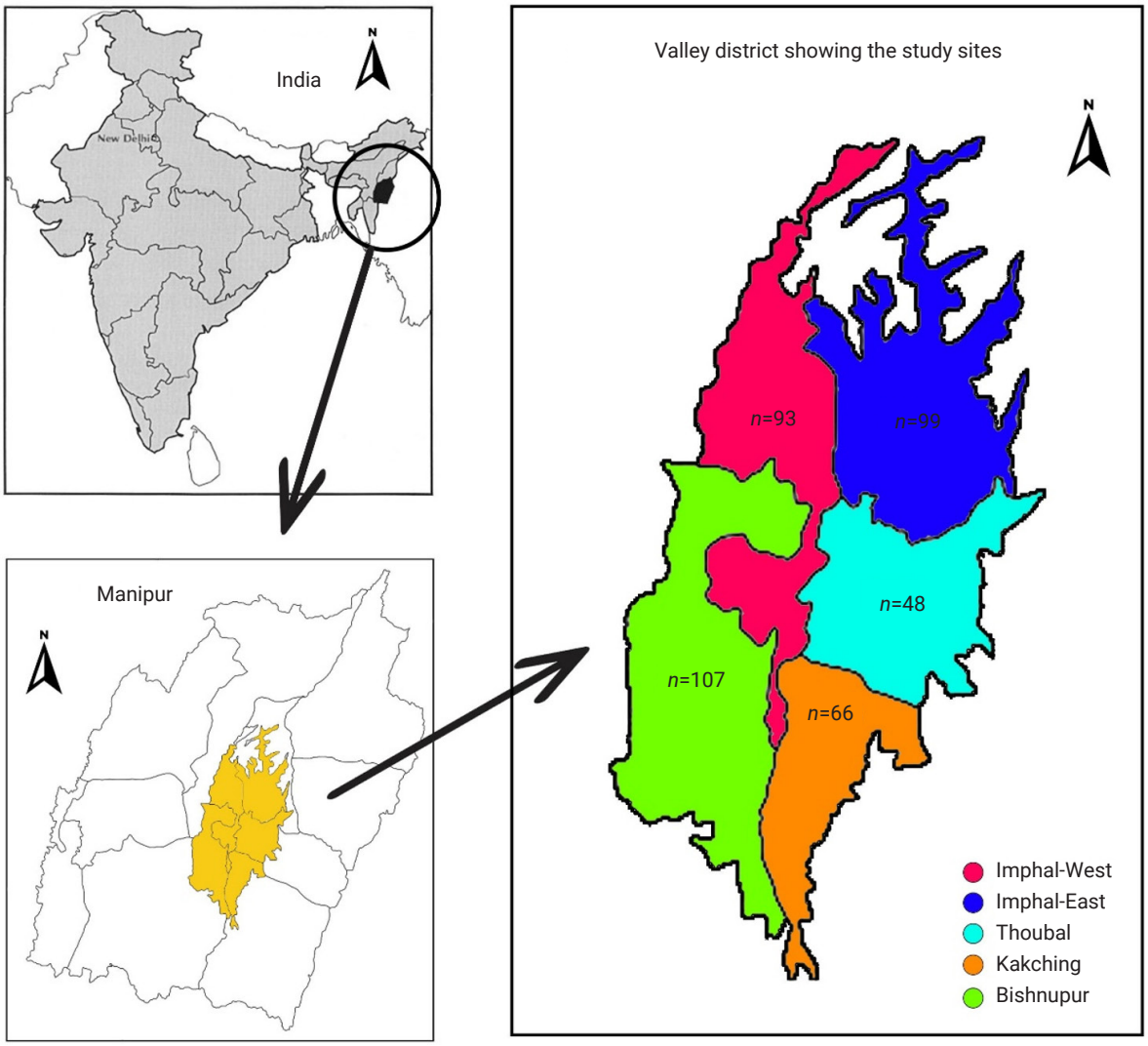


Figure 1. Geographical location of 5 valley districts of Manipur showing the study site.

household visits. Of these, 487 consented and were screened for eligibility; 465 met the inclusion criteria, and 423 completed all required assessments, including serum and random urine sample collection. Ten participants were excluded due to incomplete biological samples. Thus, the final analysis comprised 413 participants (272 females and 141 males). Reasons for non-participation included refusal ($n=22$), failure to meet inclusion criteria ($n=42$), and incomplete data collection ($n=10$).

Data Collection and Study Variables

Demographic data such as age, sex, and district of residence were collected using a structured questionnaire. Clinical data were obtained through blood and random urine samples. Serum and urine calcium and creatinine levels were considered predictor variables, along with age. Age was categorized into 2 groups: ≤40 years and >40 years, based on the mean age at which the peak prevalence of hypercalciuria is expected.

