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The **Public Health** category covers health systems, risk communication, implementation science, community-based interventions, and the prediction and prevention of public health threats. The **Infectious Diseases** category covers emerging and zoonotic infections, outbreak investigation and disease surveillance (including genomic and molecular surveillance), vaccine effectiveness, antimicrobial resistance, One Health approaches, and infectious disease prevention and control. The **Epidemiology** category covers epidemiological methods and their applications, disease surveillance methodology, data resources, and research connecting environmental factors, including climate change, with patterns of infectious and chronic diseases. The **Related Health Sciences** category covers noncommunicable diseases and healthy aging, health policy, environmental and occupational health, digital public health, and health data science.

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Editorial Office:

- Korea Disease Control and Prevention Agency
  National Center for Medical Information and Knowledge, 202 Osongsengmyung 2nd street, Osong-eup, Heungdeok-gu, Cheongju 28159, Republic of Korea. E-mail: ophrp@korea.kr

- Infolumi
  #245, 10 Jangmi-ro 48beon-gil, Bundang-gu, Seongnam 13496, Republic of Korea
  Tel: +82-31-709-0918, E-mail: osong.editorialoffice@gmail.com

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Editorial

From technological innovation to better population health

Jong-Koo Lee

National Academy of Medicine of Korea, Seoul, Republic of Korea

On September 16, 2026, the 32nd Healthcare Forum on artificial intelligence (AI) was held in Seoul under the title "How Can AI-Based Essential Healthcare Work in Regional Settings?" The event was hosted by the National AI Strategy Committee and the Ministry of Health and Welfare and organized by the National Academy of Medicine of Korea and the Korea Health Industry Development Institute [1]. The forum examined how AI could help resolve persistent challenges in regional, essential, and public healthcare. Its agenda included primary and emergency care, patient management beyond hospital settings, healthcare infrastructure, professional responsibilities, reimbursement, and institutional arrangements. These discussions also raised a question that extends beyond medical AI: how can scientific and technological advances translate into tangible improvements in population health?

AI provides a timely example of the difficulty of translating innovation into better health. Its applications are expanding rapidly in medical imaging, clinical decision support, drug discovery, health communication, and disease surveillance. Substantial investment and technological progress have generated both optimism and uncertainty among patients and the public. The central question has become whether its use improves health outcomes, strengthens healthcare systems, and reduces inequalities.

Patients' relationship with technology is also changing. Health professionals have traditionally selected medical technologies, with patients largely relying on those decisions. Increasingly, however, individuals consult generative AI directly to interpret symptoms, obtain information about medications, and reconsider clinical advice. This shift presents two distinct governance challenges: ensuring the safety and effectiveness of AI used in professional healthcare services and protecting people who independently use AI-based health information outside regulated clinical settings. Addressing both challenges requires reliable information, appropriate safeguards, and clear accountability.

Even impressive technical performance should not be equated with clinical effectiveness or benefits to population health. Gains in diagnostic accuracy, workflow efficiency, or analytical capability do not necessarily reduce mortality, improve quality of life, or increase health equity. Recent discussions in The Lancet Public Health have stressed the need to evaluate AI in relation to the broader functions and responsibilities of public health systems [2]. This evaluation should encompass real-world effectiveness, cost-effectiveness, patient experience, and the distribution of benefits and risks across population groups.

Public policy should therefore begin with the health problem to be addressed rather than with

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Corresponding author:
Jong-Koo Lee
National Academy of Medicine of Korea, 51 Seochojungang-ro, Seocho-gu, Seoul 06654, Republic of Korea
E-mail: docmohw@snu.ac.kr

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the technology. AI may help address shortages of health professionals, improve continuity of care, and strengthen disease surveillance. Introducing sophisticated technologies may nevertheless yield limited benefits if adequate personnel, reliable data, appropriate financing, and effective service delivery systems are lacking. Adoption driven by technology could even reinforce existing inequalities if it disproportionately benefits populations with better digital access, health literacy, and healthcare resources.

International frameworks offer guidance on these questions. In 2021, the World Health Organization (WHO) established six principles for the ethical governance of AI, emphasizing human autonomy, well-being and safety, transparency, accountability, inclusiveness and equity, and sustainability [3]. WHO subsequently issued guidance on the specific risks of large multimodal models [4]. The FUTURE-AI framework proposed practical standards for trustworthy AI across development, validation, deployment, and monitoring [5]. Putting these principles into practice through independent evaluation, effective regulation, and public accountability remains a substantial challenge.

In the Republic of Korea, technological innovation should form part of broader health system reform rather than be pursued as an isolated objective. Decisions about public investment, health insurance reimbursement, and institutional incentives should reflect demonstrated improvements in clinical effectiveness, population health, equity, and efficiency. Health professionals need appropriate training, and patients and communities should have a meaningful role in decisions affecting their care. These priorities are particularly important in underserved regions, where technology alone cannot resolve weaknesses in healthcare delivery.

Medical AI raises a question that applies more broadly to public health research: how can scientific advances and increasingly sophisticated analytical methods improve population health? Genomic technologies, mathematical models, environmental monitoring, and population-based health data can help us understand health risks and disease patterns. Methodological sophistication, however, is not sufficient to establish scientific or public health value. Reliable evidence, appropriate study design, reproducibility, and meaningful interpretation remain essential. The growing use of AI in research also reinforces the responsibility of researchers and journals to ensure transparency, verification, and scientific accountability.

The articles in this issue of *Osong Public Health and Research Perspectives* show how scientific evidence can help address a range of public health challenges. The perspective on surrogacy regulation in Africa highlights ethical safeguards, human rights, and institutional accountability as priorities for reproductive healthcare. A study of indoor exposure to volatile organic compounds examines associations between environmental measurements and urinary biomarkers, demonstrating the value of combining environmental monitoring with population-based health information. Mathematical modeling of Wolbachia-based dengue control explores the potential of quantitative approaches to inform disease prevention strategies. A study comparing welfare facilities for people with disabilities by coronavirus disease 2019 outbreak status emphasizes the need to prevent infection among vulnerable populations. Using national health screening statistics from 2014 to 2023, a study of metabolic syndrome components identifies changes in cardiometabolic risk patterns across age and sex groups and provides evidence for targeted prevention. Finally, a report on a foodborne outbreak associated with a festival demonstrates the practical contribution of genomic epidemiology to outbreak investigation and food safety surveillance.

Despite differences in methods and scope, these articles share the objective of generating reliable evidence to inform effective public health action. Their significance should be judged by the validity of their findings, their relevance to population health needs, and their potential to improve health outcomes, rather than by methodological sophistication or data volume alone.

The challenge is therefore to do more than accelerate scientific and technological innovation: it is to establish the conditions in which innovation produces meaningful and equitable health benefits. Meeting this challenge requires linking research to public health priorities, strengthening institutional capacity, evaluating real-world outcomes, and maintaining public accountability.

Innovation should be judged by what it achieves for population health, not merely by what technology can do. Scientific progress becomes meaningful when trustworthy evidence is put into practice to achieve effective prevention, accessible healthcare, reduced inequalities, and better health for all.

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Perspective

A bioethics-informed public health imperative for surrogacy regulation in Africa

Kavuma Sharif

Institute of Public Health, Clarke International University, Kampala, Uganda

Introduction

Surrogacy governance across Africa is highly fragmented, ranging from court-supervised statutory systems to regulatory silence that permits informal and commercially opaque arrangements [1]. This variability has important implications for maternal health, clinic accountability, psychosocial well-being, and children's legal identities, particularly in sub-Saharan Africa, where maternal mortality remains disproportionately high [2]. In settings where assisted reproductive technology (ART) services are unevenly regulated and inconsistently accessible, surrogacy may expose women and children to preventable medical, legal, and documentation-related harms [3,4].

Current debates often frame surrogacy primarily as a private contractual or reproductive-rights issue, giving insufficient attention to its broader public health and bioethical dimensions. This Perspective argues that surrogacy regulation should be understood as a bioethics-informed public health obligation that requires safeguards against exploitation, unsafe clinical practice, and legal uncertainty. We propose a governance framework that distinguishes altruistic, compensated, and commercial surrogacy and links ethical principles to enforceable protections, including clinic licensing, independent counseling and legal advice, judicial or quasi-judicial review, compensation transparency, anti-exploitation measures, and parentage and birth registration protections.

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Corresponding author:
Kavuma Sharif
Institute of Public Health, Clarke International University, Kawagga Close, off Kalungi Road, Muyenga Block 244 | Plot 8244 Bukasa Kyadondo, Kampala, Uganda
E-mail: sharifbunhanifa@gmail.com

From Private Contract to Public Health Governance

ARTs have expanded globally, but the institutional protections needed to make surrogacy safe and ethically defensible have not developed evenly across African settings [3–11]. Treating surrogacy as a purely private agreement mischaracterizes its risk profile: pregnancy is not a neutral service transaction, and surrogacy in under-resourced health systems may intensify foreseeable maternal harms, especially where antenatal continuity, emergency referral capacity, and psychosocial support are inconsistent [2,6]. The ethical and policy question is therefore not whether surrogacy is "good" or "bad," but whether governance can prevent foreseeable harm while protecting reproductive choice, child welfare, and legal certainty for intended parents.

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Africa's fertility-care context strengthens the public health case for regulation. Infertility care in much of sub-Saharan Africa is often treated as a lower priority than other reproductive-health needs despite clear demand; ART services remain concentrated, with persistent shortages of skilled personnel and limited training opportunities [12,13]. Where access is uneven, markets tend to develop in private and informal spaces, and policy often reacts to scandals rather than shaping standards proactively. This reactive cycle is visible in the continent's emerging "repronubs" and "repropreneurs," where commercial actors may expand services before enforceable safeguards are in place [14]. A credible regulatory agenda must therefore be conceptually precise, empirically grounded, and institutionally realistic.

Existing discussions of surrogacy in Africa often frame the issue as a private moral controversy, a reproductive-rights debate, or a narrow legal problem. This paper advances a different claim: surrogacy should be understood as a bioethics-informed public health governance issue because regulatory failures can produce predictable maternal, psychosocial, legal, and child-welfare harms that extend beyond private contracting. By integrating ethical analysis with population-level risk assessment and governance mechanisms, this Perspective proposes a policy-usable framework that links normative principles directly to enforceable safeguards suited to diverse African regulatory contexts.

This article is a conceptual and policy-oriented Perspective rather than a comprehensive comparative legal analysis of surrogacy regulation across African jurisdictions. Its purpose is not to provide an exhaustive doctrinal examination of national legal systems, but to develop a bioethics-informed public health framework that can guide regulatory thinking across diverse and evolving African contexts. The paper therefore uses selected jurisdictional examples illustratively to identify recurring governance challenges related to maternal health, consent, exploitation, clinic oversight, and child welfare. Given the rapid evolution and uneven availability of surrogacy legislation and ART governance across the continent, the analysis focuses primarily on normative and regulatory principles rather than detailed statutory comparison. The framework proposed here is intended to support future legal, empirical, and policy development by linking ethical principles to practical governance safeguards that can be adapted to differing institutional capacities.

HIGHLIGHTS

- Africa's surrogacy landscape is legally fragmented and requires jurisdiction-sensitive governance.
- Surrogacy should be regulated as a bioethics-informed public health issue, not only as a private contractual arrangement.
- Ethical governance must distinguish formal consent from informed, voluntary, and relationally meaningful consent.
- Cross-border reproductive travel and price differentials create risks of regulatory arbitrage and exploitation.
- This paper proposes a policy-usable framework that links ethical principles to enforceable regulatory safeguards.

A Continental Regulatory Spectrum with Real Economic Incentives

Regulatory diversity is not merely a legal anomaly; it also creates an incentive framework that shapes pricing and risk allocation. South Africa has the most coherent statutory model in Africa: surrogacy agreements require High Court pre-approval, and commercial compensation is prohibited, although expense reimbursement is allowed. However, this model has structural limitations. The financial and logistical requirements of High Court pre-approval may disadvantage lower-income intended parents, while the genetic-link rule excludes prospective parents who cannot provide gametes.

The prohibition on compensation rests partly on moral grounds, but it may also push some arrangements into informal markets. In addition, the judicial intensity of the South African model raises questions about whether it can be replicated in countries with more limited administrative and court capacity. Other African jurisdictions illustrate different points along this regulatory spectrum: Ghana has contract-based arrangements with local, court-supported pre-birth parentage mechanisms in practice; Kenya presently operates without a dedicated statutory framework, leaving surrogacy arrangements reliant on general contract law; however, the Assisted Reproductive Technology Bill 2022, which mandates altruistic-only surrogacy and prohibits commercial arrangements, passed the National Assembly in November 2025 and is currently pending Senate concurrence before proceeding to presidential assent [15]. Nigeria has an ambiguous legal landscape and reported evidence of exploitative parentage mechanisms [16,17]; Uganda has a

history of informal practice, including documented surrogate compensation and high *in vitro* fertilization costs; and Rwanda has legislative momentum but incomplete legal enforceability.

Table 1 summarizes selected African surrogacy governance positions and indicative costs [1,16–19]. Prices vary by clinic, jurisdiction, legal process, and scope of services. The cost estimates were developed from publicly available sources, including Growing Families and KinPath Surrogacy.

Ethical Foundations: Beyond Principlism to Relationally Meaningful Consent

A convincing normative argument must avoid 2 errors: romanticizing autonomy as a single, context-free attribute and denying agency by assuming that any financial consideration is inherently coercive.

At least 4 dimensions of consent can be identified in a governance-ready ethical analysis. Formal consent is the legal fact of agreement; it is necessary, but it is not sufficient. Informed consent requires comprehension of medical risks, legal terms, financial terms, and post-birth arrangements. Relational autonomy asks whether the surrogate's choice is made under conditions that permit refusal and renegotiation. Voluntariness is compromised in contexts of asymmetry when undue influence or inducements overpower meaningful choice. This distinction matters because compensation alone does not invalidate consent. Ethical concern arises when financial arrangements are opaque, coercive, or unsupported by independent counseling and enforceable protections [5–9].

Payment models also need to be distinguished. In altruistic surrogacy, compensation is limited to expense reimbursement, which may reduce the risk of commodification but can also contribute to scarcity and movement into informal markets. Compensated surrogacy may be ethically defensible when compensation is transparent, proportionate, and regulated to reflect legitimate medical, temporal, and economic burdens without creating coercive financial inducements. This distinction is not merely academic: it helps avoid criminalizing legitimate surrogacy in weakly regulated settings while also preventing commercial exploitation from being normalized [16,20,21].

Why Surrogacy Is a Public Health Issue: Accountability, not Sentiment

Surrogacy becomes a public health issue when it generates preventable harms that cannot be managed solely through private law. Sub-Saharan Africa's maternal mortality ratio remains approximately 442 per 100,000 live births, far above the Sustainable Development Goal target of 70; these baseline vulnerabilities mean that any pregnancy-related intervention requiring heightened monitoring must be governed with particular care [2]. Unregulated surrogacy may intensify avoidable risks by fragmenting antenatal care, weakening referral pathways, and allowing clinics or intermediaries to prioritize commissioning interests over maternal well-being [6,7]. Systematic reviews of its outcomes among surrogates' report that hypertensive

Table 1. Selected African surrogacy governance positions and indicative costs

Jurisdiction	Governance position	Oversight mechanism	Payment model	Indicative costs/prices
South Africa	Statutory, court-supervised	High Court pre-approval	Altruistic (expenses only)	40,000–80,000 USD
Ghana	Hybrid practice	Local court parentage orders	Compensated packages	30,000–58,000 USD
Kenya	Contract-reliant	No formal mechanism	Commercially offered, unregulated; reported coercion, fraud, and exploitative practices [19]	33,000–40,000 USD
Nigeria	Legally unclear	No effective mechanism	Commercial arrangements and exploitative ecosystems [16,17]	Highly variable
Uganda	Informal, with draft policy activity	No formal mechanism	Documented compensation	*In vitro* fertilization: 4,000–6,000 USD; surrogate compensation: 2,000–4,000 USD

Even if these prices have been obtained from sources such as; Growing Families and KinPath Surrogacy [1,18]. In this article these prices have been considered as unverified promotional figures from commercial surrogacy agencies and they are subject to change over time and jurisdiction. There are also likely to be additional costs for legal fees, medical travel, medical complications, agent fees and additional embryo-transfer cycles. Figures are given in the US dollar currencies. The Ugandan shilling figures are converted at an estimated exchange rate of near 3,700 UGX to 1 USD based on market rates as of April 2025. The entire package costs have not been quoted and the figures given represent the component costs provided by the clinics and agencies for the separate IVF cycle and surrogate payment. As price information is obtained from commercial intermediaries operating in weak regulatory environments, the figures provide an indication of transparency between jurisdictions and clinics and the actual figures provided should be interpreted as such. Price differences across jurisdictions, clinics, and legal processes and between services provided are apparent. USD, United States dollar; UGX, Ugandan shilling; IVF, *in vitro* fertilization.

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disorders are present in 3.2-10% of pregnancies [8], but the evidence base is limited to regulated jurisdictions, and there is almost a complete lack of studies of cross-border or informal arrangements [8].

Furthermore, surrogate pregnancies performed outside the supervision of a clinical protocol—marked by sporadic surveillance and lax adherence to obligatory referrals could magnify these relative risks. In such settings, the exploitation risks documented in transnational gestational surrogacy become particularly acute, as asymmetric power relations and inadequate oversight may compromise both maternal health and informed decision-making [6]. The obligation to protect children from such preventable harms is established under the Convention on the Rights of the Child, which mandates safeguards to ensure every child's right to health, dignity, and protection from exploitation [7]. On the other hand, placing surrogacy within the parameters of a reliable maternal-health surveillance system, by reference to known perinatal benchmarks, is necessary to prevent these avoidable harms.

In addition to financial harm, psychosocial harm is governance-sensitive. Public health ethics further strengthens the argument by reaffirming obligations to reduce harm and promote equity: when predictable harms are disproportionately experienced by economically vulnerable surrogates, governance inaction is an ethically significant omission rather than neutral tolerance [22].

Access barriers to ART reinforce this point. Training and practice patterns in *in vitro* fertilization clinics in sub-Saharan Africa indicate uneven workforce quality and capacity, as well as inconsistent infrastructures of care. South Africa serves as a major training hub with a small number of specialist clinics, whereas much of the rest of sub-Saharan Africa has little or no specialization, and *in vitro* fertilization care is often deprioritized. In this context, surrogacy regulation is not oversight of a niche service; it is a patient-safety intervention that establishes minimum standards for clinic accreditation, psychosocial screening, and adverse-event accountability.

Transnational Markets, "Repronubs," and the Politics of Regulatory Arbitrage

Transnational surrogacy markets are not merely economic phenomena; they show how regulatory fragmentation generates cross-border public health and ethical vulnerabilities that individual states cannot manage through private contract law alone. Cross-border reproductive travel is not incidental, but a predictable consequence of regulatory and economic disparities between jurisdictions. The direction of reproductive travel within African surrogacy markets is heterogeneous. In some contexts, demand is driven by wealthy domestic intended parents operating within highly stratified national health systems; in others, lower regulatory barriers and comparatively lower costs attract international commissioning parents seeking regulatory flexibility or reduced transactional costs. The resulting vulnerabilities arise from both internal socioeconomic inequality and transnational regulatory arbitrage. Whittaker and colleagues use the terms "repronubs" and "repropreneurs" to describe nodes where transnational demand meets local entrepreneurship, with Ghana as a well-recognized case study, often before full statutory regulation is in place. Long-term follow-up studies indicate that children born through surrogacy arrangements develop well when parentage and disclosure are handled transparently [23].

Nigeria illustrates how governance failure can undermine legitimacy. "Baby factory" ecosystems, in which pregnancy and child transfer are entangled with exploitation, have eroded public trust and blurred distinctions between surrogacy and trafficking-like practices, making prosecution difficult and polarizing ethical debate [16,17,21–24]. The critical lesson is not that surrogacy is intrinsically abusive; rather, regulatory silence invites actors who profit from opacity, coercion, and weak enforcement. Similar dynamics have been described in discussions of trafficking risks and contract disputes in cross-border surrogacy when statutory frameworks are absent or fragmented [10,11,21].

Regional coordination may help reduce cross-border exploitation, documentation inconsistencies, and regulatory arbitrage. Regional organizations such as the African Union, together with international processes addressing parentage and surrogacy, can help fill these gaps by establishing minimum standards for parentage recognition, documentation, and citizenship, in line with the Convention on the Rights of the Child [7] and the Convention on the Elimination of All Forms of Discrimination against Women. Such cooperation can narrow regulatory gaps by harmonizing minimum standards for documentation, parentage recognition, and anti-exploitation enforcement.

Child Welfare and Intended Parents: A Complete Regulatory Frame

A surrogate-only lens is ethically inadequate. Birth registration processes and pathways for establishing parentage must therefore be clear and predictable, particularly where cross-border travel is common. Standardized birth registration and reliable post-birth documentation are needed so that children

do not bear the most enduring consequences of regulatory uncertainty and so that parenthood is not contested because documentation is delayed or inconclusive.

Intended parents also have valid interests that should be regulated without displacing the welfare of the surrogate or child. Legal uncertainty can create prolonged uncertainty and liability for commissioning parents, while unlicensed clinics may involve less ethical intermediation, unclear price transparency, and inconsistent medical practice. A strong regulatory system weights these interests appropriately through reforms such as independent legal advice, judicial or quasi-judicial review, and clinic accreditation procedures, ensuring that these requirements are enforced rather than merely aspirational [6–14,16,20,21,24].

In this regard, the analysis focuses mainly on heterosexual intended parents to reflect the extent of the same-sex prohibitions in the laws of most African states. South Africa is an exception as the Children's Act 38 of 2005, explicitly provides for commissioning parents of the same sex and same-sex marriage has been allowed since 2006. Also, the discussion of regulations does not ignore the possibility of exclusion as a result of parentage and access rights. Emerging regulatory frameworks should nonetheless be examined to determine whether their parentage and eligibility provisions create discriminatory exclusions, even within current legal constraints.

A Policy-Usable Framework: Ethics Mapped to Safeguards

A conceptual diagram must do more than label overlapping domains; it must show how normative principles become governance instruments. Figure 1 therefore maps ethical principles to the specific safeguards that operationalize them: consent procedures and independent counseling for relational autonomy; clinical licensing and maternal safeguards for non-maleficence; anti-exploitation enforcement and compensation transparency for justice; limits on profit-driven intermediation and dehumanizing terms for dignity; and parentage and birth registration protections for child welfare. These distinctions are not merely conceptual; they determine the safeguards required in a workable governance framework.

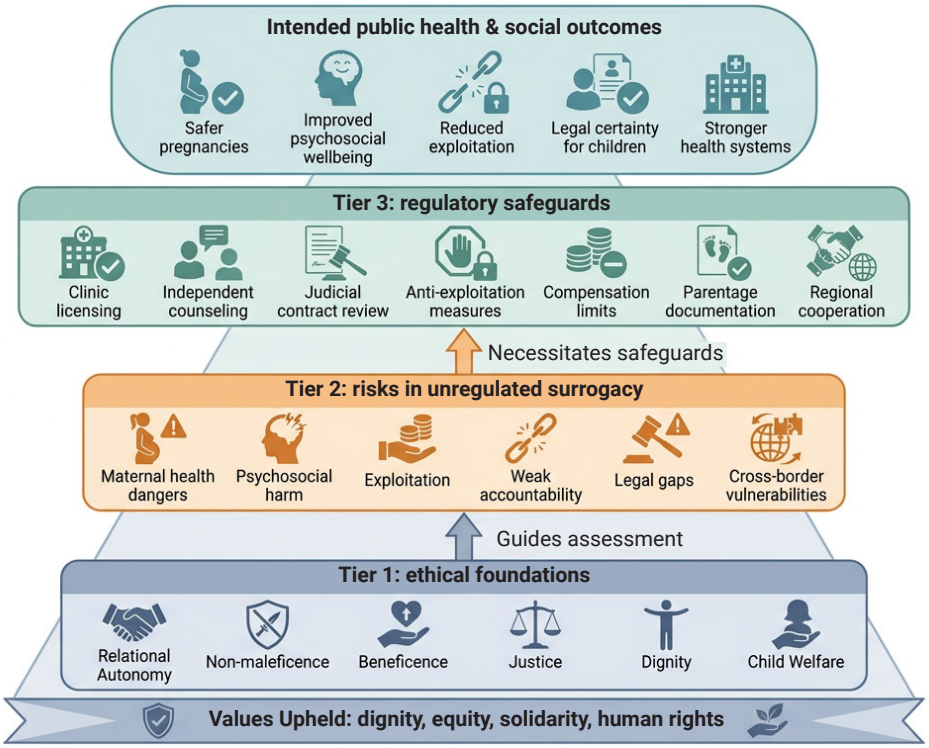


Figure 1. Principle-to-protection architecture for surrogacy regulation in Africa. This conceptual model shows how a bioethics-informed public health lens reframes surrogacy as a governance obligation rather than a private contractual transaction. Tier 1 articulates the ethical foundations for regulation; Tier 2 identifies structural maternal, psychosocial, legal, and cross-border risks produced by regulatory fragmentation; and Tier 3 outlines proportionate safeguards that operationalize ethical commitments as enforceable regulatory instruments. The framework provides a scalable, context-sensitive roadmap for strengthening surrogacy governance, improving maternal and child protections, and reducing exploitation across diverse African jurisdictions.

