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

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Editorial

The Republic of Korea's post-COVID-19 pandemic preparedness: it is time to assess the progress of pandemic preparedness

Jong-Koo Lee

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In May 2023, the Korean government announced strategic priorities as part of its mid- to long-term preparedness plan for future infectious disease pandemics. Drawing lessons from the H1N1 influenza and Middle East respiratory syndrome outbreaks, this plan emphasized the need to build advanced response capabilities to prevent future outbreaks from escalating into national security threats. Rather than perceiving the conclusion of the coronavirus disease 2019 (COVID-19) pandemic as the end of infectious disease risks, the government expressed its commitment to securing essential medical countermeasures—such as vaccines—within 100 to 200 days of an outbreak onset. Additionally, it plans to establish a scalable response system capable of handling up to 1 million daily cases and implement enhanced protections for vulnerable populations to minimize critical illness, mortality, and health inequities. To operationalize these objectives, the government's approach is structured around 5 core pillars (surveillance and prevention, preparedness and response, infrastructure, recovery, and research and development) mapped onto 10 detailed initiatives [1].

At the international level, the World Health Organization (WHO) has launched a series of legal and operational reforms aimed at strengthening global health security. In November 2022, WHO established the Working Group on Amendments to the International Health Regulations (IHR) to revise the IHR (2005). Following 8 rounds of negotiations, the agreed draft was submitted at the 77th World Health Assembly in May 2024 and is expected to enter into force without a vote in June 2025 [2]. Complementing the IHR revisions, WHO member states also reached a draft consensus on a Pandemic Agreement after more than 3 years of negotiations under the Intergovernmental Negotiating Body. This is new international legal instrument under the WHO Constitution, and is designed to enhance global collaboration on the prevention, preparedness, and response to future pandemics [3].

In parallel with these legal frameworks, there has been progress in the development of medical countermeasures for priority diseases. Notably, preparations are underway for the possible human transmission of highly pathogenic avian influenza H5N1. The Republic of Korea has increased its preparedness for highly pathogenic avian influenza H5N1. First identified in Guangdong, China, in 1996, H5N1 has caused significant outbreaks among poultry and wild birds worldwide. The emergence of the 2.3.4.4b variant since 2020 has expanded its host range to include mammals such as cats, minks, cattle, and marine mammals. Although

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human infections remain rare, asymptomatic cases have been reported, and the possibility of sustained human-to-human transmission cannot be excluded [4]. In the Republic of Korea, H5N1 was first confirmed in 2003, with additional data on wild and domestic animals recorded during the 2024–2025 season. Notably, this includes a 2023 outbreak among cats at a Seoul animal shelter and a confirmed case in a wild leopard cat in 2025. The government has responded by prioritizing surveillance of high-risk groups, stockpiling antivirals and personal protective equipment, and offering seasonal influenza vaccines to frontline workers. Concurrently, the development of mRNA vaccines against H5N1 is underway, aiming to facilitate mass vaccination within 100 days if needed [5]. Another emerging threat is Chikungunya virus (CHIKV), which has been reported in over 110 countries since its initial detection in Tanzania in 1952. Recent large-scale outbreaks have been linked to viral adaptation to Aedes mosquitoes. As of 2025, La Réunion has reported more than 20,000 cases, with local transmission confirmed in Mauritius and Mayotte [6]. These trends underscore the necessity for robust evidence regarding vaccine efficacy and deployment to effectively support international public health responses.

The Republic of Korea has adopted a 2-track approach to vaccine development. For diseases such as severe fever with thrombocytopenia syndrome, influenza, COVID-19, respiratory syncytial virus, and Hantaan virus, the goal is to develop domestic vaccines. Conversely, for diseases with lower domestic prevalence—such as Lassa fever, dengue, Nipah virus, and Chikungunya—the country plans to collaborate with the Coalition for Epidemic Preparedness Innovations and other global partners [7].

However, recent political and institutional instability threatens to undermine these efforts. Prolonged medical-professional disputes following the announcement of increased medical school quotas have led to mass withdrawals of students and residents, raising concerns that medical research and development capacity could be set back by a decade. Funding cuts prompted by public backlash against alleged research cartels have further strained the Republic of Korea's research infrastructure, contributing to an exodus of science, technology, engineering, and mathematics (STEM) talent toward the medical field. The situation was exacerbated by the impeachment of the president and a freeze on medical school enrollments in 2026, casting doubt on the future direction of the Republic of Korea's health system reform and biomedical innovation.

In light of the imminent implementation of the IHR amendments and the anticipated adoption of the Pandemic Agreement, this moment presents a critical opportunity to reassess the Republic of Korea's 2023 commitments. A renewed national review is essential to evaluate the progress of implementation and to formulate alternative strategies that ensure resilience and readiness for future global health threats.

Notes

Ethics Approval
Not applicable.

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

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Data Profile

Synthetic data production for biomedical research

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ABSTRACT

Synthetic data, generated using advanced artificial intelligence (AI) techniques, replicates the statistical properties of real-world datasets while excluding identifiable information. Although synthetic data does not consist of actual data points, it is derived from original datasets, thereby enabling analyses that yield results comparable to those obtained with real data. Synthetic datasets are evaluated based on their utility—a measure of how effectively they mirror real data for analytical purposes. This paper presents the generation of synthetic datasets through the Healthcare Big Data Showcase Project (2019–2023). The original dataset comprises comprehensive multi-omics data from 400 individuals, including cancer survivors, chronic disease patients, and healthy participants. Synthetic data facilitates efficient access and robust analyses, serving as a practical tool for research and education. It addresses privacy concerns, supports AI research, and provides a foundation for innovative applications across diverse fields, such as public health and precision medicine.

Keywords: Genomics; Life-log data; Omics-data; Public health; Synthetic data

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Introduction

Biomedical research increasingly relies on large-scale datasets, such as multi-omics data—including wearable life-log data, whole exome sequencing, whole genome sequencing, RNA sequencing (RNA-seq), and microbiome profiles—to uncover insights into human health. However, these datasets often contain sensitive information, which limits their accessibility and hampers research progress [1,2].

To address these challenges, the Healthcare Big Data Showcase Project (2019–2023) was launched to collect and integrate multi-omics and life-log data from 400 individuals, including cancer survivors, chronic disease patients, and healthy participants, thereby creating a valuable resource for healthcare research. Despite its comprehensive nature, the sensitivity of the dataset restricts its use, necessitating innovative solutions to facilitate analysis without compromising

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privacy [3].

Synthetic data have emerged as a transformative solution. By replicating the statistical properties of real data while eliminating identifiable information, synthetic datasets enable analyses that yield results comparable to those obtained with real data [1,4]. Unlike direct replicas, synthetic data are derived from original datasets and designed to mirror their statistical characteristics. Its utility is evaluated by how effectively it serves as a proxy for real data, allowing researchers to draw reliable conclusions while safeguarding privacy [5,6].

Among the various data types, life-log data were synthesized using advanced deep learning models, such as recurrent time-series generative adversarial networks (RTSGAN), due to their temporal structure and suitability for such models. Generative adversarial networks (GAN)-based approaches, such as the Wasserstein GAN, significantly improved the quality and stability of the synthesis process [7].

HIGHLIGHTS

- Each synthetic dataset includes1,000 individuals and was generated based on original datasets from 400 individuals in the Healthcare Big Data Showcase Project (2019–2023).
- Recurrent time-series generative adversarial network (RTSGAN), a state-of-the-art autoencoder-generative adversarial networks (GAN) model designed for irregularly timed medical data, was employed to generate synthetic datasets.
- Synthetic data replicate the statistical properties of real data, enabling privacy-preserving research without compromising analytical validity.
- Synthetic datasets for life-log, RNA sequencing, methyl-seq and microbiome data included 1,000 individuals each.
- Utility tests, including "train on synthesized, test on real" (TSTR) and "train on real, test on synthesized" (TRTS), demonstrated the practical value of synthetic data for predictive modeling.
- Synthetic data eliminate the need for institutional review board approval, overcoming barriers to data access and collaboration.
- Synthetic datasets enhance privacy, accessibility, offering broad societal and research benefits.

Methods

In this study, synthetic datasets comprising 1,000 individuals for each data type were generated based on original multi-omics and life-log data collected from 400 participants in the Healthcare Big Data Showcase Project (2019–2023) (Table 1).

For the life-log data, the RTSGAN model was employed to generate synthetic datasets (Supplementary Material 1). In contrast, synthetic sequencing data—including RNA-seq and methyl-seq—were generated using statistical methods tailored to each data type, whereas microbiome data were reconstructed without applying statistical perturbations.

The RTSGAN model, introduced at the 2021 Institute of Electrical and Electronics Engineers International Conference on Data Mining, is an autoencoder-based GAN architecture specifically designed for medical data with irregular time intervals, addressing limitations of conventional GAN models [8,9]. Life-log data were categorized into dynamic and static variables. Dynamic variables represent time-dependent information, such as daily weight, calories burned, and step count, whereas static variables include fixed attributes like date of birth, blood type, and gender. The RTSGAN model learns temporal and structural patterns from both types of variables, enabling the generation of synthetic data that reflects the statistical properties of the original data.

For RNA-seq data, synthetic datasets were created using 28,284 Ensembl gene IDs. Metrics such as read count, fragments per kilobase of transcript per million mapped reads (FPKM), and transcripts per million (TPM) were synthesized by introducing random errors to group-specific mean values, thereby mimicking realistic biological variability [5,9].

Synthetic methyl-seq data were generated by adding stochastic noise to group-level methylation averages, preserving statistical fidelity while introducing appropriate variation [5,10].

Microbiome datasets were generated by retaining microbial features and taxonomic classifications from original fecal and saliva samples, with all personal identifiers removed to ensure data privacy.

To assess the quality of the synthetic data, a "train on synthesized, test on real" (TSTR) evaluation was conducted (Table 2). This evaluation was performed exclusively on the synthetic life-log dataset generated using RTSGAN, owing to its temporal nature and suitability for downstream predictive modeling tasks. The results demonstrated a high degree of similarity between the synthetic and real data, as evidenced by comparable area under the receiver operating characteristic curve (AUROC) and classification accuracy in both test scenarios. Although scenario 2 showed a slight decline in performance, it remained within an acceptable range for practical applications.

In contrast, sequencing datasets such as RNA-seq, methyl-

Table 1. The Healthcare Big Data Showcase Project data

Multi-omics	Total (*n* = 399)			Normal (*n* = 99)			Chronic disease (*n* = 100)			Breast cancer (*n* = 80)			Colorectal cancer (*n* = 80)			Gastric cancer (*n* = 40)		
	1st[a)]	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd	1st	2nd	3rd
WGS	396	-	-	99	-	-	95	-	-	81	-	-	81	-	-	40	-	-
RNA-Seq	374	-	-	98	-	-	95	-	-	81	-	-	81	-	-	24	-	-
LiquidBx.	202	-	-	-	-	-	-	-	-	81	-	-	81	-	-	40	-	-
DTC genes	99	-	-	99	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Proteom	379	-	-	99	-	-	100	-	-	65	-	-	80	-	-	35	-	-
Methyl-Seq	390	44	-	99	-	-	90	-	-	81	16	-	81	-	-	39	-	-
Microbiome	353	140	168	99	79	73	89	61	40	46	-	34	79	-	21	40	-	-
Metabolume	313	165	-	92	-	49	78	-	51	30	-	-	74	65	-	39	-	-

WGS, whole genome sequencing; RNA-seq, RNA sequencing; -, not generated or not available.
[a)]The data were produced in 3 sequential stages, referred to as the first, second, and third phases.

Table 2. TSTR results (applied only to synthetic life-log data)

	Scenario 1	Scenario 2
AUROC[a)]	0.9844	0.9667
Accuracy	0.9999	0.9677

Scenario 1: The real dataset was split into a 9:1 ratio, with the model trained on 90% and evaluated on 10% of the real data; scenario 2: The model was trained on the entire synthetic dataset and tested on the real dataset to evaluate the synthetic data's utility.
TSTR, train on synthesized, test on real; AUROC, area under the receiver operating characteristic curve.
[a)]The AUROC measures a model's ability to distinguish between classes, with values closer to 1 indicating better performance.

seq, and microbiome were not subjected to TSTR validation, as these sequencing-based data types are primarily used for biological interpretation—such as differential expression and pathway analysis—rather than supervised classification. Therefore, their synthetic validity was assessed through the preservation of statistical distributions and biological patterns relative to the original data. Given these constraints, their validity was instead supported through statistical similarity assessments and the preservation of group-level trends relative to the original data. Nonetheless, the results confirm that RTSGAN-generated synthetic life-log data retain substantial analytical value and can serve as reliable proxies for real data in predictive modeling tasks [4,9].

Collection

Data Resource Area and Population Coverage

Synthetic datasets encompassing 1,000 individuals for each data type were generated based on original data collected from 400 participants in the Healthcare Big Data Showcase Project (2019–2023). These synthetic datasets provide an integrated view of microbial, genetic, and lifestyle metrics, enabling multidimensional analysis while preserving privacy.

The data were synthesized as follows: (1) microbiome data: Original fecal and saliva samples were processed using next-generation sequencing to identify microbial features and their taxonomic classifications. Synthetic datasets retained these structures without introducing additional statistical perturbations, thereby preserving the compositional integrity of the original microbiome profiles. (2) Life-log data: Activity, body composition, and sleep metrics were collected using wearable devices, providing temporal and longitudinal insights. Synthetic life-log datasets were generated using a recurrent time-series generative adversarial network (RTSGAN) to reflect irregular temporal dynamics. (3) Methyl-seq data: DNA methylation profiles covering 45,579 Ensembl gene IDs were synthesized by applying statistical noise to group-level methylation patterns to reflect epigenetic modifications. (4) RNA-seq data: Transcriptomic profiles including gene expression patterns (FPKM, read counts, TPM) were generated using 28,284 Ensembl gene IDs with random perturbations added to preserve the statistical properties of the original data.

This integrated synthetic data resource provides a comprehensive framework for exploring the relationships among microbiome composition, genetic and epigenetic features, and lifestyle behaviors in a privacy-preserving manner.

Survey Frequency

Since the dataset consisted of synthetic data, there were no actual survey dates or repeated measures.

Measures

Microbiome data: (1) feature IDs and DNA sequences: captured in the dna-seq folder; (2) feature abundance:

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stored as relative abundance in the feature table; (3) taxonomy: taxonomic classifications in the taxonomy folder.

Life-log data: (1) activity metrics: calories burned, distance, steps, activity time (vigorous, moderate, light), rest time; (2) body metrics: body mass index, body fat percentage, weight; (3) sleep metrics: awake time, rapid eye movement sleep time, light sleep time, total sleep time.

Methyl-seq data: (1) methylation matrix: Ensembl gene IDs (e.g., ENSG00000123456) and DNA methylation levels for each gene and patient; (2) summary statistics: a total of 45,579 genes analyzed and distribution of methylation values.

RNA-seq data: gene expression: Ensembl gene IDs (e.g., ENSG00000123456) and gene expression levels (FPKM, read count, and TPM) for each gene and patient with 28,284 genes.

Data Resource Use

The synthetic datasets generated from life-log, RNA-seq, Methyl-seq, and microbiome data offer a wide range of applications in predictive modeling, risk assessment, biomarker discovery, and public health research. By leveraging these datasets, researchers can address critical health challenges while maintaining privacy and data security. The expected benefits of synthetic data, combined with its versatile applications, render it a powerful tool for advancing healthcare and personalized medicine.

One of the primary applications of synthetic datasets is the development of predictive models for health monitoring and disease risk assessment. Using life-log data, researchers can identify behavioral patterns, such as physical activity levels and sleep quality, and correlate these with health outcomes like metabolic syndrome and mental health conditions. These insights are valuable for creating personalized health interventions and preventive strategies. For RNA and microbiome data, synthetic datasets enable the identification of biomarkers and predictive factors for a wide range of diseases, including cancer, chronic illnesses, and gastrointestinal disorders. By integrating RNA-seq and microbiome data with clinical information, researchers can develop robust risk stratification models to predict disease onset or progression, facilitating earlier diagnosis and targeted treatment strategies.

The multi-omics nature of the synthetic datasets facilitates the discovery of novel biomarkers by enabling the analysis of complex relationships between genetic, transcriptomic, and microbiome data. Gene expression profiles can be examined to identify transcriptional signatures specific to cancer subtypes or chronic disease conditions, thereby facilitating the discovery of potential therapeutic targets [2]. The composition of the gut microbiota can be linked to metabolic disorders or immune system dysregulation, aiding in the development of interventions to restore microbiome balance and treat related diseases. By identifying disease-specific biomarkers, synthetic data provides a foundation for population-specific biomarker identification and the development of diagnostic tools tailored to diverse demographic or health profiles. These findings can also lead to more accurate diagnostics and personalized treatments.

Synthetic datasets derived from life-log, RNA, and microbiome data also offer valuable insights for public health research. Descriptive statistics generated from these datasets can simulate national trends in health behaviors, such as physical activity, sleep patterns, and microbiome diversity. Such analyses assist researchers in estimating the prevalence of health behaviors or biological factors associated with chronic diseases, thereby informing public health interventions and policy-making. These insights are essential for developing population-level health strategies, such as campaigns to promote physical activity, improve sleep quality, or enhance gut health. Additionally, the capacity to simulate national trends aids in predicting healthcare demands and allocating resources effectively.

Combining synthetic life-log, RNA-seq, and microbiome data allows for comprehensive integrative analyses that uncover the interactions among lifestyle factors, genetic profiles, and microbial ecosystems. This multi-dimensional approach enables researchers to investigate the interplay between physical activity, gene expression, and gut health. Furthermore, lifestyle variables such as sleep patterns can influence microbiome diversity and, subsequently, health outcomes. By leveraging these datasets, researchers can uncover new biological pathways and interactions that drive disease progression, ultimately enabling the development of personalized healthcare solutions and preventive strategies. This integrative analysis is crucial for advancing precision medicine, where treatments are tailored to individuals' unique genetic, environmental, and microbiome profiles.

Synthetic datasets are also valuable for educational programs, offering realistic data for training in data analysis, model development, and simulation-based projects.

Strengths and Weaknesses

Strengths and Weaknesses of Synthetic Data

Synthetic data offers several compelling advantages that make it a valuable tool for research and analysis. First, it provides robust privacy protection by eliminating identifiable information, thereby addressing the critical privacy concerns that often accompany real-world datasets. This feature

enables researchers to work with data without violating individual confidentiality, a significant hurdle in many studies involving sensitive information.

Another key strength is the simplification of regulatory processes. Because synthetic data does not involve actual personal data, it bypasses the need for extensive ethical reviews and institutional approvals, thereby streamlining the data-sharing process. This significantly reduces the administrative burden on researchers and accelerates project initiation.

Synthetic data also demonstrates high utility by accurately reflecting the statistical properties of real-world data. This fidelity supports diverse analytical approaches and ensures that findings derived from synthetic data are comparable to those based on real data. Additionally, synthetic datasets are freely shareable for research and educational purposes, enhancing accessibility and promoting collaboration across institutions and disciplines.

Lastly, the broad applicability of synthetic data makes it an invaluable resource across various fields, including healthcare, AI development, and public health. Its versatility ensures that it can support a wide range of studies, from predictive modeling to public health surveillance.

Nonetheless, synthetic data also have notable limitations. One significant challenge is the need for thorough validation. To ensure usability and fidelity, synthetic data must be rigorously evaluated against real-world datasets. Without proper validation, insights derived from synthetic data may lack reliability, thereby limiting its effectiveness.

Another weakness is the inability of synthetic data to fully capture rare or highly complex patterns present in real data. This limitation is particularly evident when studying rare diseases or genetic variants, where the unique nuances of the original dataset may be lost during the synthetic generation process. Addressing this issue requires continuous refinement of synthetic data generation techniques to improve their ability to replicate these intricate patterns.

By understanding both the strengths and weaknesses of synthetic data, researchers can better leverage its potential while mitigating its limitations. This balanced approach ensures that synthetic data remains a powerful and reliable tool for advancing scientific and medical knowledge.

Discussion

Integration and relationship of multimodal data

To ensure that synthetic data accurately reflects real-world characteristics, different generation methods were applied, each tailored to a specific data type. For life-log data, time-series patterns were preserved using an RTSGAN model, which captures temporal dependencies and variability. For multi-omics data, synthetic RNA-seq datasets were constructed by introducing controlled variations to gene expression metrics such as read count, FPKM, and TPM. Similarly, synthetic methyl-seq data was generated by incorporating stochastic noise to maintain the statistical integrity of group-specific trends.

In contrast, microbiome datasets were generated by retaining microbial features and taxonomic classifications from original fecal and saliva profiles, without introducing statistical perturbations. All personal identifiers were removed from all data types to ensure data privacy while preserving the compositional structure of the original data.

Whole genome sequencing (WGS) and whole exome sequencing (WES) data, although originally collected as part of the Healthcare Big Data Showcase Project, were not included in this synthetic data generation study due to several practical limitations. These data types are extremely large in scale, requiring substantial storage, processing power, and computational time to handle. Moreover, the complexity of genomic variation—including rare variants, structural rearrangements, and coverage depth—makes it challenging to generate realistic synthetic equivalents.Another key limitation is the absence of widely accepted evaluation frameworks to validate the biological fidelity of synthetic WGS/WES data. Unlike expression or methylation profiles, where group-level statistical patterns can be preserved with controlled noise, genomic sequencing data require more advanced modeling techniques that are still under development. Therefore, this study focused on RNA-seq and methyl-seq data, which are more amenable to statistical synthesis approaches and allow more reliable fidelity assessments.

Collectively, these approaches support the robustness of synthetic multimodal datasets and demonstrate their potential for reliable downstream analyses.

Ethical implications of using synthetic data in biomedical research

The use of synthetic data in biomedical research presents significant ethical advantages, particularly in addressing concerns related to patient privacy and data security. One primary ethical benefit of synthetic data is its ability to mitigate the risks of re-identification and unauthorized access to sensitive personal health information. Unlike real patient data, synthetic datasets do not contain direct identifiers, thereby reducing concerns about privacy breaches and ethical dilemmas associated with data sharing.

Additionally, synthetic data facilitates broader access to biomedical datasets without compromising individual patient confidentiality. This is particularly relevant in

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collaborative research settings where data sharing across institutions or countries can be restricted by stringent privacy regulations. By providing a secure and privacy-preserving alternative, synthetic data enables researchers to conduct meaningful analyses while adhering to ethical and legal frameworks.

Moreover, the generation of synthetic datasets allows for the control or mitigation of biases inherent in real-world data, contributing to more balanced and representative analyses. This can enhance the fairness of machine learning models and prevent unintended biases in biomedical research applications.

These ethical advantages underscore the potential of synthetic data as a responsible and effective tool for advancing biomedical research while upholding the principles of patient privacy and ethical integrity.

Access

The synthetic omics data will be made publicly available as educational resources through the Clinical & Omics Data Archive (CODA) platform (https://coda.nih.go.kr/) once the validation process is complete. This validation ensures that the unique characteristics of each omics dataset are thoroughly considered, thereby preserving the fidelity and utility of the synthetic data for research and educational purposes.

Supplementary Material

Supplementary Material 1. Overview of RTSGAN. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0335.

Notes

Ethics Approval

The informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest

Hee Youl Chai has been the Journal Management Team director of *Osong Public Health and Research Perspectives*. The other authors have no conflicts of interest to declare.

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None.

Availability of Data

The datasets generated during the current study will be available in the CODA repository, https://coda.nih.go.kr/.

Authors' Contributions

Conceptualization: YGL, JEK; Data curation: YGL, MSK, DUN; Formal analysis: MSK; Funding acquisition: HYC, MSK; Project administration: HYC; Resources: HYC; Writing–original draft: YGL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Review Article

The contribution of dietary total antioxidant capacity to type 2 diabetes risk and levels of glycemic biomarkers: a systematic review

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ABSTRACT

Objectives: This study systematically reviewed and analyzed epidemiological evidence regarding the association between dietary total antioxidant capacity (DTAC) and both the risk of developing diabetes and glycemic biomarker levels.

Methods: We searched the PubMed, Scopus, ScienceDirect, and Google Scholar databases through July 2024 without imposing any date restrictions. Original studies that examined the relationship between DTAC and either the risk of developing diabetes or glycemic biomarker levels—specifically fasting blood glucose (FBG), hemoglobin A1C (HbA1C), insulin, and the homeostatic model assessment for insulin resistance (HOMA-IR)—were eligible for inclusion. After eliminating duplicates and irrelevant records, relevant studies were selected, and data were extracted through rigorous critical analysis.

Results: A total of 32 articles were included in the review. Of the 19 studies that evaluated diabetes risk, 15 reported a lower risk among subjects with higher DTAC values. All 4 studies examining prediabetes risk found lower risk in participants with high DTAC scores. Additionally, significant inverse relationships were observed between DTAC values and FBG (9/15 studies), HbA1C (1/6 studies), insulin (5/6 studies), and HOMA-IR (8/9 studies).

Conclusion: The majority of evidence indicates that high adherence to an antioxidant-rich diet may reduce diabetes risk and improve glycemic biomarkers, including FBG, insulin, and HOMA-IR.