The primary outcome was hypercalciuria, defined using the random urinary calcium-to-creatinine ratio, with interpretation as follows: <0.14 considered normal, >0.20 indicating hypercalciuria [11]. Values between 0.14 and 0.20 were classified as borderline and labeled as the "at-risk" group. Serum calcium levels were categorized as hypocalcemia (<8.5 mg/dL), normocalcemia (8.5–10.5 mg/dL), and hypercalcemia (>10.5 mg/dL) [12], enabling assessment of their relationship with urinary calcium excretion.

Specimen Collection and Laboratory Analysis

Approximately 2 mL of venous blood was collected in non-ethylenediaminetetraacetic acid coated microcentrifuge

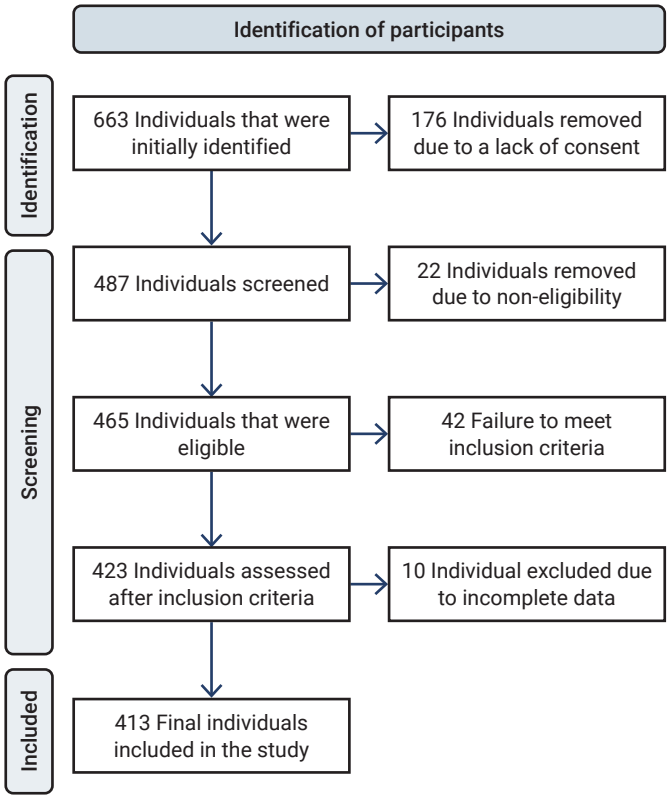


Figure 2. Flowchart showing selection of participants.

tubes. Random spot urine samples were collected on the same day in sterile containers, using the clean-catch midstream method to minimize contamination [13]. All samples were collected during household visits and processed in community settings according to the survey schedule. Collected specimens were refrigerated at 4°C until analysis. Serum and urine creatinine levels were measured using Jaffe's reaction method [14]. Urine samples were diluted with distilled water at a 1:20 ratio, and results were multiplied by 20. Serum and urine calcium levels were measured using the Arsenazo III method [15]. For urine calcium measurement, samples were diluted with distilled water at a 1:2 ratio, and the pH was adjusted to 3–4 by adding drops of 0.1 mol/L HCl; the final result was multiplied by 3. All measurements were performed using an automated biochemistry analyzer, the Erba Chem 5x (Erba), following standard operating procedures. Internal quality control checks were run before each batch of samples to ensure accuracy and reproducibility.

Statistical Methods

Statistical analyses were conducted using IBM SPSS Statistics for Windows ver. 21.0 (IBM Corp.). Data were expressed as mean ± standard deviation (SD) with 95% confidence intervals (CIs), as well as frequency and percentage. The significance of differences among the hypercalciuria, at-risk, and normal groups was assessed using analysis of variance (ANOVA) for serum creatinine, serum calcium, and random urine calcium and creatinine levels. Tukey's post hoc test was applied to evaluate differences between group pairs (hypercalciuria vs. at-risk, hypercalciuria vs. normal, and at-risk vs. normal). The chi-square test was used to examine differences in demographic variables and serum calcium status among the 3 groups. The association of urinary calcium-to-creatinine status with demographic variables and serum calcium status was analyzed using a multinomial logistic regression model. Urinary calcium-to-creatinine status was the dependent variable, with demographic variables and serum calcium status entered as covariates of interest. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive power of serum and urine calcium for hypercalciuria. The cut-off values for these parameters were determined using the maximum Youden index [16]. A p-value <0.05 was considered statistically significant.

Ethics Statement

The study was reviewed and approved by the Institutional Human Ethical Committee (IHEC) of Manipur University under reference number MU/IHEC/2020/018, with approval granted on December 14, 2020. The IHEC confirmed the use of informed consent, and all participants provided written informed consent prior to enrollment.