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Conclusion

Africa's surrogacy landscape illustrates how ethical principles, public health obligations, and reproductive governance converge in contexts marked by legal fragmentation. Strengthening regulatory safeguards is not only a regional imperative, but also part of a global shift toward cross-border child-protection norms, as reflected in Hague discussions on parentage and regulatory reforms in India, Nepal, and Cambodia. The framework proposed here may help African policymakers avoid harms observed in unregulated markets while tailoring protections to local institutional capacities. By grounding surrogacy governance in autonomy, justice, and child welfare, African states can build systems that are ethically coherent and globally aligned. This Perspective underscores the need for coherent, rights-based legislation before demand expands further into informal markets. Rather than treating ethics, maternal health, and legal governance as separate domains, this framework integrates them into a single regulatory architecture that translates bioethical principles into practical public health safeguards adaptable to diverse African institutional settings.

Recommendations

Legislate a 3-tier surrogacy model that distinguishes altruistic, compensated, and commercial arrangements, with proportionate safeguards and clear prohibitions on exploitative intermediation. Compensated arrangements should be limited to transparent, regulated reimbursement and proportionate compensation for time, medical burden, lost income, and pregnancy-related effects, while prohibiting open-market bidding, profit-driven brokerage, and uncapped financial inducements characteristic of commercial surrogacy markets.

Require independent counseling and legal advice as minimum safeguards for informed and relationally meaningful consent, supported by plain-language materials and appropriate cooling-off periods.

License and accredit ART clinics that provide surrogacy services, including mandatory standards for screening, antenatal monitoring, referral pathways, psychosocial follow-up, and adverse-event reporting.

Implement judicial or quasi-judicial review of surrogacy agreements, calibrated to institutional capacity, to secure legal clarity on parentage before embryo transfer.

Codify compensation transparency and payment caps to ensure that compensation reflects legitimate burdens without functioning as a coercive inducement, including disclosure of intermediary fees and contractual terms.

Strengthen anti-exploitation enforcement targeting coercive recruitment, trafficking-like practices, and unregulated intermediary networks operating within informal surrogacy markets.

Protect children's legal identity through clear rules on parentage determination, standardized birth registration procedures, and reliable post-birth documentation, including cross-border protections against statelessness.

Advance regional coordination through African Union model guidelines and cross-border agreements that establish minimum standards for clinic oversight, documentation, parentage recognition, and anti-exploitation enforcement.

Principle-to-Protection Architecture for Surrogacy Regulation in Africa

Integrated Bioethics-Public Health Regulatory Framework for Surrogacy Governance in Africa. The diagram in Figure 1 synthesizes 3 analytical tiers: (1) normative ethical foundations guiding surrogacy governance; (2) population-level public health risks generated by regulatory gaps; and (3) actionable safeguards that translate ethical commitments into enforceable protections. By linking principles to mechanisms such as independent counseling, clinic accreditation, judicial review, anti-exploitation enforcement, compensation transparency, and documentation protections, the framework provides a policy-usable architecture for African surrogacy regulation grounded in autonomy, equity, harm reduction, and child welfare.

Notes

Ethics Approval
Not applicable.

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

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None.

Availability of Data
Not applicable.

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Original Article

Urinary metabolites of volatile organic compounds as biomarkers of indoor exposure: evidence of sex differences in a cross-sectional study using the Korea National Health and Nutrition Examination Survey

Saerom Kim[1], Yusra Mirghani[1], Heejoon Kim[1], Seung-Ah Choe[2,3]

[1]Department of Public Health, Korea University, Seoul, Republic of Korea
[2]Department of Preventive Medicine, Korea University College of Medicine, Seoul, Republic of Korea
[3]Research and Management Center for Health Risk of Particulate Matter, Korea University, Seoul, Republic of Korea

ABSTRACT

Objectives: This study examined associations between indoor total volatile organic compound (TVOC) concentrations and urinary volatile organic compound (VOC) metabolites in Korean adults, focusing on potential sex-specific differences. We hypothesized that higher indoor TVOC exposure would be associated with higher urinary VOC metabolite concentrations and that these associations would differ by sex.

Methods: We conducted a cross-sectional analysis of the 2020–2021 Korea National Health and Nutrition Examination Survey, which included the Republic of Korea's first population-based indoor air quality survey. The analysis included 1,859 adults aged ≥19 years who participated in the indoor air quality survey from July 2020 to August 2021. Indoor TVOC concentrations (μg/m³) were measured using standardized protocols. Nine urinary VOC metabolites were quantified, creatinine-adjusted, and log-transformed. Multivariable linear regression with sex-stratified, exploratory subgroup (non-employed adults), and sensitivity analyses was performed.

Results: Indoor TVOC concentrations were positively associated with urinary 2-methylhippuric acid (2-MHA; β = 0.041; 95% confidence interval [CI], 0.029–0.052) and 3- and 4-methylhippuric acid (3,4-MHA; β = 0.040; 95% CI, 0.027–0.052) in both sexes (*p* for interaction = 0.990 and 0.728), and these associations were robust to sensitivity analyses. Among non-employed adults, estimates were larger in males (2-MHA, β = 0.110 vs. 0.024; 3,4-MHA, β = 0.130 vs. 0.031; *p* for interaction = 0.016 and 0.008), but this interaction was inconsistent across sensitivity analyses.

Conclusion: Urinary 2-MHA and 3,4-MHA may serve as biomarkers of indoor VOC exposure in both sexes; a possible sex difference among non-employed adults was inconsistent across sensitivity analyses and requires confirmation.

Keywords: Biomarkers; Environmental exposure; Indoor air quality; Sex; Volatile organic compounds

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Corresponding author:
Seung-Ah Choe
Department of Preventive Medicine, Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Republic of Korea
E-mail: seungah@korea.ac.kr

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Introduction

Background/Rationale

Volatile organic compounds (VOCs) are common indoor pollutants emitted from household products, building materials, electronic devices, and personal activities such as cooking, smoking, and solvent use [1–12]. Indoor VOC concentrations are typically 2–5 times higher than outdoor concentrations, largely because of limited ventilation, seasonal variation, and indoor activities [6,7,9–11,13]. Because people spend much of their time indoors, indoor VOC exposure is frequent and may pose public health risks [1,10,14–16]. This issue has received additional attention since the coronavirus disease 2019 (COVID-19) pandemic, when working from home, virtual meetings, and other lifestyle changes increased time spent indoors. In addition, more frequent extreme weather events may prolong indoor stays, further supporting the need for effective indoor air quality (IAQ) management [17]. International organizations, including the World Health Organization (WHO), have recognized the risks of indoor air pollution and emphasized the need for continuous monitoring and regulation of indoor air pollutants, particularly because children and adult females may be more susceptible to household air pollution [12,18].

VOCs with carcinogenic or toxic properties have received attention because of their potential health risks. These compounds are associated with a range of adverse outcomes, including eye and throat irritation, headache, respiratory and neurological disorders, endocrine disruption, and certain cancers [3,5,6,18–23]. After entering the body primarily through inhalation, ingestion, or dermal contact, VOCs are metabolized through multiple biological pathways and subsequently excreted in urine as specific metabolites [1,2,21,22,24]. These urinary VOC metabolites are commonly used as biomarkers of recent internal exposure because they may reflect both environmental concentrations and individual physiological characteristics [1–3,5,21].

Although previous studies have suggested sex-based differences in VOC exposure and metabolism, few studies have examined sex-specific differences in the association between VOC exposure and urinary biomarkers [13,18,21,25–27]. The Korea National Health and Nutrition Examination Survey (KNHANES) recently incorporated IAQ measurements, including total volatile organic compound (TVOC) concentrations, enabling population-level analyses of these associations [14,26].

In this study, TVOC was conceptualized not as a surrogate for individual parent compounds but as an integrated proxy for mixed indoor chemical exposure. This approach allowed us to assess whether between-household variability in indoor VOC mixtures was reflected in corresponding patterns of internal exposure biomarkers at the population level.

HIGHLIGHTS

- Using data from 1,859 adults in the Republic of Korea's first population-based indoor air quality survey, this study examined associations between indoor total volatile organic compound concentrations and urinary volatile organic compound metabolites.
- Indoor total volatile organic compound concentrations were positively associated with urinary 2-methylhippuric acid and 3,4-methylhippuric acid concentrations, supporting the use of these urinary metabolites as noninvasive biomarkers of indoor exposure.
- In exploratory analyses among non-employed adults, associations were stronger in males.
- Possible sex differences in these exposure–biomarker associations warrant confirmation in future studies.

Objectives

This study examined the association between indoor TVOC concentrations and urinary VOC metabolites using data from the 2020–2021 KNHANES, which included the Republic of Korea's first population-based IAQ survey. Specifically, we hypothesized that indoor TVOC exposure would be positively associated with urinary VOC metabolite concentrations and that these associations may differ by sex. The broader aim was to inform public health strategies for managing IAQ and identifying vulnerable populations based on sex-specific exposure and metabolic patterns.

Materials and Methods

Study Sample

This cross-sectional study used data from the Household IAQ and Environmental Hazardous Substances Biomarker Survey, a subsidiary survey of KNHANES conducted from July 2020 to August 2021 as part of KNHANES VIII. To assess indoor environmental exposure, a stratified subsample of approximately 1,200 households was selected using a 2-stage sampling method based on season, region, and housing type. Households that consented to IAQ monitoring were included, and the subsample was constructed through secondary extraction procedures from the primary KNHANES sample. During home visits, trained field staff measured TVOC concentrations in accordance

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with the Official Test Method for Indoor Air Quality issued by the Ministry of Environment (MOE), Republic of Korea [25]. TVOC was selected for further analysis because of its relevance to indoor chemical exposure and the availability of corresponding urinary biomarkers. For biomonitoring, only adult household members aged ≥19 years from households that participated in the IAQ survey were eligible. Of the 1,980 participants initially enrolled for biomonitoring, those with urinary creatinine concentrations outside the physiological range (<0.3 or >3.0, n=107) and those with missing urine samples (n=14) were excluded, leaving a final analytical sample of 1,859 individuals [26,27].

Indoor VOC Measurement

TVOC concentrations in residential environments were quantified according to the MOE standard protocol [25]. In-home sampling was conducted by trained personnel using solid-phase adsorption tubes within the survey window. Air samples were collected at breathing-zone height, 1.2–1.5 m above the floor, in the central area of the primary living space, defined as the living room. Samples were collected during 2 consecutive 30-minute sessions under guideline-specified normal residential operating conditions, without experimental manipulation of temperature, humidity, ventilation, or appliance use. This approach supported consistency across households and provided a standardized estimate of indoor VOC exposure. The collected samples were analyzed by thermal desorption followed by gas chromatography to quantify TVOC concentrations (μg/m³).

Urinary VOC Metabolite Measurement

Urinary VOC metabolites were analyzed according to the KNHANES biomonitoring protocol of the Korea Disease Control and Prevention Agency (KDCA) [26], using the LC-MS/MS method specified in the protocol [28]. The target indoor VOCs were benzene, toluene, ethylbenzene, xylene, and styrene. Nine metabolites were selected based on toxicological relevance and international comparability [14]: S-phenylmercapturic acid (SPMA), a metabolite of benzene; N-acetyl-S-(benzyl)-L-cysteine (BMA), a metabolite of toluene; phenylglyoxylic acid (PGA) and mandelic acid (MA), metabolites of ethylbenzene and styrene; 2-methylhippuric acid (2-MHA) and 3- and 4-methylhippuric acid (3,4-MHA), metabolites of xylene isomers; N-acetyl-S-(3-hydroxypropyl)-L-cysteine (3-HPMA), a metabolite of acrolein; N-acetyl-S-(n-propyl)-L-cysteine (BPMA), a metabolite of 1-bromopropane; and N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine (DHBMA), a metabolite of 1,3-butadiene. These abbreviations and parent-compound links were used consistently throughout the analyses. Although urinary VOC metabolites are generally more stable than parent VOCs measured in blood, they primarily reflect recent exposure because their biological half-lives are relatively short, typically ranging from several hours to approximately 1–2 days [20].

Quantification was performed using liquid chromatography–tandem mass spectrometry with an API 5500 triple quadrupole mass spectrometer (AB Sciex) coupled to a Nexera XR LC-20AD system (Shimadzu). Chromatographic separation was performed on a C18 column (2.0 μm, 2.1×150 mm), with a mobile phase consisting of 0.01% acetic acid in water and acetonitrile at a flow rate of 0.4 mL/min. Electrospray ionization enabled sensitive detection, and calibration curves (R^2 ≥0.995) were updated every 200 samples to maintain analytical robustness [29].

To account for urine dilution, metabolite concentrations were normalized to urinary creatinine (μg/g creatinine). Samples with creatinine concentrations outside the physiological range of 0.3–3.0 g/L, as defined in the WHO guideline Biological Monitoring of Chemical Exposure in the Workplace: Guidelines (1996), were excluded [27]. Values below the limit of detection (LOD) were flagged as <LOD (Table S1). For statistical analyses, these values were imputed as LOD/√2, consistent with standard practice for left-censored data [26,28]. These exclusion and imputation procedures were applied to maintain data integrity and comparability across population subgroups [26].

Covariates

Potential covariates were identified using a directed acyclic graph (Figure S1). On the basis of previous studies examining relationships between urinary VOC metabolites and metabolic outcomes, the following covariates were selected for adjustment [14,29,30]. In the conceptual causal pathway, biological factors, including sex, age, central obesity, hypertension, diabetes, and dyslipidemia; behavioral factors, including current smoking status, secondhand smoke exposure, alcohol consumption, and walking; and socioeconomic factors, including income, education, and household composition, were considered common causes of indoor TVOC exposure and urinary VOC metabolite concentrations.

Sex was categorized as male or female, and age was treated as a continuous variable. Central obesity was adjusted for using waist circumference rather than body mass index because waist circumference more directly reflects visceral adiposity, which may influence the uptake, partitioning, and clearance of lipophilic pollutants [31–33]. Central obesity was defined as a waist circumference ≥85 cm in females and ≥90 cm in males. Chronic disease status was determined

from self-reported physician diagnosis and clinical criteria. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medication. Dyslipidemia was defined as fasting total cholesterol ≥240 mg/dL after at least 12 hours of fasting, use of cholesterol-lowering medication, and/or fasting triglycerides ≥200 mg/dL. Diabetes was defined as fasting blood glucose ≥126 mg/dL, use of antidiabetic medication or insulin injections, physician diagnosis, or glycated hemoglobin ≥6.5%.

Current smoking was defined as having smoked at least 100 cigarettes during one's lifetime and currently smoking. Secondhand smoke exposure was defined as indoor exposure to tobacco smoke at home within the past 7 days. Alcohol consumption was defined as drinking alcohol at least once per month during the past year. Walking was defined as walking for at least 30 minutes per day on at least 5 days per week [26].

Monthly household income was categorized into quartiles, and educational attainment was categorized as middle school or below versus high school or above. Whereas prior studies classified marital status as married, unmarried, or other, this study operationalized household structure as a binary indicator of multiperson versus single-person households to reflect the increasing prevalence of 1-person households and growing family diversity.

Statistical Analysis

All analyses were unweighted and did not incorporate the KNHANES strata or primary sampling units, because inclusion depended on household consent to monitoring and specimen provision. Descriptive statistics were calculated for all participants and were stratified by sex. Creatinine-adjusted urinary VOC metabolite concentrations were log-transformed for analysis. Associations between indoor TVOC concentrations and urinary VOC metabolites were evaluated using general linear models adjusted for sex, age, central obesity, hypertension, diabetes, dyslipidemia, smoking status, secondhand smoke exposure, alcohol consumption, walking, household income, educational attainment, and household composition. Indoor TVOC concentrations were modeled as a continuous variable scaled by interquartile range (IQR). Sex-specific effect modification was assessed by including a sex-by-TVOC interaction term in the multivariable models (Type III test), and sex-stratified models were subsequently fitted; no adjustment was made for multiple comparisons. To explore potential nonlinear exposure–response relationships, generalized additive models with penalized spline functions were fitted separately by sex. Exposure–response curves were restricted to the common support by symmetric within-stratum trimming at the 1st and 99th percentiles, with no extrapolation beyond the observed data.

To evaluate whether occupational TVOC exposure might have contributed to exposure misclassification, a subgroup analysis was conducted among non-employed participants. Non-employed participants were those classified in the KNHANES occupation variable as having no current employment (including homemakers and students). Three sensitivity analyses were conducted *post hoc*: (1) use of household cluster-robust standard errors, because participants in the same household shared a single indoor TVOC measurement; (2) exclusion of participants whose urine was collected 1 month or more after indoor air sampling; and (3) exclusion of participants with indoor TVOC concentrations above the 99th percentile (1,777.5 μg/m³). All statistical analyses were performed using SAS ver. 9.4 (SAS Institute Inc.) and R software ver. 4.5.0 (R Foundation for Statistical Computing).

Ethics Statement

This study analyzed deidentified, publicly available data from the KNHANES, which had received annual approval from the Institutional Review Board of the KDCA (e.g., 2020–2021, approval numbers 2018-01-03-2C-A and 2018-01-03-5C-A). Written informed consent was obtained from all participants by the KDCA at the time of the KNHANES survey. As this study involved secondary analysis of publicly available, deidentified data, it was exempt from additional Institutional Review Board approval.

Results

Descriptive Data

Among the 1,859 participants, the proportion of females was slightly higher than that of males (54.6% vs. 45.4%) (Table 1). Indoor TVOC concentrations did not differ significantly by sex (median [IQR], 107.5 [39.5–235.0] μg/m³ in males vs. 105.2 [39.0–246.8] μg/m³ in females). Male participants had higher educational attainment than female participants (high school or above, 74.4% vs. 62.8%), were more likely to live in households with 2 or more members (87.6% vs. 84.2%), and had higher rates of current smoking (29.0% vs. 3.4%), monthly alcohol consumption (65.8% vs. 37.6%), central obesity (45.3% vs. 32.8%, $p<0.001$), and hypertension (30.7% vs. 23.4%). Female participants had higher rates of secondhand smoke exposure (3.8% vs. 1.7%) and reported significantly longer indoor stay durations than males (18.8 hours vs. 15.0 hours). Urinary VOC metabolite distributions were similar between males and females.

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Table 1. Sociodemographic and health characteristics of participants by sex (*n* = 1,859)

Characteristic	Overall	Male (*n* = 844, 45.4%)	Female (*n* = 1,015, 54.6%)	*p*[a]
Age (y)				0.782
19–39	431 (23.2)	190 (22.5)	241 (23.7)	
40–64	819 (44.1)	378 (44.8)	441 (43.4)	
≥65	609 (32.8)	276 (32.7)	333 (32.8)	
Monthly household income quartile				0.401
Q4 (highest)	463 (25.0)	213 (25.3)	250 (24.8)	
Q3	460 (24.8)	222 (26.4)	238 (23.6)	
Q2	466 (25.2)	209 (24.8)	257 (25.4)	
Q1 (lowest)	463 (25.0)	198 (23.5)	265 (26.2)	
High school education or above	1,265 (68.0)	628 (74.4)	637 (62.8)	<0.001
≥2-Person household	1,594 (85.7)	739 (87.6)	855 (84.2)	0.041
Central obesity[b]	713 (38.5)	382 (45.3)	331 (32.8)	<0.001
Hypertension	497 (26.7)	259 (30.7)	238 (23.4)	<0.001
Dyslipidemia	427 (23.0)	177 (21.0)	250 (24.6)	0.062
Diabetes	204 (11.0)	104 (12.3)	100 (9.9)	0.090
Current smoking[c]	278 (15.0)	244 (29.0)	34 (3.4)	<0.001
Secondhand smoke exposure[d]	53 (2.9)	14 (1.7)	39 (3.8)	0.005
Current drinker[e]	934 (50.4)	553 (65.8)	381 (37.6)	<0.001
Indoor stay time (h)	17.0 (13.0–21.0)	15.0 (12.0–20.0)	18.8 (14.0–22.0)	<0.001
Indoor TVOC (μg/m³)	106.6 (39.2–239.2)	107.5 (39.5–235.0)	105.2 (39.0–246.8)	0.911

Categorical variables are presented as unweighted *n* (%), with percentages calculated using non-missing values for each variable. Continuous variables are described with medians with 1st and 3rd quartiles.
TVOC, total volatile organic compound.
[a]The Pearson chi-square test, the Fisher exact test, and Wilcoxon rank sum test were employed according to the distribution. [b]Central obesity (abdominal obesity) was defined as a waist circumference ≥90 cm in men and ≥85 cm in women according to the 2020 Clinical Practice Guidelines for the Management of Obesity in Korea by the Korean Society for the Study of Obesity. [c]Current smoking: Defined as individuals who have smoked at least 100 cigarettes in their lifetime and currently smoke every day or some days. [d]Self-reported exposure to tobacco smoke from other people indoors at home during the past 7 days. [e]Current drinker: Defined as individuals who consumed alcohol at least once a month during the past year.

Most metabolite pairs showed weak to moderate positive correlations (ρ = 0.01–0.50). The strongest correlation was observed between 2-MHA and 3,4-MHA (ρ = 0.83), followed by the correlation between 3-HPMA and DHBMA (ρ = 0.50) (Figure 1). These coefficients were based on log-transformed, creatinine-adjusted concentrations using pairwise complete observations.

Outcome Data

This cross-sectional study evaluated indoor TVOC concentrations as the exposure and urinary VOC metabolite concentrations as the outcomes.

Main Results

Indoor TVOC concentrations were positively associated with urinary 2-MHA and 3,4-MHA concentrations in both males (β = 0.040 and 0.037, respectively) and females (β = 0.040 and 0.041, respectively), with *p* for interaction of 0.990 and 0.728, respectively (Figure 2).

In exploratory analyses, indoor TVOC concentrations were also positively associated with PGA in males (β = 0.022; 95% confidence interval [CI], 0.007–0.037), whereas this association was not evident in females (β = 0.017; 95% CI, −0.003 to 0.037). Other metabolites showed weak and statistically nonsignificant associations in both sexes (Figure 2).

In generalized additive models, the association between indoor TVOC exposure and urinary VOC metabolites did not deviate significantly from linearity. For both 2-MHA and 3,4-MHA, the exposure–response relationships were approximately linear and similar between males and females, with overlapping CIs (Figure 3).

When analyses were restricted to non-employed participants (243 males and 460–461 females), stronger associations were observed in males than in females for 2-MHA (β = 0.110; 95% CI, 0.049–0.170 vs. β = 0.024; 95% CI, 0.001–0.048; *p* for interaction = 0.016) and 3,4-MHA (β = 0.130; 95% CI, 0.067–0.193 vs. β = 0.031; 95% CI, 0.006–0.057; *p* for interaction = 0.008). However, the positive association between indoor TVOC concentrations and urinary PGA was not evident in non-employed males (Figure S2). In sensitivity analyses

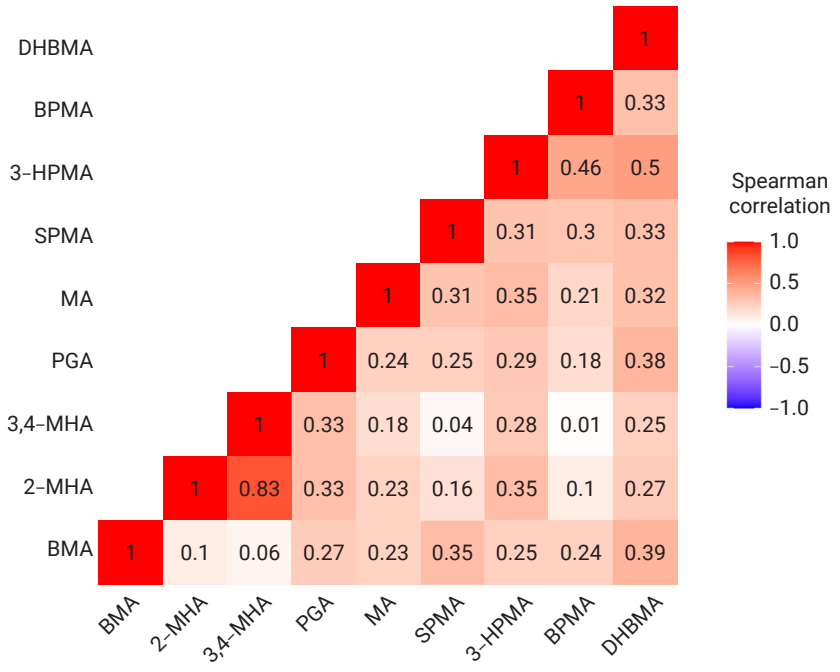


Figure 1. Pairwise correlation between the urinary volatile organic compound (VOC) metabolites.
BMA, N-acetyl-S-(benzyl)-L-cysteine; 2-MHA, 2-methylhippuric acid; 3,4-MHA, 3- and 4-methylhippuric acid; PGA, phenylglyoxylic acid; MA, mandelic acid; SPMA, S-phenylmercapturic acid; 3-HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; BPMA, N-acetyl-S-(n-propyl)-L-cysteine; DHBMA, N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine.