Keywords: Blood glucose; Diabetes mellitus; Dietary total antioxidant capacity; Glycated hemoglobin; Insulin resistance; Insulin

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Introduction

Type 2 diabetes (T2D) is a chronic condition characterized by insulin resistance and elevated blood glucose levels. As of 2021, approximately 537 million adults worldwide have diabetes, with

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more than 90% of these cases being T2D—a figure projected to rise to 643 million by 2030 [1]. In 2021, T2D accounted for an age-standardized mortality rate of 18.5 per 100,000 individuals [2] and, in 2019, a disability-adjusted life years rate of 801.5 per 100,000 individuals [2]. T2D leads to severe complications, including cardiovascular diseases, kidney damage, and neuropathy [3]. Major contributing factors include obesity, physical inactivity, and unhealthy dietary habits [4].

There is growing interest in the role of oxidative stress and inflammation in chronic conditions such as atherosclerosis, obesity, and T2D [5]. An imbalance between prooxidants and antioxidants, resulting in oxidative stress, is a key pathogenic mechanism that increases diabetes risk [6]. Hyperglycemia promotes glucose autoxidation, non-enzymatic glycation, and impairs monocyte function, all of which lead to increased free radical production [7]. In addition, reduced levels of antioxidants exacerbate oxidative stress [8], resulting in lipid and DNA damage as observed in patients with diabetes [9].

A healthy diet rich in antioxidants and anti-inflammatory compounds may reduce the risk of chronic diseases, including cardiovascular disease, diabetes, and certain cancers [10]. Dietary intake has been linked to modulation of oxidative stress [11,12], and energy restriction has been suggested to lower levels of oxidative stress intermediaries [13]. Consumption of antioxidants is proposed as a protective strategy to mitigate oxidative damage [14], and evidence indicates that dietary antioxidants reduce T2D risk by inhibiting peroxidation chain reactions [15]. Moreover, consuming fruits and vegetables is associated with reduced incidence and mortality from various chronic diseases [16,17]. One hypothesis suggests that the collective impact of antioxidants—such as vitamins C and E, carotenoids, flavonoids, and proanthocyanidins—protects cells against free radical-induced oxidative damage [18].

Recent research indicates that higher total plasma antioxidant capacity is correlated with the intake of antioxidant-rich fruits and vegetables [19,20]. Because individual antioxidant concentrations do not fully capture the overall antioxidant potential of whole foods, the concept of dietary total antioxidant capacity (DTAC) was introduced [21]. DTAC functions as a valuable indicator of the overall antioxidant status of a diet [22,23].

Over recent decades, researchers have developed various methods to assess the total antioxidant capacity (TAC) of complex materials like foods. These assays include ferric reducing-antioxidant power (FRAP), which measures the reduction of Fe^{3+} to Fe^{2+}; total radical-trapping antioxidant parameter (TRAP), which monitors protection during a controlled peroxidation reaction; Trolox equivalent antioxidant capacity (TEAC), which compares the ability of antioxidants to quench the $ABTS^{1+}$ radical with that of Trolox; and oxygen radical absorbance capacity (ORAC), which evaluates the complete reaction of antioxidants with biologically relevant free radicals [24,25].

HIGHLIGHTS

- Oxidative stress contributes to the pathophysiology of diabetes.
- An antioxidant-rich diet intake may reduce diabetes risk.
- An antioxidant-rich diet intake may improve glycemic biomarkers, including fasting blood glucose, insulin, and homeostatic model assessment for insulin resistance.

In recent years, substantial research has focused on the relationship between DTAC and T2D risk [26,27]. Although a recent systematic review examined the relationship between DTAC and cardiometabolic risk factors in diverse populations, no review has comprehensively summarized the evidence linking DTAC to T2D risk and related biomarkers such as fasting blood glucose (FBG), hemoglobin A1C (HbA1C), insulin levels, and homeostatic model assessment for insulin resistance (HOMA-IR).

Materials and Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to ensure a transparent and systematic report [28].

Search Strategy

We conducted a systematic literature search in PubMed, Scopus, ScienceDirect, and Google Scholar up to July 2024 without imposing any date restrictions. Our search strategy used specific keywords relevant to the research question: "Dietary antioxidant capacity OR Dietary antioxidant index OR Dietary antioxidant intake OR Dietary total antioxidant" in title, abstract, and keywords, combined with "Diabetes OR Glycemic indices OR Metabolic indices OR insulin resistance OR insulin OR HOMA-IR OR glucose OR sugar" in title, abstract, and keywords. Only English-language original articles were included. Details of the search strategy are provided in Table S1. Reference lists of the included studies were also reviewed to identify additional relevant articles.

The research question was: "Is there an association between DTAC and T2D risk and levels of glycemic biomarkers?" Table 1 outlines the population, exposure, comparator, outcome (PECO) approach for this review, with individuals with

Table 1. Description of the PECO strategy

Element	Description
Population	People with diabetes or at risk of diabetes
Exposure	Low dietary total antioxidant capacity
Comparator	People with high dietary total antioxidant capacity
Outcome	Diabetes risk and diabetes-related glycemic biomarkers including FBG, HbA1C, insulin, and HOMA-IR

FBG, fasting blood glucose; HbA1c, hemoglobin A1C; HOMA-IR, homeostatic model of insulin resistance.

diabetes or at risk defined as the population, low DTAC as the exposure, high DTAC as the comparator, and diabetes risk and glycemic biomarkers (FBG, HbA1C, insulin, and HOMA-IR) as the outcomes.

Eligibility Criteria

We included original articles published in English that evaluated the association between DTAC and either the risk of developing diabetes or glycemic biomarkers (including FBG, HbA1C, insulin, and HOMA-IR). Studies were excluded if they focused on a single dietary antioxidant (e.g., vitamin E or carotenoids) in relation to T2D, the effects of antioxidant supplementation on diabetes biomarkers, the impact of specific active constituents with antioxidant activity from special foods on diabetes management, interactions between DTAC and specific genotypes (e.g., the caveolin-1 gene variant, rs 3807992) on diabetes biomarkers, or the combined effect of DTAC with other factors on diabetes or glycemic biomarkers. Animal studies, theses, dissertations, conference abstracts, editorials, reviews, and posters were also excluded.

Selection of Studies

Extracted studies were transferred to an EndNote file, and duplicate articles were removed. Two independent researchers screened the remaining articles based on their titles and abstracts to identify potentially eligible studies. Full texts of the selected articles were then reviewed independently to assess eligibility and extract relevant data. Any disagreements regarding study eligibility were resolved through discussion until consensus was reached.

Data Extraction

The following information was collected: first author and year of publication, study country and design, participant demographics (including age and sex), physical condition, follow-up duration, dietary assessment method, DTAC evaluation method, covariates, and outcome measures reported as correlation indicators (odds/hazard ratios, confidence intervals, *p*-values, if available). Only results from fully adjusted models were considered.

In studies that employed multiple statistical approaches to assess the association between DTAC and T2D risk, priority was given to findings from regression analyses. When analyses were conducted separately by sex and an association was observed in only 1 sex, only the relevant sex-specific findings were documented.

Ethics Approval

The ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran, registered and approved the protocol of this study (IR.TBZMED.REC.1401.824).

Results

Selection of Studies

Initially, 314 studies were retrieved (Figure 1). After removing duplicates, 143 studies remained. A review of titles and abstracts identified 43 publications relevant to the study's scope. Following critical appraisal, 11 studies were excluded because 1 was irrelevant, 1 was unavailable, 1 was a duplicate of an already included study, 1 was a letter, 5 investigated the interaction of DTAC with other factors regarding T2D, and 2 focused on single dietary antioxidants. Ultimately, 32 studies were included in the review (comprising 8 cohort studies, 20 cross-sectional studies, and 4 case-control studies) (Figure 1).

Characteristics of the Included Studies

As shown in Table 2, the included investigations [26,27,29–58] were conducted across diverse global regions. The studies were published between 2010 and 2024, with the majority ($n=26$) published after 2015. In the cohort studies, follow-up durations ranged from 3 to 37 years, although 4 studies had excessively long follow-up periods. Most studies (23 of 32) used food frequency questionnaires (FFQs) to assess dietary intake. DTAC was measured using various methods, including FRAP (21 studies), ORAC (9 studies), TRAP (5 studies), TEAC (5 studies), a composite dietary antioxidant index (3 studies), and other methods (2 studies). Different cut-off points were employed to categorize DTAC values. Twenty-one studies focused on subjects with

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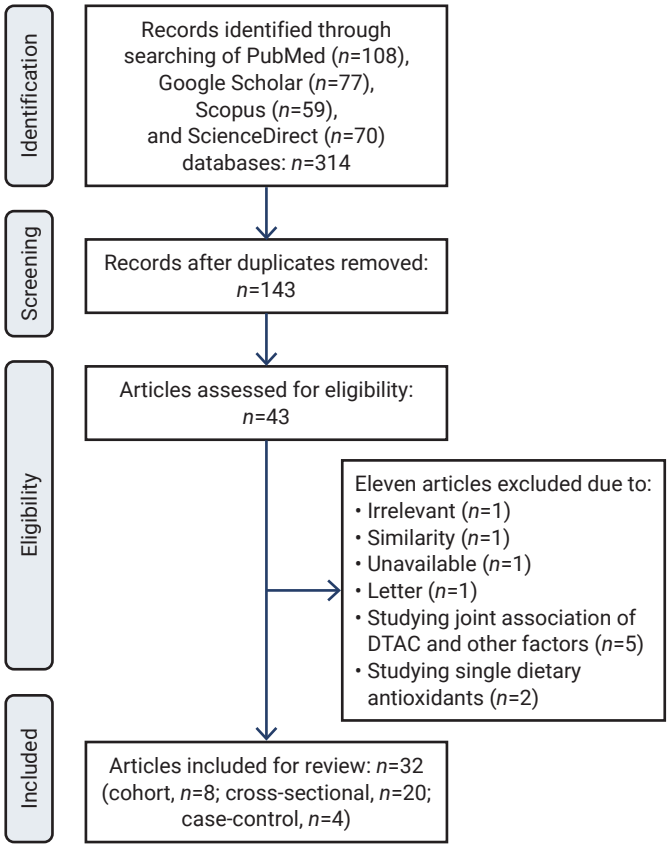


Figure 1. Flow diagram of the study. DTAC, dietary total antioxidant capacity.

diabetes or prediabetes, and most studies ($n=23$) adjusted for potential covariates in their analyses.

Relationship between DTAC and Risk of Developing Prediabetes and Diabetes

Among the 19 studies assessing the association between DTAC and diabetes risk [27,29–46], 15 reported a lower risk of diabetes in individuals with higher DTAC values [30,31,33–35,37–46]. In contrast, 4 studies found no significant association [27,29,32,36]. All 4 studies that evaluated the link between DTAC and prediabetes risk reported lower risk in individuals with higher DTAC values [27,40,47,48].

Relationship between DTAC and Glycemic Biomarkers

As shown in Table 2, out of 15 studies that evaluated the association between DTAC and FBG [26,27,29,31,43,48–57], 9 reported lower FBG levels in individuals with higher DTAC values [27,29,43,48,51–54,57]. Six studies investigated the association between DTAC and HbA1C [27,31,49,50,55,56], with only 1 study reporting lower HbA1C levels in those with higher DTAC values [27]. Furthermore, 6 studies assessed the

Table 2. Summary and characteristics of the 28 selected studies assessing the relationship of DTAC with diabetes risk and its related glycemic biomarkers

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					Statistical analysis method/considered confounders
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	
Bahadoran et al. [29]	2012	Iran/cohort	1,983 Adults (47% men)	40.4 ± 13.0	168 Food-items semiquantitative FFQ	ORAC: Q1, <842; Q2, 842–958; Q3, 959–1,080; Q4, >1,080	3	At baseline: FBG did not significantly differ across DTAC categories. DTAC was negatively associated with FBG (p-trend <0.01). After a 3 years follow-up, DTAC was not associated with FBG.	-	-	-	Hyperglycemia (FPG ≥100 mg/dL) did not differ across the DTAC quartiles and during 3-year follow-up, hyperglycemia did not significantly correlate with DTAC value.	Age, sex, BMI, physical activity, smoking status, energy and macronutrient intakes, dietary potassium intake

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	Statistical analysis method/considered confounders
Baharirad et al. [26]	2022	Iran/cross-sectional	189 T2D patients	35–65	FFQ	ORAC (tertile)	-	The mean values of FBS did not show statistically significant difference among the DTAC tertiles. There was no significant relationship between DTAC and FBS (tertile 3 vs. tertile 1: β, −0.90; 95% CI, −1.23 to 1.05; $p = 0.87$; adjusted model).	-	-	-	-	Logistic regression/age, sex, BMI, physical activity, and total caloric intake
Capas et al. [27]	2018	Turkey/descriptive	Adults with T2D; people with diabetes, $n = 29$ ($n = 20$ female); healthy subjects, $n = 15$ ($n = 10$ female)	40–70	3 Days of 24-hour food record	Modified version of the FRAP	-	In people with diabetes, a negative correlation was found between DTAC and FBG ($r = -0.406$, $p = 0.036$).	In people with diabetes, a negative correlation was found between DTAC and HbA1C ($r = -0.531$, $p = 0.004$).	-	-	DTAC did not differ between the 2 groups.	Group comparison and Spearman correlation/ not stated
Cetiner et al. [30]	2021	Turkey/cross-sectional	People with diabetes, $n = 60$ ($n = 33$ female); healthy subjects, $n = 25$ ($n = 14$ female)	Newly diagnosed T2DM, 50.8 ± 6.8; formerly diagnosed T2DM, 51.8 ± 7.4; controls, 45.6 ± 8.6	3 Days of 24-hour recall	FRAP, TEAC, TRAP, ORAC	-	-	-	-	-	DTAC was lower in diabetes than in controls ($p < 0.001$).	Groups comparison/ confounders have not been considered.
Chen et al. [31]	2023	China/cross-sectional	11,956 Participants	Mean > 42	24-Hour dietary recall	CDAI (6 dietary antioxidants)		FBS did not significantly differ among the CDAI quartiles. In full adjusted model, CDAI did not independently associate with fasting glucose.	Percentage of HbA1C was lower in the highest quartile of CDAI ($p = 0.03$). In full adjusted model, CDAI was not independently associated with HbA1C.	-	-	Percentage of people with diabetes were lower in the highest quartile of CDAI ($p < 0.001$) Compared with the lowest quartile of CDAI, the highest quartile was related to reduced risk of diabetes (OR, 0.84; 95% CI, 0.71–0.99; $p = 0.035$).	Multivariable logistic regressions/age, sex, race, education, physical activity, smoking status, hypertension, and coronary heart diseases

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	Statistical analysis method/considered confounders
Cyunczyk et al. [32]	2022	Poland/cross-sectional	413 Adults (40% male); normoglycemia, 171 (41.40%); prediabetes, 202 (48.91%); T2D, 40 (9.69%)	49.84±9.47	3 Days of 24-hour dietary recall	FRAP (Q1, ≤8.37; Q2, 8.38–11.27; Q3, 11.2–14.50; Q4, ≥14.51)	-	-	-	DTAC was inversely associated with HOMA-IR (β=−0.39, p=0.02).	-	The higher quartile of DTAC was significantly associated with a reduced odds ratio for the prevalence of prediabetes (Q3 vs. Q1; OR, 0.583; 95% CI, 0.309–0.945), but not with the risk of diabetes.	Linear regression/age, sex, family history of diabetes, education level, physical activity, dyslipidemia, hypertension, BMI, waist circumference, smoking status, daily alcohol intake and daily energy intake
Daneshzad et al. [33]	2020	Iran/case-control	Pregnant women with GDM; GDM, n=200; healthy, n=263	28.33±6.23	3 Days of a 24-hour dietary record	FRAP, TRAP, TEAC; tertile values were not stated.	-	-	-	-	-	FRAP was significantly lower in pregnant women with GDM than in controls. The risk of GDM was 85% lower among those in the highest tertile of FRAP (OR, 0.15; 95% CI, 0.08–0.29; p-trend < 0.0001). There was no significant association between the risk of GDM and TRAP as well as TEAC.	Group comparison and binary logistic regression/age, BMI, energy intake, physical activity, number of offspring, carbohydrate, fat, and protein intake, and supplementation
Daneshzad et al. [49]	2020	Iran/cross-sectional	265 T2D women	59.66±8.94	168-Item semiquantitative	FRAP (T1, <3.68; T2, 3.68–5.18; T3, >5.18); ORAC	-	FBS levels did not differ significantly across the tertiles of DTAC.	HbA1C levels did not differ significantly across the tertiles of DTAC.	-	-	-	Analysis of variance/age, BMI, energy intake, physical activity, blood pressure, medication, supplement consumption
Fagherazzi et al. [34]	2018	France/cohort	402 Women at very high risk of T2DM; women with T2DM, 117 (29%); women free of T2DM, 285 (71%)	55.7±6.65	Semiquantitative FFQ (57 predefined food groups)	FRAP	19	-	-	-	-	FRAP scores did not differ between 2 groups. A high DTAC was associated with less developing T2DM, in women with a moderate or high Western dietary pattern score.	Group comparison and regression/not stated
El Frakchi et al. [35]	2024	Morocco/cross-sectional	254 T2D outpatients	54.52±7.21	255 Food-item FFQ	FRAP; high, >10.6 mmol; low, <10.6 mmol	-	-	-	-	-	Percentage of people with diabesity was lower among those with higher DTAC (p=0.02).	Student t-test/-

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	Statistical analysis method/considered confounders
Galarregui et al. [50]	2018	Spain/cross-sectional	112 Overweight or obese adults	50.8±9	137-Item semiquantitative FFQ	FRAP (T1, <8.6; T, 8.6–11.36; T3, >11.36)	-	Glucose level did not change significantly across the tertiles of DTAC.	HgA1C level did not change significantly across the tertiles of DTAC.	Subjects with higher values of TAC had significantly lower HOMA-IR ($p=0.03$).	Subjects with higher values of TAC had significantly lower insulin concentration ($p=0.01$).	-	-
Hermsdorff et al. [51]	2011	Spain/cross-sectional	266 Healthy subjects (105 men/161 women)	22±3	Brazilian sample ($n=123$), 3 day-record; Spanish sample ($n=143$), 136 food-items semiquantitative FFQ	TEAC	-	DTAC value was inversely associated with glucose ($p<0.05$).	-	DTAC values were inversely associated with HOMA-IR ($p<0.05$).	DTAC values were inversely associated with insulin levels ($p<0.05$).	-	Multiple linear regression/ age, sex, waist circumference, energy intake, smoking habit, physical activity, and vitamin supplement use
Heshmati et al. [44]	2024	Iran/prospective cohort	1,856 pregnant women; GDM, 369	18–45	168 Food-items FFQ	FRAP	Between February 1, 2020 and August 31, 2021	-	-	-	-	The adjusted risk of GDM decreased by 34% (95% CI, 10%–52%; $p=0.023$) for each DTAC score increase. Women in the highest quartile of DTAC had a lower risk of developing GDM compared to those in the lowest quartile (adjusted RR, 0.29; 95% CI, 0.12–0.68; $p=0.005$).	Age, BMI, occupation, hypertension, diabetes, education, and working rotating shift
Jimenez-Ortega et al. [58]	2024	México/cross-sectional	830 Children and adolescents	7–18	116 Food-items FFQ	Based on the intake of 6 vitamins and minerals (vitamins A, C, E, selenium, magnesium, and zinc)		-	-	In total participants, people in the highest DAI category had low insulin resistance (OR, 0.49; 95% CI, 0.30–0.80). Female participants in the highest DAI category had significantly lower odds of developing insulin resistance than those in the lowest DAI category (OR, 0.54; 95% CI, 0.29–0.98).	-	-	Multiple logistic regression/ age, sex, BMI, smoking status, vitamin D intake, polyunsaturated intake, alcohol intake, family history of diabetes, Tanner stages, protein intake and total fat intake

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	Statistical analysis method/considered confounders
Kashino et al. [36]	2019	Japan/ prospective cohort	64,660 Adults (27,809 men and 36,851 women). During the 5-y period, 1,191 participants (692 men and 499 women) were newly diagnosed with T2D.	44–76	147 Food-items FFQ	FRAP ORAC, TRAP (quartiles)	5	-	-	-	-	DTAC was not associated with the risk of T2D in multivariate-adjusted models. Similar associations were found in men and women.	Linear and logistic regression/age, sex, study area, smoking habits, physical activity, BMI, history of hypertension, family history of diabetes mellitus, use of supplements, coffee consumption, and energy intake
Li et al. [37]	2024	China/cross-sectional	12,467 Participants (female, 65.4%); people with T2D, 1,238 (9.9%)	57.04±10.13	FFQ	FRAP	-	-	-	-	-	Higher DATC was associated with a lower T2DM risk (OR, 0.96; 95% CI, 0.80–1.17; *p*-trend = 0.024).	Logistic regression/age, sex, smoking status, alcohol consumption, physical activity, BMI, WC, TG, HDL-C, hypertension, and health supplement intake
Liu et al. [38]	2024	China/cross-sectional	2,158 Participants (male, 52.12%)	58.87±0.41	24 Hour dietary recall	CDAI	-	-	-	-	-	A negative correlation between CDAI and diabetic retinopathy (OR, 0.94; 95% CI, 0.90–0.98; $p = 0.007$).	Multivariate logistic regression/age, sex, race, drinking, smoking, body mass index (BMI), hypertension, etc.
Mancini et al. [39]	2018	Germany/ prospective cohort	64,223 Women. During 15 years of follow-up, 1,751 women had validated T2Ds.	52±7	208 Food-items dietary questionnaire	FRAP (Q1, ≤8.72; Q2, 8.73–11.29; Q3,11.30–13.93; Q4,13.94–17.55; Q5, >17.55)	15	-	-	-	-	In multivariable models, higher levels of DTAC were associated with a lower risk of T2D (OR, 0.73; 95% CI, 0.60–0.89; $p < 0.0001$).	Spline regression/ smoking status, physical activity, education level, hypertension, hypercholesterolaemia, family history of diabetes, energy intake, alcohol intake, BMI
Okubo et al. [52]	2014	United Kingdom/ cohort	Men (1,441), women (1,253)	59–73	129 Food-item FFQ	ORAC, TRAP, FRAP, TEAC	37	By all 4 assays: In women, but not in men, DTAC was inversely associated with fasting glucose ($p < 0.05$).	-	By all 4 assays: In women and men, DTAC was inversely associated with HOMA-IR ($p < 0.05$).	By all 4 assays: In women and men, DTAC was inversely associated with insulin levels ($p < 0.05$).	-	Multiple linear regression/ age, sex, BMI, smoking status and physical activity level, dietary supplement use, and energy intake
Psaltopoulou et al. [53]	2011	Greece/ epidemiological study	551 Men and 467 women; normal, $n = 771$; IFG, $n = 203$; T2D, $n = 44$	Normal, 38±11; IFG, 43±10; diabetic, 52±8	Semiquantitative FFQ	TRAP, FRAP, TEAC		Using all 3 assays, an inverse association was found between DTAC and serum log-glucose ($p = 0.001$).	-	By all 3 assays, an inverse association was found between DTAC and serum log- HOMA ($p \leq 0.001$).	By all 3 assays, an inverse association was found between DTAC and serum log- insulin ($p \leq 0.002$).	-	Multiple regression analyses/age, sex, BMI, physical activity status, smoking habits, and energy intake
Puchau et al. [54]	2010	Spain/cross-sectional	153 Healthy young adults (101 women and 52 men)	20.8±2.7	136 Food-item FFQ and 3-day food record	FRAP (low, <6.9 mmol; high, >6.9 mmol)	-	Serum glucose significantly differed between subjects with high and low DTAC values ($p = 0.006$). Serum glucose was negatively associated with DTAC ($p = 0.03$).	-	HOMA-IR did not significantly differ between subjects with high and low DTAC values.	Insulin levels did not significantly differ between subjects with high and low DTAC values.	-	Groups comparison and multiple linear regression/sex and daily energy intake