Results

Descriptive Data of General Clinical Characteristics of Participants

Table 1 presents the general characteristics of the study participants. Hypercalciuria was significantly more prevalent in the 41–60-year age group (66.2%) compared with the younger 19–40-year group (33.8%), providing strong evidence of an age-related association. By sex, females had a higher prevalence of hypercalciuria (75.3%) than males (24.7%). District-level variation was also observed, with Kakching and Imphal-West reporting the highest prevalence among the hypercalciuric group (28.6%) and Imphal-East the lowest (7.8%). With respect to serum calcium status, hypercalciuria prevalence was highest in normocalcemia (53.2%) and hypercalcemia (33.8%), and lowest in hypocalcemia (13.0%). No significant association was observed between hypercalciuria and either serum creatinine or serum calcium levels. For urine creatinine, the lowest mean value was found in the hypercalciuric group (4.67 mg/dL), while the highest was observed in the normal

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Table 1. General clinical characteristics of the participants

Characteristic	Total (*n* = 413)	Hypercalciuria (*n* = 77)	At risk (*n* = 97)	Normal (*n* = 239)	*p*
Age group (y)					< 0.001**
19–40	219 (53.0)	26 (33.8)	45 (46.4)	148 (61.9)	
41–60	194 (47.0)	51 (66.2)	52 (53.6)	91 (38.1)	
Sex					0.10
Male	141 (34.1)	19 (24.7)	32 (33.0)	90 (37.7)	
Female	272 (65.9)	58 (75.3)	65 (67.0)	149 (62.3)	
Valley district					< 0.001**
Imphal-East	93 (22.5)	6 (7.8)	13 (13.4)	74 (31.0)	
Imphal-West	99 (24.0)	22 (28.6)	30 (30.9)	47 (19.7)	
Bishnupur	107 (25.9)	19 (24.7)	28 (28.9)	60 (25.1)	
Thoubal	48 (11.6)	8 (10.4)	10 (10.3)	30 (12.6)	
Kakching	66 (16.0)	22 (28.6)	16 (16.5)	28 (11.7)	
Serum calcium status					0.002*
Hypocalcemia	27 (6.5)	10 (13.0)	7 (7.2)	10 (4.2)	
Normocalcemia	293 (70.9)	41 (53.2)	74 (76.3)	178 (74.5)	
Hypercalcemia	93 (22.5)	26 (33.8)	16 (16.5)	51 (21.3)	
Serum samples					
Serum creatinine (mg/dL)	0.91 ± 0.20	0.90 ± 0.22	0.93 ± 0.20	0.92 ± 0.22	0.64
Serum calcium (mg/dL)	10.02 ± 1.12	10.07 ± 1.35	9.92 ± 1.13	10.06 ± 0.88	0.64
Random urine samples					
Urinary creatinine (mg/dL)	7.24 ± 3.80	4.67 ± 2.69	7.18 ± 3.57	9.87 ± 5.15	< 0.001**
Urinary calcium (mg/dL)	7.05 ± 3.64	8.55 ± 4.15	7.67 ± 3.71	4.93 ± 3.07	< 0.001**
Calcium-to-creatinine ratio	0.19 ± 0.08	0.08 ± 0.03	0.16 ± 0.01	0.33 ± 0.21	< 0.001**

Data are presented as *n* (%) or mean ± standard deviation.
Significant at *$p < 0.05$, **$p < 0.001$.

group (9.87 mg/dL). Urinary calcium was highest in the hypercalciuric group (8.55 mg/dL) and lowest in the normal group (4.93 mg/dL).

Serum and urine calcium and creatinine levels by sex

Table 2 shows sex-specific mean ± SD values of serum and urine calcium and creatinine. Overall, 18.64% of participants had hypercalciuria, 23.49% were at risk, and 57.87% were within the normal range. The mean ± SD of serum creatinine was slightly higher in the risk group (0.93 ± 0.20 mg/dL), followed by the normal group (0.92 ± 0.22 mg/dL) and the hypercalciuric group (0.90 ± 0.22 mg/dL). The mean serum calcium level was marginally higher in the hypercalciuric group (10.07 ± 1.35 mg/dL), followed by the normal group (10.06 ± 0.88 mg/dL) and the risk group (9.92 ± 1.13 mg/dL). However, 1-way ANOVA indicated no statistically significant differences among the groups for serum creatinine or serum calcium. In contrast, significant differences were found in urinary parameters. Random urine creatinine increased progressively from the hypercalciuric group (4.67 ± 2.69 mg/dL) to the risk group (7.18 ± 3.57 mg/dL) and was highest in the normal group (9.87 ± 5.15 mg/dL). Significant differences were observed among all group pairs ($p < 0.001$). Conversely, urinary calcium exhibited a declining trend: highest in the hypercalciuric group (8.55 ± 4.15 mg/dL), slightly lower in the risk group (7.67 ± 3.71 mg/dL), and lowest in the normal group (4.93 ± 3.07 mg/dL). The association across groups was statistically significant ($p < 0.001$), with differences noted between hypercalciuria vs. normal and risk vs. normal, though not between hypercalciuria and risk. These patterns were consistent across both sexes, although certain variations were noted. Males had higher mean serum creatinine and urine creatinine values, whereas females had higher mean calcium levels in both the hypercalciuric and risk groups.