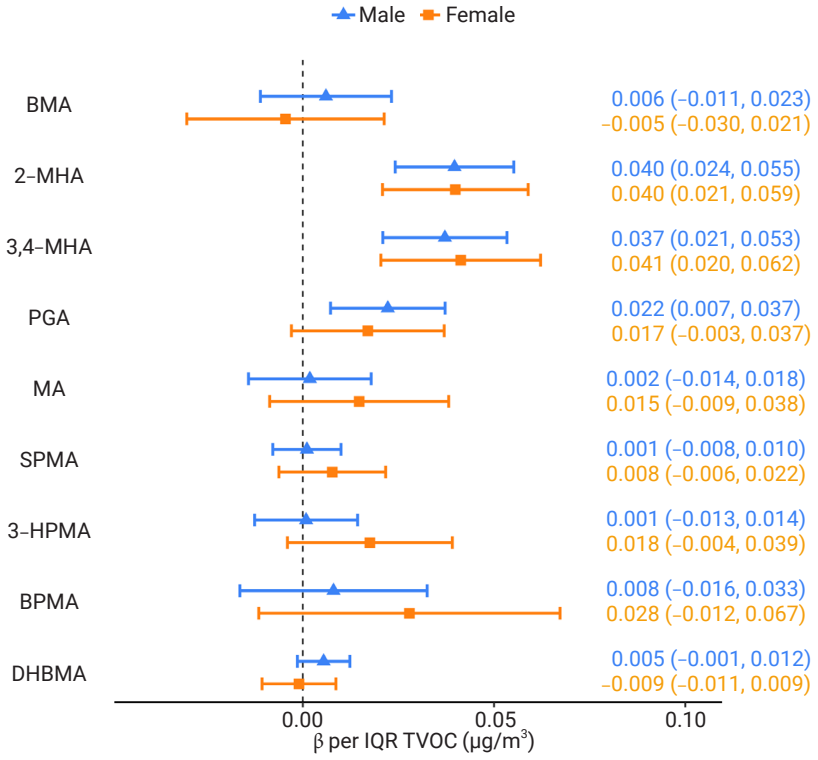


Figure 2. Linear coefficients for the association between indoor total volatile organic compound and urinary volatile organic compound metabolites, stratified by sex.
BMA, N-acetyl-S-(benzyl)-L-cysteine; 2-MHA, 2-methylhippuric acid; 3,4-MHA, 3- and 4-methylhippuric acid; PGA, phenylglyoxylic acid; MA, mandelic acid; SPMA, S-phenylmercapturic acid; 3-HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; BPMA, N-acetyl-S-(n-propyl)-L-cysteine; DHBMA, N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine.

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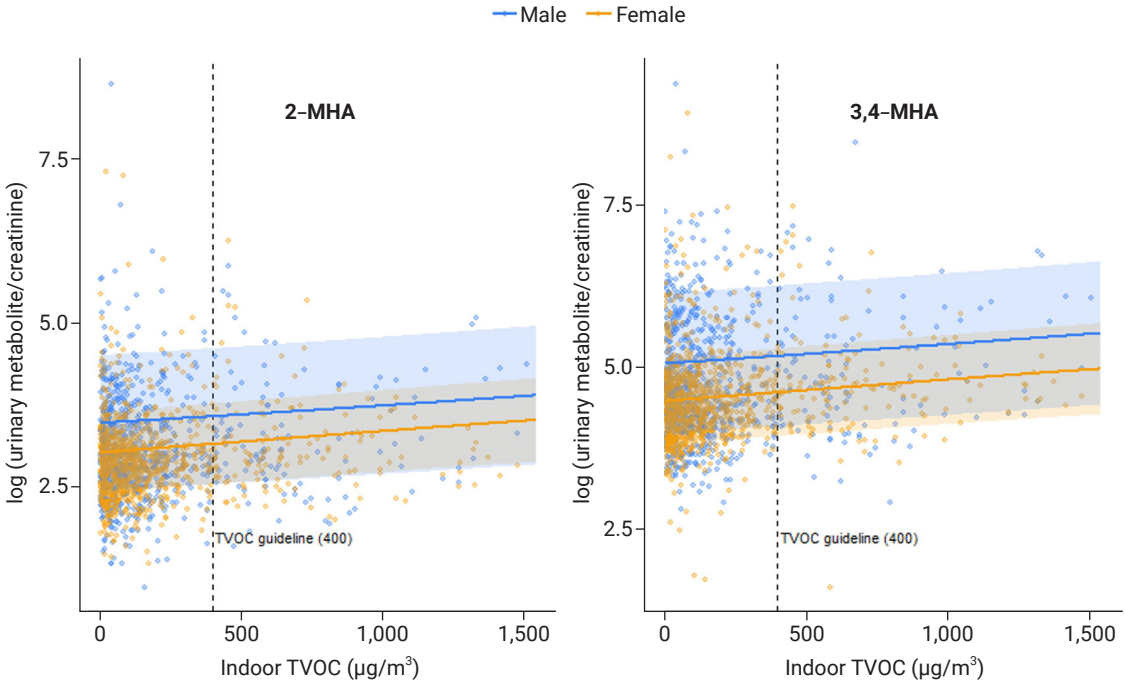


Figure 3. Generalized additive models for the association of indoor total volatile organic compound (TVOC) with urinary 2-MHA and 3,4-MHA. TVOC guideline: The vertical dashed line represents the Korean recommended indoor air quality standard for TVOC (400 μg/m³) for selected facilities, including medical institutions and childcare facilities, as specified in Article 4 and Annex 3 of the Enforcement Rule of the Indoor Air Quality Control Act.

BMA, N-acetyl-S-(benzyl)-L-cysteine; 2-MHA, 2-methylhippuric acid; 3,4-MHA, 3- and 4-methylhippuric acid; PGA, phenylglyoxylic acid; MA, mandelic acid; SPMA, S-phenylmercapturic acid; 3-HPMA, N-acetyl-S-(3-hydroxypropyl)-L-cysteine; BPMA, N-acetyl-S-(n-propyl)-L-cysteine; DHBMA, N-acetyl-S-(3,4-dihydroxybutyl)-L-cysteine.

using household cluster-robust standard errors or excluding participants with an air–urine interval of 1 month or more or with TVOC concentrations above the 99th percentile, the full-sample associations were robust, whereas the subgroup interaction was not consistent (Table S2).

Discussion

Key Results

In this KNHANES-based sample of Korean adults, indoor TVOC exposure was positively associated with the urinary xylene metabolites 2-MHA and 3,4-MHA in both males and females, with no evident overall sex-dependent difference. In non-employed participants, point estimates were larger in males, but this exploratory subgroup finding was not consistent across sensitivity analyses. These findings support the use of 2-MHA and 3,4-MHA as sensitive biomarkers of indoor VOC exposure in both sexes.

Interpretation

These findings should be interpreted within a mixture-exposure framework, in which TVOC represents an integrated proxy for combined indoor chemical exposure rather than a surrogate for individual parent compounds. Therefore, the observed associations should be understood as reflecting between-household variability in indoor VOC mixtures at the population level, as captured by corresponding urinary VOC metabolite patterns, rather than direct one-to-one metabolic relationships.

Although some epidemiological studies have not identified sex-dependent differences in VOC-related outcomes [9,13,20,23], an exploratory analysis restricted to non-employed participants in this study suggested possible sex-dependent differences in the association between indoor TVOC concentrations and urinary biomarkers. If confirmed, such differences could be related to VOC metabolism influenced by metabolic rate, hormonal regulation, or household role [9,12,34,35], or to behavioral factors, including time spent in specific rooms, ventilation practices, consumer product use, and gendered household roles such as cooking or cleaning. Contrary to expectations based on gendered patterns of household activity, point estimates were larger in males than in females. This unexpected direction may reflect differential selection by employment status (more retirees and students among non-employed males and more homemakers among non-

employed females), residual confounding by unmeasured occupational exposure, or the exploratory nature of this subgroup analysis, which was not consistent across sensitivity analyses (Table S2); because households with very high indoor TVOC concentrations may have been under-represented, whether sex differences exist at high exposure levels cannot be determined from these data. Although the models were adjusted for socioeconomic factors, education and income may lie on the causal pathway from sex to exposure, potentially attenuating potential sex-specific effects [35,36]. Future studies incorporating direct measures of time–activity patterns, household tasks, and personal product use are needed to distinguish behavioral mechanisms from biological mechanisms.

Generalizability

These findings support targeted strategies to reduce indoor VOC exposure, including improved ventilation and source control for high-emission household products [4,24]. The use of a KNHANES-based sample strengthens the generalizability of the findings, and the exploratory analysis of non-employed participants helped reduce potential confounding from occupational exposure. Public health policies should consider vulnerable populations when developing IAQ standards [20,36]. In addition, IAQ management should be integrated with outdoor pollution-control efforts to address the broader spectrum of VOC exposure [7,9,13]. As indoor environments are important determinants of health, these results support public health approaches that account for possible sex differences.

Limitations

This observational study has several limitations. The cross-sectional design limits causal inference [23]. Exposure assessment based on urinary metabolites has limitations, including the possibility that a single metabolite may arise from exposure to multiple parent compounds or from direct uptake from environmental media rather than endogenous metabolic production [3,4,37]. Spot urine samples provide only a short-term snapshot of exposure and may not fully reflect chronic exposure patterns [20,26]. Because most urinary VOC metabolites reflect short-term exposure, any time gap between indoor air sampling and urine collection may have attenuated the observed associations, particularly among participants with intermittent or highly variable exposure patterns. For 76 participants, urine was collected 1 month or more after indoor air sampling because of COVID-19–related disruptions [26]; excluding them did not materially change the results (Table S2). Future studies should consider repeated measurements and time-aligned sampling to improve the temporal resolution of exposure and outcome assessment.

Conclusion

These findings support the use of 2-MHA and 3,4-MHA as sensitive biomarkers of indoor VOC exposure in both males and females. The larger point estimates observed among non-employed males suggest a possible sex difference, but this subgroup finding was not consistent across sensitivity analyses and warrants confirmation in future studies. Drawing on the first indoor air quality survey conducted within KNHANES, these results, obtained among participants who consented to in-home monitoring, support the use of urinary biomarkers in indoor air quality surveillance.

Supplementary Material

Figure S1. Directed acyclic graph of the hypothesized relationships among indoor total volatile organic compound exposure, sex, covariates, and urinary volatile organic compound metabolites; **Figure S2.** Sex-stratified associations between indoor total volatile organic compound concentrations and urinary volatile organic compound metabolites among non-employed participants; **Table S1.** Metabolite-specific limits of detection for urinary volatile organic compound metabolites measured in the Korea National Health and Nutrition Examination Survey; **Table S2.** Sensitivity analyses of the associations between indoor total volatile organic compound concentrations and urinary 2-MHA and 3,4-MHA. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0419.

Notes

Ethics Approval

This study analyzed deidentified, publicly available data from the KNHANES, which had received annual approval from the Institutional Review Board of the KDCA, including approval numbers 2018-01-03-2C-A and 2018-01-03-5C-A for 2020–2021. The KDCA obtained written informed consent from all participants at the time of the KNHANES survey. Because this study involved secondary analysis of publicly available, deidentified data, it was exempt from additional Institutional Review Board approval.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

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Korea. The funding sources had no role in the design, conduct, or reporting of this study.

Availability of Data

The datasets generated and/or analyzed during the current study are available in the KDCA repository: https://knhanes.kdca.go.kr/knhanes/main.do

Authors' Contributions

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

Additional Contributions

This study analyzed publicly available KNHANES data collected by the KDCA.

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Original Article

Optimal control strategies for dengue transmission under varying adult prevalence of *Wolbachia*-carrying mosquitoes: a deterministic mathematical modeling study

Fadilaturrohmah Nur, Yongkuk Kim

Department of Mathematics, Kyungpook National University, Daegu, Republic of Korea

ABSTRACT

Objectives: This study aimed to develop prevalence-informed post-release dengue control strategies for settings in which *Wolbachia*-carrying *Aedes aegypti* mosquitoes have become established through population replacement and to quantify how optimal supplementary intervention intensity and duration vary with adult *Wolbachia* prevalence, p_W.

Methods: A deterministic human–mosquito model was formulated that included *Wolbachia*-free and *Wolbachia*-carrying mosquitoes and incorporated cytoplasmic incompatibility, maternal transmission, and reduced vector competence. Two bounded supplementary controls were optimized over a 3-year horizon: reduction of effective human–mosquito contact and conventional adult mosquito suppression, represented by increased adult mortality. A quadratic-cost optimal-control problem was solved numerically using the Pontryagin maximum principle and a forward/backward discrete-adjoint algorithm with bounded line search. Outcomes were compared across representative p_W scenarios and prevalence scans.

Results: The optimal policies applied high-intensity supplementary control early in the planning horizon and then relaxed control as infection pressure declined. Under the baseline control bounds and cost weights, higher p_W reduced the uncontrolled infection burden, decreased the incremental benefit of additional intervention, and shortened the duration of maximum control. In coarse scans with $u_{max} = 0.30$, the terminal dengue infection near-elimination indicator, defined as $I_H(T) \leq 10^{-4}$ at $T = 3$ years, changed between $p_W = 0.55$ and $p_W = 0.60$ for 7 of 12 tested cost-weight combinations; the other 5 did not reach the criterion on the tested grid. The transition was conditional on the assumed parameters, initial conditions, planning horizon, admissible control bounds, cost weights, and terminal criterion. A separate refined continuation example demonstrated non-monotonic mean control use and a sharp decrease in cumulative incidence.

Conclusion: Adult *Wolbachia* prevalence measured through entomological surveillance may represent an actionable index for post-release dengue management. The identified transition band is a model-based planning indicator, not a universal field threshold or evidence of mosquito population elimination.

Keywords: Dengue; Models, theoretical; *Wolbachia*

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Corresponding author:
Yongkuk Kim
Department of Mathematics, Kyungpook National University, 80 Daehak-ro, Buk-gu, Daegu 41566, Republic of Korea
E-mail: yongkuk@knu.ac.kr

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Introduction

Background

Dengue remains a major mosquito-borne public health threat in many endemic settings, with transmission driven primarily by female *Aedes aegypti* mosquitoes [1–3]. Conventional prevention strategies rely on integrated vector management, including environmental management, chemical control, and community-based measures [4].

However, sustained suppression of *Aedes aegypti* populations is difficult in practice, and dengue outbreaks may continue even when substantial vector control resources are deployed.

Wolbachia-based biocontrol has emerged as a complementary strategy for dengue prevention. In this study, the *Wolbachia* component is interpreted as a population replacement strategy rather than a population suppression approach. In this approach, *Wolbachia*-carrying *Aedes aegypti* mosquitoes are introduced so that *Wolbachia* becomes established in the local mosquito population [5–9]. Cytoplasmic incompatibility and maternal transmission support *Wolbachia* spread and persistence, whereas reduced vector competence decreases the ability of mosquitoes to transmit dengue virus [8–13].

Recent empirical studies have strengthened the evidence base for *Wolbachia*-based population replacement. A cluster-randomized trial in Yogyakarta, Indonesia, demonstrated substantial reductions in dengue incidence and dengue-related hospitalizations after deployment of wMel-infected mosquitoes [14]. Large-scale operational studies have reported similar public health benefits in real-world settings. In Niterói, Brazil, phased deployments of adult wMel-infected *Aedes aegypti* mosquitoes were associated with a substantial reduction in dengue incidence despite heterogeneous *Wolbachia* introgression across release zones [15]. In the Aburra Valley, Colombia, citywide wMel releases in Bello, Medellín, and Itagüí were associated with large reductions in notified dengue incidence after *Wolbachia* establishment [16]. Together, these studies support the relevance of adult *Wolbachia* prevalence as an operational entomological indicator for dengue control planning.

A substantial body of mathematical work has examined dengue transmission under vaccination, seasonality, vector control, and optimal intervention strategies [17–22]. Several *Wolbachia*-based mathematical models have focused on release, invasion, establishment, and persistence dynamics [10–13,23]. However, after *Wolbachia* has become established in the field, public health programs face a different operational question: how should supplementary dengue control measures be adjusted according to observed adult *Wolbachia* prevalence, p_w? This question is important because *Wolbachia* prevalence can vary across space and time, and additional interventions may be necessary when resources are limited.

HIGHLIGHTS

- Adult *Wolbachia* prevalence can inform post-release dengue control planning.
- *Wolbachia* was modeled as a population replacement strategy rather than as mosquito suppression.
- Supplementary adult mosquito suppression was represented as increased adult mortality.
- Under baseline control bounds and cost weights, higher *Wolbachia* prevalence shortened high-intensity supplementary control.
- The transition band was conditional on the assumed parameters, planning horizon, admissible control bounds, cost weights, and terminal criterion.

Objectives

This study develops prevalence-informed optimal control strategies for dengue after *Wolbachia* establishment. Adult *Wolbachia* prevalence, p_w, is used as a surveillance-based index for post-release decision-making. Two time-varying supplementary interventions are considered: (1) reduction of effective human–mosquito contact and (2) conventional adult mosquito suppression through a control-induced increase in adult mosquito mortality. The second intervention represents measures such as targeted adulticiding and is modeled separately from the *Wolbachia* population replacement mechanism.

Using a mating-structured Wolbachia–dengue model adapted from published work [23], this study solves a bounded optimal-control problem and quantifies how optimal intervention intensity, duration, and expected health gains vary across adult Wolbachia prevalence levels and representative post-release scenarios. The objective is not to propose a new optimal-control theorem but to provide a prevalence-informed planning framework that links an observable entomological metric to post-release dengue control allocation and budgeting.

Relative to the release-impact assessment in reference [23], the added analysis optimizes two bounded supplementary controls after release and compares their intensity, duration, and infection outcomes across initial adult *Wolbachia* prevalence levels.

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Materials and Methods

Study Design and Setting

This deterministic mathematical modeling study was designed to support decision-making for dengue control after *Wolbachia* establishment. No human participants, animals, or patient-level data were used.

Model Structure and Mathematical Modeling Process

The model was adapted from a published *Wolbachia*–dengue framework and reformulated for a post-release setting in which *Wolbachia*-carrying mosquitoes were already present and no explicit release program was modeled [23]. The human population was divided into susceptible, infected, and recovered classes, denoted by S_H, I_H, and R_H, respectively, with $N_H = S_H + I_H + R_H$. Mosquitoes were divided into *Wolbachia*-free and *Wolbachia*-carrying types. For each type, the model included an aquatic-stage compartment and susceptible and infected adult female compartments.

$$p_W(t) = \frac{F_W(t)}{F_U(t) + F_W(t)}, \; F_U(t) = S_U(t) + I_U(t),$$
$$F_W(t) = S_W(t) + I_W(t)$$

Mosquito recruitment incorporated mating structure, cytoplasmic incompatibility, and imperfect maternal transmission [10–13]. Human–mosquito transmission was represented using direction-specific biting and transmission parameters [8,9,24–26]. The *Wolbachia* component represented population replacement rather than population suppression. Adult mosquito suppression was modeled separately through the control $u_2(t)$, which increased adult mosquito mortality (Figure 1).

Controlled Dynamical System

The controlled model is given below. Here, $F_U = S_U + I_U$, $F_W = S_W + I_W$, and $N_H = S_H + I_H + R_H$ is constant.

$$\frac{dS_H}{dt} = \mu_H N_H - (1-u_1(t))\left(\frac{b_U \alpha_{UH} I_U}{N_H} + \frac{b_W \alpha_{WH} I_W}{N_H}\right) S_H - \mu_H S_H$$

$$\frac{dI_H}{dt} = (1-u_1(t))\left(\frac{b_U \alpha_{UH} I_U}{N_H} + \frac{b_W \alpha_{WH} I_W}{N_H}\right) S_H - (\sigma_H + \mu_H) I_H$$

$$\frac{dR_H}{dt} = \sigma_H I_H - \mu_H R_H$$

$$\frac{dA_U}{dt} = G_U(F_U, F_W)\left(1 - \frac{A_U + A_W}{K}\right) - (\tau_U + \mu_{UA}) A_U$$

$$\frac{dS_U}{dt} = \frac{\tau_U}{2} A_U - (1-u_1(t)) \frac{b_U \alpha_{HU} I_H}{N_H} S_U - (1 + \xi u_2(t)) \mu_U S_U$$

$$\frac{dI_U}{dt} = (1-u_1(t)) \frac{b_U \alpha_{HU} I_H}{N_H} S_U - (1 + \xi u_2(t)) \mu_U I_U$$

$$\frac{dA_W}{dt} = G_W(F_U, F_W)\left(1 - \frac{A_U + A_W}{K}\right) - (\tau_W + \mu_{WA}) A_W$$

$$\frac{dS_W}{dt} = \frac{\tau_W}{2} A_W - (1-u_1(t)) \frac{b_W \alpha_{HW} I_H}{N_H} S_W - (1 + \xi u_2(t)) \mu_W S_W$$

$$\frac{dI_W}{dt} = (1-u_1(t)) \frac{b_W \alpha_{HW} I_H}{N_H} S_W - (1 + \xi u_2(t)) \mu_W I_W$$

$$G_U(F_U, F_W) = \frac{\rho_U F_U^2 + \rho_W (1-\phi) F_W F_U + \rho_W (1-\gamma) F_W^2}{F_U + F_W}$$

$$G_W(F_U, F_W) = \frac{\rho_W \phi F_W F_U + \rho_W \gamma F_W^2}{F_U + F_W}$$

Interventions and Controls

Two time-dependent supplementary controls were introduced. Control $u_1(t)$ represents reductions in effective human–mosquito contact, including personal protection, community-based exposure reduction, and other measures

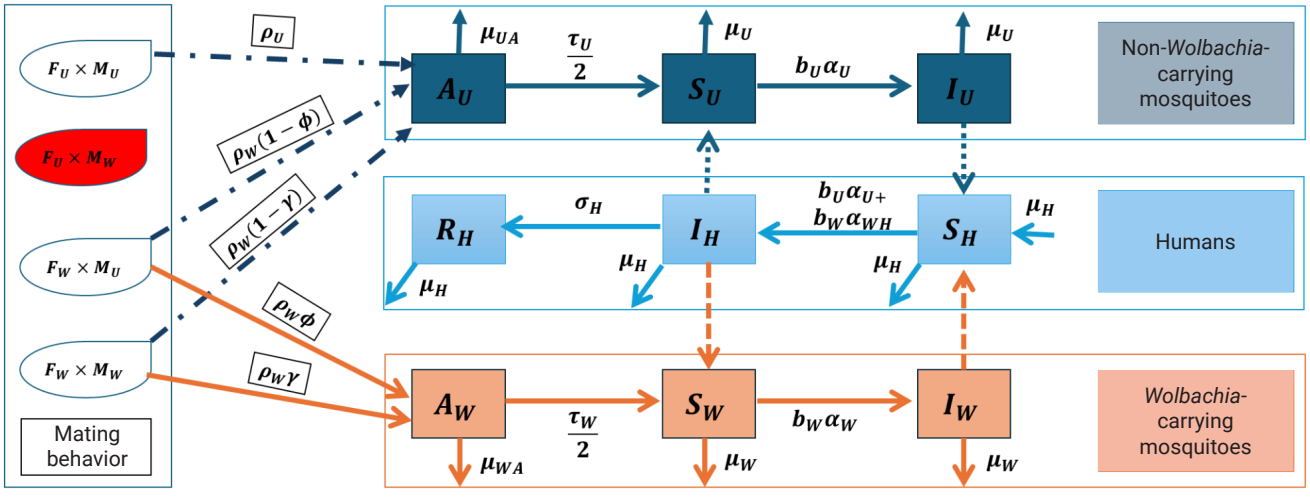


Figure 1. Interaction between human and mosquito populations in dengue transmission.

that reduce effective biting. Control $u_2(t)$ represents conventional adult mosquito suppression, such as targeted adulticiding and other interventions that increase adult mosquito mortality rates. In the controlled system, this intervention was incorporated by multiplying the baseline adult mosquito mortality rates by $(1+\xi u_2(t))$. Thus, $u_2(t)$ acts on the mortality terms for both *Wolbachia*-free and *Wolbachia*-carrying adult mosquitoes and is distinct from the *Wolbachia* population replacement mechanism.