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	Statistical analysis method/considered confounders
Rahmani et al. [47]	2021	Iran/case-control	Prediabetes, *n* = 49; healthy control, *n* = 98	47.42 ± 15.98	80 Food-item FFQ	FRAP (T1, ≤11.90; T2, 11.90–21.24; T3, >21.24)	-	-	-	-	-	Patients with prediabetes had lower DTAC scores as compared with controls. High DTAC was associated with a significantly reduced likelihood of having prediabetes (OR, 0.09; 95% CI, 0.02–0.53; *p*-trend = 0.01).	Age, sex, BMI, marital status, income, occupation, education, physical activity, dietary supplementation, family history of diabetes, and total calorie intake
Roumi et al. [45]	2024	Iran/cross-sectional	4,241 Participants; patients with T2D, *n* = 589; individuals without T2D, *n* = 3,611	35–70	FFQ	Wright's method	-	There was no significant correlation between FBG and dietary total antioxidant index.	-	-	-	Negative associations was found between T2D with total score of dietary antioxidant index (OR, 0.67; 95% CI, 0.55–0.81; *p* = 0.001).	Logistic and linear regression/age, sex, BMI, education level, marital status, occupation, physical activity, and calorie intake
Salavatizadeh et al. [55]	2022	Iran/cross-sectional	200 People with T2D	18–70	147 Food-item FFQ	FRAP		FBS was not different across DTAC tertiles (*p* = 0.44).	HbA1C did not differ across DTAC tertiles (*p* = 0.67).	People in the third tertile of DTAC had lower HOMA-IR level (*p* = 0.05).	People in the third tertile of DTAC had lower insulin level (*p* = 0.01).	-	Kruskal-Wallis test and analysis of covariance/age, sex, diabetes duration, smoking status, physical activity, BMI, waist circumference, and energy
van der Schaft et al. [40]	2019	Netherland/cohort	5,796 Men (*n* = 2,266) and women (*n* = 3,530); normoglycaemia, *n* = 4,957; prediabetes, *n* = 839	Men, 63.4; women, 64.6	170 Items semiquantitative FFQ	FRAP	15	-	-	Dietary FRAP was inversely associated with HOMA-IR (*p* < 0.001).	-	Higher FRAP score was associated with a lower risk of T2D among the total population (HR, 0.84; 95% CI, 0.75–0.95; *p* = 0.01) and among participants with prediabetes (HR, 0.85; 95% CI, 0.73–0.99; *p* = 0.03), but not with risk of prediabetes.	Cox proportional hazards regression/age, sex, BMI, hypertension, dyslipidemia, highest attained level of education, physical activity, smoking status, energy intake, daily alcohol intake and degree of adherence to guidelines for a healthy diet
Sezavar et al. [56]	2021	Iran/cross-sectional	170 Adults with morbid obesity	37.4 ± 10.17	147 Food-item FFQ	ORAC, FRAP (T1, <5.36; T2, 16.41–24.01; T3, >145.17)	-	FBS did not significantly differ across tertiles of FRAP (*p* = 0.21) and ORAC (*p* = 0.86).	HbA1C did not significantly differ across tertiles of FRAP (*p* = 0.22) and ORAC (*p* = 0.99).	-	-	-	One-way ANOVA/not stated

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	Statistical analysis method/considered confounders
Sohouli et al. [57]	2020	Iran/case-control	NAFLD, *n* = 158; healthy individuals, *n* = 357	43.9 ± 5.9	168 Food-item FFQ	ORAC (tertiles)	-	Across increasing DTAC tertiles, the FBG level reduced ($p = 0.001$).	-	-	-	-	One-factor ANCOVA test/ not stated
Sotoudeh et al. [48]	2018	Iran/case-control study	300 Individuals with and without prediabetes (*n* = 150/group)	Control, 47.7 ± 7.2; prediabetic, 47.4 ± 7.5	168 Food-items semiquantitative FFQ	ORAC (Q1, < 11,878.5; Q2, 11,878.5–16,322.1; Q3, 16,322.1–24,548.8; Q4, > 24,548.8 mmol TE/100 g)	-	Across increasing DTAC quartiles, the participants had lower FBG (p-trend < 0.001).	-	-	-	The mean DTAC was lower in individuals with prediabetes than in the control group ($p < 0.001$). Participants in the fourth quartile of DTAC were less likely to experience prediabetes compared with those in the first quartile (OR, 0.18; 95% CI, 0.07–0.49; $p < 0.001$).	Logistic regression/ BMI, physical activity, education, dietary intake of fiber, fat, energy, and coffee
Tan et al. [41]	2022	South Korean/ cohort	20,594 Participants, 332 men and 360 women with T2D	40–79	106 Food-item FFQ	Self-reported dietary data linked to the TAC database	5	-	-	-	-	DTAC was inversely associated with the development of T2D in women (HR, 0.58; 95% CI, 0.40–0.83; p-trend = 0.0004). Among men, an approximately 15% reduced risk of developing T2D was observed for an SD increment in TAC (HR, 0.85; 95% CI, 0.75–0.96).	A multivariable Cox proportional hazards regression/age, BMI, education, smoking, alcohol intake, physical activity
Zhou et al. [46]	2024	China/cross-sectional	7,982 Subjects; 48.50% male and 51.50% female; diabetic, 1,607; non-diabetic, 6,375	47.32 ± 16.77	Two 24-hour dietary recalls	CDAI	-	-	-	-	-	High CDAI was associated with reduced risk of diabetes mellitus in the female population ($p = 0.046$).	Multifactorial logistic regression models/age, sex, race, and education level
Zujko et al. [42]	2014	Poland/cross-sectional	80 Patients with and without T2D and 37 controls	40–65	24-Hour food recall and dietary database	FRAP	-	-	-	-	-	DTAC was significantly higher in control than in patients with longstanding diabetes and those with newly diagnosed diabetes ($p = 0.01$).	Groups comparison/not stated

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Table 2. Continued

Study	Year	Country/study design	Target population	Age (y)	Method of dietary intake assessment	Method of DTAC evaluation	Follow-up (y)	Findings					Statistical analysis method/considered confounders
								FBS	HbA1C	HOMA-IR	Insulin	Risk of diabetes	
Zujko et al. [43]	2018	Poland/cross-sectional	5,690 Adults (2,554 men and 3,136 women)	50.08 ± 16.44	A single 24-hour dietary recall	FRAP (tertiles)	-	In women, higher DTAC was significantly associated with reduced odds of elevated blood glucose.	-	-	-	In women, higher DTAC was associated with 27.9% lower odds of diabetes (OR, 0.721; 95% CI, 0.522–0.997).	Logistic regression/age, BMI, educational level, leisure time, physical activity, smoking, and alcohol intake

DTAC, dietary total antioxidant capacity; FBS, fasting blood sugar; HbA1c, hemoglobin A1C; HOMA-IR, homeostatic model assessment for insulin resistance; FFQ, food frequency questionnaire; ORAC, oxygen radical absorption capacity; FBG, fasting blood glucose; FPG, fasting plasma glucose; BMI, body mass index; T2D, type 2 diabetes; CI, confidence interval; T2DM, type 2 diabetes mellitus; FRAP, ferric reducing-antioxidant power; TEAC, Trolox equivalent antioxidant capacity; TRAP, total radical-trapping antioxidant potential; CDAI, composite dietary antioxidant index; OR, odds ratio; GDM, gestational diabetes mellitus; TAC, total antioxidant capacity; RR, risk ratio; DAI, dietary antioxidant index; WC, waist circumference; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; IFG, impaired fasting glucose; HR, hazard ratio; ANOVA, analysis of variance; ANCOVA, analysis of covariance; SD, standard deviation.

relationship between DTAC and insulin levels [50–55], and 5 of these found that higher DTAC values were associated with lower insulin levels [50–53,55]. Among the 9 studies evaluating DTAC and HOMA-IR [32,40,50–55,58], 8 reported lower HOMA-IR values in subjects with higher DTAC values [32,40,50–53,55,58].

Discussion

A healthy and diverse diet can enhance overall health outcomes and well-being [59,60]. Antioxidants play a critical role in maintaining health by neutralizing free radicals—highly reactive molecules that can damage cells and genetic material. These free radicals arise from metabolism, exercise, and environmental exposures such as air pollution and sunlight [61]. Evidence indicates that a diet rich in antioxidants, particularly from fruits, vegetables, and legumes, reduces the risk of chronic diseases related to oxidative stress. Epidemiological studies and meta-analyses of prospective observational studies have consistently linked higher intakes of antioxidant-rich foods with reduced risks of cardiovascular diseases, cancer, and all-cause mortality [62,63]. Thus, incorporating antioxidant-rich foods into one's diet may improve overall health and well-being [64,65].

In the present study, we reviewed both interventional and observational investigations to provide an overview of the relationship between an antioxidant-rich diet and the risk of developing diabetes or altered glycemic biomarkers. Our systematic review provides robust evidence that high DTAC is associated with decreased diabetes risk as well as improved levels of FBG, insulin, and HOMA-IR.

Oxidative stress is central to the pathophysiology of diabetes [66]. Excess production of reactive free radicals, often triggered by hyperglycemia, leads to oxidative stress, which further exacerbates diabetes and its complications [66,67]. In diabetes, oxidative stress interacts with cellular biomolecules—including proteins and lipids—resulting in harmful effects such as lipid peroxidation, which compromises cellular structure and function [68]. Genetic studies related to oxidative stress have revealed potential causal links with diabetes and microvascular complications [69]. Elevated lipid peroxidation coupled with reduced antioxidant activity has been observed in patients with diabetes [70]. Although classic antioxidants like vitamin E have not demonstrated clinical benefits in large-scale trials, a more comprehensive strategy that both prevents reactive species generation and scavenges free radicals appears promising [67]. Moreover, synergistic low-dose antioxidant blends have shown potential in reducing lipid peroxidation

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and restoring redox homeostasis [71]. Understanding the interplay among dietary antioxidants, lipid peroxidation, and hyperglycemia is essential for managing diabetes and its associated complications.

Oxidative stress also contributes significantly to the development of insulin resistance. Research has shown that systemic oxidative stress is correlated with insulin resistance. For instance, data from the Framingham Offspring Study revealed that individuals with higher levels of oxidative stress (measured by urinary 8-epi-prostaglandin F2α) had an increased prevalence of insulin resistance, even after adjusting for body mass index [72]. A similar positive association between oxidative stress markers and HOMA-IR has been reported in young adults [73]. Oxidative stress may impair insulin signaling by damaging cellular components such as proteins, lipids, and DNA, leading to reduced glucose uptake [74]. Additionally, the activation of inflammatory pathways further exacerbates insulin resistance [75]. Antioxidants help counteract this process by reducing inflammation; for example, Luu et al. [76] reported an inverse association between dietary antioxidant intake and inflammatory biomarkers in a study of 3,853 women, while Beharka et al. [77] demonstrated that prolonged dietary antioxidant supplementation reduced the production of specific inflammatory mediators in mouse macrophages.

Elevated oxidative stress can also impair insulin secretion. In both type 1 and type 2 diabetes, chronic hyperglycemia contributes to complications in target organs. High glucose levels trigger the production of reactive oxygen (ROS) and reactive nitrogen species, which damage DNA, proteins, and lipids, and activate stress-sensitive pathways such as nuclear factor kappa B (NF-κB) and p38 mitogen-activated protein kinase [78]. In T2D, elevated glucose and free fatty acid levels further activate these pathways, contributing to both insulin resistance and impaired insulin secretion [78]. Studies have reported increased oxidative and endoplasmic reticulum stress in pancreatic β-cells under hyperglycemic conditions, adversely affecting insulin production [79]. Furthermore, oxidative stress compromises insulin sensitivity and contributes to insulin resistance by impairing glucose uptake into cells [66]. Accumulating evidence indicates that oxidative stress plays a central role in β-cell dysfunction and insulin secretory failure in T2D [80,81].

Dietary bioactive compounds, including antioxidants, play a crucial role in protecting pancreatic β-cells from oxidative stress, which is a key factor in the development and progression of diabetes [82,83]. Dietary antioxidants may protect β-cells by inhibiting NF-κB activity [84] and by activating nuclear factor erythroid-derived factor 2-related factor 2 (Nrf2), a transcription factor that upregulates antioxidant and cytoprotective genes [85]. NF-κB is a transcription factor that regulates the expression of genes involved in inflammation and immune responses. The activation of NF-κB increases the production of pro-inflammatory cytokines, which can damage β-cells [86]. Meanwhile, Nrf2 is a transcription factor that regulates the expression of antioxidant and cytoprotective genes. Nrf2 activation upregulates antioxidant enzymes and proteins, which help to neutralize ROS and reduce oxidative stress [87]. Studies have shown that polyphenols and other dietary antioxidants can inhibit NF-κB activation and reduce oxidative stress [88] and activate the Nrf2 pathway [89], thereby protecting β-cells from oxidative damage and improving their function.

Dietary antioxidants also help maintain serum antioxidant levels and mitigate oxidative stress, which is essential for overall health [90]. Vahid et al. [91] reported that higher dietary antioxidant intake was associated with increased serum TAC. Similarly, Jewell et al. [92] found that an antioxidant blend—including vitamin E, vitamin C, and β-carotene—increased cellular protection and improved antioxidant status in dogs and cats. Avila-Escalante et al. [11] demonstrated that a high-antioxidant diet enhances plasma antioxidant capacity and reduces oxidative stress markers in individuals with various chronic diseases. Therefore, incorporating antioxidant-rich foods into the diet is crucial for maintaining overall health and preventing chronic diseases.

In summary, as illustrated in Figure 2, consumption of antioxidant-rich foods enhances circulating antioxidant levels and mitigates oxidative stress. This effect contributes to reduced insulin resistance, improved insulin secretion and sensitivity, and ultimately lower blood glucose levels, thereby decreasing the risk of T2D and its associated complications.

Strengths of the Study

The included investigations were conducted in diverse regions worldwide, enhancing the generalizability of the findings. The recent publication dates of most studies indicate that the topic is current. The presence of several prospective cohort studies with substantial sample sizes strengthens the statistical power of the results. Additionally, most studies accounted for potential confounders in their analyses of the DTAC–diabetes risk relationship, underscoring the independent role of DTAC.

Limitations of the Study

Several studies did not adequately consider covariates in their statistical analyses, and diverse statistical methods

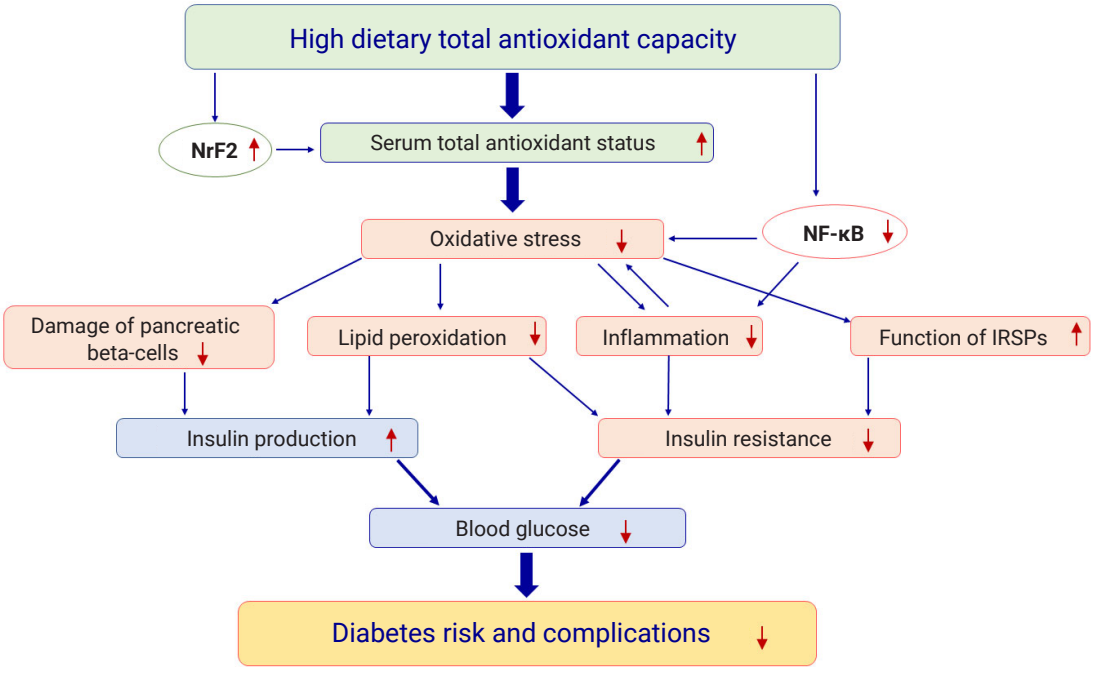


Figure 2. Potential mechanistic pathways for the association between dietary total antioxidant capacity and the diabetes risk and its related glycemic biomarkers.
NrF2, nuclear factor erythroid-derived factor 2-related factor 2; NF-κB, nuclear factor kappa B; IRSP, insulin receptor signaling pathway.

were employed across investigations. Furthermore, different techniques were used to calculate DTAC, and varying cut-off points were applied when categorizing DTAC values, which may have influenced the findings. The heterogeneity among the included studies—in terms of study populations, measured outcomes, and methodologies (including statistical analyses and DTAC evaluation methods)—precluded the performance of a meta-analysis and limited the ability to draw definitive conclusions.

Conclusion

The majority of existing evidence indicates that high adherence to an antioxidant-rich diet may reduce diabetes risk and improve glycemic biomarkers, including FBG, insulin, and HOMA-IR.

Implications of the Findings

The findings of this study have significant public health implications, particularly in managing T2D. They provide valuable insights for developing dietary recommendations aimed at preventing chronic diseases. Improved blood glucose parameters can lead to better glycemic control, reducing the risk of diabetes-related complications such as cardiovascular disease, neuropathy, and nephropathy. Enhanced glycemic control further contributes to overall metabolic health and quality of life for individuals with or at risk for T2D.

Supplementary Material

Table S1. Association between the dietary total antioxidant capacity and risk of developing diabetes or glycemic biomarkers: the database search strategy using PubMed, Scopus, Google Scholar, and ScienceDirect. Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0337.

Notes

Ethics Approval

The ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran, registered and approved the protocol of this study (IR.TBZMED.REC.1401.824).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

All study-related data are included in the publication or provided as supplementary information.

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Review Article

Global health security in the post-COVID-19 era: threats, preparation, and response

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ABSTRACT

Global health security threats in the post-coronavirus disease 2019 era include dense urban populations, increased human–animal proximity, migration driven by political or economic instability, climate change, humanitarian crises, antimicrobial resistance (AMR), and the misuse of biological research—including the accidental or intentional release of high-risk pathogens. The foundational preparation for these threats is to establish a robust, resilient public health system based on universal health coverage. The World Health Organization's International Health Regulations must continue to promote global solidarity by maintaining core capacities such as surveillance, national laboratories, and epidemiological investigations of emerging infectious diseases, with timely reporting and information sharing within the global health security community. A One Health approach is essential for addressing AMR. Infection prevention and control must be enhanced to reduce healthcare-associated infections in medical facilities. Additionally, regulations concerning biosafety and biosecurity should address dual-use research of concern as well as the accidental or intentional release of high-risk pathogens from laboratories. Global health security is a collective responsibility because these threats know no borders and require coordinated action.

Keywords: Biosecurity; Climate change; Communicable disease control; COVID-19; Emerging infectious disease; Immunization

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Introduction

The scale and socioeconomic impact of the coronavirus disease 2019 (COVID-19) pandemic was unprecedented. Most countries worldwide were completely unprepared for, and failed to respond to, this emerging infectious disease. This study reviews the global health security landscape in the post-COVID-19 era, focusing on preparation for and response to forthcoming threats, and suggests countermeasures. It investigates potential global health security

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threats such as emerging infectious diseases, antimicrobial resistance, and bioterrorism. The study examines human and environmental factors that influence water-borne and vector-borne diseases, as well as biosafety and biosecurity concerns that could facilitate bioterrorism. Additionally, it highlights antimicrobial resistance as a growing threat and discusses the impact of climate change on vector-borne and water-borne diseases.

Materials and Methods

The author conducted a qualitative content analysis to describe and categorize current global health security threats, preparations, and responses, both present and future. Materials were sourced from PubMed, Scopus, Web of Science, and Google Scholar using keywords such as "emerging infectious diseases," "global health security," "preparedness," "response," "AMR," "threat," and "climate change." This qualitative content analysis aimed to preserve expert perspectives while generating new research questions.

Global Health Security Threats

Background

Public health organizations worldwide conduct surveillance of emerging public health events. The World Health Organization (WHO) detects approximately 3,000 signals per month, although only a small fraction of these signals are genuine threats [1]. Public health experts can now identify potential threats more quickly than ever before. Advances in science, including gene-editing technologies such as CRISPR clustered regularly interspaced short palindromic repeats (CRISPR), enable the rapid identification of pathogen characteristics and the development of medical countermeasures. This technology facilitates the creation of new vaccines and treatments, as well as reducing vector populations [2].

The WHO supports the Global Outbreak Alert and Response Network, a worldwide network of institutions, and the US Centers for Disease Control and Prevention maintains a Global Rapid Response Team composed of over 400 public health experts to address outbreaks or public health emergencies of international concern [3]. The COVID-19 pandemic revealed that the global risk was far greater than anticipated. Furthermore, contemporary human lifestyles have outpaced significant scientific advances and the capacity of institutional surveillance and response. Globalization, economic development, crowded megacities, rapid international air travel, mass migrations, and intensified human–animal interactions have altered pathogen emergence and transmission, thereby amplifying the risk and severity of outbreaks. In conflict zones, fragile health systems and mass exoduses—as seen in Syria, Yemen, and the Democratic Republic of the Congo—further complicate responses. Additionally, the expansion of human populations into new geographic areas, along with climate change, deforestation, intensive farming, and large-scale food production, has fundamentally altered the interactions among humans, animals, and the environment. Recognizing these diverse drivers of disease is essential for effective planning and response.

HIGHLIGHTS

- Lessons learned from a devastating outbreak or epidemic can guide better preparation for future events.
- The next global health security threat might come from an emerging respiratory infectious disease outbreak, antimicrobial resistance, a vector-borne disease, or bioterrorism.
- We must take multisectoral, whole-of-society actions to prepare for, prevent, detect, and respond to global health security threats nationally, regionally and globally.

Rising Populations, Megacities, and the Loss of Natural Habitats

In 2017, urban populations outnumbered rural populations, with urbanization rates in Africa (48%) and Asia (51%) exceeding those of other regions [4,5]. In densely populated cities in Asia and Africa, humans and animals often live in close proximity, facilitating the transmission of novel viruses—such as COVID-19, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Ebola—from animals to humans, followed by human-to-human spread. Human activities like deforestation, logging, or mining force animals to abandon their natural habitats, thereby increasing the risk of vector-borne diseases such as malaria. Intensive poultry farming elevates the risk of zoonotic transmission, as seen with avian influenza H7N9, where transmission occurs between domesticated animals and wild birds along global migratory routes [6]. Zoonotic diseases account for more than 60% of emerging infectious diseases [7]. The Ebola outbreaks in West Africa were linked to deforestation and the resulting increased contact between humans and animals (Table 1) [4–8].

Table 1. Summary of global health security threats, preparations, and responses in WHO JEE

Factor	Threats	Preparation/response in WHO JEE [36]
Dense populations/urbanization/ deforestation/logging/mining [4–7]	Higher chance of a novel virus transmission	P5, P8, D2, R3, R4
Migration due to political/economic reason [9,10]	Poor sanitation, outbreak of water-borne diseases	P1, P2, P3, P5, P6, P8
International travel and trade [11,12]	Rapid transmission of infectious diseases	P1, P3, P5, D2, R1, R2, PoE
Climate change [13–16]	Vector-borne, water-borne disease outbreak	D1, D2, R3
Humanitarian crisis [18–20]	Breakdown of sanitation system, immunization programs	P1, P2, P3, P6, P7, P8, D1, D2, D3, R1, R2, R3, R5
Antimicrobial resistance [21–25]	Resistant to existing treatments	P4, R4
Healthcare-associated infections [26–29]	Increase in healthcare costs and antimicrobial resistance	P4, R4
Biological research and threats [30–33]	Dual-use research of concern accidental or intentional release of high-risk pathogens	P7, R2

WHO JEE, World Health Organization Joint External Evaluation; P, prevent; D, detect; R, respond; PoE, point of entry; P1, legal instruments; P2, financing; P3, International Health Regulation [IHR] coordination, national IHR focal point; P4, antimicrobial resistance; P5, zoonotic disease; P6, food safety; P7, biosafety and biosecurity; P8, immunization; D1, national laboratory system; D2, surveillance; D3, human resources; R1, health emergency management; R2, linking public health and security authorities; R3, health services provision; R4, infection prevention and control; R5, risk communication and community engagement.

Forced Migration in Conflict Zones, Rapid International Travel, and Trade

Humans can now travel anywhere within 24 hours at an affordable cost via air travel, allowing pathogens to spread rapidly through unknown hosts. Simultaneously, the world is experiencing a historic migration crisis as refugees cross borders from conflict zones. Approximately 20 million people are fleeing political crises in South Sudan, Syria, and Afghanistan [9]. In January 2020, China imposed a lockdown on 60 million people in Hubei Province, the origin of COVID-19; however, 5 million travelers had already departed for domestic and international destinations in the weeks preceding the lockdown (Table 1) [9,10]. In 2016, the United States reported approximately 5,500 travel-related cases of Zika originating from the Caribbean and Latin America [11]. In May 2015, a man returning from the Middle East introduced MERS to South Korea, resulting in 186 confirmed cases and 38 deaths. Additionally, Mexico reported the first cases of novel influenza A (H1N1) in April 2009, with the WHO declaring a pandemic just 9 weeks after the initial case (Table 1) [11,12].

Climate Change

Climate change can expand the geographic distribution of vector-borne diseases such as chikungunya, dengue, and Zika to previously unexposed populations, as well as water-borne diseases. Increased rainfall and rising temperatures create more breeding grounds for mosquitoes and disrupt sanitation systems [13]. Yemen experienced a cholera outbreak in 2019. Haiti has suffered from cholera since 2010, which is believed to have been introduced by United Nations relief workers [14]. Furthermore, climate change could release bacteria and viruses trapped in Arctic ice [15]. In August 2016, an anthrax outbreak occurred in the Yamal Peninsula in the Arctic after a long-dead reindeer infected with anthrax bacteria was discovered (Table 1) [13–16]. Anthrax outbreaks occur sporadically, primarily among cows, goats, and other herbivorous mammals [17].