Urinary calcium excretion by demographic and serum calcium levels

Table 3 summarizes the association of urinary calcium excretion with demographic variables and serum calcium status. A significant relationship between age and urinary calcium excretion was observed ($p < 0.001$), indicating that older individuals were more likely to be hypercalciuric. Within the hypercalciuric group, 66.2% were aged 41–60 years, compared with 33.8% in the 19–40 group. Similarly, in the risk group, 53.6% were in the 41–60 group versus

Table 2. Mean distribution of serum and urine calcium and creatinine among the studied population

Characteristic		Hypercalciuria (*n* = 77, 18.6)	At risk (*n* = 97, 23.5)	Normal (*n* = 239, 57.9)	*p*	*Post hoc* Tukey HSD		
						Hypercalciuria: risk	Hypercalciuria: normal	Risk: normal
Serum creatinine (mg/dL)	Male	1.05 ± 0.21	1.06 ± 0.22	1.06 ± 0.21	0.96	0.96	0.95	0.99
	Female	0.85 ± 0.20	0.87 ± 0.15	0.83 ± 0.18	0.37	0.88	0.72	0.36
	Total	0.90 ± 0.22	0.93 ± 0.20	0.92 ± 0.22	0.64	0.61	0.79	0.87
Serum calcium (mg/dL)	Male	9.84 ± 1.54	10.3 ± 1.31	10.11 ± 0.77	0.49	0.45	< 0.05	0.45
	Female	10.15 ± 1.29	9.78 ± 0.99	10.03 ± 0.95	0.11	0.11	0.74	0.21
	Total	10.07 ± 1.35	9.92 ± 1.13	10.06 ± 0.88	0.64	0.71	0.99	0.65
Random urine creatinine (mg/dL)	Male	4.78 ± 2.93	7.18 ± 3.19	11.64 ± 5.81	< 0.001**	0.14	< 0.001**	< 0.001**
	Female	4.63 ± 2.63	7.18 ± 3.76	8.80 ± 4.40	< 0.001**	< 0.001**	< 0.001**	< 0.05*
	Total	4.67 ± 2.69	7.18 ± 3.57	9.87 ± 5.15	< 0.001**	< 0.001**	< 0.001**	< 0.001**
Random urine calcium (mg/dL)	Male	8.43 ± 4.19	7.34 ± 3.15	5.35 ± 3.25	< 0.001**	0.4	< 0.001**	< 0.05*
	Female	8.59 ± 4.17	7.84 ± 3.98	4.68 ± 2.94	< 0.001**	0.37	< 0.001**	< 0.001**
	Total	8.55 ± 4.15	7.67 ± 3.71	4.93 ± 3.07	< 0.001**	0.14	< 0.001**	< 0.001**

Data are presented as mean ± standard deviation unless otherwise stated.
HSD, honestly significant difference.
Significant at *$p < 0.05$, **$p < 0.001$.

Table 3. A comparative analysis of urinary calcium excretion with demographic variables and serum calcium status using the chi-square test

Characteristic	Hypercalciuria (*n* = 77)	At risk (*n* = 97)	Normal (*n* = 239)	*p*
Sex				0.109
Male (*n* = 141)	19 (24.7)	32 (33.0)	90 (37.7)	
Female (*n* = 272)	58 (75.3)	65 (67.0)	149 (62.3)	
Age group (y)				< 0.001**
19–40	26 (33.8)	45 (46.4)	148 (61.9)	
41–60	51 (66.2)	52 (53.6)	91 (38.1)	
Serum calcium status				0.002*
Hypercalcemia (*n* = 93)	26 (33.8)	16 (16.5)	51 (21.3)	
Hypocalcemia (*n* = 27)	10 (13.0)	7 (7.2)	10 (4.2)	
Normocalcemia (*n* = 293)	41 (53.2)	74 (76.3)	178 (74.5)	

Data are presented as *n* (%).
Significant at *$p < 0.05$, **$p < 0.001$.

46.4% in the 19–40 group. In contrast, among the normal group, the majority (61.9%) were younger (19–40 years), while 38.1% were in the 41–60 group. Serum calcium status was also significantly associated with urinary calcium excretion ($p < 0.05$). Among the hypercalciuric group, 13.0% were hypocalcemic, 33.8% hypercalcemic, and 53.2% normocalcemic. In the risk group, 7.2% were hypocalcemic, 16.5% hypercalcemia, and 76.3% normocalcemic. In contrast, among individuals with normal urinary calcium excretion, 74.5% were normocalcemic, 21.3% hypercalcemic, and 4.2% hypocalcemic. Sex differences were also noted: among females, 75.3% were hypercalciuric, 67.0% at risk, and 62.3% normal. Among males, 24.7% were hypercalciuric, 33.0% at risk, and 37.7% normal. However, no statistically significant association was found between sex and urinary calcium status.