Controls were bounded by operational limits. Unless otherwise stated, the bounds were $0 \le u_1(t) \le u_{1,max} = 0.75$ and $0 \le u_2(t) \le u_{2,max} = 0.75$. In the coarse prevalence scans used to summarize near-elimination transitions, a tighter common bound, $u_{max} = 0.30$, was also considered.

Objective Functional and Computation

A weighted objective was minimized that consisted of the time-integrated infected-human burden and quadratic intervention costs:

$$J(u_1, u_2) = \int_0^T \left[AI_H(t) + \frac{c_1}{2} u_1(t)^2 + \frac{c_2}{2} u_2(t)^2 \right] dt.$$

Cumulative incidence was computed separately as an epidemiological outcome to compare controlled and uncontrolled scenarios. Necessary optimality conditions were derived using the Pontryagin maximum principle, yielding projection expressions for $u_1(t)$ and $u_2(t)$. The discretized problem was solved in Python using fourth-order Runge–Kutta forward integration, backward discrete-adjoint sweeps, and a bounded line search. Final states were recomputed using the returned controls and checked for population balance, cumulative-incidence consistency, and numerical stationarity. Details of the derivation, adjoint system, and switching functions are provided in Supplementary Material 1. Disease-free equilibria and the basic reproduction number are provided in Supplementary Material 2.

Initial Conditions, Parameter Sources, and Scenario Design

The planning horizon was $T = 3 \times 365$ days. The baseline human initial conditions were $S_H(0) = 9{,}999$, $I_H(0) = 1$, and $R_H(0) = 0$, with $N_H = 10{,}000$. Assumed non-equilibrium post-release totals of 30,000 aquatic and 84,225 adult female mosquitoes were partitioned according to the prescribed initial adult Wolbachia prevalence, $p_W(0)$. Scans varied $p_W(0)$; subsequent $p_W(t)$ evolved under the model. Unless otherwise stated, a small initial number of infected mosquitoes was introduced for each adult mosquito type, with $I_U(0) = I_W(0) = 10$.

The representative scenarios $p_W(0) = 0.20$, 0.40, and 0.45 were chosen to represent low, intermediate, and higher initial *Wolbachia* prevalence levels. The baseline admissible bounds were $0 \le u_1(t) \le 0.75$ and $0 \le u_2(t) \le 0.75$, representing high but imperfect operational efficacy. In the coarse prevalence scans, a tighter common bound, $u_{max} = 0.30$, was also used to examine whether a near-elimination transition could occur under more restrictive intervention feasibility. The baseline objective weights were $A = 100$ and $c_1 = c_2 = 0.001$. The mortality-scaling parameter xi (ξ) was set to 1 in the baseline simulations.

Parameter values were taken from published dengue and *Wolbachia* modeling studies whenever available. Parameters for which directly comparable field estimates were unavailable were treated as baseline illustrative values and are identified as assumed values in Table 1 [8,9,12,24–29]. These assumed values were not intended as site-specific estimates; rather, they defined a reference setting for comparing prevalence-indexed control scenarios. Aquatic density limitation, human recovery, mosquito demographic quantities, and carrying-capacity assumptions are supported by studies of *Aedes* container ecology and dengue modeling [26–29].

Outcome Measures

The primary reported epidemiological outcome was

Table 1. Parameter descriptions and values

Parameter	Description	Value	Source
b_U	Biting rate (*Wolbachia*-free mosquitoes)	0.35	[24]
b_W	Biting rate (*Wolbachia*-carrying mosquitoes)	0.95 b_U	[25]
τ_U	Maturation rate (U)	1/10	[26]
τ_W	Maturation rate (W)	1/10	[26]
α_{UH}	Per-bite transmission (U to human)	0.15	Assumed
α_{HU}	Per-bite transmission (human to U)	0.15	Assumed
α_{WH}	Per-bite transmission (W to human)	0.084	[8]
α_{HW}	Per-bite transmission (human to W)	0.15	Assumed
μ_U	Adult death rate (U)	0.034	[26]
μ_W	Adult death rate (W)	1.1 μU	[9]
N_H	Total human population	10,000	Assumed
μ_{UA}	Aquatic death rate (U)	0.02	[12]
μ_{WA}	Aquatic death rate (W)	0.02	[12]
μ_H	Human birth/death rate	3.9×10^{-5}	Assumed
σ_H	Human recovery rate	1/14	[28]
ρ_W	Oviposition rate parameter (W)	11	[9]
ρ_U	Oviposition rate parameter (U)	13	[9]
K	Aquatic carrying capacity	3 N_H	[29]
γ	W-offspring proportion (W×W)	0.95	[9]
φ	W-offspring proportion (W×U)	0.95	[9]
ξ	Mortality-control scaling factor	1	Assumed

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cumulative incidence over the planning horizon, defined as

$$\text{CumInf} = \int_0^T (1 - u_1(t)) \left[\frac{b_U \alpha_{UH} I_U(t)}{N_H} + \frac{b_W \alpha_{WH} I_W(t)}{N_H} \right] S_H(t)\, dt$$

This quantity integrates the incidence rate in persons/day and represents the cumulative number of new human infections (persons) over [0,T], excluding $I_H(0)$. For concision, this quantity is denoted as CumInf in the tables and figures. CumInf(OFF) denotes the uncontrolled baseline, and CumInf(ON) denotes the optimal-control case.

By contrast, the time-integrated infected-human burden, $\int_0^T I_H\left(t\right) dt$ was reported separately in the broad prevalence scan (Figure 2). Writing $B(T) = \int_0^T I_H\left(t\right) dt$, this burden has units person-days, and $\text{CumInf} = I_H(T) - I_H(0) + (\sigma_H + \mu_H) B(T)$.

A terminal dengue infection near-elimination indicator was also evaluated. In this study, near elimination was defined operationally as the infected-human state variable satisfying $I_H(T) \leq 10^{-4}$ at T = 3 years. Because the model is deterministic, $I_H(t)$ is treated as a continuous state variable; therefore, this criterion should be interpreted as the infected-human compartment being numerically close to zero at the terminal time. It refers to the near elimination of dengue infection in the human population, not the elimination of the *Aedes aegypti* mosquito population.

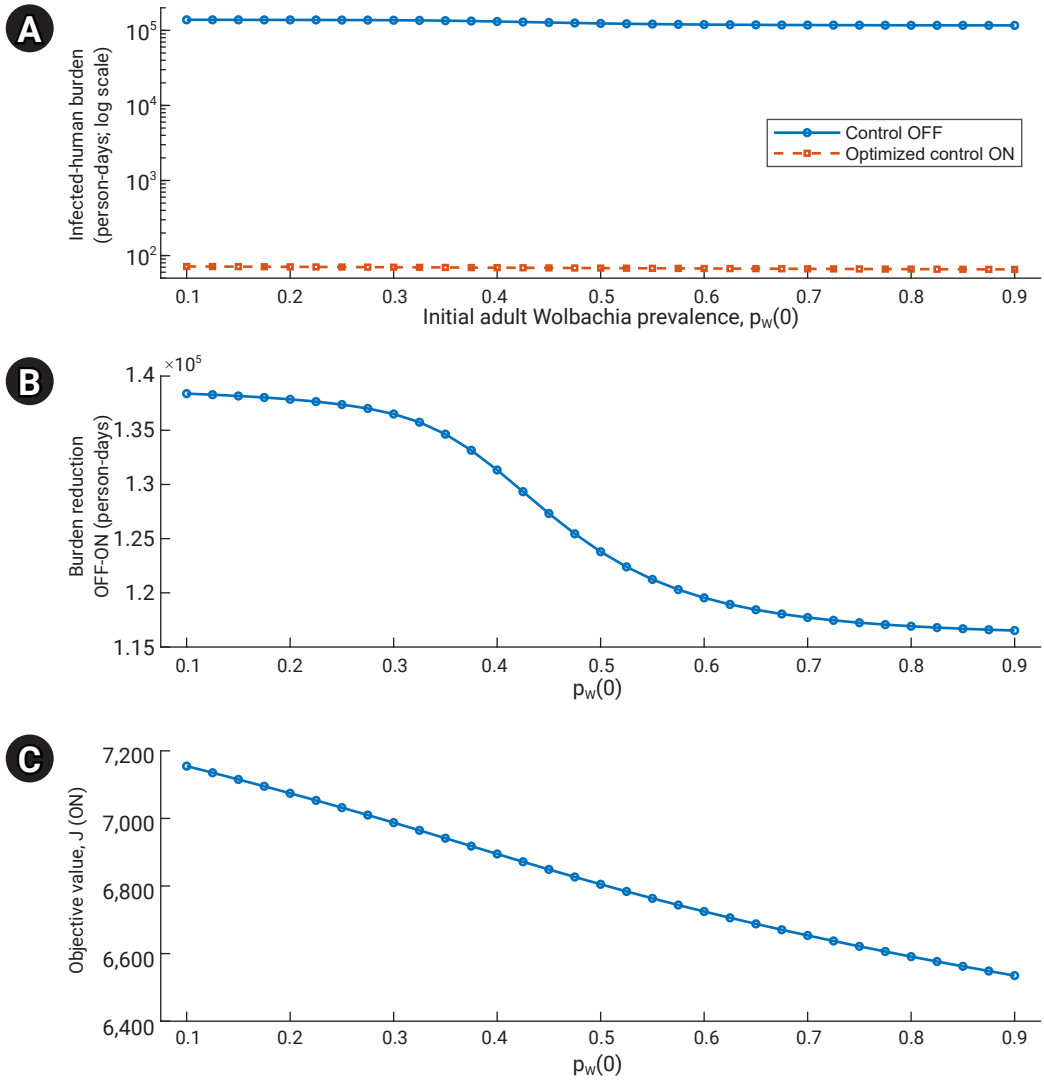


Figure 2. Prevalence scan over the initial adult Wolbachia proportion, $p_W(0)$. (A) Comparison of the uncontrolled baseline (Control OFF) and optimal intervention (Control ON) in terms of the time-integrated infected-human burden, $\int_0^T I_H(t)dt$, in person-days (logarithmic scale). (B) Reduction in this burden (OFF−ON), in person-days. (C) Total objective cost under control ON. The grid is $p_W(0) = 0.10, 0.125, \ldots, 0.90$, with A = 100, $c_1 = c_2 = 0.001$, and $u_{1,max} = u_{2,max} = 0.75$.

Clinical Trials

Not applicable. This study did not involve clinical trials, laboratory animals, or pathogens requiring institutional biosafety review.

Sex and Gender

Not applicable. The study did not include human participants, animals, or cell lines.

IRB/IACUC Approval

Not applicable. Institutional review board approval and informed consent were not required for this modeling study.

Results

Across representative post-release scenarios, the optimal supplementary controls generally began at or near their admissible maximum values and were then relaxed as infection pressure declined. This early-intensive pattern was observed for both contact reduction, $u_1(t)$, and conventional adult mosquito suppression, $u_2(t)$. The 3 representative adult *Wolbachia* prevalence scenarios are listed in Table 2, and quantitative summaries of scenario-specific outcomes and optimal-control use are provided in Table 3.

Scenario-specific comparisons showed that increasing adult *Wolbachia* prevalence lowered the uncontrolled cumulative incidence and reduced the incremental benefit of additional supplementary intervention. Under the baseline admissible bounds, $u_{1,max} = u_{2,max} = 0.75$, the total duration at maximum control decreased as p_W increased. In practical terms, when *Wolbachia* was already established at a higher adult prevalence, the model did not require maximum-intensity supplementary control to be maintained for as long. For example, as p_W increased from 0.20 to 0.45, the time at maximum contact reduction decreased from approximately 379 to 308 days. The time at maximum adult mosquito suppression decreased from approximately 286 to 252 days. This pattern reflects the lower effective transmission potential of mosquito populations with higher *Wolbachia* prevalence and the resulting diminishing marginal benefit of prolonged maximum-intensity intervention (Figure 3).

Additional heatmap summaries of the duration at the upper bound under parameter scans are provided in Figures S1–S3.

The scenario summaries also showed that optimal control substantially reduced cumulative incidence compared with the uncontrolled baseline. However, the magnitude of the incremental reduction decreased as p_W increased. This pattern indicates that higher established *Wolbachia* prevalence already provides a lower-transmission baseline, such that additional supplementary control yields smaller marginal gains. This result supports the use of p_W as a prevalence-indexed planning variable for determining whether sustained maximum-intensity intervention is warranted.

In the broad prevalence scan over p_W, the uncontrolled time-integrated infected-human burden declined as adult *Wolbachia* prevalence increased. Optimal control further reduced the burden across the scanned range, but the reduction achieved by optimal control relative to no additional intervention decreased with increasing p_W. The optimal objective value also decreased with increasing p_W.

These findings indicate that the operational value of supplementary intervention is greatest at lower or intermediate *Wolbachia* prevalence and becomes smaller once *Wolbachia* is more strongly established (Figure 2).

Empirical threshold intervals from the coarse prevalence scan are reported in Table 4. Under the tighter common

Table 2. Adult mosquito prevalence scenarios after *Wolbachia* release

Scenario	*Wolbachia*-free adult mosquitoes (%)	*Wolbachia*-carrying adult mosquitoes (%)
1	80	20
2	60	40
3	55	45

Table 3. Scenario-specific quantitative comparison of optimal strategies

Scenario	p_W	Time at max u_1 (d)	Time at max u_2 (d)	CumInf(OFF)	CumInf(ON)	OFF–ON	J*
1	0.20	379	286	9,856	4.0557	9,852	7,074.4
2	0.40	312	256	9,390	3.9274	9,386	6,894.8
3	0.45	308	252	9,103	3.8947	9,099	6,849.0

$T(u_i = u_{i,max})$ denotes the total time, in days, for which the control was at its upper bound, evaluated using $u_i(t) \geq u_{i,max} - 10^{-4}$ and rounded to the nearest day. CumInf is cumulative new human infections (persons), excluding IH(0); OFF and ON denote uncontrolled and numerically optimized cases, and OFF–ON is their difference. J* denotes the best verified numerical objective, not a global optimality certificate. $A = 100$, $c_1 = c_2 = 0.001$, $u_{1,max} = u_{2,max} = 0.75$, and $T = 1,095$ days.

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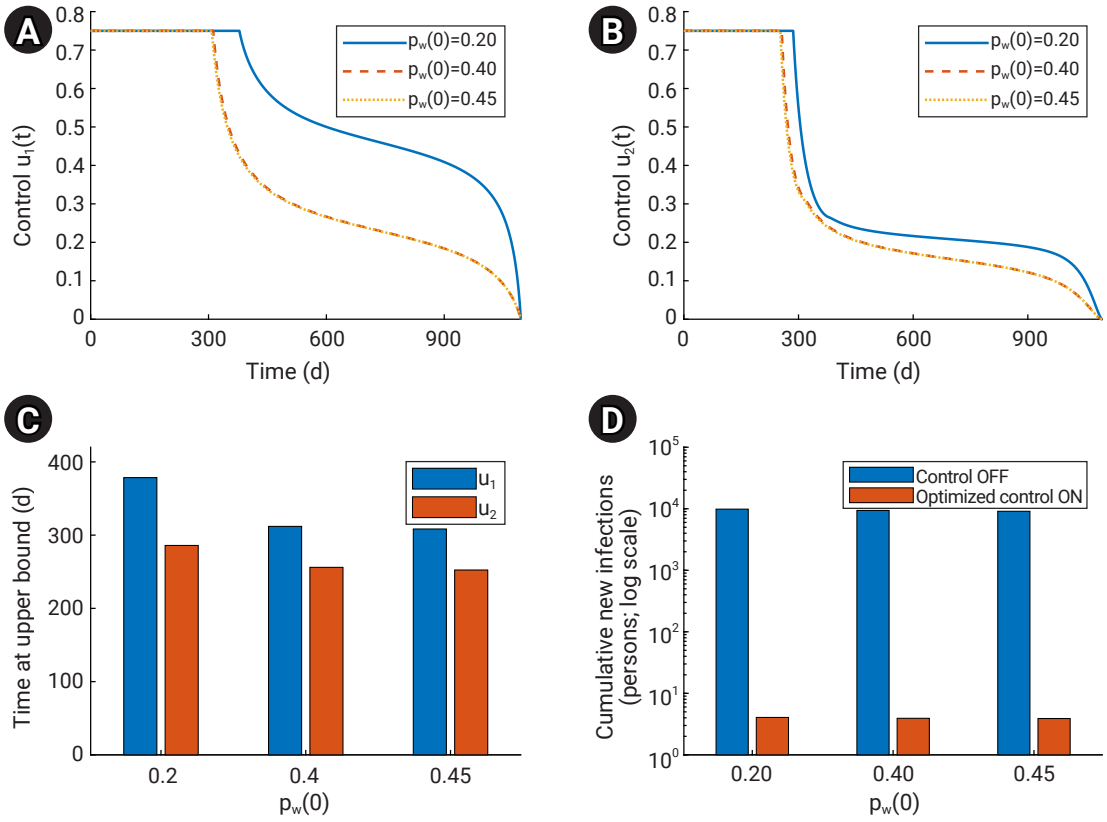


Figure 3. Scenario-specific optimal-control summary under representative post-release Wolbachia prevalence levels. (A) Contact-reduction control, $u_1(t)$. (B) Adult-mortality control, $u_2(t)$. (C) Duration of maximum-intensity control, as defined in Table 3. (D) Cumulative new human infections (persons) under Control OFF and control ON, shown on a logarithmic scale. A = 100, $c_1 = c_2 = 0.001$, and $u_{1,max} = u_{2,max} = 0.75$.

control bound $u_{max} = 0.30$, the terminal dengue infection near-elimination indicator changed between $p_W = 0.55$ and $p_W = 0.60$ for 7 of the 12 tested cost-weight combinations; the other 5 did not reach the criterion on the tested grid. Here, near elimination refers to the terminal infected-human state satisfying $I_H(T) \leq 10^{-4}$ at T = 3 years. This criterion refers to dengue infection in the human population in the deterministic model and does not imply elimination of the *Aedes aegypti* mosquito population.

A separate refined continuation example showed that mean control use can vary non-monotonically and that CumInf(ON) may decrease sharply over a narrow p_W interval. Because this refined scan reports cumulative incidence and mean control levels rather than the terminal near-elimination flag, it complements rather than replaces the coarse-grid threshold summary in Table 4 (Figure 4). The terminal criterion was not reached on the refined grid.

Table 4. Empirical transition intervals for terminal dengue infection near elimination

Cost weight c	A = 20	A = 50	A = 100
0.001	[0.55, 0.60]	[0.55, 0.60]	[0.55, 0.60]
0.003	[0.55, 0.60]	[0.55, 0.60]	[0.55, 0.60]
0.01	NR	NR	[0.55, 0.60]
0.03	NR	NR	NR

Near elimination was defined by $I_H(T) \leq 10^{-4}$ individuals at T = 3 years. The intervals bracket adjacent grid values at which the indicator changed from 0 to 1 in $p_W(0) = 0.10, 0.15, \ldots, 0.60$, with $u_{1,max} = u_{2,max} = u_{max} = 0.30$ and $c = c_1 = c_2$. NR means that the criterion was not reached anywhere on this grid; it does not imply a threshold outside the grid. This is a deterministic human-infection criterion, not mosquito-population elimination.

Discussion

This study provides a quantitative framework for post-release dengue management when *Wolbachia*-carrying mosquitoes are already established. By treating adult *Wolbachia* prevalence, p_W, as an index observable through routine entomological surveillance, the model links a practical field metric to time-dependent control decisions and expected health gains.

The results should be interpreted in the context of the growing field evidence for *Wolbachia*-based population

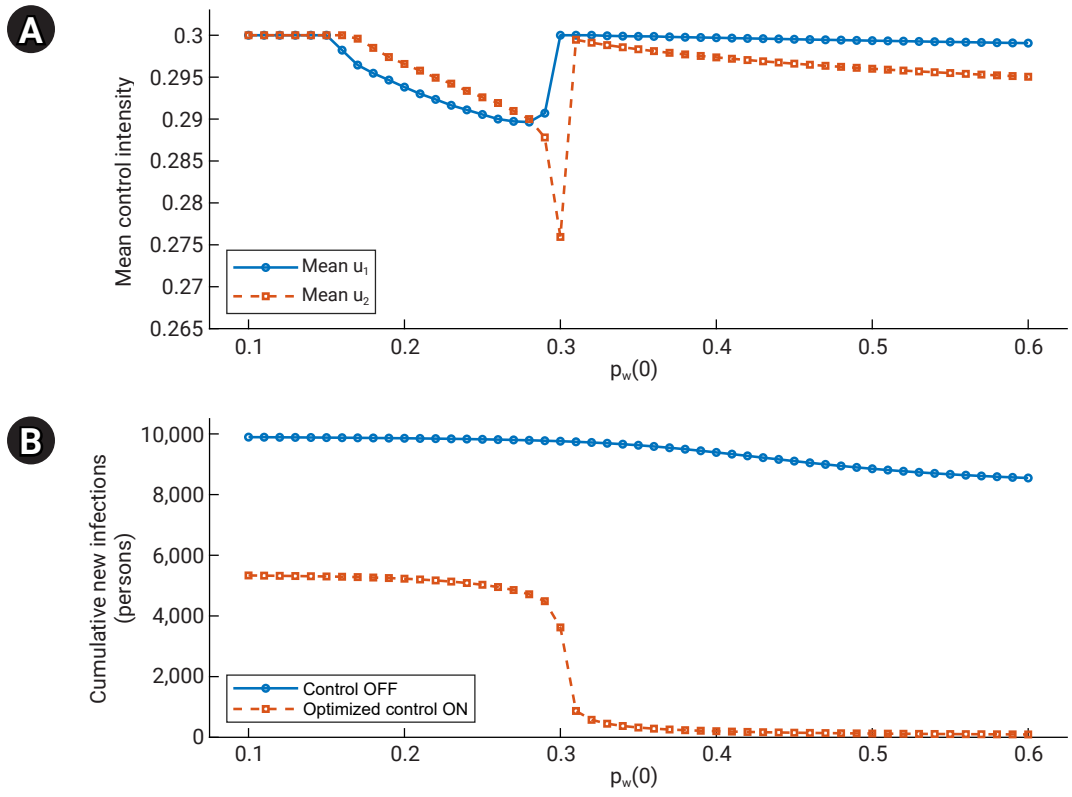


Figure 4. Refined continuation scan under bounded controls. (A) Mean control levels $\bar{u}_1(p_W)$ and $\bar{u}_2(p_W)$, defined as time averages over the planning horizon. (B) Cumulative new human infections (persons) versus initial $p_W(0)$ under Control OFF and control ON. The grid is $p_W(0) = 0.10,0.11,\ldots,0.60$, with $A = 50$, $c_1 = c_2 = 0.01$, and $u_{1,max} = u_{2,max} = 0.30$. The terminal criterion $I_H(T) \leq 10^{-4}$ was not reached on this grid.

replacement. Recent studies from Indonesia, Brazil, and Colombia have shown that *Wolbachia* establishment can be associated with substantial reductions in dengue incidence in operational settings [14–16]. These studies support the practical relevance of using *Wolbachia* prevalence as a surveillance-based planning indicator. At the same time, the prevalence threshold band identified in the simulations should not be interpreted as a universal field threshold. Rather, it is a model-based operational indicator under the assumed parameter set, initial conditions, time horizon, admissible control bounds, cost weights, and terminal criterion.

Under the baseline control bounds and cost weights, the diminishing marginal benefit of additional intervention as p_W increases has operational implications. When baseline p_W is high, intensified post-release measures may yield relatively small incremental reductions in infections, and earlier relaxation may be justified. Alternative parameter values or terminal thresholds may shift the interval or prevent the criterion from being reached; the band alone therefore cannot justify relaxing control. Broader sensitivity assessment and local calibration are needed before operational use.

The near-elimination transition band should be interpreted as an operational, model-based indicator rather than a declaration of epidemiological elimination. Specifically, it brackets adjacent tested p_W values between which the terminal criterion $I_H(T) \leq 10^{-4}$ changes from unmet to met under the stated conditions. It does not imply extinction of *Aedes aegypti* or universal elimination of dengue transmission in field settings.