Humanitarian Crisis with Weak Government

Recent humanitarian crises have left 20 million people facing famine in countries such as Nigeria, South Sudan, Somalia, and Yemen [9]. In regions where states collapse or are unable to govern, public health systems deteriorate, leading to the absence of proper sanitation and immunization programs [18]. Wild poliovirus has re-emerged in countries like Afghanistan, Pakistan, Syria, and Nigeria [19]. Mass population movements, driven by violence and exacerbated by congested refugee camps with poor hygiene conditions, further increase the risk of cross-border disease transmission. Standard countermeasures like social distancing and handwashing are often impractical in refugee camps. Local COVID-19 transmission was reported by 122 refugee-hosting countries in April 2020 (Table 1) [18–20].

Antimicrobial Resistance

Antimicrobial resistance (AMR) is among the most concerning threats in the modern world. AMR arises from prophylactic antibiotic use in farmed animals, indiscriminate medical prescribing, and inadequate infection control in hospitals [21]. Overused antibiotics and other antimicrobials can persist due to genetic mutations, rendering treatable infections, such as

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hospital-acquired infections (HAIs), malaria, and tuberculosis, resistant to current treatments [22]. Hundreds of thousands of people die annually from multidrug-resistant and extremely drug-resistant tuberculosis, particularly in India, South Asia, and sub-Saharan Africa, with future projections reaching millions each year [23]. AMR also affects the wealthiest countries and world-class health facilities; tens of thousands of Americans die from AMR-related infections each year [24]. Additionally, the use of falsified and substandard drugs sold at street markets, which deliver sub-therapeutic doses, further contributes to the development of resistance (Table 1) [21–25].

Healthcare-Associated Infections

Hospitalization carries the risk of healthcare-associated or HAIs, many of which are highly resistant to treatment. HAIs not only increase healthcare costs due to prolonged hospital stays, long-term disability, loss of income, and even death, but also contribute to the development of AMR [26]. Although HAIs are widespread, their burden is higher in low- and middle-income countries compared to high-income countries. In Europe and North America, serious HAIs occur in 5% to 10% of hospitalizations [27], while this proportion rises to 40% in Asia, sub-Saharan Africa, and Latin America [27]. Older adults, patients in intensive care units, and those undergoing invasive procedures are particularly susceptible. Healthcare facilities can significantly reduce the risk by modifying the physical environment and culture, such as promoting handwashing, using personal protective equipment, and ensuring the safe disposal of medical waste [28]. The WHO and UNICEF offer resources to guide health professionals [29]. Hospitals must adopt a systemic approach to ensure cleanliness and safety for all individuals, including doctors, nurses, technicians, and patients (Table 1) [26–29].

Biological Research and Threats: Biosecurity and Biosafety

Modern biotechnology presents potentially deadly threats. Biosecurity refers to measures taken to protect humans, animals, and the environment from the intentional release of harmful biological pathogens or substances from research laboratories [30]. Dual-use research of concern (DURC) involves studies intended to generate knowledge, products, or technologies that could, if misused, pose serious risks to public health, animal health, and the environment. There are currently no official international biosecurity norms or institutions governing DURC. However, existing international agreements—such as the Geneva Protocol (1925), the Biological Weapons Convention (1975), United Nations (UN) Security Council Resolution 1540 (2004), UN Security Council Resolution 2325 (2016), and the WHO's Responsible Life Sciences Research for Global Health Security (2010)—can help manage DURC [31]. Biosafety, in contrast, involves the secure operation of biological research facilities to prevent the accidental release of hazardous materials to laboratory workers or the public. The advent of genomic science has ushered in a new era of biosafety challenges. The widespread sharing of genetic sequencing data, advances in pathogen creation, and the democratization of biological information available online create scenarios with potentially grave consequences. This potential for misuse has led policymakers and scientists to pause or even ban certain types of biological research [32]. Concerns over biothreats have also fueled distrust among nations. For instance, during the COVID-19 pandemic, issues of biosecurity and biosafety arose regarding the origin of the SARS coronavirus 2 (SARS-CoV-2) virus, with some alleging it originated from a Chinese laboratory—either as a manmade virus or through an accidental release—although these claims were denied by scientists, epidemiologists, and intelligence agencies [33]. With proper regulations for biosecurity and biosafety, risks can be monitored, mitigated, and managed. National governments, international organizations, and scientists should engage in a regulatory process that advances biosafety and biosecurity while fostering promising scientific advancements and enhancing global health security (Table 1) [30–33].

Global Health Security Preparation and Response

Robust, Resilient, and Equitable Public Health Systems

The world requires robust, resilient, and equitable public health systems that incorporate effective risk communication with the public.

Universal health coverage

Universal health coverage is essential for global health security. Universal access to public health services enables early detection and surveillance, facilitating rapid responses to contain potential outbreaks. Newly diagnosed individuals can be isolated, and their contacts can be traced promptly. Robust health systems also prevent and manage chronic illnesses, reducing the risk of severe outcomes in individuals with underlying conditions. Furthermore, health systems must implement effective risk communication strategies to build public trust and encourage adherence to surveillance and contact tracing measures, as demonstrated by the Republic of Korea during the COVID-19 pandemic [34]. These systems should also address the needs of marginalized

populations. Health equity is critical—not only as a matter of human rights but also for early disease detection and rapid, agile responses. Access to healthcare enables timely testing, treatment, and effective contact tracing, which is key to containing outbreaks at the community level. The health system should protect both health workers and patients by ensuring robust infection prevention and control measures in healthcare settings. Moreover, systems must have surge capacity to rapidly scale up services during health emergencies, including maintaining stockpiles of personal protective equipment, essential vaccines, medicines, and ventilators. Plans should also address the supply of health workers and invest in local manufacturing capacity to mitigate global supply chain disruptions in medical resources.

WHO's International Health Regulations core capacities

The WHO's International Health Regulations (IHRs) require all member states to develop core public health capacities—including laboratories, surveillance systems, and rapid notification and response mechanisms. States are expected to submit a States Parties Self-Assessment Annual Report (SPAR) and are encouraged to participate in the voluntary Joint External Evaluation [35,36]. The development of laboratory capacities must also incorporate biosafety and biosecurity measures, including risk classification frameworks, containment protocols, and other safety measures (Figure 1) [36]. Health security extends beyond healthcare, encompassing public health services and education, which are vital for disease detection, response, and vaccine rollout. It is crucial for member states to notify the WHO of any public health event that may constitute a public health emergency of international concern [35]. Improving sanitation with access to clean water and soap is essential for protecting against water-borne diseases like cholera. Effective vector control, particularly for mosquitoes, is central to managing vector-borne diseases. Routine vaccinations protect against a wide range of infectious diseases, and food safety measures—extending from farming practices to manufacturing—are critical for early detection and recall of foodborne outbreaks.

Research and development

COVID-19 underscored the critical role of research and development in health security. Although it is not feasible to prepare vaccines in advance for every emerging infectious disease, more investment is needed in developing medical technologies—including new antibiotics to combat resistance, universal flu vaccines, and innovative platforms for vaccine discovery. Policies such as public funding, advanced market commitments, technology transfer, and patent pooling are essential to incentivize investment in new antibiotics. Furthermore, the cost of diagnostics, therapies, and vaccines must be affordable. Policymakers should collaborate with companies to plan for rapid scaling of manufacturing in the event of a widespread outbreak, epidemic, or pandemic.

One Health

One Health—an integrated approach recognizing the interconnectedness of human, animal, and environmental health—is essential. The COVID-19 pandemic was spurred by a novel coronavirus transmitted from animals to humans, followed by human-to-human spread. Similarly, bird populations can carry novel influenza viruses during migratory flights, while mosquitoes can expand their geographic range due to climate change, facilitating the spread of diseases such as malaria, Zika, and dengue.

Climate change and biodiversity

Climate change expands the distribution of disease vectors, influences ecosystems, and creates conditions favorable for water-borne infections. Transitioning to carbon-free or

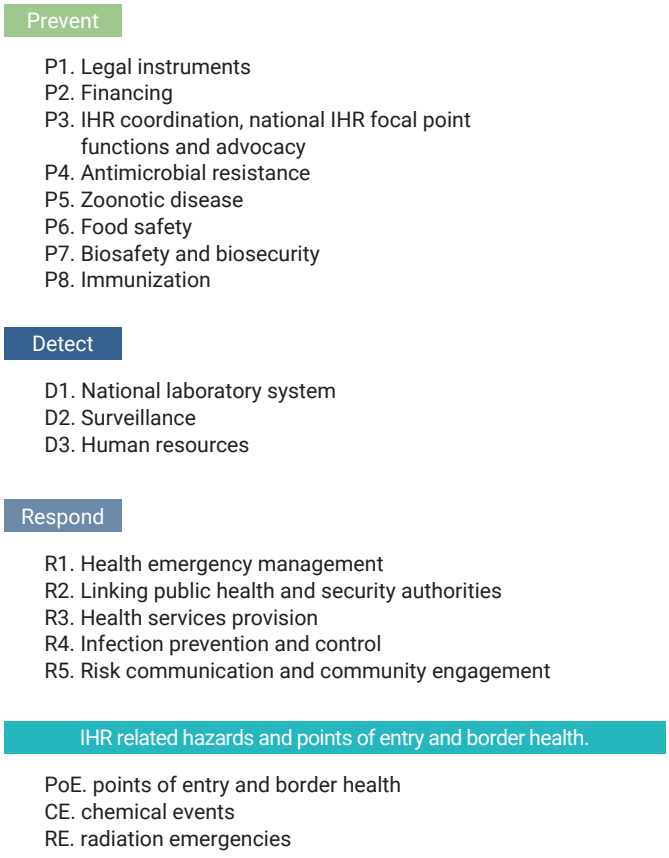


Figure 1. International Health Regulations core capacities. IHR, International Health Regulation. Based on [36].

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renewable energy using advanced technologies to reduce production costs is imperative. Securing global biodiversity—including protecting forests—is crucial for global health security, as plants and animals provide important sources of new antimicrobials and therapies. Global solidarity, exemplified by agreements such as the Paris Agreement, is essential for collective action.

Factory farms, wet markets, and animal pathogen surveillance

Farmers in factory farms use antibiotics in their animals, supplying consumers with inexpensive meat that may contain antibiotic-resistant bacteria [37]. Sustainable and humane agricultural practices are needed, which may also encourage a shift toward plant-based diets as meat prices rise. Markets selling live wildlife present additional risks [38]. The sale of live wildlife should be banned, and the wildlife trade curtailed [39]. However, a ban alone is insufficient; significant resources are required for enforcement, as the illegal wildlife trade is a multibillion-dollar criminal enterprise [39]. Furthermore, the sale of domesticated animals for consumption requires strict health and safety measures, such as physically separating live animals from people, as well as rigorous meat-handling protocols with strong enforcement [40].

Understanding animal pathogens is critical for identifying and responding to zoonotic diseases, including the development of vaccines and therapies. Increased investment in virus surveillance is needed to track the movement of zoonotic pathogens among species and toward human populations [41]. This information is valuable for preventing human diseases and developing effective interventions. Zoonotic pathogen research must adhere to strict biosafety and biosecurity standards to prevent accidental or intentional releases.

Equity

No one is safe from infectious diseases unless everyone is safe. In an interconnected world, equity in health security is paramount. Every country and population plays a role in preventing and responding to infectious diseases. Equal access to health benefits and the equitable distribution of burdens must be achieved both domestically and internationally [42]. Global health security should ensure that vaccines and treatments are affordable and available to everyone [43]. Poor and vulnerable populations, including low-paid workers, foreign migrants, and refugees, must be adequately supported in terms of health and hygiene during epidemics or pandemics.

WHO Governance Reform

Reforming the governance of the WHO must begin by providing it with sufficient funding to fulfill its global mandate and the flexibility to allocate resources toward the most urgent global health security issues. With increased funding and flexibility, the WHO can assist low- and middle-income countries in meeting IHR obligations, thereby enhancing their capacities to detect, report, and respond to novel infections. This support would enable all member states to detect, report, and rapidly respond to public health events that may constitute a public health emergency of international concern. Currently, there are no penalties for member states that do not comply with WHO recommendations on travel, trade, and quarantine, and most have not developed the IHR-required core capacities. The WHO should be granted stronger enforcement powers, which might include withdrawing voting rights from non-compliant member states, developing an inspection system with enforcement authority, and establishing global norms for AMR in collaboration with the World Organisation for Animal Health (WOAH) and for biosafety/biosecurity. Additionally, WHO should lead and coordinate global health security efforts alongside international partners such as WOAH and the Food and Agriculture Organization. Enhancing WHO's global governance could also involve establishing health accountability among member states through a new treaty backed by feasible funding [44].

Preparing for the Next Pandemic

Healthier and more resilient cities

More than half of the world's population currently lives in urban areas, and this is projected to increase to two-thirds by 2050 [45]. Densely populated cities have proven to be hotspots for contagions like SARS-CoV-2, as viruses can easily spread in crowded apartment buildings, subways, and buses, and on busy sidewalks. Constant human-to-human contact amplifies pandemic risks, and during outbreaks, dense populations hinder social distancing—making it nearly impossible to maintain safe practices without causing major social and economic disruptions. COVID-19 forced unprecedented changes in major metropolitan areas. In the post-COVID-19 era, cities could re-emerge as more resilient, healthier—both physically and mentally—and more sustainable, with increased green spaces, walking paths, and bike lanes.

The new mode of consumerism

During COVID-19, online shopping increased by 75% [46], with online grocery shopping becoming a primary source of purchases [47]. Rather than dining in restaurants, people

preferred take-out or delivery. Additionally, healthcare has shifted toward remote access; 76% of US hospitals now use telehealth technologies to contact, diagnose, and treat patients [48].

Schools and workplaces in a virtual world

At all levels of education, instruction has moved online, with teachers and professors delivering lectures virtually and evaluating assignments and exams remotely. Similarly, many workplaces have adopted telework arrangements.

Sanitary social behaviors

During the COVID-19 era, common social behaviors—such as shaking hands, hugging, and large gatherings—nearly vanished, replaced by new habits like frequent hand hygiene, proper cough etiquette, and mask wearing. In the post-COVID-19 world, these sanitary behaviors may reduce the transmission of many common respiratory diseases, such as colds and flu. However, they may also alter human intimacy by limiting the expression of facial emotions, physical touch, and social interaction.

International travel

Air travel and tourism are expected to rebound in the post-COVID-19 era; approximately 1.1 billion tourists traveled internationally in the first 9 months of 2024 [49]. However, we continue to face the potential for rapid international disease transmission and the challenges of climate change. It remains uncertain whether future travel will be more environmentally sustainable.

A safer and more equitable society

The COVID-19 pandemic exposed significant health inequities both domestically and internationally, particularly in access to healthcare services and social safety nets. Poor populations and low-income countries experienced disproportionately high hospitalization and death rates. In the post-COVID-19 era, addressing health inequalities stemming from disparities in wealth and political power is essential to creating a more equitable society.

Discussion

How Failures of the IHR Implementation Have Impacted Pandemic Response: Lessons Learned from Previous Emerging Infectious Diseases such as SARS and MERS

The 2015 MERS outbreak in the Republic of Korea led to improvements in the country's national emergency system for emerging infectious diseases [50]. Similarly, Hong Kong, Singapore, and Taiwan—having experienced the 2003 SARS outbreak—responded effectively during the early stages of the COVID-19 pandemic, strengthening their emerging infectious disease response systems [51].

Between 2018 and 2020, the Republic of Korea achieved high WHO SPAR scores of 94 compared to the global average of 61 following reforms to its national public health emergency system (Figure 2) [35]. For emerging infectious diseases, early detection and rapid response were key to containing outbreaks (Figure 2) [35]. However, the world was largely unprepared to detect and respond to emerging infectious diseases, with only a few countries having effective management systems in place [51]. The roles of health authorities and relevant ministries must be clearly defined [52]. Moreover, effective information-sharing systems for the public were lacking, and communication, cooperation, and collaboration between different levels of government were insufficient [50]. Additionally, there was a shortage of well-trained healthcare workers and epidemiologists [50].

How the WHO Should Be Reformed

The WHO has struggled to fulfill its mandate to guide and coordinate its member states, resulting in uncoordinated responses. Three key points should be considered for reform: (1) Sanctions: Although the IHR mandates that member states notify the WHO of any potential public health emergencies of international concern and cooperate accordingly, the WHO currently lacks legal enforcement power. The IHR should include sanctions against non-compliant member states, similar to the World Trade Organization, which can impose sanctions on member states that violate its rules [52]. (2) Innovative Funding Mechanisms: The WHO requires more innovative financing mechanisms, such as those employed by Gavi, the Vaccine Alliance, the Global Fund, or UNITAID [52]. (3) Public-Private Partnership Governance: The governance structure of the WHO should incorporate alternative voices, including those from civil society and private philanthropists, as seen with the Global Fund [25].

Implementing these reforms will require strong commitment and extensive coordination among member states. The WHO must be empowered with greater authority and coordination capacity to effectively combat the next pandemic.

Conclusion

The world must prepare for all health security threats, including emerging respiratory infectious diseases, such as novel coronaviruses, avian influenza, or Ebola virus. Lessons learned from devastating outbreaks or epidemics can help us better prepare for future events,

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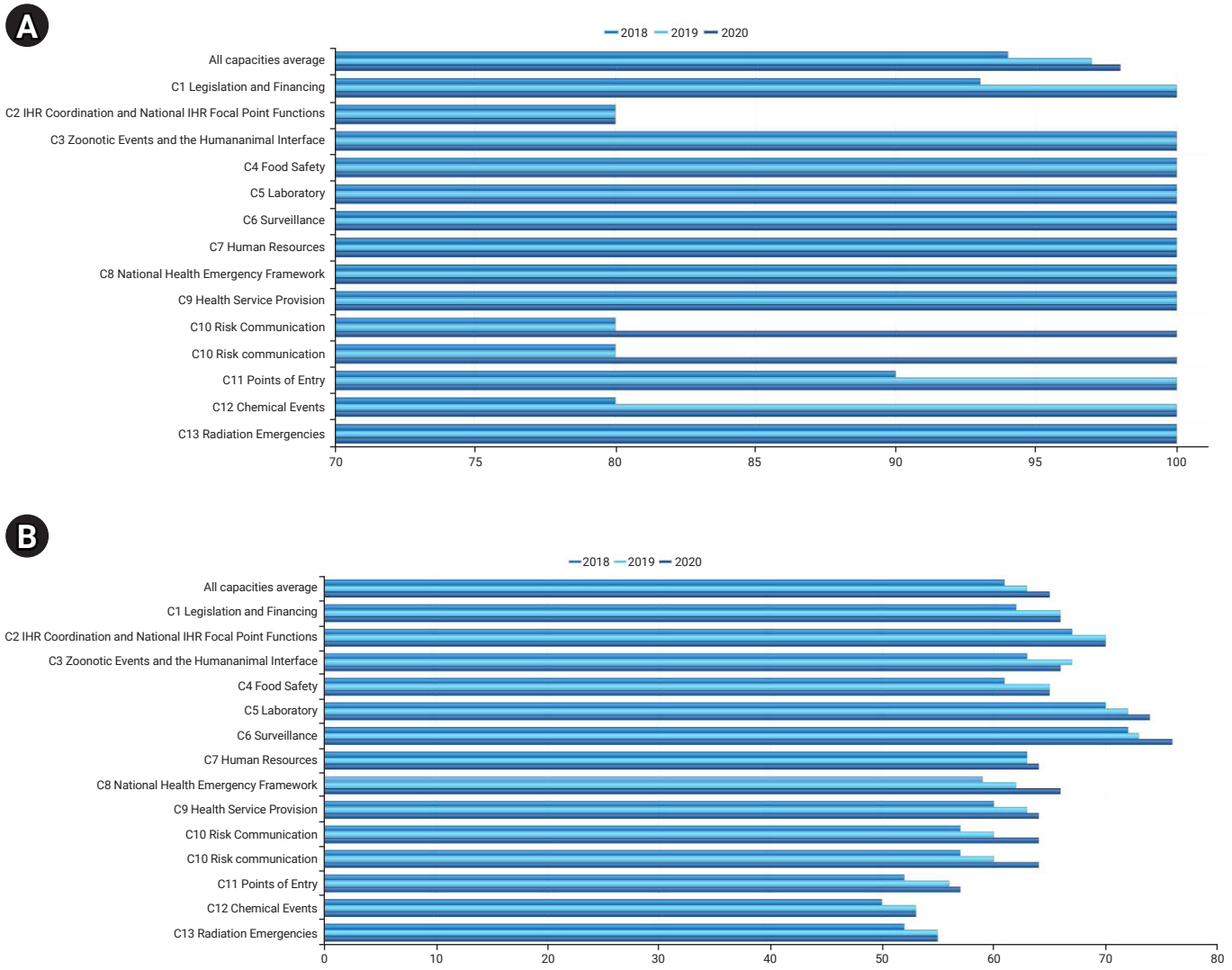


Figure 2. International Health Regulations capacity progress from the states parties' self-assessment annual report in 2018–2020 (Republic of Korea) (A) and all the countries (B). IHR, International Health Regulation. Based on [35].

as evidenced by the responses to COVID-19 in countries that had previously experienced SARS or MERS. The next global health security threat may arise from an emerging respiratory infectious disease outbreak, AMR, a vector-borne disease, or bioterrorism. Additionally, slower but increasingly significant threats, such as cholera outbreaks in refugee camps within conflict zones, continue to pose risks. To address these potential threats, multisectoral, whole-of-society actions are necessary to prepare for, prevent, detect, and respond at national, regional, and global levels. By applying the lessons learned from COVID-19—in particular, the insight that the pandemic was largely preventable with better preparedness—we can achieve global health security with justice for all.

Notes

Ethics Approval

The informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest

Chaeshin Chu has been a managing editor of *Osong Public Health and Perspectives* since 2011.

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None.

Availability of Data

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

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Original Article

A comparison of health-related quality of life using the World Health Organization Quality of Life–BREF and 5-Level EuroQol-5 Dimensions in the Malaysian population

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ABSTRACT

Objectives: This study aimed to describe and compare health-related quality of life (QoL) as measured by the World Health Organization Quality of Life–BREF (WHOQoL-BREF) and the EuroQol-5 Dimensions (EQ-5D) among the Malaysian population, examining differences by sociodemographic characteristics including age, income, sex, ethnicity, educational level, and occupation.
Methods: This cross-sectional study used data from 19,402 individuals collected as part of a health and demographic surveillance system survey conducted in the Segamat district of Malaysia in 2018–2019. Descriptive statistics and measures of central tendency were produced. Differences in QoL among demographic sub-groups were examined using the t-test and analysis of variance, while the correlations between the WHOQoL-BREF and EQ-5D were evaluated using Pearson correlation coefficients.
Results: Based on complete case analysis (n=19,129), the average scores for the 4 WHOQoL-BREF domains were 28.2 (physical), 24.1 (psychological), 12.0 (social relationships), and 30.4 (environment). The percentages of participants not in full health for each EQ-5D dimension were 12.8% (mobility), 3.1% (self-care), 6.9% (usual activities), 20.9% (pain/discomfort), and 6.8% (anxiety/depression). Correlations between the 4 WHOQoL-BREF domains and the 5 EQ-5D dimensions were relatively weak, ranging from −0.06 (social relationships with self-care and pain/discomfort; p<0.001) to −0.42 (physical with mobility; p<0.001).
Conclusion: Although health-related QoL as measured by the WHOQoL-BREF and the EQ-5D are correlated, these 2 measures should not be considered interchangeable. The choice between them should be guided by the specific research questions and the intended use of the data.

Keywords: Community participation; Developing countries; Health inequities; Quality of life; Surveys and questionnaires

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Introduction

The World Health Organization (WHO) defines quality of life (QoL) as an individual's perception of their position in life within the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns [1]. This broad concept encompasses multiple layers of an individual's life, including physical health, psychological state, social relationships, and interactions with the surrounding environment. When QoL is applied to the measurement of health status and disease, it is termed health-related QoL, reflecting subjective health, well-being, and life satisfaction among the population [2].

Several instruments are widely used to measure health-related QoL, 2 of which are the focus of this study. The first is the WHO Quality of Life Scale–BREF (WHOQoL-BREF) [1], which assesses 4 QoL domains: physical, psychological, social, and environmental. The second instrument is the EuroQol-5 Dimensions (EQ-5D) [3], which covers 5 health state dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition to these 5 dimensions, the EQ-5D includes a visual analog scale (VAS) for rating overall health status. Both measures have been translated and employed in clinical and community studies worldwide [4,5].

Despite their similar aim of measuring an individual's health-related QoL, the WHOQoL-BREF and EQ-5D are based on different conceptual frameworks [6]. The WHOQoL-BREF is a profile-based measure constructed to evaluate specific domains using multiple items [7]. This profile-based approach is valuable in assessing health or its domains from the patient's perspective, particularly in clinical trials where detailed information and sensitivity to clinical changes are required [6].

In contrast, the EQ-5D is a preference-based measure designed to capture health states and facilitate the calculation of quality-adjusted life years (QALYs) [8]. Self-reported information from the 5 domains is converted into an index score (or utility value) using country-specific public preferences for various health states—hence, it is classified as a preference-based measure [9]. Similar to profile-based measures, preference-based measures assess health from the patient's perspective; however, the utility values produced by the EQ-5D can also be used for economic analyses of health interventions [6,7].