Odds of Hypercalciuria by Demographics and Serum Calcium Levels

Table 4 displays the odds ratios (ORs) for hypercalciuria relative to demographic variables and serum calcium status, using normal urinary calcium as the reference. Females had 1.4-fold higher odds (OR, 1.43; 95% CI, 0.77–2.63; $p = 0.26$) of developing hypercalciuria compared with males. Individuals aged 41–60 years had a threefold higher risk (OR, 3.19; 95% CI, 1.86–5.47; $p < 0.001$) compared with those aged 19–29 years. District-wise analysis showed significant associations. Compared with Imphal-East, individuals from Imphal-

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Table 4. Results of multinomial logistic regression in hypercalciuric and risk groups with normal calcium excretion as the reference population in the analysis

Urine calcium and creatinine status	Variable	Category	OR (95% CI)	*p*
Hypercalciuria	Sex	Female	1.43 (0.77–2.63)	0.26
		Male	0	
	Age group (y)	41–60	3.19 (1.86–5.47)	< 0.001**
		19–40	0	
	Districts	Imphal-West	5.77 (2.18–15.28)	0.00*
		Thoubal	3.28 (1.05–10.28)	0.41
		Kakching	9.69 (3.55–26.39)	0.00*
		Bishnupur	3.90 (1.46–10.39)	0.006
		Imphal-East	0	
	Serum calcium status	Hypercalcemia	2.10 (1.15–3.84)	0.02*
		Hypocalcemia	3.52 (1.33–9.31)	0.01*
		Normocalcemia	0	
At risk	Sex	Female	1.11 (0.66–1.85)	0.69
		Male	0	
	Age group (y)	41–60	1.88 (1.16–3.02)	0.01*
		19–40	0	
	Districts	Imphal-West	3.63 (1.72–7.65)	0.001*
		Thoubal	1.89 (0.75–4.79)	0.176
		Kakching	3.25 (1.38–7.62)	0.001*
		Bishnupur	2.65 (1.26–5.57)	0.010*
		Imphal-East	0	
	Serum calcium status	Hypercalcemia	0.73 (0.39–1.38)	0.34
		Hypocalcemia	1.52 (0.55–4.20)	0.41
		Normocalcemia	0	

OR, odds ratio; CI, confidence interval.
Significant at *$p < 0.05$, **$p < 0.001$.

West had 5.77-fold higher odds (OR, 5.77; 95% CI, 2.18–15.28; $p < 0.001$), Kakching 9.69-fold higher odds (OR, 9.69; 95% CI, 3.55–26.39; $p < 0.001$), and Bishnupur 3.90-fold higher odds (OR, 3.90; 95% CI, 1.46–10.39; $p = 0.006$). Thoubal showed no significant difference, although its OR was 3.28 (95% CI, 1.05–10.28; $p = 0.41$). Comparing calcium status, hypocalcemic individuals had 3.5-fold higher odds of hypercalciuria (OR, 3.52; 95% CI, 1.33–9.31; $p = 0.01$) relative to normocalcemic individuals. Hypercalcemic individuals also had significantly higher odds (OR, 2.10; 95% CI, 1.15–3.84; $p = 0.02$). In the at-risk category, females had slightly higher odds (OR, 1.11; 95% CI, 0.66–1.85; $p = 0.69$) compared with males. Participants aged 41–60 years had 1.8-fold higher odds (OR, 1.88; 95% CI, 1.16–3.02; $p = 0.01$) compared with those aged 19–29 years. District-wise associations in the risk group were also significant: Imphal-West (OR, 3.63; 95% CI, 1.72–7.65; $p = 0.001$), Kakching (OR, 3.25; 95% CI, 1.38–7.62; $p = 0.001$), and Bishnupur (OR, 2.65; 95% CI, 1.26–5.57; $p = 0.01$). Thoubal showed no significant association (OR, 1.89; 95% CI, 0.75–4.79; $p = 0.17$). Individuals with hypocalcemia had 1.5-fold higher odds of being in the risk category (OR, 1.52; 95% CI, 0.55–4.20; $p = 0.41$), while those with hypercalcemia had lower odds (OR, 0.73; 95% CI, 0.39–1.38; $p = 0.03$) compared with normocalcemic individuals.