This study has several limitations. The analysis was based on literature-derived parameter values rather than site-specific calibration, and it did not explicitly incorporate seasonal or climate-driven variation in vector abundance or transmission. In addition, the control set was restricted to contact reduction and adult mosquito suppression. Future work should incorporate uncertainty quantification and sensitivity analyses, calibrate the model to local entomological and epidemiological surveillance data, include explicit seasonality or climatic forcing, and examine complementary strategies, such as larval habitat reduction and spatially targeted interventions, to improve generalizability and programmatic relevance.

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Conclusion

Adult *Wolbachia* prevalence may serve as a surveillance-based index for prevalence-informed post-release dengue control. Under the baseline control bounds and cost weights, higher p_w reduced the marginal benefit of supplementary intervention and shortened the duration of maximum-intensity control, supporting earlier relaxation within these model scenarios. The identified transition band should be interpreted as a model-based planning indicator for terminal dengue infection near-elimination, not as a universal field threshold or as evidence of elimination of the *Aedes aegypti* mosquito population. Linking routine *Wolbachia* surveillance to control intensity and duration may help guide post-release dengue management and resource allocation when resources are limited.

Supplementary Material

Supplementary Material 1. Pontryagin maximum principle details; **Supplementary Material 2.** Disease-free equilibria and basic reproduction number; **Figure S1.** Heatmaps of the duration at the upper bound for scenario 1; **Figure S2.** Heatmaps of duration at the upper bound: scenario 2; **Figure S3.** Heatmaps of duration at the upper bound: scenario 3. Supplementary data are available at https://doi.org/10.24171/j.phrp.2026.0110.

Notes

Ethics Approval
Not applicable.

Conflicts of Interest
Yongkuk Kim 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 author has no conflicts of interest to declare.

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Availability of Data
All data generated or analyzed during this study are included in this article and its supplementary materials. Additional computational files are available from the corresponding author upon reasonable request.

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Original Article

Comparative analysis of associations between facility structure and air quality managers' knowledge, attitudes, and practices by COVID-19 outbreak status in welfare facilities for persons with disabilities: a cross-sectional survey study in the Republic of Korea

Mi Yu[1], Bryan Inho Kim[2], Jungyeon Yu[3], Sanghwan Bae[3], Seyoung Kim[4], Su Jin Kang[4], Sangwon Lee[5], Sang-Eun Lee[6]

[1]Division of Disease Control Capacity Building, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[2]Division of Emerging Infectious Disease Response, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[3]Korea Institute of Civil Engineering and Building Technology (KICT), Goyang, Republic of Korea
[4]Department of Public Health Science, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[5]Department of Disease Data Science, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[6]Division of Infectious Disease Control and Response, Gyeongnam Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency, Busan, Republic of Korea

ABSTRACT

Objectives: This study investigated associations between building structure and managers' knowledge, attitudes, and practices (KAP) regarding indoor air quality in welfare facilities for persons with disabilities, comparing facilities with and without coronavirus disease 2019 (COVID-19) cluster outbreaks.

Methods: A web-based survey was conducted among managers of 242 welfare facilities for persons with disabilities in the Republic of Korea. Facilities were recruited from a national sampling frame of approximately 3,000 facilities, yielding a response rate of 8.1%. The 80-item questionnaire assessed building characteristics and air quality-related KAP scores. Logistic regression was used to identify factors associated with cluster outbreaks.

Results: Of the 242 facilities, 50.8% had experienced cluster outbreaks. Facilities in complex/multi-use buildings had higher odds of outbreaks than those in detached buildings did (adjusted odds ratio, 2.21; 95% confidence interval, 1.25–3.91; $p = 0.006$). For managerial factors, facilities with outbreaks tended to have lower attitude scores ($p = 0.02$); however, this association did not remain statistically significant after Bonferroni correction (adjusted $\alpha = 0.0083$). No significant differences were observed in knowledge or practice scores.

Conclusion: Building structure, particularly complex/multi-use configuration, was associated with COVID-19 cluster outbreaks. Managerial KAP scores were not definitively associated with outbreaks under the conservative significance threshold, but the observed trends suggest that institutional support, ventilation guidance, and practical training for facility managers may help strengthen future infection-prevention efforts.

Keywords: Air pollution, indoor; COVID-19; Health knowledge, attitudes, practice; Logistic models

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Corresponding author:
Sang-Eun Lee
Division of Infectious Disease Control and Response, Gyeongnam Regional Center for Disease Control and Prevention, Korea Disease Control and Prevention Agency, 1090 Jungang-daero, Yeonje-gu, Busan 47596, Republic of Korea
E-mail: ondalgl@korea.kr

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

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Introduction

Early in the coronavirus disease 2019 (COVID-19) pandemic, transmission was primarily attributed to respiratory droplets and direct contact [1]. As the pandemic progressed, however, frequent cluster outbreaks in enclosed, crowded, and close-contact settings indicated that additional transmission routes were involved [2,3]. Substantial evidence, including the comprehensive analysis by Greenhalgh et al. [4], has since identified airborne transmission as an important pathway, and this route is now recognized by the World Health Organization (WHO) and the U.S. Centers for Disease Control and Prevention [5]. Although the physical dynamics of airflow are well documented, recent studies indicate that the effectiveness of mitigation measures also depends on managerial and institutional factors, including leadership commitment, resource allocation, and facility safety culture [6].

In the Republic of Korea, suspected inter-room and intra-room airborne transmission has been reported in settings including call centers, fitness centers, and residential complexes, underscoring the importance of structural and mechanical factors in indoor ventilation [7–10].

Beyond physical infrastructure, facility managers' knowledge, attitudes, and practices (KAP) may influence outbreak prevention. Previous studies suggest that knowledge is often high when standardized manuals are available, whereas practices may be limited by staffing shortages, budget constraints, and insufficient specialized training in environmental engineering [11].

Research conducted in April 2022 on long-term care facilities in the Republic of Korea found that systematic ventilation management remained inadequate and that professional guidance on ventilation equipment operation was needed [12].

Welfare facilities for persons with disabilities are infection-vulnerable environments with operational characteristics that differ from those of medical settings. These facilities often involve active physical engagement and social interaction, which may increase respiratory emission rates. Effective indoor ventilation is therefore a practical intervention for reducing infection risk in these settings [13]. The rationale for focusing on disability welfare facilities stems from their distinction from other high-risk settings, such as long-term care hospitals. Whereas long-term care hospitals are clinical environments that often serve passive or bedbound populations, disability welfare facilities are more home-like settings characterized by active physical engagement, communal dining, and social rehabilitation activities [14]. These behavioral factors may increase respiratory emissions and make consistent mask wearing more difficult. Unlike hospitals, which operate under more strictly regulated medical protocols, environmental management in disability welfare facilities often depends on the discretion of nonclinical managers.

HIGHLIGHTS

- Facility structure was associated with coronavirus disease 2019 cluster outbreaks: facilities in complex/multi-use buildings had 2.21 times higher odds of outbreaks than those in detached buildings.
- Managers of facilities with prior cluster outbreaks had lower attitude scores for indoor air quality management than managers of facilities without outbreaks, although this association did not remain statistically significant after Bonferroni correction.
- Future infection-response planning for welfare facilities for persons with disabilities should consider facility layout, building type, and institutional support for ventilation and indoor air quality management.

As part of the 2022 national initiative "Analysis of Indoor Ventilation Risk Factors in High-Risk Multi-Use Facilities," the Korea Disease Control and Prevention Agency (KDCA) conducted a nationwide survey of ventilation managers. The present study analyzed data from managers of welfare facilities for persons with disabilities to compare air quality-related KAP according to COVID-19 cluster outbreak history. By identifying these associations, this study provides evidence to support targeted indoor air quality management programs and future infection-response planning.

Materials and Methods

Study Population and Selection

The study focused on welfare facilities for persons with disabilities, including residential facilities, community rehabilitation facilities such as daycare centers, vocational rehabilitation facilities, and shelters for victims. These facilities were designated as high-risk settings requiring intensive surveillance because of the potential for severe outcomes and frequent cluster outbreaks [15,16]. Of the 249 facilities initially identified, 242 were included in the final analysis after 7 were excluded because of refusal to participate or incomplete responses (Figure 1).

The sample size was determined using a pragmatic recruitment strategy during the COVID-19 pandemic. The study aimed to maximize participation within a 3-week period through official KDCA communication channels. Of

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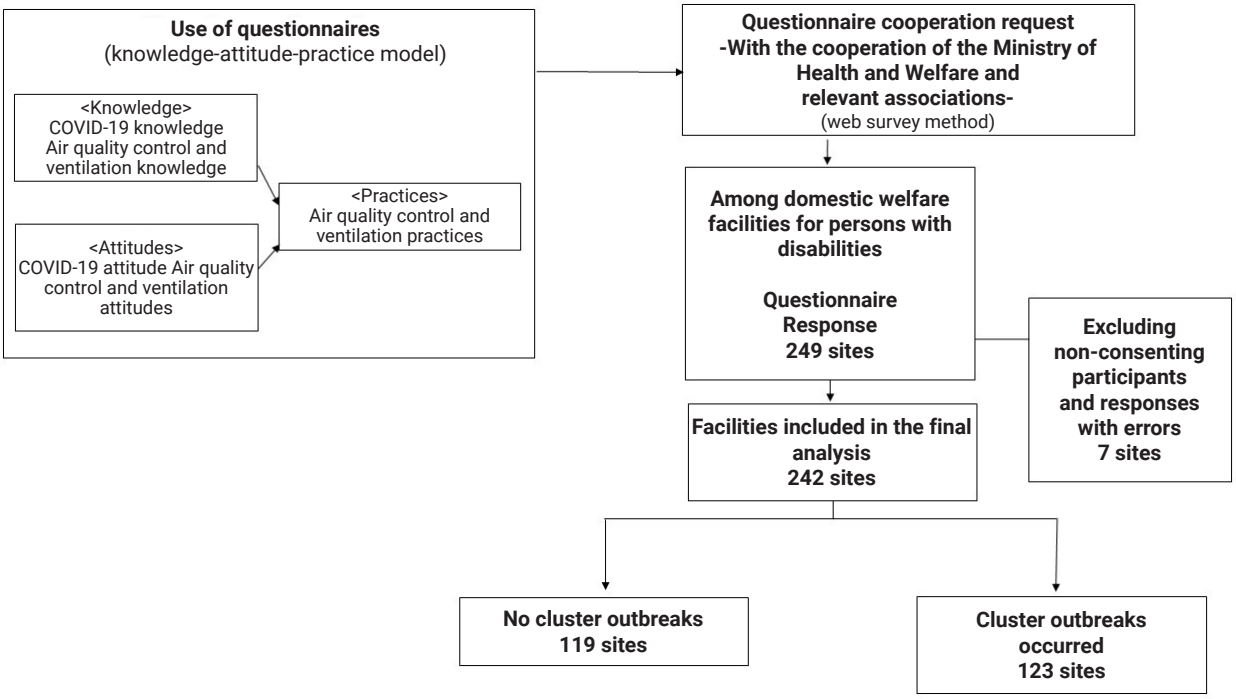


Figure 1. Survey procedure and number of participating facilities.

approximately 3,000 facilities nationwide, 242 responded, yielding a response rate of approximately 8.1% and representing both complex/multi-use and detached structures across the Republic of Korea.

Data Collection

A web-based survey was conducted in collaboration with 3 major organizations: the Korea Association of Disability Welfare Facilities, the Korea Association of Daycare Facilities for the Disabled, and the Korea Association of Vocational Rehabilitation Facilities for the Disabled. Formal cooperation requests were sent to each facility to encourage participation.

Survey Instrument: The KAP Model

The survey instrument was developed specifically for this study by the research team at the Seoul National University Institute of Health and Environment and was based on the KAP model [17]. Because no validated tools were available for assessing ventilation-related KAP among Korean welfare facility managers, a structured item-generation process was used. The item pool was drawn from current WHO and KDCA guidelines on COVID-19 and indoor ventilation, scientific literature on airborne transmission, and expert consensus review by the research team before survey deployment. The framework was used to assess managers' understanding of ventilation, attitudes toward air quality management, and implementation of ventilation practices.

Measurement and Variables

The 80-item survey instrument was structured into 4 domains.

Knowledge (31 items)

Items assessed factual understanding of COVID-19 transmission and clinical features (10 items) and indoor ventilation principles (21 items). Each item was presented as a true/false/"don't know" statement and scored dichotomously: correct answers were assigned 1 point, and incorrect or "don't know" responses were assigned 0 points. Example items included "The main clinical symptoms of COVID-19 are fever, fatigue, dry cough, and muscle aches" for the COVID-19 knowledge subscale and "Ventilation volume is unrelated to infection risk," which was reverse-scored, for the ventilation knowledge subscale. Internal consistency, mathematically equivalent to Kuder–Richardson Formula 20 for binary items, was $\alpha = 0.308$ for COVID-19 knowledge and $\alpha = 0.550$ for ventilation knowledge.

Attitudes (38 items)

Items evaluated perceptions of COVID-19 severity and personal susceptibility, perceived effectiveness of prevention measures, barriers to guideline compliance, and attitudes toward indoor ventilation management. All items used a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). For analysis, attitude scores were converted to a 10-point scale. Negatively worded items,

such as "Even if infected, the impact on my workplace would be small," were reverse-coded before summing so that higher scores consistently reflected more favorable attitudes toward prevention and ventilation management. Example items included "I am well aware of the government's indoor ventilation guidelines and manage accordingly" and "I follow COVID-19 prevention guidelines faithfully." Internal consistency was good for the COVID-19 attitude subscale (α = 0.814, *n* = 242) and acceptable for the ventilation attitude subscale (α = 0.713, *n* = 242).

Practices (6 items)

Items assessed implementation of ventilation management behaviors using binary yes/no responses (yes = 1, no = 0). Example items included "Is regular performance inspection and maintenance of ventilation equipment and air purifiers conducted?" and "Is periodic ventilation of 30 minutes or more per session being practiced?" Higher scores indicated greater adherence to recommended practices. Internal consistency was α = 0.544 (*n* = 117); this modest value may reflect the limited number of items and right-skewed item distributions, because most facilities reported adherence to most practices.

Facility characteristics and outbreak history (5 items)

Items captured key building characteristics, including facility type, corridor configuration, and the presence of air purification systems. The occurrence and frequency of COVID-19 cluster outbreaks at each facility were also assessed. In accordance with the COVID-19 response guidelines in effect at the time, a cluster outbreak was defined as an occurrence involving 10 or more confirmed COVID-19 cases. The reference period for outbreak history extended from the beginning of the COVID-19 pandemic to the time of the survey. Information on cluster outbreak history was obtained solely through self-reported responses from facility managers and was not independently verified against official public health surveillance records.

Reliability statistics, including Cronbach's alpha values for all domains, are summarized in Table 1. Missing responses were addressed using domain-specific listwise deletion. Complete-case sample sizes were 242 for the knowledge and attitude domains, whereas the analysis for the Practice domain was restricted to 117 respondents who completed all six items, resulting in a total of 702 valid item-level responses. This reduction in the analytical sample size for the Practice domain was primarily driven by non-responses on specific items, most notably the facility performance inspection question. Data were analyzed to identify associations between facility characteristics and KAP scores, with a focus on comparing facilities with and without a history of cluster outbreaks.

Definitions

The following are the definitions of several terms used in this study: (1) Detached building: A structure utilized exclusively by the welfare facility, with no shared space or ventilation systems with other commercial or residential entities. (2) Complex/multi-use building: A structure shared with other businesses or residential units, often involving shared common areas or integrated building systems. (3) Single-corridor layout: A design where rooms are situated on only 1 side of the corridor, typically allowing for better natural light and potential cross-ventilation. (4) Double-corridor layout: A design featuring a central corridor with rooms arranged on both sides, which may limit natural airflow compared to single-corridor designs. (5) Infection-vulnerable facilities (healthcare facilities): Healthcare and social welfare settings—including long-term care institutions, mental health facilities, and disability welfare facilities—characterized by a high risk of severe clinical outcomes and frequent cluster outbreaks, thus requiring intensive surveillance and rapid response protocols. (6) Air purification device (air purifier): Equipment designed to improve indoor air quality by removing pollutants through filtration or neutralizing airborne microbes via sterilization units. This category encompasses both mechanical air cleaners and specialized air sterilizers.

Table 1. Internal consistency reliability (Cronbach's alpha) by knowledge, attitudes, and practices domain

Domain	Item type	Items (k)	Analyzed respondents (*n*)	Total observed data points (*n*×k)	Cronbach's α
COVID-19 knowledge	Binary (0/1)	10	242	2,420	0.308
Ventilation knowledge	Binary (0/1)	21	242	5,082	0.550
COVID-19 attitude	5-Point Likert	20	242	4,840	0.814
Ventilation attitude	5-Point Likert	18	242	4,356	0.713
Practice	Binary (0/1)	6	117	702	0.544

For binary items, Cronbach's alpha is mathematically equivalent to Kuder-Richardson Formula 20 (KR-20). Benchmarks: ≥ 0.90, excellent; ≥ 0.80, good; ≥ 0.70, acceptable; ≥ 0.60, questionable; ≥ 0.50, poor; < 0.50, unacceptable. *n* represents the number of facility managers who completed all items within the corresponding domain after listwise deletion.

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Survey Period
The survey was conducted from November 24, 2022, to January 16, 2023.

Statistical Analysis
Because 6 primary independent variables were compared, this study was exploratory. To control the overall type I error rate, a Bonferroni correction was applied, setting the significance threshold at α = 0.0083. Results with *p*-values between 0.0083 and 0.05 were interpreted cautiously as suggestive trends rather than definitive associations.

Institutional Review Board Approval
This study received final approval from the Institutional Review Board (IRB) of Seoul National University Institute of Health and Environment (IRB No: 2301/002-011). Before participation, all respondents were informed of the study objectives and the voluntary nature of participation. Informed consent was obtained electronically from all facility managers before they proceeded to the survey questions. All data were anonymized to protect the privacy and confidentiality of participants and their facilities.

Results

Internal consistency reliability for the KAP subscales was evaluated using complete cases for each domain (Table 1). For binary knowledge items, Cronbach's alpha (KR-20) was 0.308 for COVID-19 knowledge (k = 10, *n* = 242, total 2,420 data points) and 0.550 for ventilation knowledge (k = 21, *n* = 242, total 5,082 data points). For Likert-scale attitude domains, internal consistency was good for COVID-19 attitude (α = 0.814, k = 20, *n* = 242) and acceptable for ventilation attitude (α = 0.713, k = 18, *n* = 242). Practice behaviors demonstrated relatively low internal consistency (α = 0.544, k = 6, *n* = 117).

Building Structure, Air Purification, and COVID-19 Outbreaks
Analysis of 242 welfare facilities showed associations between building structural characteristics and COVID-19 cluster outbreaks. Among the 119 facilities without outbreaks, 50 (42.0%) were detached buildings and 69 (58.0%) were complex/multi-use buildings. In contrast, among the 123 facilities with cluster outbreaks, 89 (72.4%) were complex/multi-use buildings. After adjustment for corridor type, presence of air purifiers, and manager KAP scores, facilities in complex/multi-use buildings had higher odds of cluster outbreaks than detached buildings did (adjusted odds ratio, 2.21; 95% confidence interval [CI], 1.25–3.91; *p* = 0.006).

While facilities with double-corridor layouts showed a slightly higher outbreak rate (54.7%) compared to those with single-corridor layouts (48.3%), this difference was not statistically significant. Similarly, facilities without air purifiers had an outbreak rate 9.5 percentage points higher (56.3%) than those with air purifiers (46.8%), but this difference also did not reach statistical significance.

Managerial KAP Scores and Outbreak Experience
Knowledge and practice scores did not differ significantly between managers of facilities with and without cluster outbreaks; mean scores were approximately 23 points for knowledge and 3.7 points for practices in both groups. After adjustment for knowledge and practice levels, however, higher manager attitude scores were associated with lower odds of cluster outbreaks (*p* = 0.02) (Table 2), although this finding did not meet the Bonferroni-corrected significance threshold.

KAP Scores by Frequency of Outbreaks
When facilities were categorized according to the frequency of COVID-19 cluster outbreaks (0, 1, or ≥2), knowledge, attitude, and practice scores showed no statistically significant differences across the groups. Although small numerical variations were observed, these differences were not considered meaningful (Figure 2).

Discussion

Infection-vulnerable settings, including disability welfare facilities, face elevated risks of rapid pathogen transmission because of congregate living and behavioral factors such as frequent social interaction and difficulty maintaining consistent mask wearing [18–22]. Indoor air quality management, including adequate ventilation as emphasized in the WHO roadmap, is therefore an important component of infection prevention in these populations [23].

This study provides evidence that facility infrastructure is associated with COVID-19 cluster outbreaks. After adjustment for potential confounders, facilities in complex/multi-use buildings had 2.21 times higher odds of outbreaks than detached buildings did (95% CI, 1.25–3.91). This increased vulnerability may be related to the absence of dedicated heating, ventilation, and air conditioning systems, shared common areas with commercial occupants, and limited centralized environmental management. These findings are consistent with previous research suggesting that detached structures may allow more controlled ventilation environments and may reduce inter-building transmission of infectious particles [24,25].

Table 2. COVID-19 cluster outbreaks in welfare facilities for persons with disabilities, grouped by structural features of the facilities and knowledge, attitudes, and practices of the managers

Feature	Facilities with outbreaks	Facilities without outbreaks	Adjusted OR (95% CI)[a)]	*p*
Total	123 (100.0)	119 (100.0)		
Building structure				
Complex/multi-use building	89 (72.4)	69 (58.0)	2.21 (1.25–3.91)	0.006
Detached building	34 (27.6)	50 (42.0)	Ref.	
Corridor type				
Double-corridor	52 (42.3)	43 (36.1)	1.57 (0.90–2.75)	0.11
Single-corridor	71 (57.7)	76 (63.9)	Ref.	
Presence of air purifier				
Absent	58 (47.2)	45 (37.8)	1.49 (0.85–2.61)	0.17
Present	65 (52.8)	74 (62.2)	Ref.	
Knowledge	23 ± 3.61	23 ± 3.77	1.02 (0.95–1.11)	0.57
Attitude	7.29 ± 0.65	7.45 ± 0.60	0.58 (0.37–0.92)	0.02
Practice	3.72 ± 1.51	3.73 ± 1.54	1.04 (0.86–1.26)	0.67

Data are presented as *n* (%) or mean ± standard deviation unless otherwise stated.
COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; ref, reference.
[a)]Adjusted for building structure, corridor type, presence of air purifiers, and knowledge, attitudes, and practices of the facility managers.

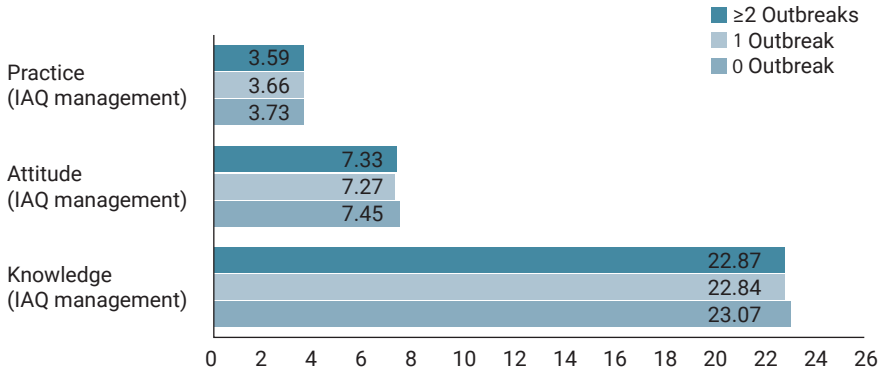


Figure 2. Knowledge, attitudes, and practices of facility managers, grouped by number of COVID-19 cluster outbreaks. IAQ, indoor air quality.

Regarding managerial factors, the uncorrected analysis showed lower attitude scores in facilities with outbreaks ($p = 0.02$), but this association did not remain statistically significant after Bonferroni correction (adjusted $\alpha = 0.0083$). The results therefore suggest a possible directional pattern but should be interpreted cautiously. The lack of significant differences in knowledge and practice scores may reflect knowledge saturation after prolonged pandemic-related education, whereas implementation of practices may have been constrained by structural, staffing, and budget limitations rather than by lack of intent. The observed attitude pattern may also reflect the emotional and physical burden accumulated during outbreak responses. Consistent with previous research indicating that attitudes may more directly influence COVID-19 preventive behaviors than knowledge alone, these findings support policies that combine technical training with psychological and organizational support for facility managers [26,27].