Numerous studies have explored the health-related QoL of populations beyond the Global North, where these instruments were originally developed. Both the WHOQoL-BREF and the EQ-5D have been translated and validated in Malaysia, ensuring their cultural and linguistic appropriateness. For example, the WHOQoL-BREF has demonstrated good psychometric properties in studies assessing the QoL of rural residents, where income levels were found to be associated with QoL [10]. Similarly, the EQ-5D has been validated for the Malaysian population, with country-specific value sets developed to reflect local health preferences. It has also been used to assess the QoL of both young and elderly Malaysians with low-income backgrounds [11], while country-specific utility value sets were developed in India [12] and Indonesia [13], facilitating cross-cultural comparisons. Together, these instruments allow for a comprehensive assessment of health-related QoL in Malaysia by capturing both broad subjective aspects (WHOQoL-BREF) and specific health state descriptions with economic utility (EQ-5D) relevant to Malaysia's diverse ethnic landscape and healthcare system.

However, the association between these 2 measures remains unclear. One study in Thailand mapped the WHOQoL-BREF onto the EQ-5D and found that only the physical domain of the WHOQoL-BREF was associated with EQ-5D utility values, though that study was limited to patients with chronic diseases [5]. Therefore, this study aimed to describe and compare WHOQoL-BREF and EQ-5D results using QoL data from a community-dwelling Malaysian population, examining differences across various sociodemographic characteristics. Malaysia's ethnic classification system is unique, incorporating 3 interrelated terms. "Bumiputera," meaning "sons of the soil," is a political designation that includes ethnic Malays and indigenous peoples, granting them certain legal and economic privileges [14]. Malays, the largest ethnic group, are automatically considered Bumiputera and are predominantly Muslim with distinct cultural and linguistic heritage. "Orang Asli" refers specifically to the indigenous peoples of Peninsular Malaysia who, despite their Bumiputera status, often

HIGHLIGHTS

- Both the World Health Organization Quality of Life–BREF (WHOQoL-BREF) and the EuroQol-5 Dimensions (EQ-5D) consistently indicated a relatively good health-related QoL among Malaysians.
- Although the domains of the WHOQoL-BREF and the dimensions of the EQ-5D were associated, the correlations were weak, indicating that the 2 measures are not interchangeable.
- The decision to use one measure or both in a study should consider the study's objectives and participant characteristics.

encounter greater socioeconomic challenges than Malays. This complex classification system significantly influences Malaysia's social, economic, and political landscape. Although comparing health-related QoL measures is not a new concept, this study adds to our understanding of the cultural relevance and applicability of the WHOQoL-BREF and EQ-5D in the Malaysian context. Our findings provide valuable insights for stakeholders selecting appropriate QoL measures for population-based studies in Malaysia and similar multicultural Asian settings.

Materials and Methods

Study Setting and Participants

This observational population study was conducted in the Segamat District of Johor State, Malaysia (Figure S1) [15]. Segamat hosts a longitudinal health and demographic surveillance system known as the South East Asia Community Observatory (SEACO), launched in November 2011 [15]. The district covers 2,851 km2 and has a population comprised of 50.6% men and 49.4% women; 67.5% of residents are aged 15 to 64 years. The majority of residents are of Malay and Bumiputera heritage (53.9%), followed by Chinese (31.9%) and Indian (8.3%) ethnic groups [16]. This population structure closely resembles the national profile (51.4% male; 67.3% aged 15 to 64; 61.9% Malay and Bumiputera, 22.5% Chinese, and 6.7% Indian). Participants who consented during the 2017 SEACO census were invited to participate in the 2018 Health Survey [17], which provided the data that were analyzed in this study.

Data Collection

This cross-sectional study used data from the SEACO 2018 Health Survey [17], conducted every 5 years. Data were collected in 2018–2019 by trained enumerators who visited consenting households. Using handheld electronic devices, enumerators conducted interviews, encrypted the data, and uploaded it to a secure server. Further details on data collection are provided in previous reports [10,18]. The collected explanatory variables are presented in Table 1 [19,20].

Outcome Measures

The WHOQoL-BREF [1] was introduced in 1996 and has been translated into many languages worldwide, including Malay [21]. This instrument contains 26 items covering overall QoL and general health (2 items), physical health (7 items), psychological (6 items), social relationships (3 items), and the environment (8 items). Each item is scored on a scale from 1 (very poor) to 5 (very good), with higher total domain scores indicating better conditions in that domain. Domain scores may be compared with the full WHOQoL-100 by transforming the raw scores according to the user's manual [1]. The internal consistency (α) of each domain was 0.47 for physical health, 0.66 for psychological, 0.76 for social relationships, and 0.70 for environment.

The EQ-5D has evolved into a family of instruments designed for specific purposes. The original version, the EQ-5D-3L, comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 3 levels per domain (3). In 2009, the instrument was updated to the EQ-5D-5L, which features 5 levels of responses: no problem (1), slight (2), moderate (3), severe (4), and extreme/unable to do (5). This study used the latest version, which offers improved discriminatory power and responsiveness compared to the 3L version.

Table 1. Explanatory variables

Variable	Description
Age	Participants were asked for their age, which then was categorized into 9 age groups from 16–17, then 5-year intervals, to older than 84 years old.
Monthly household income	Monthly household income was categorized into 3 categories that were recognized nationally, including bottom-40% (B40, <MYR 4,360), middle-40% (M40, MYR 4,360–MYR 9,619), and top-20% (T20, >MYR 9,619, USD 1.0≈MYR 4.1 in 2016) based on the information from the Department of Statistics Malaysia in 2016 [19,20].
Sex	Participants were asked about their sex with 3 options, but only 2 categories were reported by them, including male and female (none chose "other").
Ethnicity	Ethnicity groups were categorized into Malay, Chinese, Indian, Orang Asli (indigenous people), other, and non-citizen.
Educational level	Participants' educational levels were categorized into no formal education, primary, secondary, tertiary, and other/do not know/refused to answer.
Occupation	Participants were asked about their work in the past 30 days, with responses categorized into 4 groups: working full-time, home-makers (including housewife/househusband), self-employed, and other (including too young to work, student, not working, casual jobs, working part-time, and pensioner).

MYR, Malaysian ringgit; USD, United States dollar.

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Participants selected the health status for each domain on the day they completed the questionnaire using these 5 levels. The combination of responses yields a 5-digit health profile; for example, a profile of 11111 indicates perfect health, while 55555 indicates extreme problems in all dimensions. This profile is then linked to an estimated utility value (EUV); for this study, we used the Malaysian value set from previous studies, with a possible range from −0.442 to 1 [22–24]. The reliability (α) of the EQ-5D-5L in this study was 0.79. In addition to the 5 dimensions, participants rated their overall health on a VAS ranging from 0 (the worst imaginable state) to 100 (the best imaginable state).

Despite their common goal of assessing QoL, the 2 measures differ in design and purpose. The WHOQoL-BREF provides a broader assessment, including domains such as environment and social relationships that are not directly addressed by the EQ-5D, and it employs multiple items per domain for a more nuanced evaluation. In contrast, the EQ-5D uses single items for each dimension, which may limit its sensitivity to subtle variations. The measures also differ temporally: the WHOQoL-BREF typically reflects experiences over the past 2 weeks, whereas the EQ-5D focuses on the current day. Furthermore, the WHOQoL-BREF was developed with cross-cultural applicability in mind, potentially capturing cultural nuances in perceptions of QoL more effectively than the EQ-5D. Finally, the EQ-5D is designed to generate utility values for economic evaluation, a feature not present in the WHOQoL-BREF.

Data Analysis

Descriptive analyses were performed to summarize central tendency measures. For inferential analyses, raw domain scores were used rather than transformed scores because their equal-interval properties allow for more direct comparisons with other international measures [6]. Transformed domain scores (Tables S1–S6) were used solely for descriptive comparisons between domains. The user's manual provided guidance for managing missing values; however, since a small percentage of participants (n = 273, 1.41%) did not complete the scale—particularly Item 21 ("How satisfied are you with your sex life?")—these participants were excluded from the analysis.

The transformed WHOQoL-BREF domain scores and EQ-5D scores were cross-tabulated with demographic variables (e.g., age group) to visually inspect differences among sub-groups. Normality was assessed using Kolmogorov-Smirnov tests and verified visually with histograms and Q-Q plots (Tables S7, S8; Figures S2, S3). The tests indicated that the overall QoL and general health items, all 4 WHOQoL-BREF domains, and all 5 EQ-5D items were not normally distributed (p < 0.05), with skewness coefficients ranging from −4.7 to 8.3. However, non-normality is common in large samples, where even small deviations from normality become statistically significant [25].

The t-test and one-way analysis of variance were conducted to examine differences in QoL among demographic sub-groups, including age, monthly household income, sex, and ethnicity. Effect sizes were calculated using Cohen's d and partial eta squared. Correlations between the WHOQoL-BREF and the EQ-5D were evaluated using the Pearson correlation coefficient. All analyses were conducted using IBM SPSS version 27.0 (IBM Corp.), with a 2-tailed p-value of 0.05 indicating statistical significance.

Ethics Approval

This study was approved by the Monash University Human Research Ethics Committee (MUHREC, Project ID 2018-13142) and followed the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. Written informed consent was obtained for publication of this study and accompanying images.

Results

Participant Characteristics

A total of 19,402 people provided consent to participate in the study. After removing 273 participants (1.41%) who did not complete the WHOQoL-BREF questionnaire, data from 19,129 participants were included in the analysis. Demographic information is presented in Table 2, organized by age group. Participants ranged in age from 16 to 99 years, with an average age of 48.5 years (standard deviation [SD], 18.7); the gender distribution was relatively balanced, with 44.0% male and 56.0% female. The majority belonged to the B40 income group (79.7%) and were of Malay ethnicity (62.7%), reflecting semi-urban and rural population characteristics.

Quality of Life: WHOQoL-BREF

The WHOQoL-BREF results indicated average perceived general QoL and health scores of 3.82 (SD, 0.60) and 3.85 (SD, 0.60), respectively, suggesting relatively good overall QoL and satisfaction with health. Figure 1 visually display the 4 WHOQoL-BREF domains across sub-groups defined by age, ethnicity, household income, and age group, using a standardized 100-point scale (Tables S1–S6). The environment domain (Domain 4: mean, 71.7; SD, 11.3) was slightly lower than the physical health (Domain 1: mean, 75.7; SD, 11.7), psychological (Domain 2: mean, 75.8; SD, 10.7), and social relationships (Domain 3: mean, 75.4; SD, 11.4) domains. The data also indicate that men perceive their physical health slightly more favorably than women. In other panels, ethnic

Table 2. Demographic characteristics of participants (*n* = 19,129)

Characteristic	16–17 y (*n* = 952)	18–24 y (*n* = 1,886)	25–34 y (*n* = 2,481)	35–44 y (*n* = 2,448)	45–54 y (*n* = 2,976)	55–64 y (*n* = 4,120)	65–74 y (*n* = 2,952)	75–84 y (*n* = 1,142)	>84 y (*n* = 172)	Total (*n* = 19,129)
Age (y)	16.5 ± 0.5	20.5 ± 2.0	29.8 ± 2.8	39.5 ± 2.9	49.8 ± 2.9	59.7 ± 2.8	68.7 ± 2.7	78.7 ± 2.7	88.1 ± 3.0	48.5 ± 18.7
Household income /mo, MYR)	2,687 ± 2,658	3,575 ± 2,802	3,659 ± 2,833	3,415 ± 2,942	3,205 ± 2,943	2,717 ± 2,463	2,066 ± 1,923	1,696 ± 1,935	1,912 ± 1,961	2,919 ± 2,671
Household income category										
B40	789 (82.9)	1,366 (72.4)	1,726 (69.6)	1,819 (74.3)	2,294 (77.1)	3,405 (82.6)	2,644 (89.6)	1,048 (91.8)	153 (89.0)	15,244 (79.7)
M40	139 (14.6)	452 (24.0)	665 (26.8)	538 (22.0)	565 (19.0)	633 (15.4)	287 (9.7)	84 (7.4)	19 (11.0)	3,382 (17.7)
T20	24 (2.5)	68 (3.6)	90 (3.6)	91 (3.7)	117 (3.9)	82 (2.0)	21 (0.7)	10 (0.9)	0 (0.0)	503 (2.6)
Sex										
Male	440 (46.2)	910 (48.3)	1,085 (43.7)	1,002 (40.9)	1,206 (40.5)	1,719 (41.7)	1,473 (49.9)	525 (46.0)	66 (38.4)	8426 (44.0)
Female	512 (53.8)	976 (51.7)	1,396 (56.3)	1,446 (59.1)	1,770 (59.5)	2,401 (58.3)	1,479 (50.1)	617 (54.0)	106 (61.6)	10,703 (56.0)
Ethnicity										
Malay	634 (66.6)	1,361 (72.2)	1,783 (71.9)	1,589 (64.9)	1,833 (61.6)	2,471 (60.0)	1,697 (57.5)	558 (48.9)	73 (42.4)	11,999 (62.7)
Chinese	212 (22.3)	253 (13.4)	236 (9.5)	382 (15.6)	672 (22.6)	1,128 (27.4)	970 (32.9)	501 (43.9)	85 (49.4)	4,439 (23.2)
Indian	77 (8.1)	181 (9.6)	239 (9.6)	253 (10.3)	325 (10.9)	447 (10.8)	252 (8.5)	74 (6.5)	9 (5.2)	1,857 (9.7)
Orang Asli	24 (2.5)	59 (3.1)	79 (3.2)	72 (2.9)	60 (2.0)	33 (0.8)	18 (0.6)	6 (0.5)	2 (1.2)	353 (1.8)
Other	4 (0.4)	9 (0.5)	13 (0.5)	17 (0.7)	12 (0.4)	15 (0.4)	8 (0.3)	1 (0.1)	0 (0.0)	79 (0.4)
Non-citizen	1 (0.1)	23 (1.2)	131 (5.3)	135 (5.5)	74 (2.5)	26 (0.6)	7 (0.2)	2 (0.2)	3 (1.7)	402 (2.1)
Educational level										
No formal education	5 (0.5)	29 (1.5)	97 (3.9)	147 (6.0)	284 (9.5)	839 (20.4)	992 (33.6)	719 (63.0)	138 (80.2)	3,250 (17.0)
Primary (Pendidikan rendah)	22 (2.3)	107 (5.7)	263 (10.6)	442 (18.1)	624 (21.0)	1,528 (37.1)	1,310 (44.4)	306 (26.8)	22 (12.8)	4,624 (24.2)
Secondary (Pendidikan menengah rendah; menengah atas)	158 (16.6)	918 (48.7)	1,427 (57.5)	1,462 (59.7)	1,875 (63.0)	1,597 (38.8)	588 (19.9)	94 (8.2)	9 (5.2)	8,128 (42.5)
Tertiary (Pendidikan tinggi)	2 (0.2)	222 (11.8)	534 (21.5)	302 (12.3)	151 (5.1)	137 (3.3)	43 (1.5)	15 (1.3)	0 (0.0)	1,406 (7.4)
Other/do not know/ refused to answer	765 (80.4)	610 (32.3)	160 (6.4)	95 (3.90)	42 (1.4)	19 (0.5)	19 (0.6)	8 (0.7)	3 (1.7)	1,721 (9.0)
Work (in the past 30 days)										
Working full-time	35 (3.7)	708 (37.5)	1,289 (52.0)	1,136 (46.4)	1,080 (36.3)	717 (17.4)	250 (8.5)	19 (1.7)	1 (0.6)	5,235 (27.4)
Home-makers	3 (0.3)	99 (5.2)	651 (26.2)	735 (30.0)	1,001 (33.6)	1,623 (39.4)	930 (31.5)	308 (27.0)	31 (18.0)	5,381 (28.1)
Self-employed	7 (0.7)	99 (5.2)	280 (11.3)	356 (14.5)	512 (17.2)	582 (14.1)	377 (12.8)	67 (5.9)	3 (1.7)	2,283 (11.9)
Other	907 (95.3)	980 (52.0)	261 (10.5)	221 (9.0)	383 (12.9)	1,198 (29.1)	1,395 (47.3)	748 (65.5)	137 (79.7)	6,230 (32.6)

Data are presented as mean ± standard deviation or frequency (%).
MYR, Malaysian ringgit.

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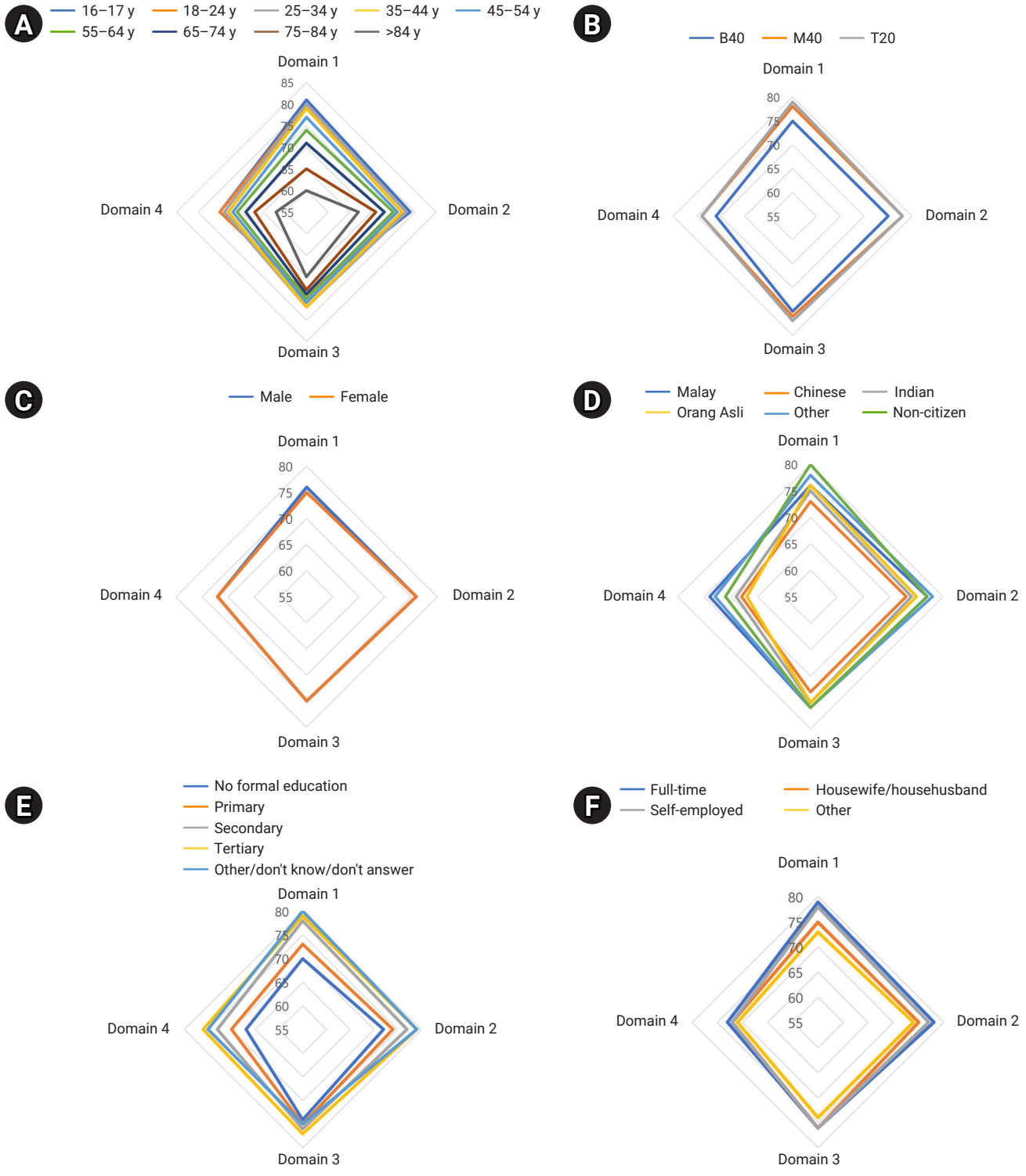


Figure 1. Four World Health Organization Quality of Life–BREF (WHOQoL-BREF) domains of quality of life in based on age group (A), household income category (B), sex (C), ethnicity (D), educational level (E), and occupation (F). Domain 1, physical health (mean, 75.7; standard deviation [SD], 11.7); Domain 2, psychological (mean, 75.8; SD, 10.7); Domain 3, social relationships (mean, 75.4; SD, 11.4); Domain 4, environment (mean, 71.7; SD, 11.3). Domain 4 had lower scores than the other 3 domains. Men perceive their physical health as slightly higher than women. Ethnic minority sub-groups (e.g., Chinese, Indian, and Orang Asli), B40 sub-group, and older sub-groups (i.e., ≥ 65 years) showed lower scores in all 4 domains than the more privileged sub-groups (i.e., Malay, T20, and younger sub-groups).

minority sub-groups (e.g., Chinese, Indian, and Orang Asli), the B40 sub-group, and older participants (i.e., ≥65 years) scored lower on all 4 domains compared with more privileged sub-groups (i.e., Malay, T20, and younger groups).

Quality of Life: EQ-5D

The EQ-5D findings revealed that participants generally experienced more intense problems in Dimension 4 (pain/discomfort; mean, 1.25; SD, 0.54; 20.9%) compared with other dimensions: mobility (mean, 1.18; SD, 0.53; 12.8%), self-care (mean, 1.05; SD, 0.32; 3.1%), usual activities (mean, 1.10; SD, 0.44; 6.9%), and anxiety/depression (mean, 1.08; SD, 0.33; 6.8%) (Table S9). The VAS indicated that participants generally reported good health (mean, 83.3; SD, 14.3), with an average EUV of 0.9402 (SD, 0.1495); additionally, 83.7% of participants reported no problems in all 5 dimensions. As with the WHOQoL-BREF, Figure 2 illustrates that ethnic minority groups (e.g., Chinese, Indian, and Orang Asli), the B40 sub-group, and older participants (i.e., ≥65 years) experienced more intense problems across all 5 dimensions compared with more privileged sub-groups (i.e., Malay, T20, and younger groups).

Correlation between WHOQoL-BREF and EQ-5D

Overall QoL and general health scores were positively correlated with all 4 WHOQoL-BREF domains ($p < 0.001$) and negatively correlated with all 5 EQ-5D dimensions ($p < 0.001$) (Table 2). Similarly, the EUV was positively correlated with all WHOQoL-BREF domains ($p < 0.001$) but showed a strong negative correlation with all EQ-5D dimensions (r ranging from −0.50 to −0.85; $p < 0.001$) (Table 3). While there were mild positive correlations among the 4 WHOQoL-BREF domains (r ranging from 0.43 to 0.66) and mild to moderate positive correlations among the 5 EQ-5D dimensions (r ranging from 0.23 to 0.69), the physical domain (Domain 1) of the WHOQoL-BREF demonstrated a mild negative correlation with the mobility dimension of the EQ-5D ($r = -0.42$, $p < 0.001$) and a mild positive correlation with self-rated health ($r = 0.42$, $p < 0.001$) and the EUV ($r = 0.45$, $p < 0.001$).

Explanatory Variables

Tables 4 and 5 present detailed results of participants' QoL as measured by both the WHOQoL-BREF and EQ-5D, stratified by demographic characteristics such as age, household income category, sex, and ethnicity. Differences in QoL among these sociodemographic sub-groups are described in the following paragraphs and Tables S10–S21.

Age

In general, QoL scores, along with the associated domains and dimensions, self-rated health, and EUVs, were lower in older age groups. Post-hoc tests revealed further differences within age sub-groups, with the level of health-related problems increasing with age. For instance, the percentage of participants with perfect health (11111) was 99.1% among 16- to 17-year-old, dropping to 57.8% among those aged 65 to 74. Moreover, effect size analyses indicated that physical health consistently exhibited the highest effect, as shown by the physical domain of the WHOQoL-BREF ($\eta^2 = 0.15$) and the mobility dimension of the EQ-5D ($\eta^2 = 0.12$).

Monthly household income

Analysis by household income category revealed that QoL and health conditions were consistently lower in the B40 group compared with the M40 and T20 groups across all domains and dimensions. However, the effect sizes were very small: physical ($\eta^2 = 0.01$), psychological ($\eta^2 = 0.01$), environment ($\eta^2 = 0.01$), and social relationships ($\eta^2 < 0.01$) for WHOQoL-BREF domains; and pain/discomfort ($\eta^2 = 0.01$), mobility ($\eta^2 < 0.01$), self-care ($\eta^2 < 0.01$), usual activities ($\eta^2 < 0.01$), and anxiety/depression ($\eta^2 < 0.01$) for EQ-5D dimensions.

Sex

Comparisons by sex indicated that women reported higher overall perceived QoL than men (95% confidence interval (CI), −0.06 to −0.02). However, women rated their general health and EUV lower than men (95% CI, 0.01–0.04 and 95% CI, 0.01–0.02; respectively). The effect size differences between sexes were relatively small: physical ($d = 0.09$) and psychological ($d = 0.07$) for WHOQoL-BREF domains; and mobility ($d = -0.07$), pain/discomfort ($d = -0.09$), and anxiety/depression ($d = -0.08$) for EQ-5D dimensions.