ROC Curve Analysis

Table 5 summarizes the ROC curve analysis, evaluating the predictive utility of serum and urine calcium for hypercalciuria. Urinary calcium had an area under the ROC curve (AUC) of 0.70, with a predictive cut-off value of 23.07 mg/dL, sensitivity of 58.40%, and specificity of 75%. In contrast, serum calcium had a much lower predictive value, with an AUC of 0.52.

Discussion

Key Results

This study is among the few conducted to investigate the prevalence of hypercalciuria in Manipur. We assessed its frequency among Meitei adults aged 19 to 60 years residing in the valley districts. Globally, hypercalciuria affects 5% to 10% of adults and occurs in approximately one-third of individuals with calcium stones [17]. Idiopathic hypercalciuria accounts for about 40% to 50% of recurrent calcium stone

Table 5. Receiver operating characteristic curve analysis: cut-off points, sensitivity, and specificity of serum calcium and random urine calcium

Variable	AUC	*p*	Cut-off (mg/dL)	Sensitivity (%)	Specificity (%)
Serum calcium	0.52	0.51	10.76	29.9	87.5
Urine calcium	0.70	0.00*	23.07	58.4	75.0

AUC, area under the receiver operating characteristic curve.
Significant at *$p < 0.05$.

cases [18]. In our study, the prevalence of hypercalciuria was 75.3% among females and 24.7% among males, yielding an overall prevalence of 18.64%, which is higher than the global average.

Hypercalciuria is well recognized as a major risk factor for kidney stone formation. The prevalence of kidney stone disease in Manipur is notably high. Marak et al. [19] reported a prevalence rate of 22.4%, whereas Konjengbam et al. [20] reported a slightly lower rate of 11.24%. This high prevalence of kidney stones in Manipur may be partly explained by the elevated incidence of hypercalciuria observed in this population. Beyond stone formation, hypercalciuria also poses broader health risks, including urinary tract infections and reductions in bone mineral density, leading to osteopenia or osteoporosis.

In this study, random urine samples were used, with calcium levels expressed relative to creatinine. A low urine creatinine combined with relatively high urine calcium can result in a proportionally elevated calcium excretion, potentially reflecting factors such as reduced muscle mass or impaired renal function [21]. Our findings showed low urine creatinine levels with high urine calcium, yielding elevated calcium-to-creatinine ratios. This observation is consistent with other studies, which have also reported that individuals with low creatinine and high calcium levels demonstrate increased calcium-to-creatinine ratios, indicative of hypercalciuria [22].

Age emerged as a significant factor influencing hypercalciuria prevalence. Previous studies have demonstrated age-related variations, with hypercalciuria being common in children and adolescents. For example, a study reported that hypercalciuria is frequent among children aged 2 to 16 years, with younger children more likely to develop the disorder [23]. Another study noted that 39% of healthy adolescents exhibit hypercalciuria [24]. In contrast, our study showed that older adults were more susceptible. Participants aged 41 to 60 years had 3.19-fold higher odds of hypercalciuria compared with those aged 19 to 40 years. Similar findings have been reported in older adults, particularly postmenopausal women, who often take calcium supplements for osteoporosis prevention or treatment. Excess absorbed calcium may subsequently be excreted in the urine, contributing to hypercalciuria [25]. Reports indicate that up to 40% of postmenopausal women exhibit high urinary calcium levels [26]. Another study found elevated urinary calcium in 19% of postmenopausal women, further supporting a high prevalence in this subgroup [27]. In older men, elevated urinary calcium may be influenced by diet, bone mineral density, and underlying medical conditions. Notably, higher urinary calcium excretion in older men has been linked to reduced trabecular bone mineral density, potentially leading to bone loss [10]. Additionally, urinary sodium excretion has been correlated with calcium excretion, suggesting that dietary salt intake may influence calcium homeostasis [28]. However, metabolic, developmental, and hereditary factors must also be considered to fully explain the association between age and hypercalciuria. Several studies have reported that calcium absorption, vitamin D levels, and nephrolithiasis risk increase around mid-adulthood (approximately 40 years), which may indirectly contribute to hypercalciuria [29,30].

Sex-related differences in hypercalciuria have also been reported. Golovanov et al. [31] observed that men typically excrete more urinary calcium and exhibit a higher likelihood of oxalate stone formation, whereas women excrete less calcium overall, regardless of lithogenic factors. By contrast, our study found that women were more likely to have hypercalciuria, although the association was not statistically significant. Within the hypercalciuric group, females had 1.4 times greater odds than males, and within the at-risk group, females had 1.1 times greater odds. Women also exhibited higher urinary calcium excretion, often accompanied by lower creatinine excretion. These findings are consistent with previous reports suggesting that postmenopausal women are more prone to elevated urinary calcium [27]. Men, in contrast, generally excrete less calcium but significantly higher amounts of creatinine, which may reduce their apparent susceptibility to hypercalciuria [6,8]. This sex-specific pattern may be partly explained by differences in renal calcium handling: women demonstrate reduced distal calcium reabsorption [32], while men exhibit diminished proximal tubular calcium reabsorption.