No meaningful differences in KAP scores were observed across groups categorized by outbreak frequency. These findings do not support a clear association between repeated outbreak experience and managerial KAP levels. Nevertheless, previous studies suggest that continuous decision support and repeated education can support more effective environmental management [28,29]. Future policies should move beyond manual distribution alone and include regular indoor ventilation training across infection-vulnerable sectors. However, because this study was cross-sectional, the direction of the observed associations cannot be determined. Although lower attitude scores were associated with higher outbreak frequency, reverse causation remains possible. The emotional and physical burden of managing a cluster outbreak, including

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emergency response stress and responsibility for resident safety, may have reduced managers' perceived efficacy and attitudes toward practice. These scores may therefore reflect the psychological aftermath of an outbreak rather than a purely predictive baseline factor.

This study has several limitations. First, the cross-sectional design precludes determination of temporal precedence. Second, the study may be subject to selection bias because only 242 of approximately 3,000 facilities participated, and reporting bias is possible because the survey was web-based.

Nonresponse bias is also possible because facilities that voluntarily participated may have differed from nonparticipating facilities in infection-control capacity, interest in indoor air quality, or available administrative resources. In addition, because this study focused on the welfare system of the Republic of Korea, the findings may have limited generalizability to other countries or to other types of high-risk institutions. Furthermore, detailed information on the characteristics of nonresponding facilities, including facility type, geographic location, and facility size, was not available for direct comparison with the participating facilities. Therefore, potential differences between responding and nonresponding facilities could not be assessed, and the representativeness of the study sample may be limited. These factors should be considered when interpreting and generalizing the study findings.

Third, this study did not account for individual demographic characteristics of facility managers, such as age, professional experience, or educational background, because these data were not available from the primary survey. The absence of these individual-level covariates may have resulted in residual confounding. To address the risk of false-positive findings associated with multiple testing, a Bonferroni correction was applied to support a more conservative statistical interpretation.

Fourth, type I error cannot be entirely ruled out despite use of the Bonferroni correction. Because this was an exploratory analysis of a specific subset of facilities, findings with marginal *p*-values, including the attitude-score result, should be viewed as hypothesis generating. Confirmatory studies with larger sample sizes are needed to validate these associations. Fifth, there is potential for residual confounding by facility size and regional COVID-19 incidence. Larger facilities may have had a higher probability of experiencing cluster outbreaks because of greater numbers of residents or users at risk. In addition, complex/multi-use buildings may be more frequently located in urban or high-density areas with different levels of community transmission. Because these variables were not available for adjustment in the present analysis, the observed association between building structure and cluster outbreaks (adjusted OR, 2.21) should be interpreted cautiously and should not be considered evidence of a causal relationship.

A final limitation concerns the psychometric properties of the survey instrument, which was developed specifically for this study and has not been validated against an external criterion. Internal consistency was robust for the COVID-19 attitude domain (α = 0.814) and acceptable for the ventilation attitude domain (α = 0.713), but reliability was more modest for the knowledge domains (α = 0.308–0.550) and the practice scale (α = 0.544). The relatively low Cronbach's alpha coefficients for the knowledge domains may reflect heterogeneity in item content, weak inter-item correlations, or measurement limitations of the study-specific questionnaire. Although ceiling effects may reduce internal consistency under certain conditions, the available data do not provide sufficient evidence to establish knowledge saturation as the primary explanation. Therefore, the knowledge-related findings should be interpreted cautiously. This pattern is consistent with the knowledge saturation interpretation discussed above and does not necessarily indicate poor construct validity. Nevertheless, modest reliability in the knowledge and practice domains may have introduced measurement error that biased regression coefficients toward zero. The modest internal consistency of the knowledge and practice domains may have introduced measurement error, potentially affecting the precision and magnitude of the estimated associations. Consequently, the absence of statistically significant associations for these domains should be interpreted cautiously. The extent and direction of any measurement-error bias cannot be determined from the available data. Future research should prioritize the development and validation of psychometrically robust instruments for this population and may incorporate objective measures, such as behavioral observation or administrative records, to supplement self-reported data.

Nonetheless, this study examined associations among facility structure, managerial attitudes, and documented COVID-19 cluster outbreaks in welfare facilities for persons with disabilities in the Republic of Korea. The findings can inform systematic monitoring approaches and future quantitative research on whether ventilation compliance reduces respiratory infection outbreaks over time.

Notes

Ethics Approval

This study received final approval from the Institutional Review Board of Seoul National University Institute of Health and Environment (IRB No. 2301/002-011).

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 not publicly available due to privacy and institutional policy constraints but are available from the corresponding author upon reasonable request.

Authors' Contributions
Writing–original draft: MY, BIK, SEL; Conceptualization: MY, SL, SEL; Formal analysis: MY, SL; Software: MY, JY, SB, SK, SJK, SEL; Supervision: BIK, SL, SEL; Validation: MY, SEL; Methodology: MY, BIK, SL, SEL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Age- and sex-specific patterns in the prevalence of metabolic syndrome components in the Republic of Korea, 2014–2023: a repeated cross-sectional study of national health screening statistics

Yu-Mi Jang, Woo-Hyeon Son

Design Institute, Inje University, Gimhae, Republic of Korea

ABSTRACT

Objectives: This study described 10-year trends in the prevalence of 5 metabolic syndrome (MetS) components and examined age- and sex-specific patterns in the Republic of Korea using aggregated national health screening statistics from 2014 to 2023.

Methods: This repeated cross-sectional study used publicly available aggregated data from the National Health Screening Statistical Yearbook of the National Health Insurance Service. Annual prevalence estimates were summarized overall and by age group and sex. Linear and segmented regression summarized trends, and age- and sex-standardized prevalence was estimated. The 2018 yearbook tabulated risk factors only for examinees receiving the dyslipidemia panel (restricted from 2018 to men aged ≥24 years and women aged ≥40 years); therefore, 2018 was excluded, and lipid indicators were analyzed for 2014–2017.

Results: From 2014 to 2023, crude prevalence increased for abdominal obesity (21.0% to 25.5%) and hyperglycemia (34.7% to 40.1%), mainly before 2019, and for hypertension (42.3% to 45.1%), although less after age standardization. In 2014–2017, hypertriglyceridemia increased (30.0% to 32.2%), whereas low high-density lipoprotein (HDL) cholesterol changed little (22.5% to 22.1%). Prevalence was higher in older age groups, especially for hypertension and hyperglycemia. Men had a higher prevalence of 4 components, and women of low HDL cholesterol.

Conclusion: MetS components showed heterogeneous temporal, age-specific, and sex-specific patterns in Korean national health screening statistics. Increases in abdominal obesity and hyperglycemia, mainly before 2019, support earlier age- and sex-tailored cardiometabolic prevention, whereas lipid indicators were comparable only for 2014–2017. Individual-level longitudinal studies are needed to clarify these trends.

Keywords: Age factors; Cross-sectional studies; Metabolic syndrome; National health programs; Prevalence; Republic of Korea

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Corresponding author:
Woo-Hyeon Son
Design Institute, Inje University,
197 Inje-ro, Gimhae 50834,
Republic of Korea
E-mail: physical365@gmail.com

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Introduction

Metabolic syndrome (MetS) comprises a cluster of cardiometabolic abnormalities, including abdominal obesity, elevated blood pressure, dysglycemia, and dyslipidemia, that together increase the risks of cardiovascular disease, type 2 diabetes, and premature mortality. Standard definitions, such as the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, define MetS as the presence of at least 3 of 5 component abnormalities [1]. Beyond the composite diagnosis, each component is clinically relevant because its prevalence pattern may vary by age, sex, and calendar period [2]. Accordingly, surveillance of individual MetS components may provide more actionable public health information than assessment of the overall prevalence of MetS alone.

In the Republic of Korea, the prevalence of MetS and related cardiometabolic risk factors has reportedly increased in association with dietary westernization, reduced physical activity, and population aging [3]. However, much of the existing evidence focuses on adults and is based on cross-sectional snapshots or component distributions within restricted age ranges. Kim et al. [4] reported an increase in MetS prevalence using data from the Korea National Health and Nutrition Examination Survey from 2008 to 2017; however, their analysis was restricted to adults aged 20–79 years, resulting in underrepresentation of adolescents and the oldest age groups. In addition, many studies have focused primarily on the overall prevalence of MetS, limiting insight into component-specific and age-specific patterns.

Recent Korean epidemiological studies and national fact sheets indicate that cardiometabolic risk remains a major public health concern. Analyses of Korea National Health and Nutrition Examination Survey data have documented changes in MetS and related cardiometabolic risk factors among Korean adults, particularly around the coronavirus disease 2019 pandemic [5]. National diabetes and dyslipidemia fact sheets similarly indicate that diabetes and lipid disorders remain highly prevalent among Korean adults, with substantial variation by age, sex, obesity status, and comorbid conditions [6,7]. Collectively, these findings support continued surveillance of individual MetS components rather than reliance solely on the composite MetS diagnosis.

A life-course perspective can provide a useful framework for interpreting differences in cardiometabolic risk across age groups and social life stages. However, when aggregated repeated cross-sectional statistics are used, these patterns should be interpreted as population-level differences among age groups rather than as within-person life-course changes.

HIGHLIGHTS

- Metabolic syndrome components showed heterogeneous prevalence patterns over the 10-year study period in the Republic of Korea.
- Prevalence differed substantially across age groups and between men and women.
- Lipid-related indicators were comparable only for 2014–2017 because the dyslipidemia screening schedule changed in 2018.
- Aggregated screening statistics characterize population-level patterns rather than individual life-course changes.

Biological aging processes may contribute to the higher prevalence of elevated blood pressure and hyperglycemia in older age groups. Sex-specific biological and social factors may also contribute to differences in abdominal obesity, triglyceride levels, and high-density lipoprotein (HDL) cholesterol across age groups [8]. Age-related increases in vascular stiffness and insulin resistance, together with declining pancreatic β-cell function, may differentially affect blood pressure and glucose regulation [9]. Sex differences are also substantial: men often have higher levels of abdominal obesity and triglyceride-related risk, whereas women may experience accelerated cardiometabolic changes after menopause because of hormonal changes and reduced estrogen-related cardiovascular protection [10,11]. These differences may contribute to sex crossover patterns at older ages, in which prevalence among women exceeds that among men for specific indicators.

Accordingly, this study analyzed publicly available nationwide aggregated statistics from the National Health Insurance Service (NHIS) health screening statistical yearbook for 2014–2023 to: (1) describe annual trends in the prevalence of 5 MetS components; (2) summarize age-specific patterns using average annual prevalence by age group; and (3) examine sex-specific prevalence differences, endpoint changes, and descriptive sex-by-age crossover patterns.

Materials and Methods

Data Source and Study Design

A secondary descriptive epidemiological analysis was performed using publicly available aggregated data from the NHIS health screening statistical yearbook for 2014–2023 [12]. The yearbooks are published by the NHIS and report distributions of major health screening indicators among

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participants in the national health screening program. The data were downloaded from the NHIS health screening statistical yearbook website on February 6 and April 3, 2026, and last accessed on June 8, 2026. The values analyzed were taken from the yearbook tables "Statistics on the Metabolic Risk Factors by Age and Gender" (Table VIII-6 in the 2014–2017 yearbooks; Table VII-6 in the 2018–2023 yearbooks) and are provided by year, sex, and age group in Table S1. Because the dataset consists of aggregated repeated cross-sectional statistics, the unit of analysis was an aggregated prevalence estimate defined by year, sex, and age group rather than an individual participant.

The reported values were crude prevalence estimates derived from aggregated NHIS screening statistics. Overall annual prevalence was calculated as a sex-weighted estimate using sex-specific examinee counts as weights, with the total number of male and female examinees as the denominator. Age-specific and sex-specific prevalence estimates were calculated within the corresponding aggregated strata. Directly age- and sex-standardized prevalence was also calculated for each year using a fixed standard population, defined as the pooled number of examinees by sex and 15 five-year age bands across the analyzed years (Table S2).

From 2018, the dyslipidemia panel (total, HDL, and low-density lipoprotein cholesterol and triglycerides) of the general health screening was provided at 4-year intervals to men aged ≥24 years and women aged ≥40 years, instead of at every biennial screening. As reflected in the 2018 yearbook [12], the metabolic risk-factor tables for that year were compiled only for examinees who received this panel (5,000,434 examinees, consistent with the 5,002,693 lipid-tested examinees in the yearbook's triglyceride distribution table [Table VI-22], compared with 13.1–17.5 million examinees in the other years), and almost no women younger than 40 years were included. From 2019 onward, the tables again used all examinees as the denominator, whereas abnormal triglyceride and HDL cholesterol levels could be identified only among examinees who received the lipid panel or reported dyslipidemia medication. Therefore, the 2018 estimates for all 5 components refer to a different, age- and sex-restricted population, and the lipid indicators from 2018 onward are not comparable with those for 2014–2017. Accordingly, 2018 was excluded from all analyses, and hypertriglyceridemia and low HDL cholesterol were analyzed for 2014–2017 only (Table S1). The number of examinees aged 20–39 years also increased from 2019 (Table S1).

The study was designed as a secondary descriptive epidemiological analysis of aggregated repeated cross-sectional national screening statistics. The unit of analysis was the aggregated prevalence estimate by year, age group, and sex rather than the individual participant. Accordingly, the findings describe population-level distributions and temporal patterns in screening statistics and should not be interpreted as within-person longitudinal changes or causal life-course trajectories.

Age Grouping for Descriptive Analysis

The yearbook reports age distributions in 15 five-year bands ranging from ≤19 to ≥85 years. For age-specific descriptive analyses, these categories were reclassified into 7 broader age groups: ≤19, 20–29, 30–39, 40–49, 50–59, 60–69, and ≥70 years. These categories were used to summarize population-level prevalence patterns across broad life stages rather than to infer individual life-course trajectories. Examinees aged ≤19 years are a small, selected subset of this age group (eligible individuals: 31,269 in 2014 and 14,008 in 2023; examinees: 10,655–28,843 per year), and examinees aged 20–29 years (1.2–1.9 million per year; eligible individuals: 1,375,413 in 2014 and 2,667,545 in 2023) also represent a restricted subset of the age group (yearbook Table I-3 [12]). Estimates for these age groups are therefore not representative of the corresponding general population.

Measures: MetS Components

MetS components were used as defined in the yearbook guide for the tables "Statistics on the Metabolic Risk Factors by Age and Gender" (NCEP-ATP III criteria with Asian cutoffs) [13–15]. The original yearbook variable names are given in quotation marks. (1) Abdominal obesity ("Abdominal Obesity"): waist circumference ≥90 cm in men and ≥85 cm in women. (2) Hypertension ("High Blood Pressure"): systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, or current antihypertensive medication reported in the screening questionnaire. (3) Hyperglycemia ("High Blood Sugar"): fasting glucose ≥100 mg/dL or current antidiabetic medication reported in the questionnaire. (4) Hypertriglyceridemia ("Hypertriglyceridemia"): triglycerides ≥150 mg/dL or current dyslipidemia medication reported in the questionnaire. (5) Low HDL cholesterol ("Low HDL Cholesterolemia"): HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, or current dyslipidemia medication reported in the questionnaire. The medication criteria are stated in the 2014 yearbook guide [15]; later guides list only the laboratory thresholds, but the yearbook counts continued to exceed counts based on laboratory thresholds alone in the yearbook's distribution tables (e.g., hyperglycemia in 2023, ratio 1.03), whereas counts for abdominal obesity, which has no medication criterion,

matched exactly (ratio 1.00), indicating that medication-treated examinees continued to be counted (Table S3).

In this study, "hypertension" and "hyperglycemia" are used as variable labels consistent with the NHIS National Health Screening Statistical Yearbook and denote the component thresholds defined above rather than clinical diagnoses.

Statistical Analysis

Because this study used aggregated repeated cross-sectional statistics, the results reflect population-level prevalence distributions rather than within-person longitudinal trajectories. Accordingly, all analyses were ecological and descriptive in nature. Linear regression with year as a continuous predictor was used to summarize the direction and magnitude of observed temporal trends across the 9 analyzed annual observations (2014–2017 and 2019–2023) for abdominal obesity, hypertension, and hyperglycemia. To examine whether trends differed before and after 2018, a 2-segment (piecewise) linear model was also fitted: prevalence = b0+b1(year−2014)+b2D+b3D(year−2019), where D = 1 for 2019–2023; this yields period-specific annual changes for 2014–2017 and 2019–2023 and a test of the change in slope. Because only 4 comparable annual observations (2014–2017) were available for hypertriglyceridemia and low HDL cholesterol, no trend estimates were calculated for these indicators, and their values are reported descriptively. The regression coefficient (B) and coefficient of determination (R^2) were used to summarize temporal patterns, whereas *p*-values were interpreted cautiously given the small number of annual observations and were not considered evidence of causal, predictive, or individual-level longitudinal change. Time-series autocorrelation was not formally assessed because of the limited number of annual data points; the lack of formal assessment was considered a methodological limitation. In addition, because many individuals undergo screening repeatedly across years, the annual estimates are not independent; ordinary least squares confidence intervals and p-values are therefore likely to be too narrow and are presented descriptively. Age- and sex-standardized prevalence was summarized in the same way.

Overall annual prevalence was calculated as a sex-weighted average using sex-specific examinee counts as weights. The denominator for overall prevalence was the total number of examinees in each year (men and women).

All analyses were performed using Python 3.13 (SciPy 1.18 and statsmodels 0.15; Python Software Foundation) and IBM SPSS ver. 28.0 (IBM Corp.), with 2-sided $p < 0.05$ considered to indicate statistical significance.

Use of Generative Artificial Intelligence

During the preparation of this manuscript, the authors used Claude (Anthropic) for English-language editing, reference checking, and figure editing. The authors reviewed and edited all outputs and take full responsibility for the content of the publication.

Results

Annual Prevalence Trends (2014–2023)

Abdominal obesity increased from 21.0% in 2014 to 25.5% in 2023 (+4.5 percentage points; B = +0.497 percentage points per year, $R^2 = 0.87$), hyperglycemia from 34.7% to 40.1% (+5.4 percentage points; B = +0.698, $R^2 = 0.80$), and hypertension from 42.3% to 45.1% (+2.9 percentage points; B = +0.332, $R^2 = 0.94$) (Table 1; Figure 1). Most of the increases in abdominal obesity and hyperglycemia occurred before 2019: in the 2-segment model, the annual change was larger in 2014–2017 (B = +0.938 and +1.198 percentage points per year, respectively) than in 2019–2023 (B = +0.118 and −0.043; *p* for slope change = 0.007 and 0.030), whereas hypertension increased at a similar rate in both periods (B = +0.423 and +0.374; $p = 0.798$). After direct age and sex standardization, the 2014–2023 increase was similar for abdominal obesity (+4.4 percentage points) and hyperglycemia (+4.8 percentage points) but smaller for hypertension (+1.8 percentage points) (Table S2). Between 2014 and 2017, hypertriglyceridemia increased from 30.0% to 32.2% (+2.2 percentage points), whereas low HDL cholesterol changed little (22.5% to 22.1%; −0.5 percentage points).

Including the 2018 values, which refer only to the lipid-tested subgroup, changed the hypertension estimates substantially (B = +0.299, $R^2 = 0.21$, $p = 0.181$, vs. B = +0.332, $R^2 = 0.94$ without 2018), showing that the trend estimates were sensitive to a single non-comparable observation; 2018 was therefore excluded from all analyses.

Age-Specific Prevalence Patterns Based on Average Annual Prevalence

Average prevalence generally increased across older age groups, although the pattern was not strictly monotonic for all components. Abdominal obesity prevalence was 14.4% in the ≤19-year group and 35.5% in the ≥70-year group, although prevalence decreased slightly between the 30–39 and 40–49 age groups. Hypertension and hyperglycemia showed the clearest age-related gradients, increasing from 17.5% to 76.4% and from 14.6% to 56.4%, respectively, between the youngest and oldest age groups. Estimates for the ≤19- and 20–29-year groups are based on restricted subsets of these age groups. These findings demonstrate substantial differences in population-level prevalence

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Table 1. Crude prevalence, endpoint change, and descriptive trend estimates for metabolic syndrome components

Component	Year	2014 (%)	Last year (%)	Change (%p)	B (95% CI)	R^2	B, 2014–2017 (95% CI)	B, 2019–2023 (95% CI)	*p* for slope change
Abdominal obesity	2014–2023[a]	21	25.5	4.5	+0.497 (+0.326 to +0.668)	0.87	+0.938 (+0.55 to +1.32)	+0.118 (−0.16 to +0.39)	0.007
Hypertension	2014–2023[a]	42.3	45.1	2.9	+0.332 (+0.254 to +0.410)	0.94	+0.423 (+0.04 to +0.81)	+0.374 (+0.10 to +0.64)	0.798
Hyperglycemia	2014–2023[a]	34.7	40.1	5.4	+0.698 (+0.387 to +1.008)	0.80	+1.198 (+0.33 to +2.06)	−0.043 (−0.65 to +0.57)	0.030
Hypertriglyceridemia	2014–2017	30	32.2[b]	2.2	-	-	-	-	-
Low HDL cholesterol	2014–2017	22.5	22.1[b]	−0.5	-	-	-	-	-

Overall prevalence was calculated from yearbook counts for men and women combined (equivalent to a sex-weighted estimate). Linear and segmented regressions were used descriptively; B indicates the annual change in prevalence in percentage points. Because the same individuals are screened repeatedly across years, annual estimates are not independent, and the confidence intervals and p-values are likely to be too narrow. Age- and sex-standardized estimates are shown in Table S2.

%p, percentage points; CI, confidence interval; HDL, high-density lipoprotein.

[a]Nine annual observations (2014–2017 and 2019–2023). 2018 was excluded because the 2018 yearbook table was compiled only for examinees who received the dyslipidemia panel. Segmented model: prevalence = b0+b1(year−2014)+b2D+b3D(year−2019), where D = 1 for 2019–2023. [b]2017 value. Lipid indicators are reported for 2014–2017 only, without trend estimates, because the dyslipidemia screening schedule changed in 2018.

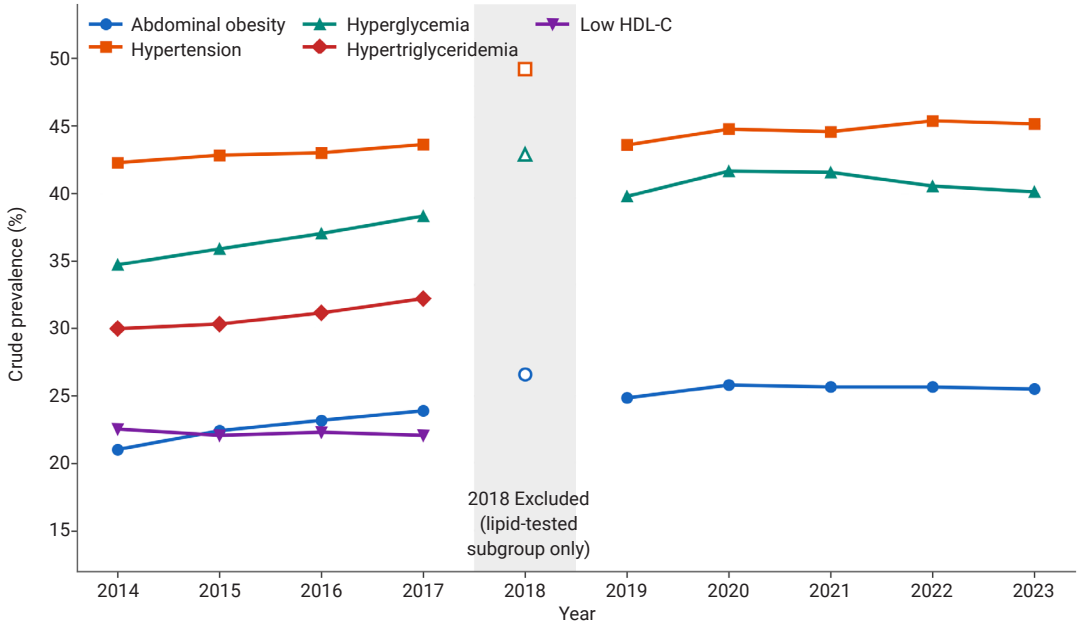


Figure 1. Annual crude prevalence of metabolic syndrome components, 2014–2023. Prevalence was calculated from yearbook counts for men and women combined. Open symbols show the 2018 values, which refer only to examinees who received the dyslipidemia panel and were excluded from all analyses. Hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) are shown for 2014–2017 only because the dyslipidemia screening schedule changed in 2018.

across age groups rather than within-person changes over time (Table 2; Figure 2).