Ethnicity

Ethnic sub-groups reported varying scores for overall QoL, its domains and dimensions, self-rated health, and EUVs. Post-hoc tests indicated that the overall QoL of the Orang Asli group was lower than that of other ethnic sub-groups (p ranging from <0.001 to 0.02). The Chinese ethnic group reported lower satisfaction with general health compared with other ethnic groups (p ranging from <0.001 to 0.03), except when compared with the Orang Asli group ($p = 0.21$). However, analyses of each WHOQoL-BREF domain consistently showed that the Malay group had higher scores than the ethnic minority groups (i.e., Chinese, Indian, and Orang Asli). Similarly, analyses of each EQ-5D dimension revealed that Malays perceived a lower intensity of problems compared with ethnic minority groups. The Orang Asli group reported lower self-rated health than other sub-groups

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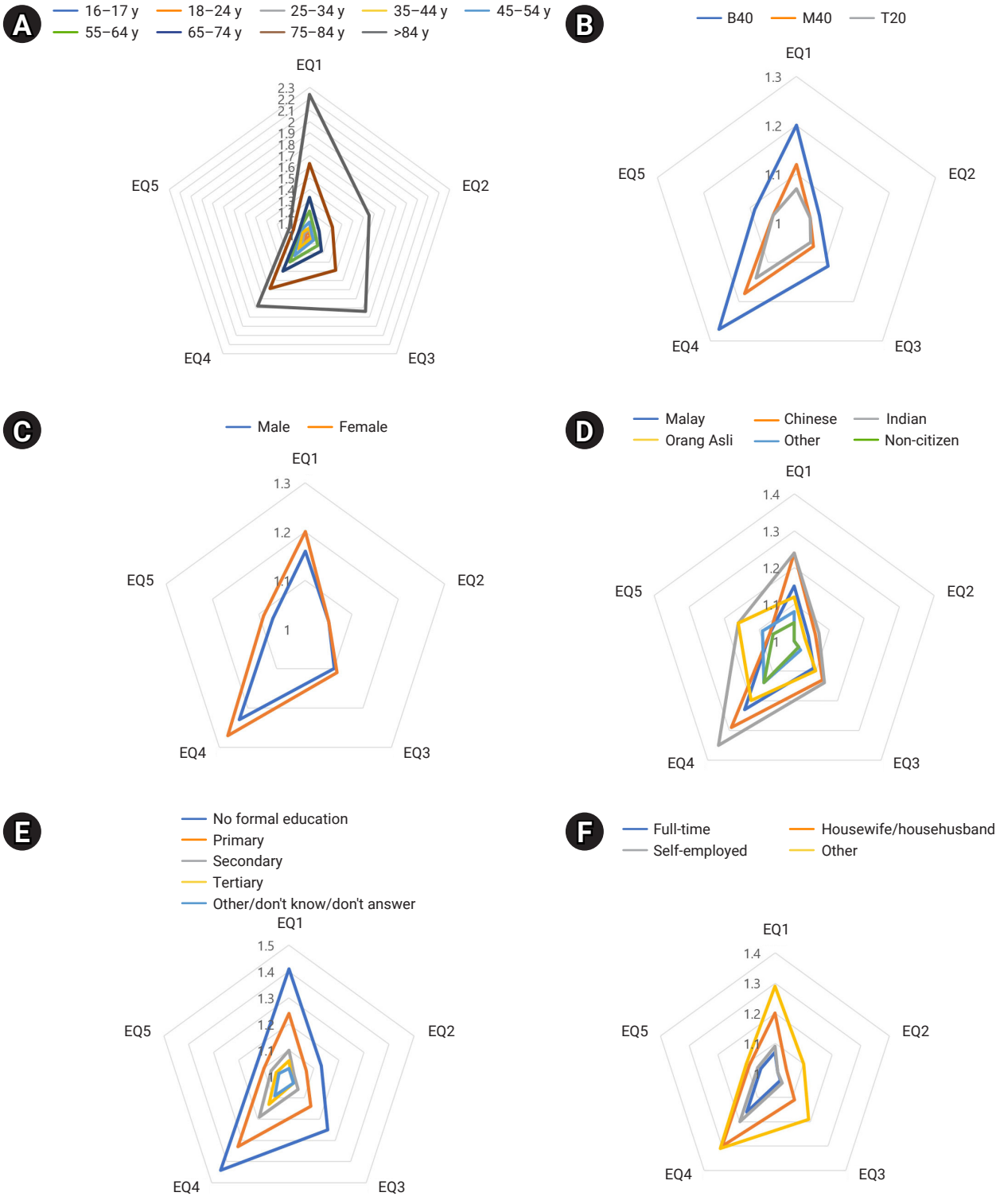


Figure 2. Five EuroQol-5 Dimensions (EQ-5D) dimensions of quality of life in based on age groups (A), household income category (B), sex (C), and ethnicity (D), educational level (E), and occupation (F). EQ1, mobility (mean, 1.18; standard deviation [SD], 0.53); EQ2, self-care (mean, 1.05; SD, 0.32); EQ3, usual activities (mean, 1.10; SD, 0.44); EQ4, pain/discomfort (mean, 1.25; SD, 0.54); EQ5, anxiety/depression (mean, 1.08; SD, 0.33). Ethnic minority groups (e.g., Chinese, Indian, and Orang Asli), B40 sub-group, and older sub-groups (i.e., 65 years and above) showed more intense conditions in all 5 dimensions than the more privileged sub-groups (i.e., Malay, T20, and younger sub-groups).

Table 3. Correlational analyses between WHOQoL-BREF domains (raw score) and EQ-5D dimensions

QoL	Overall QoL (Q1)	General health (Q2)	Domain 1	Domain 2	Domain 3	Domain 4	EQ1	EQ2	EQ3	EQ4	EQ5	VAS	EUV
Overall QoL (Q1)	1.00	0.36***	0.25***	0.35***	0.27***	0.33***	−0.11***	−0.08***	−0.10***	−0.11***	−0.11***	0.20***	0.14***
General health (Q2)		1.00	0.43***	0.39***	0.25***	0.31***	−0.22***	−0.16***	−0.21***	−0.23***	−0.15***	0.31***	0.26***
Domain 1			1.00	0.58***	0.43***	0.49***	−0.42***	−0.29***	−0.38***	−0.35***	−0.21***	0.42***	0.45***
Domain 2				1.00	0.54***	0.66***	−0.22***	−0.15***	−0.19***	−0.17***	−0.20***	0.26***	0.24***
Domain 3					1.00	0.59***	−0.07***	−0.06***	−0.08***	−0.06***	−0.07***	0.13***	0.09***
Domain 4						1.00	−0.16***	−0.11***	−0.13***	−0.13***	−0.12***	0.23***	0.18***
EQ1							1.00	0.57***	0.68***	0.52***	0.27***	−0.36***	−0.85***
EQ2								1.00	0.69***	0.36***	0.23***	−0.24***	−0.71***
EQ3									1.00	0.47***	0.28***	−0.32***	−0.80***
EQ4										1.00	0.29***	−0.38***	−0.77***
EQ5											1.00	−0.20***	−0.50***
VAS												1.00	0.41***
EUV													1.00

WHOQoL-BREF, World Health Organization Quality of Life–BREF; EQ-5D, EuroQol-5 Dimensions; QoL, quality of life; Domain 1, physical health; Domain 2, psychological; Domain 3, social relationships; Domain 4, environment; EQ1, mobility; EQ2, self-care; EQ3, usual activities; EQ4, pain/discomfort; EQ5, anxiety/depression; VAS, visual analogue scale/self-rated health; EUV, estimated utility value.
***$p < 0.001$.

($p < 0.001$), while the Indian group reported a lower EUV compared with other ethnic groups (p ranging from < 0.001 to 0.01).

Educational level

QoL findings varied based on educational sub-groups. *Post-hoc* tests consistently showed that participants with no formal education had lower QoL than those with some formal education (p ranging from < 0.001 to 0.02), regardless of whether QoL was measured using the WHOQoL-BREF or the EQ-5D.

Occupation

Differences in QoL were also observed across occupational sub-groups. *Post-hoc* tests of the WHOQoL-BREF indicated that participants engaged in full-time work generally reported better QoL than those in other occupational categories (p ranging from < 0.001 to 0.02), except in the social relationships domain, where scores were comparable to those of home-makers ($p = 0.99$). *Post-hoc* analyses for the EQ-5D showed that full-time workers generally had better QoL than other sub-groups (p ranging from < 0.001 to 0.01), although their scores were comparable to those of self-employed participants, particularly for mobility ($p = 0.23$), self-care ($p = 0.97$), usual activities ($p = 0.87$), and anxiety/depression ($p = 0.99$) domains.

Discussion

Using large community data representative of Malaysia's national demographics, this study aimed to describe and compare health-related QoL as measured by the WHOQoL-BREF and the EQ-5D across various sociodemographic characteristics. Both measures consistently indicated a relatively good quality of health and health status, which aligns with previous studies on the validation of the Malaysian EQ-5D and the development of its utility value sets [24,26]. Furthermore, correlational analyses revealed that all 4 WHOQoL-BREF domains and all 5 EQ-5D dimensions were significantly correlated; however, these correlations were relatively weak . The weak correlations may be attributed to the fundamental differences in purpose between the 2 measures. The physical health domain (Domain 1 of the WHOQoL-BREF) showed the strongest correlation with the EQ-5D dimensions, followed by the psychological (Domain 2), environmental (Domain 4), and social relationships (Domain 3) domains. On one hand, these findings support the results of a mapping study among chronic patients in Thailand, in which only physical health was associated with the EQ-5D [5]. On the other hand, our study of a large community sample indicates that the other 3 domains are also correlated with the EQ-5D.

Similar to previous studies among rural [10] and older Malaysians [11], this study found that QoL was lower in older

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Table 4. Demographic characteristics and quality of life measured with WHOQoL-BREF

Demographic characteristic	Overall QoL (Q1)	General health (Q2)	Domain 1	Domain 2	Domain 3	Domain 4
Age group (y)						
16–17 (*n* = 952)	3.99 ± 0.60	4.03 ± 0.60	29.56 ± 3.19	24.85 ± 2.83	11.88 ± 1.77	31.65 ± 3.96
18–24 (*n* = 1,886)	3.92 ± 0.59	3.99 ± 0.60	29.46 ± 2.95	24.8 ± 2.53	11.89 ± 1.62	31.38 ± 3.57
25–34 (*n* = 2,481)	3.89 ± 0.61	3.93 ± 0.59	29.29 ± 2.94	24.67 ± 2.50	12.21 ± 1.45	31.16 ± 3.63
35–44 (*n* = 2,448)	3.82 ± 0.60	3.88 ± 0.60	29.1 ± 2.85	24.52 ± 2.47	12.18 ± 1.38	30.73 ± 3.53
45–54 (*n* = 2,976)	3.77 ± 0.60	3.83 ± 0.60	28.63 ± 2.88	24.25 ± 2.41	12.16 ± 1.25	30.49 ± 3.43
55–64 (*n* = 4,120)	3.81 ± 0.59	3.81 ± 0.59	27.65 ± 2.92	23.95 ± 2.39	12.06 ± 1.19	30.21 ± 3.43
65–74 (*n* = 2,952)	3.76 ± 0.58	3.76 ± 0.59	26.8 ± 3.14	23.55 ± 2.45	11.92 ± 1.22	29.62 ± 3.52
75–84 (*n* = 1,142)	3.71 ± 0.59	3.63 ± 0.60	25.27 ± 3.37	22.95 ± 2.51	11.72 ± 1.36	28.8 ± 3.26
> 84 (*n* = 172)	3.65 ± 0.61	3.48 ± 0.62	23.84 ± 3.90	22.12 ± 2.76	11.39 ± 1.59	27.43 ± 3.99
Household income category						
B40 (*n* = 15,244)	3.80 ± 0.60	3.83 ± 0.61	28.02 ± 3.28	24.05 ± 2.55	12.01 ± 1.35	30.25 ± 3.61
M40 (*n* = 3,382)	3.91 ± 0.58	3.90 ± 0.57	28.69 ± 3.07	24.57 ± 2.44	12.13 ± 1.42	31.12 ± 3.48
T20 (*n* = 503)	4.00 ± 0.57	3.90 ± 0.66	29.02 ± 2.94	24.59 ± 2.51	12.24 ± 1.34	31.3 ± 3.42
Sex						
Male (*n* = 8,426)	3.80 ± 0.61	3.86 ± 0.60	28.32 ± 3.25	24.25 ± 2.51	12.03 ± 1.35	30.4 ± 3.55
Female (*n* = 10,703)	3.84 ± 0.59	3.83 ± 0.61	28.04 ± 3.24	24.08 ± 2.56	12.04 ± 1.38	30.45 ± 3.64
Ethnicity group						
Malay (*n* = 11,999)	3.81 ± 0.60	3.85 ± 0.60	28.39 ± 3.15	24.47 ± 2.31	12.13 ± 1.33	31.01 ± 3.40
Chinese (*n* = 4,439)	3.82 ± 0.62	3.80 ± 0.61	27.54 ± 3.44	23.45 ± 2.89	11.79 ± 1.51	29.33 ± 3.93
Indian (*n* = 1,857)	3.88 ± 0.58	3.86 ± 0.65	27.93 ± 3.37	23.72 ± 2.69	12.02 ± 1.22	29.66 ± 3.36
Orang Asli (*n* = 353)	3.65 ± 0.69	3.88 ± 0.62	28.34 ± 3.04	23.85 ± 2.48	11.97 ± 1.13	29.01 ± 3.25
Other (*n* = 79)	3.89 ± 0.55	4.01 ± 0.49	28.96 ± 2.71	24.77 ± 2.18	12.16 ± 1.35	30.97 ± 3.61
Non-citizen (*n* = 402)	3.79 ± 0.53	3.97 ± 0.46	29.31 ± 2.47	24.47 ± 2.33	12.08 ± 1.27	30.14 ± 3.30
Educational level						
No formal education (*n* = 3,250)	3.73 ± 0.59	3.74 ± 0.59	26.56 ± 3.41	23.32 ± 2.54	11.82 ± 1.31	29.00 ± 3.48
Primary (*n* = 4,624)	3.77 ± 0.60	3.8 ± 0.60	27.55 ± 3.17	23.78 ± 2.49	11.99 ± 1.24	29.87 ± 3.50
Secondary (*n* = 8,128)	3.82 ± 0.60	3.87 ± 0.60	28.7 ± 2.98	24.42 ± 2.44	12.12 ± 1.36	30.84 ± 3.46
Tertiary (*n* = 1,406)	3.99 ± 0.58	3.95 ± 0.59	29.26 ± 2.95	24.95 ± 2.39	12.29 ± 1.47	31.86 ± 3.43
Other/do not know/refused to answer (*n* = 1,721)	3.99 ± 0.58	3.99 ± 0.61	29.42 ± 3.11	24.8 ± 12.64	11.99 ± 1.64	31.51 ± 3.76
Work (in the past 30 days)						
Working full-time (*n* = 5,235)	3.86 ± 0.59	3.92 ± 0.58	29.07 ± 2.80	24.58 ± 2.40	12.15 ± 1.34	30.82 ± 3.44
Home-makers (*n* = 5,381)	3.82 ± 0.59	3.83 ± 0.60	27.87 ± 3.09	24.05 ± 2.45	12.15 ± 1.24	30.44 ± 3.58
Self-employed (*n* = 2,283)	3.76 ± 0.62	3.87 ± 0.57	28.73 ± 2.82	24.38 ± 2.30	12.09 ± 1.29	30.56 ± 3.36
Other (*n* = 6,230)	3.82 ± 0.61	3.79 ± 0.64	27.46 ± 3.65	23.80 ± 2.74	11.83 ± 1.48	30.05 ± 3.80
Total (*n* = 19,129)	3.82 ± 0.60	3.85 ± 0.60	28.17 ± 3.25	24.15 ± 2.54	12.04 ± 1.37	30.43 ± 3.60

Data are presented as mean ± standard deviation.
WHOQoL-BREF, World Health Organization Quality of Life–BREF; QoL, quality of life; Domain 1, physical health; Domain 2, psychological; Domain 3, social relationships; Domain 4, environment.

age groups, particularly in the physical health domain (e.g., physical and mobility aspects). This finding supports a recent systematic review of population-based QoL assessments, which recommended active aging to prevent QoL decline due to sedentary lifestyles [4]. Effect size analyses suggest that studies focusing on psychological health differences between age groups might consider using the WHOQoL-BREF over the EQ-5D, as the former appears more sensitive to psychological changes, as also found in a systematic review on QoL among older adults [27]. Conversely, if the study's focus is on the level of health-related problems and utility values, the EQ-5D may be preferable for comparing age groups. For instance, a study in South Korea using the 2021 Community Health Survey found that older adults experienced a decline in health-related QoL during the coronavirus disease 2019 (COVID-19) pandemic, as measured by the EQ-5D [28].

The less privileged B40 group consistently showed lower QoL compared with higher economic groups across

Table 5. Demographic characteristics and quality of life measured with EQ-5D

Demographic characteristic	EQ1	EQ2	EQ3	EQ4	EQ5	VAS	Full health (11111)	EUV
Age group (y)								
16–17 (*n* = 952)	1.01 ± 0.14	1.01 ± 0.14	1.02 ± 0.18	1.08 ± 0.35	1.04 ± 0.22	90.96 ± 12.1	867 (91.1)	0.989 ± 0.045
18–24 (*n* = 1,886)	1.02 ± 0.19	1.01 ± 0.13	1.01 ± 0.16	1.08 ± 0.31	1.03 ± 0.20	89.87 ± 11.79	1,709 (90.6)	0.989 ± 0.044
25–34 (*n* = 2,481)	1.05 ± 0.28	1.01 ± 0.14	1.03 ± 0.22	1.12 ± 0.41	1.05 ± 0.25	88.42 ± 11.81	2,112 (85.1)	0.982 ± 0.059
35–44 (*n* = 2,448)	1.06 ± 0.33	1.01 ± 0.17	1.03 ± 0.26	1.16 ± 0.43	1.07 ± 0.30	86.83 ± 11.95	1,992 (81.4)	0.976 ± 0.066
45–54 (*n* = 2,976)	1.11 ± 0.38	1.02 ± 0.18	1.06 ± 0.33	1.23 ± 0.50	1.09 ± 0.34	83.81 ± 12.83	2,189 (73.6)	0.965 ± 0.079
55–64 (*n* = 4,120)	1.21 ± 0.54	1.05 ± 0.32	1.12 ± 0.47	1.3 ± 0.58	1.1 ± 0.37	80.77 ± 14.15	2,725 (66.1)	0.946 ± 0.111
65–74 (*n* = 2,952)	1.33 ± 0.68	1.09 ± 0.41	1.18 ± 0.57	1.4 ± 0.64	1.1 ± 0.36	77.75 ± 14.3	1,705 (57.8)	0.926 ± 0.132
75–84 (*n* = 1,142)	1.63 ± 0.90	1.21 ± 0.65	1.39 ± 0.80	1.59 ± 0.76	1.15 ± 0.45	71.44 ± 15.63	476 (41.7)	0.871 ± 0.179
> 84 (*n* = 172)	2.24 ± 1.17	1.55 ± 1.04	1.84 ± 1.15	1.78 ± 0.85	1.19 ± 0.47	66.95 ± 16.55	42 (24.4)	0.772 ± 0.240
Household income category								
B40 (*n* = 15,244)	1.2 ± 0.55	1.05 ± 0.34	1.11 ± 0.46	1.27 ± 0.56	1.09 ± 0.34	82.65 ± 14.61	10,737 (70.4)	0.951 ± 0.111
M40 (*n* = 3,382)	1.12 ± 0.44	1.03 ± 0.24	1.06 ± 0.35	1.18 ± 0.45	1.05 ± 0.25	85.42 ± 12.69	2,659 (78.6)	0.969 ± 0.083
T20 (*n* = 503)	1.07 ± 0.35	1.03 ± 0.27	1.05 ± 0.32	1.14 ± 0.41	1.05 ± 0.26	87.46 ± 11.87	421 (83.7)	0.976 ± 0.083
Sex								
Male (*n* = 8,426)	1.16 ± 0.51	1.05 ± 0.32	1.1 ± 0.44	1.23 ± 0.52	1.07 ± 0.30	83.31 ± 14.28	6,338 (75.2)	0.960 ± 0.103
Female (*n* = 10,703)	1.2 ± 0.54	1.05 ± 0.32	1.11 ± 0.45	1.27 ± 0.56	1.09 ± 0.35	83.23 ± 14.27	7,479 (69.9)	0.951 ± 0.108
Ethnicity group								
Malay (*n* = 11,999)	1.15 ± 0.51	1.04 ± 0.3	1.09 ± 0.43	1.23 ± 0.52	1.07 ± 0.31	84.17 ± 13.89	8,950 (74.6)	0.960 ± 0.100
Chinese (*n* = 4,439)	1.24 ± 0.58	1.06 ± 0.36	1.13 ± 0.48	1.29 ± 0.56	1.07 ± 0.29	81.03 ± 14.44	3,022 (68.1)	0.946 ± 0.114
Indian (*n* = 1,857)	1.24 ± 0.61	1.07 ± 0.40	1.14 ± 0.50	1.35 ± 0.64	1.16 ± 0.47	82.81 ± 15.28	1,192 (64.2)	0.936 ± 0.131
Orang Asli (*n* = 353)	1.12 ± 0.43	1.03 ± 0.26	1.1 ± 0.38	1.20 ± 0.49	1.16 ± 0.44	78.04 ± 17.58	263 (74.5)	0.962 ± 0.087
Other (*n* = 79)	1.08 ± 0.27	1 ± 0	1.03 ± 0.16	1.14 ± 0.35	1.09 ± 0.29	84.91 ± 12.36	60 (75.9)	0.975 ± 0.050
Non-citizen (*n* = 402)	1.05 ± 0.26	1 ± 0.07	1.02 ± 0.20	1.14 ± 0.42	1.06 ± 0.27	87.30 ± 11.56	330 (82.1)	0.979 ± 0.058
Educational level								
No formal education (*n* = 3,250)	1.41 ± 0.76	1.13 ± 0.50	1.25 ± 0.64	1.44 ± 0.69	1.13 ± 0.41	76.56 ± 15.83	1,778 (54.7)	0.880 ± 0.210
Primary (*n* = 4,624)	1.24 ± 0.60	1.07 ± 0.37	1.14 ± 0.52	1.33 ± 0.60	1.10 ± 0.37	80.72 ± 14.61	2,987 (64.6)	0.920 ± 0.170
Secondary (*n* = 8,128)	1.10 ± 0.40	1.02 ± 0.22	1.06 ± 0.34	1.19 ± 0.47	1.07 ± 0.29	85.15 ± 12.93	6,330 (77.9)	0.960 ± 0.110
Tertiary (*n* = 1,406)	1.06 ± 0.31	1.01 ± 0.13	1.03 ± 0.20	1.13 ± 0.38	1.05 ± 0.24	88.01 ± 11.43	1,186 (84.4)	0.980 ± 0.070
Other/do not know/refused to answer (*n* = 1,721)	1.03 ± 0.24	1.01 ± 0.18	1.03 ± 0.23	1.09 ± 0.36	1.04 ± 0.21	90.02 ± 11.77	1,536 (89.3)	0.980 ± 0.080
Work (in the past 30 days)								
Working full-time (*n* = 5,235)	1.07 ± 0.29	1.01 ± 0.14	1.03 ± 0.24	1.16 ± 0.43	1.05 ± 0.26	86.52 ± 12.55	4,260 (81.4)	0.970 ± 0.080
Home-makers (*n* = 5,381)	1.20 ± 0.52	1.04 ± 0.26	1.11 ± 0.42	1.30 ± 0.57	1.09 ± 0.35	82.28 ± 14.12	3,609 (67.1)	0.930 ± 0.140
Self-employed (*n* = 2,283)	1.09 ± 0.35	1.01 ± 0.16	1.04 ± 0.24	1.20 ± 0.47	1.06 ± 0.28	83.61 ± 12.92	1,760 (77.1)	0.960 ± 0.090
Other (*n* = 6,230)	1.29 ± 0.70	1.10 ± 0.48	1.19 ± 0.61	1.31 ± 0.62	1.10 ± 0.37	81.25 ± 15.69	4,188 (67.2)	0.910 ± 0.200
Total (*n* = 19,129)	1.18 ± 0.53	1.05 ± 0.32	1.10 ± 4.7	1.25 ± 0.54	1.08 ± 0.33	83.27 ± 14.28	13,817 (72.2)	0.955 ± 0.106

Data are presented as mean ± standard deviation or frequency (%).
EQ-5D, EuroQol-5 Dimensions; EQ1, mobility; EQ2, self-care; EQ3, usual activities; EQ4, pain/discomfort; EQ5, anxiety/depression; VAS, visual analog scale/self-rated health; EUV, estimated utility value.

both measures, supporting previous studies among lower-income households and rural communities in Malaysia [10,11,29]. Although both the WHOQoL-BREF and the EQ-5D proved useful, effect size analyses suggest that studies focusing on pain or discomfort outcomes might benefit more from using the EQ-5D, as observed in a previous cross-sectional study on determinants of health-related QoL in the Philippines [30]. Additionally, a study among Korean adults with cardiovascular disease found that lower income, unemployment, and lower education levels were significantly associated with reduced health-related QoL [31]. These factors, likely prevalent among the B40 group in our study, may help explain their lower QoL scores. This parallel finding underscores the importance of considering both sociodemographic and health-related factors when assessing QoL across different populations and health

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conditions.