Individuals with increased urinary calcium excretion in

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the absence of serum calcium abnormalities or identifiable disorders are generally classified as having idiopathic hypercalciuria [33]. In our study, 53.2% of participants were normocalcemic with hypercalciuria, while the risk of hypercalciuria among normocalcemic individuals was 76.3%. Elevated urinary calcium load in such cases may result from increased intestinal absorption of calcium, reduced renal calcium reabsorption, and a tendency toward bone calcium loss [34]. Nevertheless, hypercalciuria remains a complex polygenic trait in which diet plays a major role, and it may also result from heightened vitamin D responsiveness. In our study, 13.0% of participants exhibited hypocalcemic hypercalciuria, with a 3.5-fold higher odds of hypercalciuria. Tsuji et al. [35] reported that hypocalcemia with hypercalciuria can arise from autosomal dominant hypocalcemia (ADH) caused by functional mutations in calcium-sensing receptors. In such cases, vitamin D deficiency may mask the typical hypercalciuria associated with ADH. Other studies have also linked hypocalcemia with hypercalciuria to genetic mutations affecting calcium-sensing mechanisms and related pathways [36,37]. Our findings indicate that hypocalcemia is statistically associated with increased odds of hypercalciuria, though this does not establish a direct causal relationship between low serum calcium and elevated urinary calcium excretion. The observed association could instead reflect common factors such as vitamin D deficiency, malnutrition, or hormonal disturbances that alter calcium balance. While rare genetic syndromes may contribute, they are unlikely to account for most cases in this population. Given the cross-sectional design of our study, serum and urinary calcium values were measured at a single time point, so some participants may have been misclassified due to transient fluctuations in calcium levels. Thus, our findings should be interpreted as associative rather than causal, and further studies are warranted to elucidate underlying mechanisms. Hypercalcemia with hypercalciuria represents another important clinical condition, with each disorder potentially influencing the other depending on genetic, metabolic, and therapeutic factors. In our study, 33.8% of participants had hypercalcemia with hypercalciuria, and individuals with hypercalcemia were 2.1 times more likely to develop hypercalciuria compared with normocalcemic individuals. According to Auron and Alon [38], hypercalcemia with hypercalciuria often reflects disruptions in mineral homeostasis and may lead to acute kidney injury and renal calcifications. Jacobs et al. [39] reported that impaired inactivation of vitamin D metabolites, due to CYP24A1 mutations, increases calcium absorption and can cause concurrent hypercalcemia and hypercalciuria. Although these 2 conditions frequently coexist, they may also occur independently, underscoring the need for individualized assessment and treatment strategies. Our analysis also revealed notable geographic differences in hypercalciuria prevalence across the valley districts. Significant associations were observed in Imphal-West, Bishnupur, and Kakching, with Kakching showing the highest odds (9.69) compared to other districts. Although our study did not examine contextual factors such as diet, environmental exposures, or healthcare access, these may contribute to the observed regional variation. Larger multi-district studies incorporating these variables are needed to clarify the drivers of such differences.

Regarding predictive analysis, AUC values greater than 0.9 indicate high accuracy, values between 0.7 and 0.9 indicate moderate accuracy, and values between 0.5 and 0.7 suggest low accuracy [40]. In this study, urinary calcium excretion demonstrated moderate predictive ability for hypercalciuria (AUC, 0.70; $p < 0.001$). The predictive cut-off value of urinary calcium was 23.07 mg/dL, with 58.40% sensitivity and 75% specificity, both within acceptable ranges [41]. By contrast, a prior study reported a lower cut-off of 10.15 mg/dL for urinary calcium to define hypercalciuria [42]. While hypercalciuria may also result from elevated serum calcium leading to increased urinary excretion, our findings suggest that serum calcium alone does not reliably predict hypercalciuria, although it remains a useful marker of overall calcium homeostasis.

Strengths and Limitations of the Study

This investigation has both strengths and limitations. A key strength is that it is one of the few studies to examine hypercalciuria prevalence in Manipur, providing novel data on the frequency and risk of hypercalciuria using random urinary calcium-to-creatinine ratios among Meitei adults aged 19–60 years. The study demonstrated significant associations with age group and serum calcium status. However, limitations must be acknowledged. Factors such as environmental influences, dietary patterns, and detailed nutritional assessment were not measured, and these may affect calcium levels. Additionally, reliance on random urine samples rather than 24-hour urine collections may have introduced variability. The absence of food intake data is another limitation.