The age gradient was steepest for hypertension (17.5% in the ≤19-year group vs. 76.4% in the ≥70-year group), followed by hyperglycemia (14.6% vs. 56.4%). These gradients may be associated with age-related physiological changes in vascular and glycemic regulation.

Sex-Specific Average Prevalence and Endpoint Change

Men had a higher average prevalence of abdominal obesity (28.8% vs. 19.2%), hypertension (50.4% vs. 36.7%), hyperglycemia (45.1% vs. 31.9%), and hypertriglyceridemia (38.4% vs. 22.3%; 2014–2017), whereas women had a higher prevalence of low HDL cholesterol (27.8% vs. 17.5%; 2014–2017) (Table 3; Figure 3). The increase in abdominal obesity between 2014 and 2023 was substantially greater among men (23.6% to 31.8%; +8.1 percentage points) than among women (17.9% to 18.8%; +0.9 percentage points). Between 2014 and 2017, hypertriglyceridemia increased among both men (+2.3 percentage points) and women (+2.5 percentage points), whereas low HDL cholesterol changed little among

Table 2. Prevalence of metabolic syndrome components by age group (average of annual estimates)

Age group (y)	Abdominal obesity	Hypertension	Hyperglycemia	Hypertriglyceridemia	Low HDL cholesterol
≤19	14.4	17.5	14.6	7.2	10.6
20–29	14.5	18.8	15.1	13.4	9.9
30–39	23.3	27.9	25.5	28.2	14.4
40–49	22.5	36	35.5	30.8	18.6
50–59	23.1	48.1	45.5	34.2	24.0
60–69	28.8	62.0	52.1	36.7	32.3
≥70	35.5	76.4	56.4	35.8	38.3

Fifteen 5-year age bands in the National Health Insurance Service yearbooks were reclassified into 7 age groups. Within each year, age-group prevalence was calculated using examinee counts in the corresponding strata as denominators. Values are arithmetic means of the annual estimates: abdominal obesity, hypertension, and hyperglycemia, 2014–2017 and 2019–2023 (9 years; 2018 excluded); hypertriglyceridemia and low HDL cholesterol, 2014–2017 (4 years). These estimates are crude and were not age-standardized. Examinees aged ≤19 years are a small, selected subset (10,655–28,843 per year), and estimates for this group are not representative.
HDL, high-density lipoprotein.

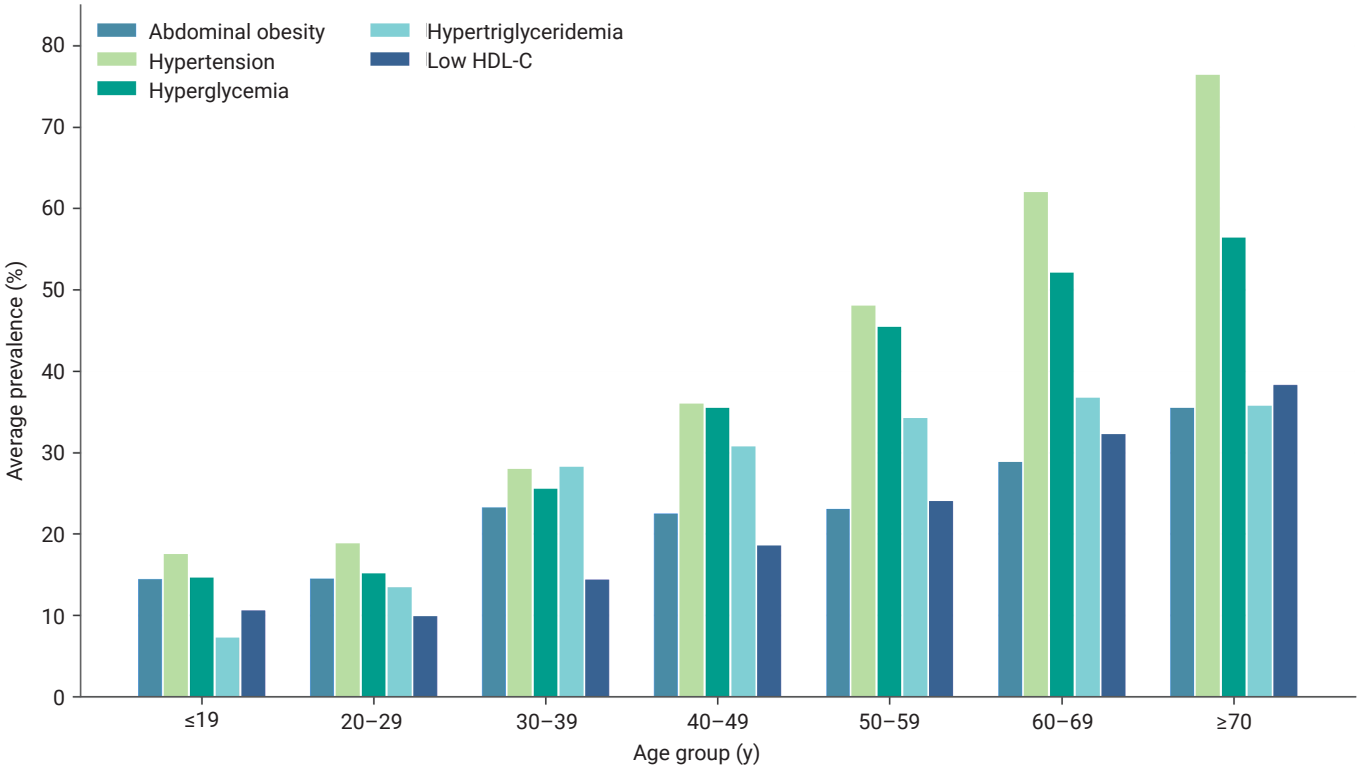


Figure 2. Age-specific prevalence of metabolic syndrome components (average of annual estimates). Abdominal obesity, hypertension, and hyperglycemia: mean of 2014–2017 and 2019–2023; hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C): mean of 2014–2017. Prevalence generally increased across older age groups, particularly for hypertension and hyperglycemia, although abdominal obesity decreased slightly between the 30–39- and 40–49-year age groups.

men (+0.5 percentage points) and decreased among women (–1.8 percentage points).

Sex-by-Age Crossover Patterns in Older Ages

To characterize crossover patterns in which prevalence among women exceeded that among men, age-specific prevalence was compared between men and women for the 3 indicators showing such patterns: abdominal obesity, hypertriglyceridemia, and low HDL cholesterol (Table 4; Figure 4). Sex-by-age crossover patterns were identified descriptively by comparing average prevalence between men and women within each age group. Because the data were aggregated, these crossover patterns were not formally tested using individual-level statistical models.

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Table 3. Sex-specific prevalence of metabolic syndrome components and endpoint changes

Component	Period	Men, average (%)	Women, average (%)	Men–women (%p)	Men, change (%p)	Women, change (%p)
Abdominal obesity	2014–2023	28.8	19.2	+9.5	+8.1	+0.9
Hypertension	2014–2023	50.4	36.7	+13.7	+4.2	+2.2
Hyperglycemia	2014–2023	45.1	31.9	+13.2	+6.9	+4.4
Hypertriglyceridemia	2014–2017	38.4	22.3	+16.1	+2.3	+2.5
Low HDL cholesterol	2014–2017	17.5	27.8	−10.2	+0.5	−1.8

Averages are arithmetic means of the annual estimates over the period shown (2014–2017 and 2019–2023 for abdominal obesity, hypertension, and hyperglycemia; 2014–2017 for lipid indicators). Positive male–female differences indicate higher prevalence among men. Endpoint change is the absolute percentage-point difference between 2014 and 2023 (non-lipid indicators) or between 2014 and 2017 (lipid indicators) within each sex. Differences were calculated from unrounded values.
%p, percentage points; HDL, high-density lipoprotein.

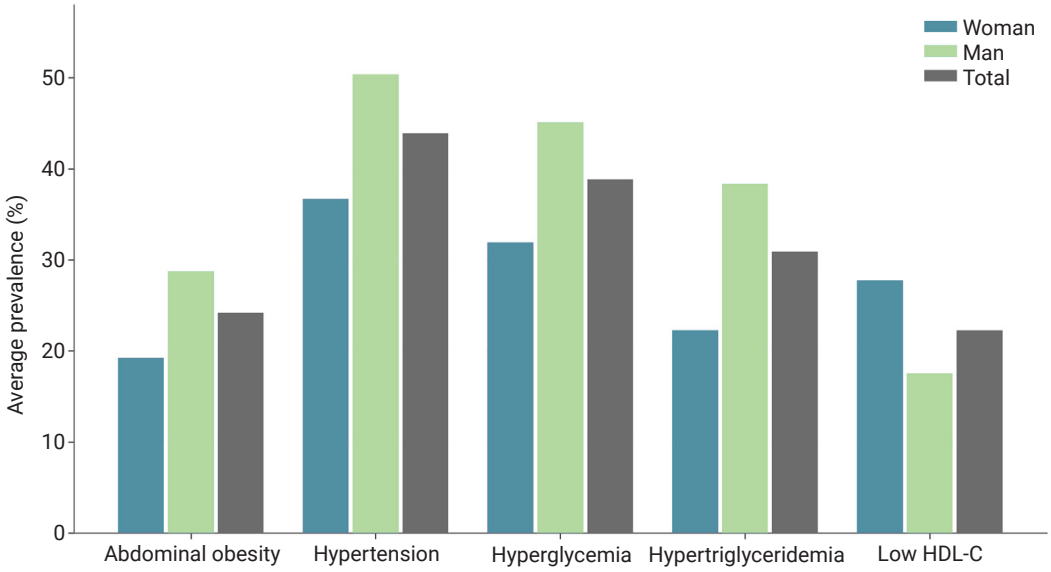


Figure 3. Sex-specific average prevalence of metabolic syndrome components. Bars represent the average of annual crude prevalence (%) for women, men, and the total screened population (abdominal obesity, hypertension, and hyperglycemia: 2014–2017 and 2019–2023; hypertriglyceridemia and low high-density lipoprotein cholesterol [HDL-C]: 2014–2017). Men had a higher prevalence of abdominal obesity, hypertension, hyperglycemia, and hypertriglyceridemia, whereas women had a higher prevalence of low HDL-C.

Abdominal obesity showed a descriptive crossover in the ≥70-year age group, in which prevalence was higher among women than among men. For hypertriglyceridemia (2014–2017), a crossover occurred in the ≥70-year group in the 7-group classification; in 5-year age bands (Figure 4), prevalence among men peaked at 45–49 years (44.9%) and then declined, whereas prevalence among women increased steadily with age and exceeded that among men from 65–69 years (38.4% vs. 35.1%). Low HDL cholesterol (2014–2017) was more prevalent among women than among men in every age group.

Discussion

This study provides a national descriptive profile of 5 MetS components in the Republic of Korea based on aggregated repeated cross-sectional screening statistics from 2014 to 2023. Three main findings emerged. First, abdominal obesity and hyperglycemia increased, mainly before 2019; hypertension increased in both periods, partly reflecting the older age composition of examinees; and during the comparable period (2014–2017), hypertriglyceridemia increased, whereas low HDL cholesterol changed little. Second, prevalence differed substantially across age groups, particularly for hypertension and hyperglycemia. Third, sex-specific differences were pronounced, with men showing a higher prevalence of most components and older women showing descriptive crossover patterns for selected lipid-related indicators.

The observed increases in abdominal obesity and hyperglycemia

Table 4. Age-specific sex comparison of prevalence for key crossover indicators

Age group (y)	Abdominal obesity (men)	Abdominal obesity (women)	Hypertriglyceridemia (men)	Hypertriglyceridemia (women)	Low HDL cholesterol (men)	Low HDL cholesterol (women)
20–29	21.2	7.8	21.1	5.2	8.9	10.9
30–39	30.5	11.8	37.8	9.3	13.9	15.3
40–49	29.7	13.8	44.7	14.2	16.7	20.7
50–59	27.8	18.3	41.9	26.2	19.3	29.0
60–69	29.8	28.0	37.2	36.3	22.6	41.6
≥70	32.0	38.4	30.8	39.8	25.4	48.9

Values are averages of annual estimates: abdominal obesity, 2014–2017 and 2019–2023; lipid indicators, 2014–2017. Crossover patterns were identified descriptively from observed average prevalence values and were not formally tested using individual-level statistical models. Crossover was defined as an age group in which prevalence among women exceeded that among men for the corresponding component. The ≤19-year group (shown in Table 2) is omitted because examinees in this group are a small, selected subset (10,655–28,843 per year) whose estimates are not representative.
HDL, high-density lipoprotein.

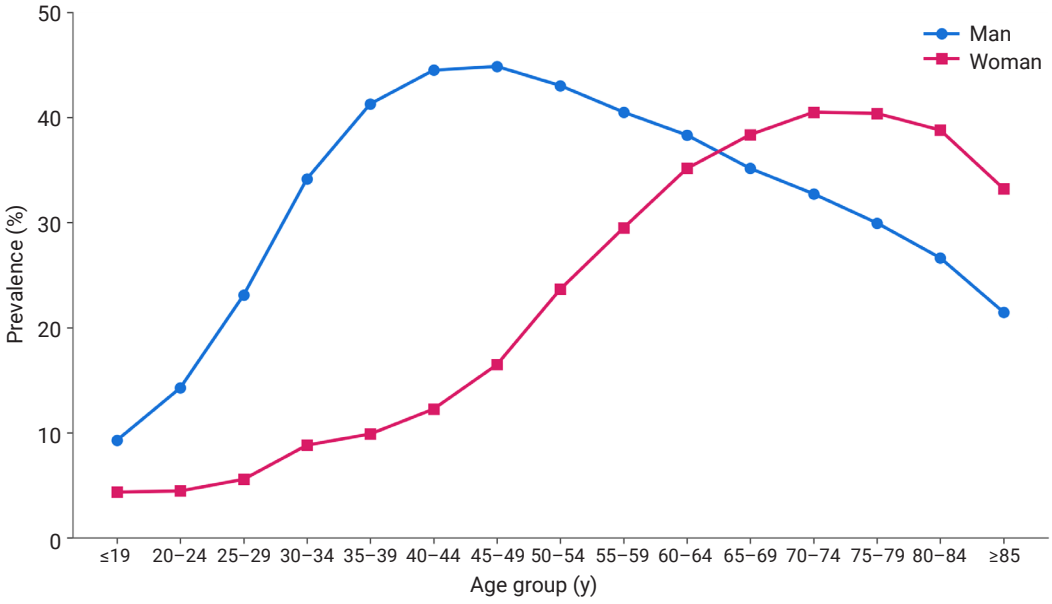


Figure 4. Age-specific sex crossover pattern in hypertriglyceridemia prevalence by 5-year age band (average of 2014–2017). Prevalence among men peaked at 45–49 years (44.9%) and declined thereafter, whereas prevalence among women increased with age and exceeded that among men from 65–69 years.

are consistent with recent Korean epidemiological evidence indicating a persistent or increasing cardiometabolic burden [5,16]. National diabetes surveillance has shown that diabetes remains highly prevalent among Korean adults, particularly older adults, and frequently coexists with obesity, hypertension, and hypercholesterolemia [6]. National dyslipidemia surveillance likewise indicates that lipid disorders remain common in the Republic of Korea, although awareness, treatment, and control have improved [7]. Collectively, these findings indicate that the observed increases in adiposity- and glycemia-related indicators are epidemiologically plausible, whereas lipid-related indicators after 2017 could not be compared because of the change in the dyslipidemia screening schedule.

Comparability of Screening Statistics Across 2018

The apparent decline in lipid-related indicators in the yearbook series reflected a change in the screening program rather than an epidemiological change. From 2018, the dyslipidemia panel was provided at 4-year intervals to men aged ≥24 years and women aged ≥40 years. The 2018 yearbook compiled its metabolic risk-factor tables only for examinees who received the panel, so that year's estimates for all 5 components refer to an age- and sex-restricted subgroup that included almost no women younger than 40 years; from 2019, all examinees were used as the denominator, whereas lipid abnormalities could be identified only among those tested or treated. In the comparable period (2014–2017), hypertriglyceridemia

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increased, whereas low HDL cholesterol changed little; thus, the screening statistics provide no consistent evidence of improvement in lipid-related indicators. Monitoring lipid indicators from routine screening statistics therefore requires denominators restricted to examinees who received the lipid panel. Including the 2018 values also changed the hypertension trend estimate substantially, illustrating how sensitive estimates from short annual series are to a single non-comparable observation.

Divergent Component Trends: Adiposity and Glycemia Increases

Abdominal obesity and hyperglycemia increased over the study period, mainly before 2019, and changed little during 2019–2023, indicating greater population-level burdens of central adiposity and dysglycemia than at the start of the period. Because the composition of examinees changed in 2019 (the number of examinees aged 20–39 years increased), the later plateau should be interpreted cautiously; however, the pattern was similar after age and sex standardization. These patterns are epidemiologically important because central adiposity and glycemic dysregulation are major contributors to cardiovascular disease and diabetes risk. The findings suggest that prevention and management efforts may need to place greater emphasis on weight-related behaviors and the early identification of glycemic risk across age groups.

Age-Specific Patterns and Implications for Prevention

Average prevalence generally increased across older age groups, although the pattern was not strictly monotonic for all components. Hypertension and hyperglycemia showed the steepest age-related gradients, which may partly reflect age-related physiological changes in vascular stiffness, insulin resistance, and glucose regulation. These patterns are consistent with established age-related increases in vascular stiffness and insulin resistance and with declining β-cell function [9].

For abdominal obesity, the largest difference between adjacent age groups was observed between the 20–29- and 30–39-year groups (8.8 percentage points).

The age-specific findings should be interpreted as differences among population age groups rather than as evidence of within-person life-course progression. The higher prevalence of abdominal obesity in the 30–39-year group than in the 20–29-year group may be associated with variation in lifestyle and social factors across early adulthood, including work patterns, physical activity, dietary habits, and other health behaviors. However, these explanations remain hypothetical because the study did not include individual-level behavioral or socioeconomic variables. The observed age-group pattern may therefore identify a potentially important period for prevention at the population level but should not be interpreted as evidence of specific causal mechanisms. Moreover, because the analysis was based on aggregated screening statistics, it cannot determine whether the pattern reflects individual weight gain, cohort differences, changes in screening participation, or unmeasured behavioral and socioeconomic factors.

Sex Differences and Targeted Prevention Priorities

Sex-stratified results showed that men had a higher prevalence of abdominal obesity, hypertension, hyperglycemia, and hypertriglyceridemia, whereas women had a higher prevalence of low HDL cholesterol.

The increase in abdominal obesity between 2014 and 2023 was substantially greater among men (+8.1 percentage points) than among women (+0.9 percentage points).

These findings are consistent with reported sex differences in visceral adipose tissue accumulation and metabolic risk [17].

Age-specific analyses further suggested that the higher prevalence of abdominal obesity among men was particularly pronounced in mid-adulthood (30s and 40s). This pattern suggests that screening and lifestyle programs directed toward men in these age groups may have substantial population-level relevance.

Sex Crossover in Older Women and the Role of Menopausal Transition

The sex crossover patterns observed for abdominal obesity (≥70 years) and hypertriglyceridemia (from 65–69 years), together with the higher prevalence of low HDL cholesterol among women in all age groups, suggest that prevalence varies by sex across age groups and becomes higher among women for some indicators in midlife or older age.

These patterns are consistent with menopause-related hormonal changes, including declining estrogen levels, that have been associated with changes in lipid metabolism and cardiovascular risk profiles [10,11].

From a clinical and public health perspective, these findings support consideration of more proactive dyslipidemia monitoring and management in perimenopausal and postmenopausal women, with risk communication that accounts for life-stage changes.

Strengths, Limitations, and Future Research Directions

A key strength of this study is the use of nationwide screening

statistics spanning the full age spectrum over a 10-year period, which enabled large-scale descriptive assessment of age- and sex-specific prevalence patterns. Identification of the 2018 change in the denominator of the yearbook tables and restriction of the analyses to comparable years also improve the validity of the temporal comparisons.

This study has several limitations. First, the analysis was based on aggregated repeated cross-sectional screening statistics; therefore, ecological fallacy is possible, and within-person changes, incidence, cumulative exposure, and causal pathways could not be assessed. Second, although direct age and sex standardization was performed, changes in screening eligibility and participation (e.g., the increase in examinees aged 20–39 years from 2019) may have altered the composition of examinees beyond age and sex. Third, individual-level behavioral, clinical, and socioeconomic factors, including diet, physical activity, smoking, alcohol use, medication use, income, education, and comorbidities, could not be accounted for. Fourth, screening participation bias may have affected the observed prevalence estimates because the data included only individuals who participated in the national health screening program. Fifth, only 9 annual observations (4 for lipid indicators) were available, time-series autocorrelation was not formally assessed, and because many individuals are screened repeatedly across years, the annual estimates were not independent; the reported confidence intervals and p-values are therefore likely to be too narrow. Finally, because of the 2018 change in the dyslipidemia screening schedule, lipid indicators could be compared only for 2014–2017. In addition, examinees aged ≤19 and 20–29 years represent restricted subsets of these age groups, so the estimates for these groups are not representative of the general population.

Future research should use denominators restricted to examinees who received the lipid panel when monitoring lipid indicators from screening statistics.

These findings have several public health implications. First, the increases in abdominal obesity and hyperglycemia suggest potential benefits of earlier cardiometabolic risk screening and lifestyle intervention, particularly from young adulthood through midlife. Second, the higher prevalence of abdominal obesity, hypertension, hyperglycemia, and hypertriglyceridemia among men suggests that workplace- and community-based prevention programs directed toward men in early and middle adulthood may warrant consideration. Third, the descriptive crossover patterns observed among older women for abdominal obesity and lipid-related indicators support consideration of more proactive cardiometabolic monitoring before and after the menopausal transition. Finally, surveillance systems should continue to monitor individual MetS components while explicitly documenting changes in screening participation, reporting procedures, and institutional rules that could affect temporal comparability.

Conclusion

From 2014 to 2023, the prevalence of MetS components in Korean national screening statistics showed heterogeneous temporal, age-specific, and sex-specific patterns. Abdominal obesity and hyperglycemia increased, mainly before 2019, suggesting the potential value of earlier cardiometabolic prevention efforts, whereas lipid-related indicators were comparable only for 2014–2017, when hypertriglyceridemia increased and low HDL cholesterol changed little. The higher prevalence observed in older age groups and the distinct sex-specific patterns support consideration of age- and sex-tailored prevention strategies, including screening in early adulthood, workplace-based lifestyle interventions, and targeted cardiometabolic monitoring in midlife and older women. Because this study used aggregated repeated cross-sectional data, the findings should be interpreted as descriptive population-level patterns rather than as individual life-course changes or causal trajectories. Future studies incorporating individual-level longitudinal analyses and lipid-panel-specific denominators are needed to further clarify changes in cardiometabolic risk patterns in the Republic of Korea.

Supplementary Material

Table S1. Values extracted from the NHIS National Health Screening Statistical Yearbooks, 2014–2023; **Table S2.** Crude and directly age- and sex-standardized prevalence (%) of metabolic syndrome components by year; **Table S3.** Risk-factor counts compared with laboratory-threshold counts, 2018 and 2023. Supplementary data are available at https://doi.org/10.24171/j.phrp.2026.0195.

Notes

Ethics Approval

This study used publicly available aggregated data from the NHIS National Health Screening Statistical Yearbook and did not involve individually identifiable information. Therefore, institutional review board approval was not required.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Korea and the National Research Foundation of Korea (grant number: NRF-2020S1A5C2A02092454).

Availability of Data

The values extracted from the NHIS National Health Screening Statistical Yearbooks (Table VIII-6, 2014–2017; Table VII-6, 2018–2023) by year, sex, and age group are provided in Table S1, together with the yearbook table numbers and access dates.