Sex-based analyses revealed mixed results: women reported higher overall QoL (as per question 1 of the WHOQoL-BREF) but lower general health (question 2 of the WHOQoL-BREF) and lower utility values on the EQ-5D compared with men. A previous study among low socioeconomic Malaysians also found that women had nearly twice the risk of poor health status compared with men [29]. Thus, overall QoL may not reliably indicate an individual's general health, as correlational analyses demonstrated a stronger association between general health and the physical and psychological domains than with overall QoL. Both measures showed similar patterns, with differences in physical and psychological health between sexes. However, if a study focuses on personal pain and discomfort differences between sexes, the EQ-5D might be preferred over the WHOQoL-BREF.

Our study suggests that the WHOQoL-BREF may offer advantages in assessing health-related QoL among ethnic minorities and indigenous populations, particularly when evaluating social relationships and environmental factors. The environment domain exhibited the most significant variations across ethnic groups. Both the WHOQoL-BREF and the EQ-5D indicated lower QoL scores for ethnic minority groups compared with the majority, aligning with previous research showing that non-Malays are at higher risk for poorer health status than Malays [10,11,29]. It would be interesting, however, to compare the QoL of ethnic minorities in Malaysia with that of the same ethnic groups in other countries. For example, the VAS score for the Indian ethnic group in Malaysia (82.81) was higher than that reported for the general population in India (75.18) [12].

Our findings also showed that the Orang Asli consistently reported lower QoL scores compared with other ethnic groups, including Malays. This suggests that despite their shared Bumiputera status [14], substantial disparities in lived experiences and access to resources affect their QoL. These distinctions are crucial for understanding the nuanced ethnic landscape in Malaysia and interpreting the QoL differences observed in our study. Future research could further explore how political and social classifications correlate with health outcomes and access to healthcare services. Notably, our study found that Orang Asli, or indigenous people in Peninsular Malaysia, reported the lowest health-related QoL, particularly in environment-related health. One possible explanation is that the Orang Asli community's intimate connection with the land and communal lifestyle has been severely impacted by modernization [32,33]. Similar effects of environmental change on QoL have been observed among indigenous people in Chile and native senior citizens in Hong Kong [34,35].

Participants with no formal education consistently reported lower QoL on both measures, a finding also noted in a study among low socioeconomic Malaysians where individuals with lower education had a 3-fold higher risk of inadequate health status compared with those with higher education [29]. However, for studies focusing on psychological health, researchers might consider using the WHOQoL-BREF over the EQ-5D because it may be more sensitive to capturing psychological status differences among educational groups, as shown in mapping studies among chronic psychiatric patients and individuals with diabetes [36,37]

When comparing occupational groups, QoL findings were relatively similar between the 2 measures. However, effect size analyses suggest that the WHOQoL-BREF may be more sensitive than the EQ-5D when the primary participants are home-makers whose QoL is compared with that of full-time workers, who might score higher on items related to work capacity [6]. Alternatively, if the primary participants are self-employed, the EQ-5D might be the preferred measure.

Practical Implications

Given the differing foundational perspectives of the WHOQoL-BREF and the EQ-5D, these measures are not intended to be used interchangeably, as also demonstrated in a study among chronic disease patients in Thailand [5]. Researchers should base their choice on the primary aims and participant characteristics of their study. Specifically, the WHOQoL-BREF may be more appropriate for comprehensive clinical assessments, whereas the EQ-5D may be preferable for economic evaluations. For instance, if the primary aim is to explore pain or discomfort in individuals with chronic diseases, the EQ-5D would be more suitable. Conversely, for studies examining QoL through psychological, social, and environmental lenses, the WHOQoL-BREF is likely a better fit. Moreover, our study suggests that the WHOQoL-BREF may be particularly well-suited for investigating QoL among ethnic minority and indigenous groups due to its broader scope in assessing social and environmental factors.

An alternative perspective is to use a complementary approach, combining both measures to achieve a richer understanding of an individual's or population's health status and QoL. The WHOQoL-BREF offers a comprehensive, in-depth assessment across 4 domains with multiple items, capturing subjective perceptions and being sensitive to psychological changes and cultural nuances. It excels in clinical trials and the evaluation of healthcare treatments. In contrast, the EQ-5D focuses on 5 specific health dimensions and produces concise, preference-based utility values, making it particularly useful for economic evaluations and health technology assessments that calculate QALYs.

Moreover, the EQ-5D is especially sensitive to issues of mobility and pain/discomfort, notably when comparing income groups, while the WHOQoL-BREF may better capture social relationships and environmental factors among ethnic minority and indigenous populations.

Beyond informing the selection of interventions, these findings can assist stakeholders in improving healthcare delivery and policy in Malaysia. The consistent differences in QoL across demographic groups suggest a need for targeted healthcare interventions. For example, lower QoL scores among older adults, particularly in physical domains, indicate the need for enhanced geriatric care and active aging programs. The high prevalence of pain/discomfort reported in the EQ-5D suggests that primary care services should emphasize pain management and chronic disease care. Furthermore, differences in psychological domains and anxiety/depression dimensions across groups underscore the importance of accessible mental health services for vulnerable populations. Lower QoL scores among lower-income groups (B40) and ethnic minorities highlight health disparities that policymakers should consider when allocating healthcare resources and designing public health initiatives to improve health equity. Similarly, the observed differences in QoL across educational levels point to a need for improved health literacy programs, especially among those with less formal education. Finally, differences in QoL between ethnic groups emphasize the importance of culturally competent healthcare for minority and indigenous populations.

Strengths and Limitations

This study is one of the first in Southeast Asia to evaluate the appropriateness of the 2 QoL measures [WHOQoL-BREF and EQ-5D) for population-based research. The use of valid and reliable instruments strengthens the study's validity. Moreover, data were collected from 19,129 participants with diverse sociodemographic characteristics that are common among residents in the Southeast Asia region. However, because of the convenience sampling technique, the results may be limited to a relatively healthier segment of the population, particularly those of lower socioeconomic status. Additionally, as this was not a longitudinal study, we were unable to fully assess the comparative sensitivity and suitability of the WHOQoL-BREF and EQ-5D over time. Future research would benefit from a longitudinal design that includes test–retest reliability for both instruments, thereby providing more robust evidence regarding their sensitivity to change and long-term reliability. It is also important to note that the choice of instrument may affect study outcomes; future studies might consider comparing results across different EQ-5D versions (e.g., the EQ-5D-3L).

Another limitation is that the data were collected in 2018–2019, which may not fully reflect the current health-related QoL landscape in Malaysia. The time gap between data collection and publication could affect the relevance of the findings, as socioeconomic conditions, health policies, and population demographics may have evolved. Furthermore, the COVID-19 pandemic, which began after the data collection period, has likely impacted various aspects of QoL, potentially limiting the applicability of pre-pandemic data to the current context. However, given that QoL measures tend to change gradually over time [28], some concerns regarding the use of older data may be mitigated.

Conclusion

This study described and compared health-related QoL as measured by the WHOQoL-BREF and the EQ-5D among the Malaysian population, based on their sociodemographic characteristics. Overall, the 2 measures produced consistent results for a relatively healthy community-based population; however, the association between them was relatively weak, indicating that they are not interchangeable. Researchers should select between these measures based on their specific research questions and intended data use, as each instrument has fundamental differences in design and purpose. While the WHOQoL-BREF provides a more comprehensive assessment of overall QoL—including psychosocial and environmental factors—the EQ-5D may be more appropriate for economic evaluations and for capturing specific health state descriptions.

Supplementary Material

Figure S1. Map of Segamat district (top left area in Johor State). **Figure S2.** (A) Histogram of general QoL. (B) Q-Q plot of general QoL. (C) Histogram of health satisfaction. (D) Q-Q plot of health satisfaction. (E) Histogram of WHOQoL-BREF Domain 1. (F) Q-Q plot of WHOQoL-BREF Domain 1. (G) Histogram of WHOQoL-BREF Domain 2. (H) Q-Q plot of WHOQoL-BREF Domain 2. (I) Histogram of WHOQoL-BREF Domain 3. (J) Q-Q plot of WHOQoL-BREF Domain 3. (K) Histogram of WHOQoL-BREF Domain 4. (L) Q-Q plot WHOQoL-BREF Domain 4. **Figure S3.** (A) Histogram of EQ-5D Dimension 1. (B) Q-Q plot of EQ-5D Dimension 1. (C) Histogram of EQ-5D Dimension 2. (D) Q-Q plot of EQ-5D Dimension 2. (E) Histogram of EQ-5D Dimension 3. (F) Q-Q plot of EQ-5D Dimension 3. (G) Histogram of EQ-5D Dimension 4. (H) Q-Q plot of EQ-5D Dimension 4. (I) Histogram of EQ-5D Dimension 5. (J) Q-Q plot of EQ-5D Dimension 5. **Table S1.** WHOQoL-BREF converted score

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100 points (age). **Table S2.** WHOQoL-BREF converted score 100 points (income). **Table S3.** WHOQoL-BREF converted score 100 points (sex). **Table S4.** WHOQoL-BREF converted score 100 points (ethnicity). **Table S5.** WHOQoL-BREF converted score 100 points (education). **Table S6.** WHOQoL-BREF converted score 100 points (occupation). **Table S7.** Normality tests and histograms: WHOQoL-BREF. **Table S8.** Normality tests and histograms: WHOQoL-BREF. **Table S9.** Demographic characteristics and quality of life measured with EQ-5D-5L. **Table S10.** *Post-hoc* WHOQoL-BREF (age). **Table S11.** *Post-hoc* EQ-5D (age). **Table S12.** *Post-hoc* WHOQoL-BREF (income). **Table S13.** *Post-hoc* EQ-5D (income). **Table S14.** *Post-hoc* WHOQoL-BREF (sex). **Table S15.** *Post-hoc* EQ-5D (sex). **Table S16.** *Post-hoc* WHOQoL-BREF (ethnicity). **Table S17.** *Post-hoc* EQ-5D (ethnicity). **Table S18.** *Post-hoc* WHOQoL-BREF (education). **Table S19.** *Post-hoc* EQ-5D (education). **Table S20.** *Post-hoc* WHOQoL-BREF (occupation). **Table S21.** *Post-hoc* EQ-5D (occupation). Supplementary data are available at https://doi.org/10.24171/j.phrp.2024.0076.

Notes

Ethics Approval

This study was approved by the Monash University Human Research Ethics Committee (MUHREC, Project ID 2018-13142) and followed the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. Written informed consent was obtained for publication of this study and accompanying images.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets are not publicly available but are available from the corresponding author upon reasonable request to the South East Asia Community Observatory (SEACO): https://www.monash.edu.my/seaco/research-and-training/how-to-collaborate-with-seaco.

Authors' Contributions

Conceptualization: RN, TTS, DR; Data curation: DR, TTS; Formal analysis: AL, HJC, RN; Funding acquisition: DR, TTS; Methodology: AL, HJC, RN, TTS; Writing–original draft: AL; Writing–review & editing: AL, HJC, VV, RN, DR, TTS. All authors read and approved the final manuscript.

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Original Article

A retrospective study on blood microbiota as a marker for cognitive decline: implications for detecting Alzheimer's disease and amnestic mild cognitive impairment in Republic of Korea

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ABSTRACT

Objectives: This study aimed to investigate the relationship between blood microbiota, specifically bacterial DNA, and cognitive decline in individuals with subjective cognitive decline (SCD) and amnestic mild cognitive impairment (aMCI). The objective was to identify potential microbial signatures that could serve as biomarkers for cognitive deterioration.

Methods: Forty-seven participants were recruited, including 13 with aMCI, 20 with SCD, and 14 normal cognition (NC). Blood samples were collected, and microbial DNA was analyzed using 16S rRNA sequencing on the Illumina MiSeq platform. Bioinformatics analyses—including α- and β-diversity measures and differential abundance testing (using edgeR)—were employed to assess microbial diversity and differences in bacterial composition among groups. Logistic regression models were used to evaluate the predictive impact of the microbiota on cognitive decline.

Results: Microbial diversity differed significantly between groups, with NC exhibiting the highest α-diversity. Both the aMCI and SCD groups showed reduced diversity. Taxa such as Bacteroidia, Alphaproteobacteria, and Clostridia were significantly decreased in the aMCI group compared to NC ($p < 0.05$). In contrast, Gammaproteobacteria increased significantly in the aMCI group compared to both NC and SCD, indicating progressive microbial changes from SCD to aMCI. No significant differences were found between the NC and SCD groups.

Conclusion: Distinct bacterial taxa—particularly the increase in Gammaproteobacteria along with decreases in Bacteroidia, Alphaproteobacteria, and Clostridia—are associated with the progression of cognitive decline. These findings suggest that blood microbiota could serve as potential biomarkers for the early detection of aMCI. However, the small sample size and the lack of control for confounding factors such as diet and medication limit the findings. Larger studies are needed to validate these results and further explore the role of microbiota in neurodegeneration.

Keywords: Brain-gut axis; Cognitive dysfunction; Microbiota

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Introduction

Based on findings from the World Alzheimer Report, it is estimated that approximately 47 million individuals worldwide are currently affected by dementia. Projections indicate that this number may increase to around 131 million by 2050 [1,2]. Alzheimer's disease (AD), the most prevalent form of dementia, is characterized by the gradual degeneration of neurons and cognitive function [3]. In the Republic of Korea, AD is recognized as a primary contributor to dementia, as supported by scholarly research [4]. AD typically progresses through 3 distinct stages: the preclinical stage, amnestic mild cognitive impairment (aMCI), and dementia. aMCI, the most common form of mild cognitive impairment, has a high likelihood of progressing to AD [5]. Decades of research have consistently demonstrated that the accumulation of amyloid beta (Aβ) peptide is closely associated with the onset of AD. Furthermore, subsequent pathological changes—such as the abnormal phosphorylation of tau protein—contribute to AD progression by promoting inflammation-induced neurodegeneration [6]. Nonetheless, the etiology of AD remains uncertain [7].

Recent studies indicate that gut dysbiosis, which influences brain immune homeostasis via the microbiota–gut-brain axis, may play a significant role in the etiology of neurodegenerative disorders [8]. Increased gut permeability may serve as the primary source of bacterial DNA in the bloodstream, in addition to contributions from the skin, oral cavity, and reproductive and respiratory tracts. Although the concentration of bacterial DNA in blood is not linked to sepsis, its elevation may precipitate various brain-related pathologies, including Alzheimer's and Parkinson's diseases [9]. Evidence indicates that bacterial DNA can alter the blood-brain barrier (BBB), hyperactivate the innate immune system, and provoke neuroinflammation—ultimately leading to cognitive impairment [10–12].

This study seeks to examine the correlation between bacterial 16S rRNA in blood—measured using next-generation sequencing technology—and cognitive deterioration in individuals with SCD and aMCI [13].

HIGHLIGHTS

- Significant shifts in blood microbiota were observed between normal cognition and individuals with amnestic mild cognitive impairment (aMCI), including decreases in Bacteroidia, Alphaproteobacteria, and Clostridia.
- A significant increase in Gammaproteobacteria was identified in the aMCI group, suggesting its potential as a biomarker for cognitive decline.
- The findings emphasize the potential of blood microbiota in the early detection and improved understanding of Alzheimer's disease and cognitive impairments.

Materials and Methods

Clinical Demographics

The objectives of this study were explained to all participants or their legally authorized caregivers, and informed consent was obtained from all subjects. The research received approval from the ethical committee of Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea. A total of 47 participants were recruited, including 13 individuals with aMCI, 20 with SCD, and 14 normal cognition (NC).

The participants' ages ranged from 47 to 85 years, and each had at least 6 years of formal education. All participants underwent a comprehensive review of their medical history, along with neurological and cognitive assessments, including the administration of the Mini-Mental State Examination (MMSE). The assessment tools employed in this study included the MMSE, the clinical dementia rating (CDR), and *APOE* testing via whole exome sequencing (Table 1).

Sample Collection and DNA Extraction

Participants were instructed to provide a complete blood sample using sterile collection containers. The samples were promptly transported to the laboratory at 4 °C. Because several chemicals used in the real-time polymerase chain reaction (PCR) and sequencing pipeline contain significant quantities of bacterial DNA, there exists a potential for erroneous identification of contaminant DNA in the samples [14]. DNA extraction was conducted with meticulous care to mitigate the risk of cross-contamination or researcher-induced contamination. All extractions were performed by a single individual over 3 consecutive days. DNA was extracted from peripheral blood leukocytes using a conventional phenol/chloroform extraction method as previously described [15]. Following ethanol precipitation, the DNA was resuspended in double-distilled water (ddH_2O) and stored at −80 °C until use. All extractions were conducted within a Class II biological safety cabinet. Genomic DNA concentration in each blood sample was quantified using a NanoDrop 2000 spectrophotometer (Thermo Scientific).

16S rRNA Amplicon Sequencing

The V3–V4 regions of the 16S rDNA were amplified using universal primers (341F and 806R) linked to indices and sequencing adapters. PCR amplification was performed

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Table 1. Demographic characteristics of study participants

Patient ID	Diagnosis	Age (y)	Sex	MMSE	CDR score
PRM12_0003	NC	66	Male	28	0.5
PRM12_0004	NC	82	Male	27	0.5
PRM12_0008	NC	60	Female	29	0.5
PRM12_0010	NC	66	Female	29	0
PRM12_0012	NC	82	Female	24	0.5
PRM12_0013	NC	50	Male	30	0
PRM12_0016	NC	56	Male	28	0.5
PRM12_0019	NC	64	Female	26	0
PRM12_0022	NC	67	Male	24	0
PRM12_0024	NC	77	Female	27	0.5
PRM12_0094	SCD	66	Female	27	0
PRM12_0117	aMCI	61	Female	27	0
PRM12_0127	aMCI	76	Male	24	0.5
PRM12_0136	aMCI	69	Male	24	0
PRM12_0138	aMCI	82	Female	24	0.5
PRM12_0177	SCD	86	Male	27	0.5
PRM12_0178	SCD	62	Female	24	0.5
PRM12_0189	SCD	59	Male	29	0.5
PRM12_0194	NC	82	Male	27	0.5
PRM12_0195	SCD	80	Female	28	0
PRM12_0197	aMCI	87	Male	20	0.5
PRM12_0200	SCD	79	Male	28	0.5
PRM12_0202	SCD	73	Female	26	0.5
PRM12_0203	NC	60	Female	29	0.5
PRM12_0205	NC	66	Female	29	0
PRM12_0207	SCD	51	Female	29	0.5
PRM12_0209	SCD	71	Female	24	0.5
PRM12_0210	aMCI	76	Female	25	0.5
PRM12_0213	SCD	72	Female	28	0.5
PRM12_0214	SCD	68	Female	26	0.5
PRM12_0215	SCD	50	Female	27	0.5
PRM12_0216	SCD	76	Female	23	0.5
PRM12_0217	SCD	78	Female	25	0.5
PRM12_0221	aMCI	79	Male	26	0.5
PRM12_0222	SCD	78	Female	26	0.5
PRM12_0223	SCD	70	Female	25	0.5
PRM12_0226	SCD	60	Female	24	0.5
PRM12_0228	SCD	68	Female	27	0.5
PRM12_0231	SCD	56	Female	24	0.5
PRM12_0233	SCD	55	Female	26	0.5
PRM12_0240	aMCI	74	Male	24	0.5
PRM12_0245	NC	82	Female	24	0.5
PRM12_0263	aMCI	72	Female	19	0.5
PRM12_0267	aMCI	66	Female	25	0.5
PRM12_0271	aMCI	78	Female	26	0.5
PRM51_0019	aMCI	73	Female	20	0.5
PRM66_0018	aMCI	71	Female	26	0.5

For each participant, the following variables are recorded: ID, diagnosis, age, sex, MMSE score, and CDR score.
MMSE, Mini-Mental State Examination; CDR, clinical dementia rating; NC, normal control; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment.

in 20-μL reactions containing 15× polymerase mix (Life Technologies), 20 μM of both forward and reverse primers, and 30 ng of template DNA. The resulting libraries were sequenced on an Illumina MiSeq platform, generating paired-end reads of 250 base pairs in length.

Bioinformatic Analysis

The reads were clustered into operational taxonomic units (OTUs) based on a 97% sequence similarity threshold. Taxonomic classification of the OTUs was determined using Quantitative Insights Into Microbial Ecology and compared against the Greengenes database version 13.8 [16]. The downstream data analysis was performed using the EasyAmplicon v1.21 Pipeline (https://github.com/YongxinLiu/EasyAmplicon) [17]. Bacterial diversity was assessed using α-diversity metrics such as Shannon's index, Simpson index, Chao1, and ACE, along with β-diversity analysis via principal coordinates analysis (PCoA) [18]. Analysis of variance (ANOVA) was conducted to compare α-diversity across groups, and PERMANOVA was employed to assess the clustering of microbial communities via PCoA.

Statistical analyses were performed using STAMP software (https://beikolab.cs.dal.ca/software/STAMP) [19], and functional differences in orthologs between groups were evaluated with 1-way ANOVA followed by Tukey–Kramer multiple comparisons using IBM SPSS ver. 27.0 (IBM Corp.). To evaluate the potential predictive impact among NC, SCD, and aMCI groups, multivariable logistic regression models were constructed using a stepwise approach (likelihood backward) based on the relative abundance of the blood microbiota. Inclusion and exclusion thresholds were set at 0.05 and 0.01, respectively.

Statistical significance was determined using the Student t-test or Mann-Whitney U-test for comparisons between 2 groups, and 1-way ANOVA or the Kruskal-Wallis test for comparisons among more than 2 groups. The Pearson chi-square test, followed by a *post-hoc* test, was used to compare categorical variables. Correlations between variables were computed using edgeR [20].

Ethics Approval

This study protocol was reviewed and approved by the institutional review board (IRB) of Soonchunhyang University Bucheon Hospital (SCHBC-2020-03-016-002). All participants signed an informed consent form approved by the IRB prior to participation.

Results

Clinical Demographics

The demographic and clinical characteristics of the participants in the 3 groups are presented in Table 1. The results indicate no statistically significant differences among the NC, aMCI, and SCD groups in terms of age, sex, *APOE* ε4 carrier status, MMSE scores, CDR scores, or CDR-sum of boxes (SB) (Table 1). It is important to note, however, that substantial disparities existed among the groups with respect to educational backgrounds and MMSE scores [21]. Participants diagnosed with aMCI were identified using previously established criteria [22]. These criteria included a confirmed memory complaint (validated by an informant), the ability to perform daily activities without significant impairment, MMSE scores ranging from 24 to 30, and a CDR score of 0.5. Healthy controls were selected to ensure proportional representation of sex and age within the community. Most of these controls were spouses of patients who had cohabited for at least 20 years and shared similar dietary patterns. These individuals exhibited MMSE scores between 24 and 30, CDR scores of 0, and no notable memory-related concerns.

Comparison of Clinical and Demographic Variables

A comprehensive comparison of clinical and demographic variables was conducted between the NC, SCD, and aMCI groups, with key differences observed in cognitive function, genetic risk factors, and certain clinical scores.

Regarding age, no significant differences were noted between the NC and SCD groups (mean difference = 0.671, $p = 0.842$), nor between the NC and aMCI groups (mean difference = −5.582, $p = 0.142$). However, a trend towards a younger age in the aMCI group compared to the SCD group was observed (mean difference = −6.254, $p = 0.077$), although this did not reach statistical significance. This suggests that age may not be a primary distinguishing factor between the NC and SCD groups, but it might be relevant in differentiating aMCI from SCD.

In the sex comparison, no significant differences were found between the NC and aMCI groups (mean difference = −0.044, $p = 0.803$), or between the SCD and aMCI groups (mean difference = −0.235, $p = 0.157$), suggesting that sex does not significantly influence the classification of these groups. However, a near-significant trend was observed between the NC and SCD groups (mean difference = −0.279, $p = 0.088$), indicating potential but not definitive sex-related differences.

The MMSE, a widely used tool for assessing cognitive function, revealed significant differences in cognitive performance between the groups. Specifically, the aMCI group showed significantly lower MMSE scores than the NC group (mean difference = 3.368, $p < 0.001$), while the SCD group also had significantly lower MMSE scores compared to the aMCI group (mean difference = 2.304, $p = 0.004$). However, no significant difference was found between the NC and SCD groups (mean difference = 1.064, $p = 0.157$). These findings highlight that MMSE scores are sensitive to cognitive changes, particularly between the NC and aMCI groups, with the SCD group showing intermediate scores.

In the CDR score, no significant differences were observed between the NC and SCD groups (mean difference = −0.129, $p = 0.067$), or between the NC and aMCI groups (mean difference = −0.102, $p = 0.184$). Similarly, no significant difference was found between the SCD and aMCI groups (mean difference = 0.027, $p = 0.702$). These results suggest that CDR scores alone may not be sufficient for distinguishing between these groups, as they reflect more subtle cognitive impairments.

The CDR-SB score, which provides a more detailed assessment of cognitive decline, revealed significant differences between the NC and SCD groups (mean difference = −0.621, $p = 0.035$) and between the NC and aMCI groups (mean difference = −0.725, $p = 0.026$). However, no significant difference was found between the SCD and aMCI groups (mean difference = −0.104, $p = 0.720$). These findings suggest that the CDR-SB may be more sensitive than the CDR score in detecting subtle cognitive changes, particularly in the early stages of cognitive decline.