Conclusion

In summary, this study highlights a higher prevalence of hypercalciuria compared with global estimates. The risk of hypercalciuria increased with age, with older adults more likely to be affected than younger individuals. A significant association was also found between serum calcium

status and urinary calcium excretion, with hypocalcemic individuals showing a greater likelihood of hypercalciuria than normocalcemics. Although no statistically significant sex differences were observed, females exhibited higher prevalence rates. These findings, specific to Meitei adults in Manipur, may serve as a basis for further research in other populations to assess whether similar trends exist. Hypercalciuria should be regarded as an important factor in understanding calcium metabolism, bone health, renal function, and associated diseases. From a public health perspective, routine screening and monitoring of urinary calcium can improve outcomes by identifying at-risk groups, promoting preventive healthcare, and enabling earlier interventions.

Notes

Ethics Approval

The study was reviewed and ethically approved by the IHEC of Manipur University under reference number MU/IHEC/2020/018. All the participants signed an informed consent form approved by IHEC prior to participation.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

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

Authors' Contributions

Conceptualization: YMS, RSA, HK; Data curation: RSA, EP, MY; Formal analysis: YMS, RSA; Funding acquisition: YMS, SSH; Investigation: RSA; Methodology: RSA; Project administration: YS, RSA; Resources: RSA; Software: RSA; Supervision: YMS; Validation: YMS, SH; Writing–original draft: RSA; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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- The Editorial Office of PHRP receives and reviews all submitted manuscripts, and all submitted manuscripts are considered confidential. The submitted manuscripts are initially screened for formatting. Once the manuscript is provisionally accepted, it is sent to the 2 most relevant reviewers for review.
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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	1,500	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.

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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).

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

Main Body

- **Introduction** should provide concise yet sufficient background information about the study to provide the readers with a better understanding of the study, avoiding a detailed literature survey or a summary of the results.
- **Materials and methods** should contain detailed procedures of the study or experiment including investigation period, methods of subject selection, and information on subjects such as age, sex or gender, and other significant features, in order to enable the experiment to be repeated. A procedure that has been already published or standardized should be described only briefly using literature citations. Clinical trials or experiments involving laboratory animals or pathogens must elaborate on the animal care and use and experimental protocols, in addition to mentioning approval from the relevant committees. The sources of special equipment and chemicals must be stated with the name of the manufacturer. All statistical procedures used in the study and criteria for determining significance levels must be described. Ensure correct use of the terms "sex" (when reporting biological factors) and "gender" (identity, psychosocial or cultural factors). Unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study involved an exclusive population (only one sex, for example), authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity, and justify its relevance. Institutional Review Board approval and informed consent procedures can be described as follows: The study protocol was approved by the Institutional Review Board of OOO (IRB No: OO-OO-OO). Informed consent was obtained by all participants (or the participant's legal guardian) / Informed consent was waived by the IRB.
- **Results** should be presented in logical sequence. Only the most important observations should be emphasized or summarized, and the main or the most important

findings should be mentioned first. Tables and figures must be numbered in the order they are cited in the text, kept to a minimum, and should not be repeated. Supplementary materials and other details can be separately presented in an appendix. The authors should state the statistical method used to analyze the results (statistical significance of differences) with the probability values given in parentheses.

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

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

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- Other types of references not described below should follow the ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Please refer to the following examples.

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

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Tables should be simple, self-explanatory, and supplemental, and should not duplicate the text or figures. Each table must be on a separate page, not exceeding 1 page when printed, and have a concise and informative title. The tables should be numbered with Arabic numerals in consecutive order.

Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table ([a], [b], [c], [d]...), and notes on level of probability (*, **, *** for *p*).

Figures should be numbered with Arabic numerals consecutively in figure legends. The figures must not be interfered and must be clearly seen. The legend for each light microscopic image should include name of the stain and magnification. Electron microscopic images should contain an internal scale marker. All figures may be altered in size by the editor. The legends should briefly describe the data shown, explain abbreviations or reference points, and identify all units, mathematical expressions, abscissas, ordinates, and symbols.

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When tables and figures are mentioned together in the text, they should be presented in parentheses as follows: (Table 1; Figure 1), (Tables 1, 2; Figures 1–3).

Appendix and Supplemental Data

If any materials are not enough to be included in the main text such as questionnaires, they can be listed in the Appendix. Any supplementary materials that help the understanding of readers or contain too great an amount of data to be included in the main text may be placed as supplementary data. Not only a recording of the abstract, text, audio or video files, but also data files should be added here.

FINAL PREPARATION FOR PUBLICATION

Final Version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher-resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

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Minor errors will be corrected directly in the online version of the article. An indication of the correction, along with the date it was made, will be added to the article information in both the HTML and PDF versions. A separate correction note will not be published.

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Author's checklist

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- ▫ The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
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- ▫ The abstract does not exceed 250 words (Objectives, Methods, Results, Conclusion) for original articles and 200 words for reviews. Up to 3–6 keywords are listed at the bottom of the abstract.

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References

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