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Brief Report

Genomic insight into a festival-linked foodborne outbreak caused by enterotoxigenic *Staphylococcus aureus* ST1-*t321* in the Republic of Korea

Yu-Jin Park[1], Joohyun Han[1], Wooju Kang[1], Yeongeun Seo[1], Mooneui Hong[1], Soo Young Lee[2], Jaeil Yoo[1], Junyoung Kim[1], Eunkyung Shin[1]

[1]Division of Bacterial Diseases, Department of Laboratory Diagnosis and Analysis, Korea Disease Control and Prevention Agency, Cheongju, Republic of Korea
[2]Chungcheongnam-do Institute of Health and Environmental Research, Hongseong, Republic of Korea

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Corresponding author:
Eunkyung Shin
Division of Bacterial Diseases, Department of Laboratory Diagnosis and Analysis, Korea Disease Control and Prevention Agency, 187 Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju 28159, Republic of Korea
E-mail: ekshin1090@korea.kr

Co-Corresponding author:
Junyoung Kim
Division of Bacterial Diseases, Department of Laboratory Diagnosis and Analysis, Korea Disease Control and Prevention Agency, 187 Osongsaengmyeong 2-ro, Osong-eup, Heungdeok-gu, Cheongju 28159, Republic of Korea
E-mail: Jun49@korea.kr

ABSTRACT

Objectives: This study investigated a large-scale foodborne outbreak caused by *Staphylococcus aureus* during a local festival in the Republic of Korea and performed genomic and molecular epidemiological analyses using whole-genome sequencing (WGS).
Methods: Microbiological identification was performed using clinical, food, and environmental samples. Molecular characterization included pulsed-field gel electrophoresis (PFGE), multilocus sequence typing, and *spa* typing. WGS was conducted to evaluate clonal relatedness, virulence factors, and antimicrobial resistance genes.
Results: A total of 141 suspected cases and 18 laboratory-confirmed cases were identified, and 24 *S. aureus* isolates were recovered (18 from patients, 3 from food samples, and 3 from environmental samples). All 17 isolates included in the genomic analysis carried the *sea* and *sec* genes and belonged to ST1-*t321*, with pairwise differences of 8–33 SNPs, consistent with a clonal origin. These isolates exhibited a previously unreported PFGE pattern (STAS16.170) in the Republic of Korea. Virulence profiling identified hemolysin genes (*hlgA*, *hlgB*, *hlgC*), leukocidin genes (*lukD*, *lukE*), and immune evasion genes (*sak*, *scn*). In addition, all isolates were methicillin-susceptible and lacked *mecA* and *mecC*.
Conclusion: This large-scale foodborne outbreak demonstrated that a single contaminated food source can result in widespread illness during mass gatherings. Genomic analysis clarified the clonal relatedness of the outbreak strains and highlighted the value of genomic surveillance for the early detection and prevention of *S. aureus* outbreaks.

Keywords: Disease outbreaks; Electrophoresis, gel, pulsed-field; Foodborne diseases; *Staphylococcus aureus*; Whole genome sequencing

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Introduction

Foodborne outbreaks have increased in scale and complexity because of changing dietary habits, climate change, and expanding interregional exchange [1–3]. These outbreaks can affect many people within a short period and impose substantial socioeconomic burdens. *Staphylococcus aureus* is a major cause of foodborne illness because it produces staphylococcal enterotoxins (SEs) [4–6]. Genomic studies have also described the diversity, adaptive evolution, and antibiotic-resistant lineages of foodborne *S. aureus*, supporting continued surveillance in food safety programs [7].

SEs are resistant to heat and proteolytic enzymes and remain stable across a broad pH range, allowing them to persist in foods, ingredients, cooked meals, and contaminated utensils after cooking or reheating [8,9]. More than 20 SE genes have been identified [5]. Among the classical SEs, SEA, SEB, SEC, SED, and SEE have been implicated in staphylococcal food poisoning outbreaks [10,11], with SEA reported most frequently [4,8,12]. In the Republic of Korea, the *sea* gene was identified in approximately 90% of outbreak-associated isolates collected between 1999 and 2002 [12]. Staphylococcal food poisoning typically causes abdominal pain, vomiting, diarrhea, and fever after an incubation period of 0.5–8 hours [5,13].

In the Republic of Korea, *S. aureus* food poisoning outbreaks are reported almost annually and are mainly associated with mass food preparation, including school meal services, industrial catering, and community events [13,14]. Contributing factors include inadequate hygiene during food preparation, improper storage, contaminated ingredients or utensils, and poor food-handler hygiene.

In April 2025, a large foodborne *S. aureus* outbreak occurred among attendees of a local festival in Chungcheong Province who had consumed boxed meals from a local supplier. This study characterized the outbreak-associated isolates using microbiological, molecular epidemiological, and whole-genome sequencing (WGS) analyses to describe their toxin profiles, genetic relatedness, virulence determinants, and antimicrobial resistance features.

HIGHLIGHTS

- A large-scale foodborne outbreak occurred during a festival in Chungcheong Province, and *Staphylococcus aureus* was isolated from specimens obtained from 18 patients, 3 food samples and 3 environmental samples from food-preparation areas.
- Seventeen outbreak-associated isolates harbored the *sea* and *sec* genes and exhibited a novel pulsed-field gel electrophoresis pattern (STAS16.170) that had not previously been reported in the Republic of Korea.
- Whole-genome sequencing (WGS)-based analysis revealed that these 17 isolates belonged to ST1-*t321* and differed by 8–33 single-nucleotide polymorphisms, consistent with a clonal origin.
- This study highlights the importance of WGS-based surveillance for the rapid identification and control of *S. aureus* outbreaks during large public gatherings.

Materials and Methods

Bacterial Isolation from Clinical, Food, and Environmental Samples

On April 16, 2025, during a public festival in Chungcheong Province, Republic of Korea, multiple attendees developed acute gastrointestinal symptoms after consuming lunch boxes from a local food supplier. Among 862 exposed individuals (819 festival participants, 38 industrial workers, and 5 food handlers), clinical specimens (stool samples or rectal swabs) were collected from 39 symptomatic individuals and 5 food handlers. In addition, 12 nonclinical specimens were obtained, including 5 cooking-utensil specimens (1 knife, 2 cutting boards, 1 dishcloth, and 1 pair of kitchen shears), 5 food items (stir-fried pork, rolled omelet, soybean paste soup with mallow, stir-fried anchovies, and braised tofu), and 2 water samples (drinking and cooking water). Clinical specimens were collected through local public health centers because symptomatic individuals resided in multiple areas. Food and environmental specimens were obtained from the City F supplier that delivered the implicated lunch boxes. All specimens were screened at the Chungcheongnam-do Institute of Health and Environmental Research according to standardized protocols for 18 bacterial and 7 viral intestinal pathogens. *S. aureus* was cultured on Mannitol Salt Agar and subcultured on Tryptic Soy Agar overnight at 37 °C. Ultimately, 24 *S. aureus* isolates were recovered: 18 from patients, 3 from food samples (rolled omelet, stir-fried anchovies, and braised tofu), and 3 from environmental sources (1 knife and 2 cutting boards). Isolates were stored at −20 °C until transfer to the Korea Disease Control and Prevention Agency for molecular and genomic analysis.

Identification of *S. aureus* and Detection of Toxin Genes

Isolates were identified using the VITEK II system (bioMérieux). Multiplex polymerase chain reaction targeting 8 SE genes

(*sea*, *seb*, *sec*, *sed*, *see*, *seg*, *seh*, and *sei*) was performed using the PowerChek *Staphylococcus aureus* Toxin ID Detection Kit (Kogene Biotech).

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing (AST) was performed using broth microdilution. Initial minimum inhibitory concentration (MIC) testing used a customized KRCDCM plate (Trek Diagnostic Systems) that included imipenem, meropenem, doripenem, ciprofloxacin, levofloxacin, cefoxitin, oxacillin, vancomycin, amikacin, tobramycin, and teicoplanin to screen for methicillin and vancomycin resistance. Expanded AST used the GPALL1F panel (Trek Diagnostic Systems) to determine MICs for chloramphenicol, daptomycin, gentamicin, linezolid, rifampin, trimethoprim-sulfamethoxazole, quinupristin-dalfopristin, tetracycline, erythromycin, oxacillin, ampicillin, penicillin, vancomycin, levofloxacin, tigecycline, moxifloxacin, clindamycin, streptomycin, ciprofloxacin, and nitrofurantoin. Results were interpreted according to Clinical and Laboratory Standards Institute guidelines [15].

Pulsed-Field Gel Electrophoresis

Pulsed-field gel electrophoresis (PFGE) was performed according to the PulseNet International protocol to assess genetic relatedness among strains. Plug fragments were incubated with 40 U of *SmaI* (Roche Diagnostics) at 25 °C for 5 hours. Electrophoresis was performed at 6 V/cm for 18 hours with pulse times of 5.16–40.17 seconds. PFGE similarity was analyzed using the Dice coefficient with a 1.5% band tolerance in BioNumerics v7.5 (Applied Maths).

Whole-Genome Sequencing Analyses

WGS was performed on 17 isolates with the *sea-sec* enterotoxin profile. Genomic DNA was extracted using the DNeasy Blood & Tissue Kit (Qiagen). Libraries were prepared with the Nextera DNA Prep Kit (Illumina Inc.) and sequenced on an Illumina MiSeq platform. Reads were quality-checked using FastQC v0.12.0 (Babraham Bioinformatics) and processed, trimmed, and assembled *de novo* using CLC Genomics Workbench ver. 25 (Qiagen). Multilocus sequence typing (MLST), *spa* typing, and staphylococcal cassette chromosome *mec* (SCC*mec*) element detection were performed using MLST, *spa*Typer, and SCC*mec*Finder from the Center for Genomic Epidemiology. Virulence-associated genes were identified using VirulenceFinder and the Virulence Factor Database at a ≥90% identity threshold. WGS-based single nucleotide polymorphism (SNP) analysis was performed using CSI Phylogeny ver. 1.4 (Center for Genomic Epidemiology) for phylogenetic inference with the default settings: minimum depth at SNP positions, 10X; minimum relative depth at SNP positions, 10%; minimum distance between SNPs (prune), 10 bp; minimum SNP quality, 30; minimum read-mapping quality, 25; and minimum Z-score, 1.96. S. aureus subsp. aureus NCTC 8325 (GenBank accession NC_007795; 2,821,361 bp) was used as the reference genome. A total of 2,589,737 positions, corresponding to 91.79% of the reference genome, were shared and trusted across all 17 isolates and were used for pairwise SNP calling; the proportion of the reference genome covered by individual isolates ranged from 92.34% to 92.46%.

Results

Characteristics of Isolates

Laboratory-confirmed cases were reported in six counties or cities across Chungcheong Province: A ($n=4$), B ($n=2$), C ($n=4$), D ($n=2$), E ($n=3$), and F ($n=3$). Additional isolates were recovered in City F from environmental swabs ($n=3$; 1 knife and 2 cutting boards) and food samples ($n=3$; rolled omelet, stir-fried anchovies, and braised tofu) (Table 1). In total, 24 *S. aureus* isolates were recovered: 18 from patient specimens, 3 from environmental swabs, and 3 from food samples. Among these, 17 had the *sea-sec* profile, whereas 7 carried *seg* and *sei*. All isolates were susceptible to oxacillin, cefoxitin, and vancomycin and were classified as methicillin- and vancomycin-susceptible *S. aureus*. Expanded AST was performed on two representative isolates, one from each enterotoxin-gene cluster, using GPALL1F panel. The *sea-sec*–positive isolate was resistant to chloramphenicol and penicillin, intermediate to gentamicin, and susceptible to

Table 1. The number of *Staphylococcus aureus* isolates obtained from each region and enterotoxin gene profile

County (city)	Origin	SE gene profile	
		sea-sec	*seg-sei*
A	Patient	4	-
B	Patient	1	1
C	Patient	2	2
D	Patient	1	1
E	Patient	2	1
F	Patient	2	1
	Food	2	1
	Environment	3	-
Total		17	7

The gene profile was identified by multiplex polymerase chain reaction. Most isolates were obtained in City F, where the implicated food supplier was located.
-, not detected.

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the other tested antibiotics; the *seg-sei*–positive isolate was resistant to chloramphenicol and penicillin but susceptible to all other tested antibiotics.

PFGE Pattern Characterization

PFGE analysis identified two patterns among the 24 isolates: STAS16.170 (n=17) and STAS16.065 (n=7), with 68.68% similarity. The STAS16.170 isolates shared the *sea-sec* profile and had not previously been reported in the Republic of Korea according to the national PulseNet Korea *S. aureus* database (Figure 1). The STAS16.065 isolates carried *seg* and *sei*. STAS16.170 was found in isolates from 12 patients, 2 food samples (rolled omelet and stir-fried anchovies), and 3 cooking utensils, whereas STAS16.065 was found in isolates from 6 patients and 1 food sample (braised tofu).

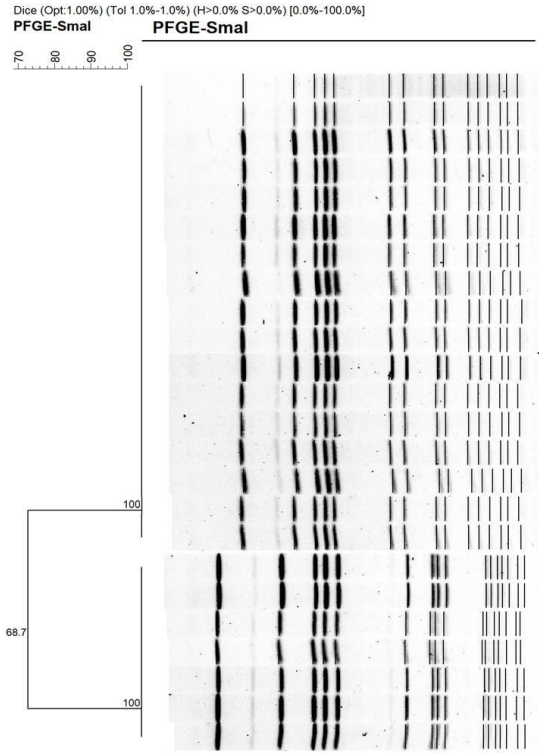
Genomic Characterization and SNP-Based Phylogenetic Relatedness

WGS analysis was performed on the 17 STAS16.170 isolates, the predominant PFGE cluster. All belonged to sequence type (ST) 1 and *spa* type *t321*. Genome-based screening identified virulence-associated genes *hlgA*, *hlgB*, *hlgC*, *lukD*, *lukE*, *sak*, and *scn* in all 17 isolates. SNP analysis showed close genetic relatedness, with pairwise differences of 8–33 SNPs (Figure 2).

Discussion

This study identified a large *S. aureus* foodborne outbreak at a festival in Chungcheong Province. Patients had typical symptoms of *S. aureus* food poisoning, including vomiting, abdominal pain, and diarrhea [5]. Food samples from the City F supplier were implicated, and molecular epidemiological analysis grouped all isolates into two PFGE patterns detected among patient, food, and environmental isolates.

The 17 isolates in the major PFGE pattern, STAS16.170, carried *sea* and *sec* (Figure 1). This finding is consistent with reports that SEA is the most frequent enterotoxin in staphylococcal food poisoning [4,13]. SEC, first identified in the 1960s [16,17], continues to be detected in recent outbreak studies [18,19]. Similar *sea*- and *sec*-positive *S. aureus* outbreaks have been reported at a university festival in Japan involving crêpes [20] and among more than 300 students in Vietnam who consumed chicken dishes [21]. These cases indicate that *S. aureus* strains carrying *sea* and *sec* can cause large outbreaks in mass catering or public-event settings.



No.	Strain ID	PFGE pattern	Toxin ID	Region	Source
1	KRSTA25-358	STAS16.170	sea, sec	A	patient
2	KRSTA25-359	STAS16.170	*sea, sec*	A	patient
3	KRSTA25-360	STAS16.170	*sea, sec*	A	patient
4	KRSTA25-361	STAS16.170	*sea, sec*	A	patient
5	KRSTA25-363	STAS16.170	*sea, sec*	B	patient
6	KRSTA25-365	STAS16.170	*sea, sec*	C	patient
7	KRSTA25-366	STAS16.170	*sea, sec*	C	patient
8	KRSTA25-368	STAS16.170	*sea, sec*	D	patient
9	KRSTA25-370	STAS16.170	*sea, sec*	E	patient
10	KRSTA25-371	STAS16.170	*sea, sec*	E	patient
11	KRSTA25-374	STAS16.170	*sea, sec*	F	patient
12	KRSTA25-375	STAS16.170	*sea, sec*	F	patient
13	KRSTA25-376	STAS16.170	*sea, sec*	F	Environment
14	KRSTA25-377	STAS16.170	*sea, sec*	F	Environment
15	KRSTA25-378	STAS16.170	*sea, sec*	F	Environment
16	KRSTA25-379	STAS16.170	*sea, sec*	F	Food
17	KRSTA25-380	STAS16.170	*sea, sec*	F	Food
18	KRSTA25-362	STAS16.065	*seg, sei*	B	patient
19	KRSTA25-364	STAS16.065	*seg, sei*	C	patient
20	KRSTA25-367	STAS16.065	*seg, sei*	C	patient
21	KRSTA25-369	STAS16.065	*seg, sei*	D	patient
5	KRSTA25-372	STAS16.065	*seg, sei*	E	patient
6	KRSTA25-373	STAS16.065	*seg, sei*	F	Patient
7	KRSTA25-381	STAS16.065	*seg, sei*	F	Food

Figure 1. Pulsed-field gel electrophoresis (PFGE) results for the 24 isolates associated with the outbreak. Two PFGE patterns were identified, STAS16.170 (n=17) and STAS16.065 (n=7), with 68.68% similarity between the 2 clusters.

Isolates		Genome data				Virulence factors									SNP matrix															
No.	Strain ID	Genome size (bp)	% GC	No. of contigs	Coverage (x)	*hlgA*	*hlgB*	*hlgC*	*lukD*	*lukE*	*sea*	*sec*	*sak*	*scn*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1	KRSTA25-358	2,726,684	33.0	28	64.22											27	28	22	14	15	22	27	11	18	11	9	28	17	18	21	22
2	KRSTA25-359	2,727,512	33.0	27	68.75										27		9	25	29	26	27	24	26	33	26	24	17	32	25	16	15
3	KRSTA25-360	2,727,575	32.5	28	62.45										28	9		22	26	23	20	21	21	30	23	25	14	31	22	15	14
4	KRSTA25-361	2,728,911	33.0	27	50.12										22	25	22		20	15	16	19	19	22	15	19	22	21	14	17	22
5	KRSTA25-363	2,727,788	32.0	26	50.97										14	29	26	20		15	22	25	13	16	11	11	26	15	18	21	24
6	KRSTA25-365	2,727,373	32.0	26	58.65										15	26	23	15	15		17	26	10	17	10	10	23	16	21	22	19
7	KRSTA25-366	2,729,755	33.0	25	54.18										22	27	20	16	22	17		21	13	18	19	21	22	25	12	21	18
8	KRSTA25-368	2,727,966	32.0	28	50.17										27	24	21	19	25	26	21		24	27	20	24	31	26	13	16	29
9	KRSTA25-370	2,730,387	32.0	26	57.86										11	26	21	19	13	10	13	24		17	10	12	23	14	19	20	17
10	KRSTA25-371	2,728,469	32.0	29	61.38										18	33	30	22	16	17	18	27	17		15	15	30	15	14	27	28
11	KRSTA25-374	2,728,430	33.0	28	63.19										11	26	23	15	11	10	19	20	10	15		8	25	14	15	18	25
12	KRSTA25-375	2,728,144	32.0	25	75.06										9	24	25	19	11	10	21	24	12	15	8		27	16	15	20	21
13	KRSTA25-376	2,726,795	32.5	28	60.26										28	17	14	22	26	23	22	31	23	30	25	27		27	24	25	12
14	KRSTA25-377	2,729,343	32.0	26	59.07										17	32	31	21	15	16	25	26	14	15	14	16	27		21	26	25
15	KRSTA25-378	2,728,549	32.0	33	78.10										18	25	22	14	18	21	12	13	19	14	15	15	24	21		17	22
16	KRSTA25-379	2,727,570	32.0	27	46.17										21	16	15	17	21	22	21	16	20	27	18	20	25	26	17		25
17	KRSTA25-380	2,728,812	33.0	26	58.86										22	15	14	22	24	19	18	29	17	28	25	21	12	25	22	25	

Figure 2. Whole-genome sequencing analysis results and isolate information for the 17 isolates carrying the *sea-sec* genes among the 24 isolates associated with the outbreak. The single nucleotide polymorphism (SNP) matrix indicates the number of SNP differences among isolates, with increasing red-shading intensity representing greater genetic distance. The sequenced genomes have been registered with National Center for Biotechnology Information under BioProject PRJNA1455267, and the BioSample numbers are SAMN57359915 and SAMN57359925–SAMN57359940.
hlg A/B/C, hemolysin A/B/C; *luk D/E*, leukocidin D/E; *sak*, staphylokinase; *scn*, staphylococcal complement inhibitor.

In the present study, WGS confirmed that all 17 analyzed isolates belonged to ST1-*t321* and differed by only 8–33 SNPs, consistent with a clonal origin consistent with the PFGE results. SNP-level variation detected by WGS also revealed microevolutionary differences within the ST1 lineage that traditional subtyping could not resolve [22,23]. ST1 is one of the most frequently reported staphylococcal food poisoning clones in the Republic of Korea [12]. Although ST1-*t321* has been reported sporadically in China, Kuwait, and Malaysia [24–26], it has not been reported in the Republic of Korea, possibly because WGS-based *spa* typing data for domestically circulating *S. aureus* remain limited. Thus, the strain may have been recently introduced or may have circulated at low levels before this outbreak. Continued genomic surveillance is needed to clarify the prevalence, geographic distribution, and enterotoxin-gene associations of ST1-*t321* and related ST1 clones.

Virulence gene analysis showed that all outbreak isolates carried hemolysin genes (*hlgA*, *hlgB*, *hlgC*), leukocidin genes (*lukD*/*lukE*), and immune evasion cluster genes (*sak* and *scn*). These genes encode factors associated with erythrocyte and epithelial cell membrane damage, leukocyte pore formation, and immune evasion through complement interference and reduced opsonization [27–30]. Their presence indicates that the ST1-*t321* outbreak lineage carried multiple virulence-associated determinants.

AST results showed that all isolates were susceptible to oxacillin, cefoxitin, and vancomycin, and no *mecA* or *mecC* genes were detected, confirming that the isolates were methicillin-susceptible and vancomycin-susceptible *S. aureus*. Representative isolates were resistant to penicillin and chloramphenicol; however, because resistance to these 2 agents is relatively common in *S. aureus*, these findings should be interpreted as supportive phenotypic information. Although antimicrobial resistance was not a defining feature of this outbreak, multidrug-resistant (MDR) and methicillin-resistant *S. aureus* in food-related transmission settings remain public health concerns [31,32]. Continued AST-based monitoring can support surveillance for emerging MDR *S. aureus* strains.

These findings should be interpreted in light of several limitations. Because this study was based on isolates from a single festival-associated outbreak, generalizability may be limited. In addition, individual-level food-consumption histories, exact symptom-onset times, and complete data on food preparation, storage, transport, and distribution were unavailable, preventing definitive matching of patients to specific contaminated foods. Although SNP-based genomic analysis showed close relatedness among isolates from patients, foods, and food-contact surfaces, these data alone could not determine the direction of contamination. Furthermore, WGS focused primarily on the predominant *sea-sec*–positive cluster; therefore, the epidemiological significance of the *seg-sei*–positive isolates requires further clarification. SNP distances were estimated against a non-ST1 reference genome (NCTC 8325) without recombination

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filtering, which may have inflated pairwise differences; the 8–33 SNP range should therefore be interpreted together with the concordant PFGE and sequence-typing results.

Despite these limitations, this study identified a clonal group of enterotoxin-producing *S. aureus* ST1-*t321* strains associated with a festival-related foodborne outbreak. The isolates shared a PFGE pattern (STAS16.170) that had not previously been identified in the national PulseNet database used for routine *S. aureus* surveillance in the Republic of Korea. These findings show that mass food preparation at public gatherings requires strict hygiene control to reduce the risk of *S. aureus* foodborne outbreaks.

Continued PFGE- and WGS-based surveillance, supported by sequencing capacity, bioinformatics expertise, and genomic epidemiology training, can help detect emerging variants, monitor virulence and antimicrobial resistance, and guide outbreak control.

Notes

Ethics Approval
Not applicable.

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 may be obtained from the corresponding author upon reasonable request.

Authors' Contributions
Conceptualization: JK, ES, JY; Data curation: MH; Formal analysis: YJP; Investigation: SYL, YJP, JH, WK, YS; Project administration: JK, ES, JY; Resources: SYL; Supervision: JY; Writing–original draft: YJP; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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OSONG PUBLIC HEALTH AND RESEARCH PERSPECTIVES

Instruction for authors

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

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Contact Us

Editorial Office: Korea Disease Control and Prevention Agency National Center for Medical Information and Knowledge, 202 Osongsengmyung 2nd street, Osong-eup, Heungdeok-gu, Cheongju 28159, Korea
E-mail: ophrp@korea.kr

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ARTICLE PROCESSING CHARGES

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

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

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

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

Table 1. Key features and limits of articles

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

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Title Page

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  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.
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  1. Park HY. The role of the thrombomodulin gene in the development of myocardial infarction [dissertation]. Yonsei University; 2000.

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