Finally, the APOE genotype comparison showed significant differences between the NC and aMCI groups (mean difference = −0.308, $p = 0.034$) and between the SCD and aMCI groups (mean difference = −0.358, $p = 0.009$), indicating a stronger association of the APOE ε4 allele with aMCI. This supports previous research linking the APOE ε4 allele with increased risk of Alzheimer's disease and other forms of cognitive impairment. No significant difference in the APOE genotype was found between the NC and SCD groups (mean difference = 0.05, $p = 0.694$), suggesting that the APOE genotype is more relevant for distinguishing between aMCI and the other two groups.

These results collectively highlight the differences in clinical and demographic variables across the NC, SCD, and aMCI groups, with significant findings related to cognitive function (MMSE, CDR-SB) and genetic risk factors (APOE genotype). These variables could serve as important markers for distinguishing between different stages of cognitive decline, particularly in identifying individuals at risk for progressing from SCD to aMCI (Table 2).

Landscape of the Microbiome in Blood Sample

Alpha diversity analyses of the blood microbiota revealed significant differences in microbial richness and evenness

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Table 2. Comparison of clinical and demographic variables

	Comparison	Mean difference	SE	95% CI	*p*
Age	NC vs. SCD	0.671	3.346	−6.162 to 7.504	0.842
	NC vs. aMCI	−5.582	3.698	−13.134 to 1.970	0.142
	SCD vs. aMCI	−6.254	3.421	−13.241 to 0.733	0.077
Sex	NC vs. SCD	−0.279	0.158	−0.602 to 0.044	0.088
	NC vs. aMCI	−0.044	0.175	−0.401 to 0.313	0.803
	SCD vs. aMCI	−0.235	0.162	−0.566 to 0.096	0.157
MMSE	NC vs. SCD	1.064	0.733	−0.433 to 2.561	0.157
	NC vs. aMCI	3.368	0.81	1.714 to 5.022	< 0.001
	SCD vs. aMCI	2.304	0.749	0.774 to 3.834	0.004
CDR score	NC vs. SCD	−0.129	0.068	−0.268 to 0.010	0.067
	NC vs. aMCI	−0.102	0.075	−0.255 to 0.051	0.184
	SCD vs. aMCI	0.027	0.07	−0.116 to 0.170	0.702
CDR-SB	NC vs. SCD	−0.621	0.281	−1.195 to −0.047	0.035
	NC vs. aMCI	−0.725	0.31	−1.358 to −0.092	0.026
	SCD vs. aMCI	−0.104	0.287	−0.690 to 0.482	0.720
APOE genotype	NC vs. SCD	0.05	0.126	−0.270 to 0.307	0.694
	NC vs. aMCI	−0.308	0.139	−0.592 to −0.024	0.034
	SCD vs. aMCI	−0.358	0.128	−0.619 to −0.097	0.009

The results of *post-hoc* comparisons between the NC, SCD, and aMCI groups for several key clinical and demographic variables, including age, gender, MMSE score, CDR score, CDR-SB score, and *APOE* genotype. The table includes mean differences between each pair of groups, the standard error of the mean difference, *p*-values, and 95% confidence intervals.

SE, standard error; CI, confidence interval; NC, normal cognition; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment; MMSE, Mini-Mental State Examination; CDR, clinical dementia rating; CDR-SB, clinical dementia rating sum of boxes.

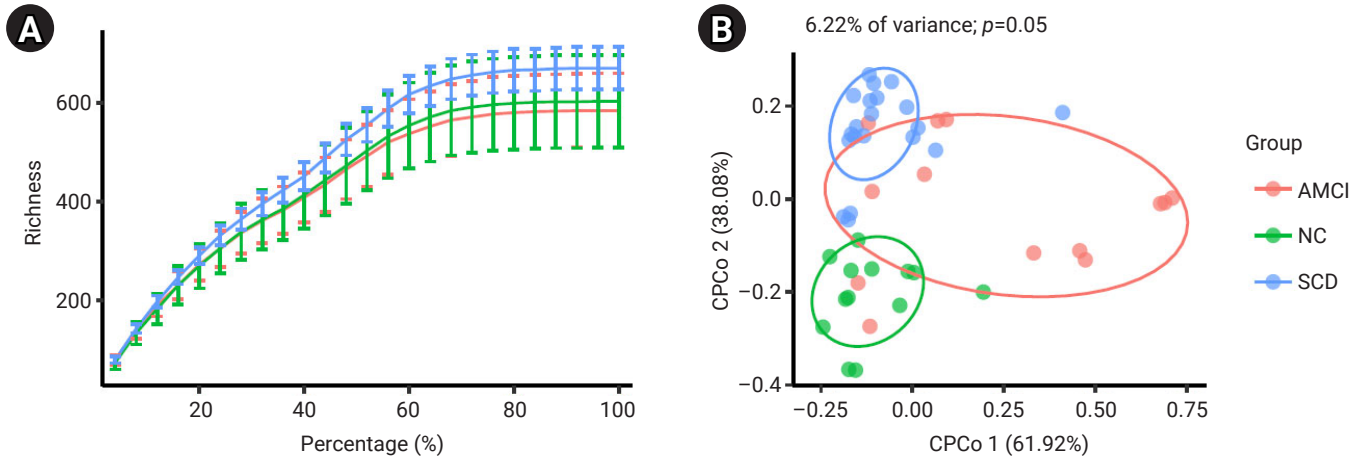


Figure 1. Alpha and beta diversity analysis. (A) Alpha rarefaction curve; richness increases with sequencing depth, approaching saturation, indicating adequate sampling. Variations in curve trajectories suggest differences in biodiversity among the groups (amnestic mild cognitive impairment [aMCI], normal cognition [NC], and subjective cognitive decline [SCD]). (B) Beta diversity (CPCoA): CPCoA shows differences in community composition between groups. Ellipse overlaps indicate similarities, while separations highlight microbial divergence, with 6.22% of variance explained ($p = 0.05$).

among the NC, aMCI, and SCD groups. The Shannon index and Chao1 index were used to assess diversity (Figure 1A). NC exhibited the highest alpha diversity, while both the aMCI and SCD groups demonstrated significantly lower diversity. One-way ANOVA results indicated significant differences in microbial diversity and richness across the 3 groups, and *post-hoc* Tukey honest significant difference tests confirmed pairwise differences, with NC showing the highest diversity, followed by SCD and aMCI. This gradient of reduced microbial diversity may be linked to disease progression

Table 3. Microbial diversity and richness metrics across groups

Metric	*n*	Mean ± SD	ANOVA (*p*)	Significant difference (Tukey HSD)
Chao1			< 0.001	NC > SCD, NC > aMCI, SCD > aMCI
0	14	832.5 ± 24.4		
1	20	607.5 ± 13.33		
2	13	416.92 ± 20.97		
Richness			< 0.001	NC > SCD, NC > aMCI, SCD > aMCI
0	14	1,460.71 ± 21.56		
1	20	1,031.5 ± 31.5		
2	13	660.31 ± 39.4		
Simpson			< 0.001	NC > SCD, NC > aMCI, SCD > aMCI
0	14	0.5526 ± 0.0372		
1	20	0.4554 ± 0.0141		
2	13	0.3064 ± 0.024		

The table summarizes microbial diversity and richness indices across 3 groups (NC, SCD, aMCI). Significant differences ($p < 0.05$) were found between groups for all indices based on ANOVA. Tukey honest significant difference *post-hoc* tests confirmed pairwise differences, indicating that group 0 consistently had the highest diversity, followed by group 1, and group 2 with the lowest (0 = NC, 1 = SCD, 2 = aMCI).
SD, standard deviation; ANOVA, analysis of variance; HSD, honest significant difference; NC, normal cognition; SCD, subjective cognitive decline; aMCI, amnestic mild cognitive impairment.

(Table 3). The decrease in microbial diversity observed in the aMCI and SCD groups may reflect early alterations in blood microbiota composition associated with cognitive decline. These findings are consistent with previous studies suggesting that reduced microbial diversity correlates with neurodegenerative diseases.

These results highlight the potential of blood microbiome composition as a biomarker for distinguishing between healthy aging and the early stages of cognitive decline, such as aMCI and SCD. The clear separation observed in beta diversity analysis underscores the possibility of identifying microbial signatures indicative of neurodegenerative changes. Further studies are needed to explore the mechanisms driving these microbiome shifts and their potential role in cognitive impairment. Both analytical methods yielded consistent results, underscoring the robustness of the findings. This progressive decline in microbial diversity suggests that gut dysbiosis may contribute to cognitive impairment and that blood microbiome analysis could serve as a valuable tool for identifying biomarkers and elucidating the mechanisms underlying neurodegeneration.

Differential Abundance of Bacterial Taxonomy

A differential abundance analysis of bacterial taxa between the NC and aMCI groups was conducted using edgeR. The results revealed several significant shifts in bacterial composition. Specifically, Bacteroidia, Alphaproteobacteria, and Clostridia were significantly decreased in the aMCI group compared to NC, whereas Gammaproteobacteria showed a significant increase in abundance in the aMCI group (Figure 2). These findings suggest that specific bacterial taxa may be associated with the progression from normal cognitive function to aMCI, with alterations in microbial communities potentially contributing to the underlying pathophysiology of the condition.

Additionally, the analysis revealed a significant increase in the abundance of Gammaproteobacteria in the aMCI group compared to the SCD group ($p < 0.05$) (Figure 3A). However, no significant differences in bacterial abundance were observed between the NC and SCD groups (Figure 3B). These findings suggest that while microbial changes are evident between NC and aMCI, there are no major shifts between NC and SCD. Gammaproteobacteria may serve as a key marker in the transition from SCD to aMCI (Figure 3C). These observations underscore the importance of further exploring specific bacterial taxa as potential biomarkers for the early detection and monitoring of cognitive decline.

Discussion

This study represents one of the initial attempts to characterize the blood microbiome in older Korean patients exhibiting symptoms of aMCI. It specifically aimed to compare microbial composition across clinical phases, including aMCI, SCD, and NC. Our findings revealed significant differences in the microbiome composition of patients in the early stages of cognitive decline compared to NC. These differences underscore the potential role of blood microbiota in the pathophysiology of cognitive decline and neurodegenerative diseases.

Our results demonstrated a decreased abundance of Bacteroidia in aMCI and AD patients. This class of bacteria is

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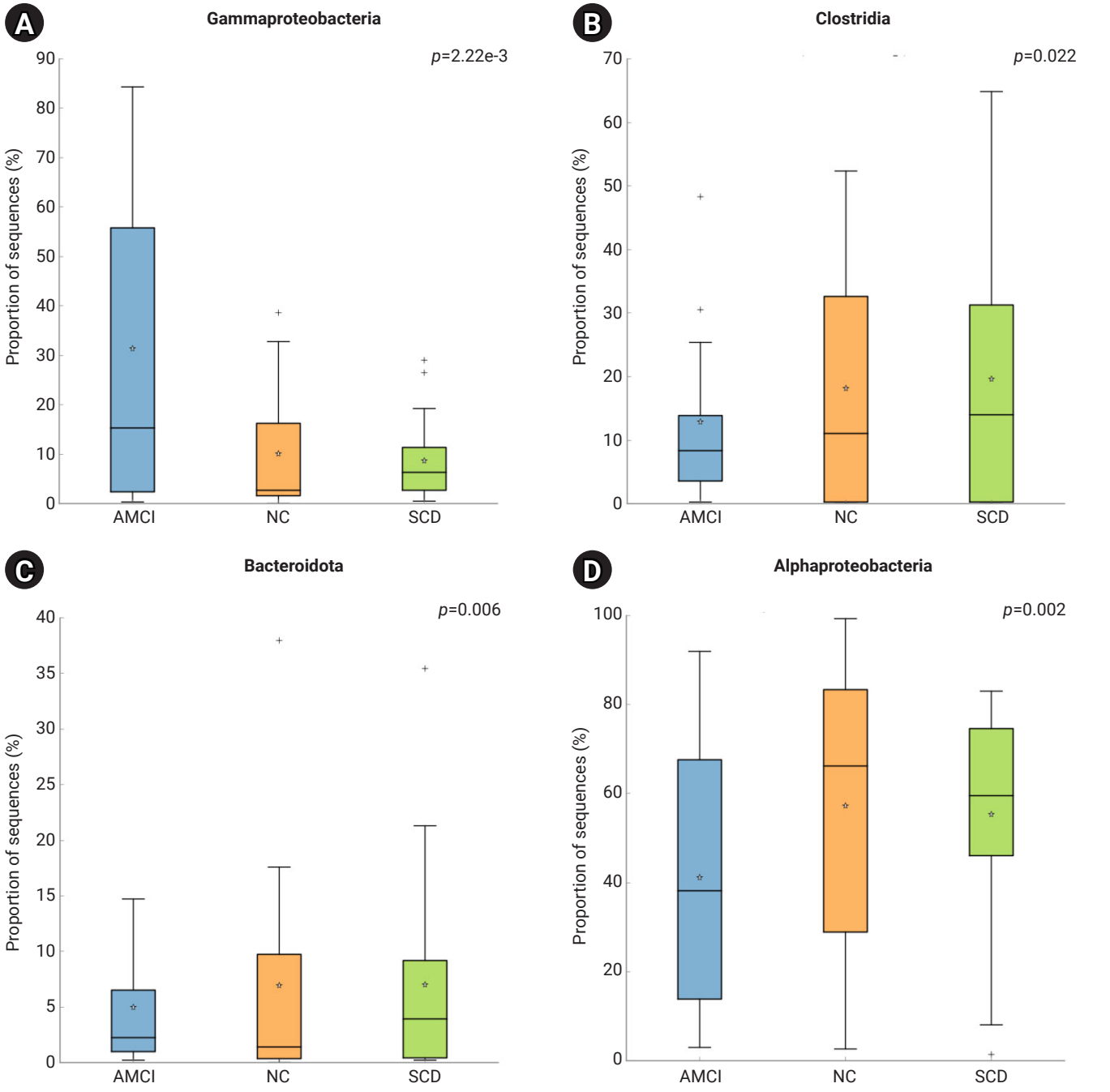


Figure 2. Relative abundances of bacterial taxa in the amnestic mild cognitive impairment (aMCI), normal cognition (NC), and subjective cognitive decline (SCD) groups based on STAMP analysis of blood 16S rRNA sequencing. (A) Gammaproteobacteria: significantly higher in aMCI ($p < 0.002$). (B) Clostridia: higher in NC and SCD than in aMCI ($p = 0.022$). (C) Bacteroidota: more abundant in NC ($p = 0.006$). (D) Alphaproteobacteria: highest in NC, followed by SCD and aMCI ($p = 0.002$). Box plots represent median (line inside the box), mean (◇), interquartile range (IQR; box edges), and whiskers indicating 1.5×IQR. Plus sign (+) indicates an outlier.

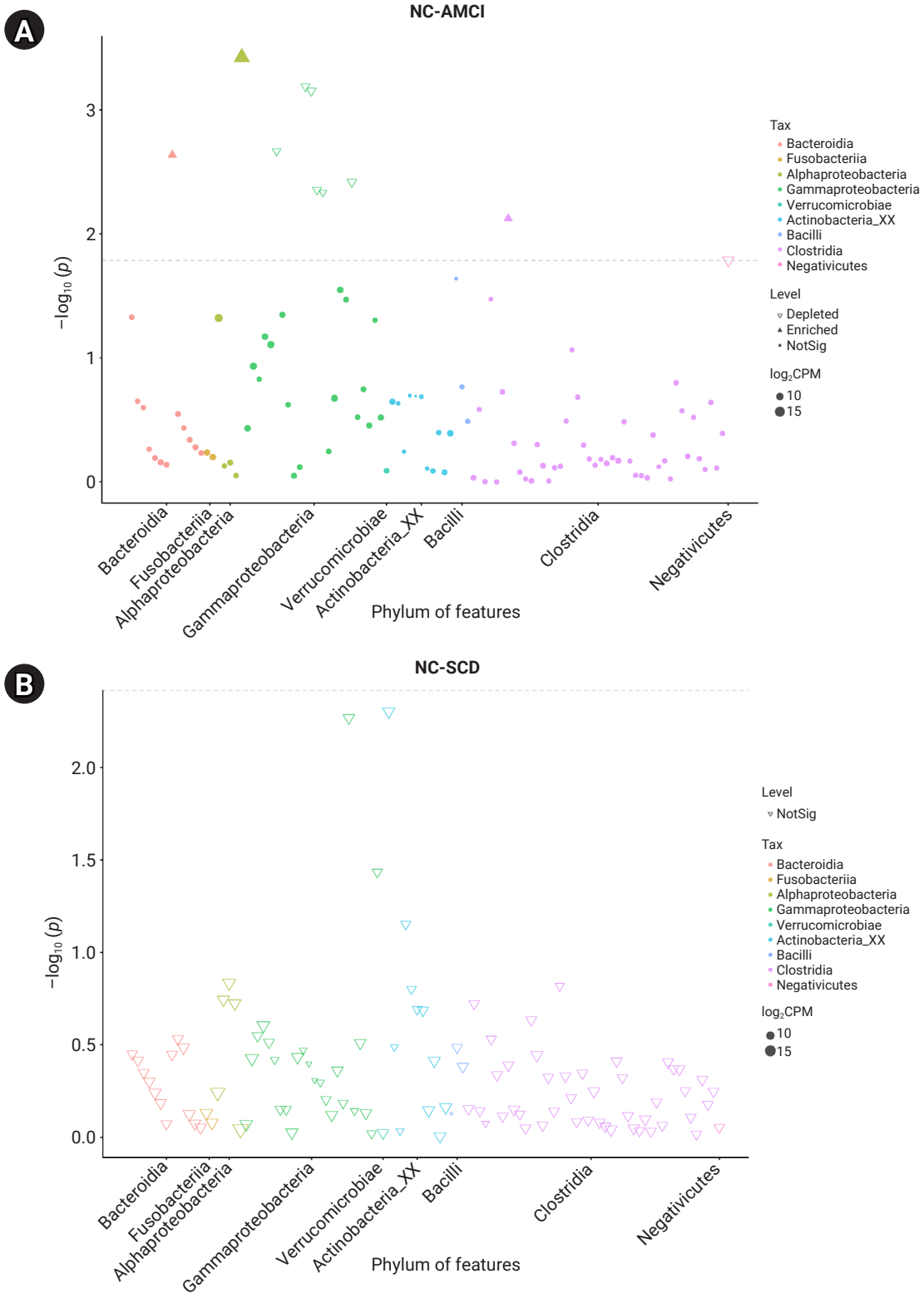


Figure 3. (Continued on next page.)

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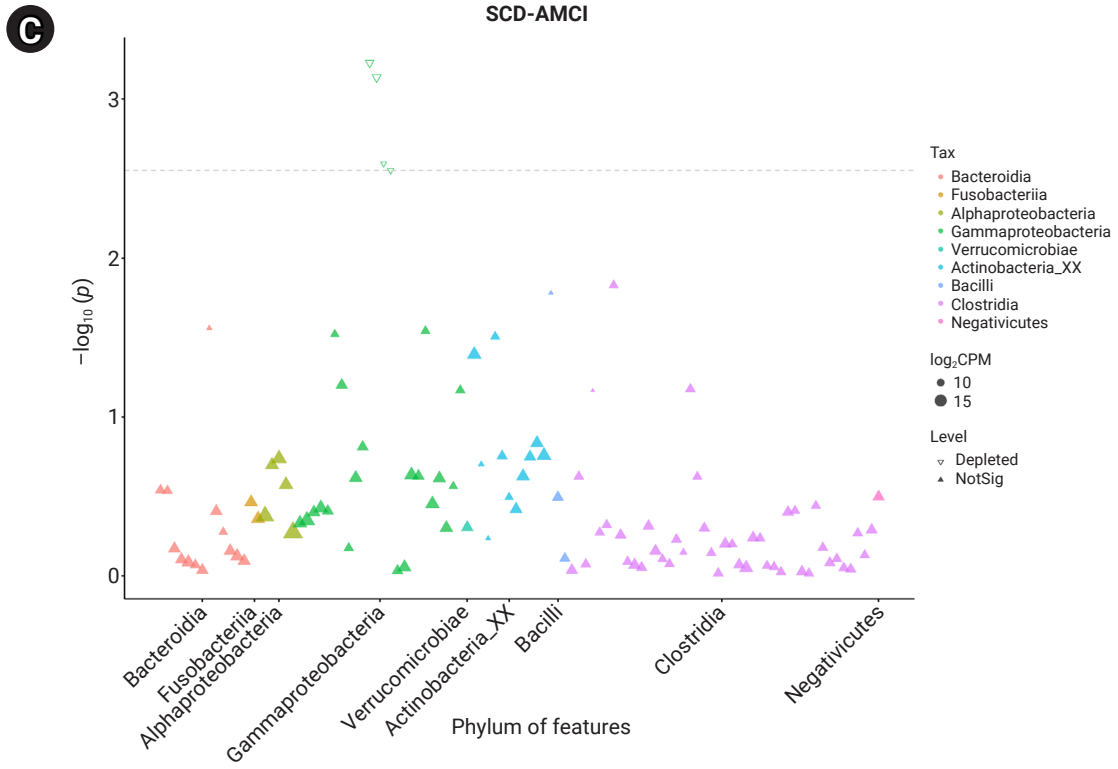


Figure 3. Manhattan plot of bacterial abundance associations. (A) Normal cognition (NC) vs. amnestic mild cognitive impairment (aMCI): increased Alphaproteobacteria (beneficial symbionts) and decreased Gammaproteobacteria (opportunistic pathogens) in aMCI. (B) NC vs. subjective cognitive decline (SCD): no significant bacterial associations ($p > 0.05$), indicating minimal microbiome differences. (C) SCD vs. aMCI: significant decrease in Gammaproteobacteria in aMCI, reflecting microbiome changes with cognitive decline. The x-axis represents taxa (log2CPM), and the y-axis shows −log10 p-values. Significant associations are highlighted above the threshold.

associated with inflammatory processes in the gut, systemic inflammation, and disruptions to the gut-brain axis, which may influence the progression of dementia [23]. Similarly, Alphaproteobacteria—which promote cytokine production and exacerbate neuroinflammation—were significantly decreased in aMCI and AD patients [24]. Interestingly, Clostridia, known for their role in producing short-chain fatty acids (SCFAs), exhibited a complex influence; while SCFAs possess neuroprotective properties, a reduction in Clostridia populations could lead to increased gut permeability and systemic inflammation [25]. Conversely, we observed a significant increase in Gammaproteobacteria, bacteria linked to dysregulation of gut homeostasis, suggesting a shift toward a dysbiotic state in aMCI and AD patients [26].

These findings emphasize the critical role of gut and blood microbiota in maintaining the integrity of the gut-brain axis. Dysbiosis may promote chronic neuroinflammation, disrupt the BBB, and impair the production of neuroactive metabolites, all of which contribute to cognitive decline [27,28]. The identification of microbial signatures specific to aMCI and AD may inform the development of novel diagnostic tools and therapeutic strategies targeting the gut-brain axis.

Conclusion

This research highlights the potential of blood microbiota as biomarkers and therapeutic targets for AD and aMCI. By identifying specific microbial signatures associated with these conditions, the study lays the foundation for developing novel strategies to prevent, diagnose, and treat neurodegenerative diseases. Addressing the limitations discussed and expanding future research to include dietary, medication, and genetic influences will further enhance our understanding of the gut-brain axis and its role in cognitive health.

Diet and Medication as Confounders

This study did not account for the influence of diet and medication on microbiome composition and cognitive decline. Both factors significantly shape microbial populations and could confound the associations observed in this research [29]. Future studies should employ statistical methods to adjust for these variables or directly investigate

their impact on the microbiome and cognitive function.

Technical Limitations

While 16S rRNA sequencing provided valuable insights, it has inherent limitations. The resolution of this method may not detect low-abundance taxa that play critical roles in systemic and neurological processes [30]. Additionally, contamination during sample collection and sequencing remains a challenge [31]. To mitigate these issues, we employed stringent protocols, including sterile collection methods, precise DNA extraction techniques, and advanced bioinformatics pipelines. Nonetheless, future work should explore metagenomic or metatranscriptomic approaches for more comprehensive microbiome profiling.

Genetic Factors

This study did not investigate genetic factors that could influence microbiome composition and the risk of cognitive decline. Variants in host genes, particularly those involved in immune response and gut permeability, may play significant roles in shaping microbial populations and mediating their effects on the brain [32]. Future research should incorporate genetic analyses to explore these interactions and provide a more holistic understanding of the microbiome's role in neurodegeneration.

Notes

Ethics Approval

This study protocol was reviewed and approved by the institutional review board of Soonchunhyang University Bucheon Hospital (SCHBC-2020-03-016-002). All participants signed an informed consent form approved by the IRB prior to participation.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

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

Authors' Contributions

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

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Original Article

SWOT strategy for future global health security: insights from Indonesia, Cambodia, Vietnam, Dominican Republic, Ghana, and the Republic of Korea using the World Health Organization International Health Regulations monitoring tool

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ABSTRACT

Objectives: The study aimed to analyze the core capacities to implement World Health Organization International Health Regulations (IHR) in 6 countries: Indonesia, Cambodia, Vietnam, the Dominican Republic, Ghana, and the Republic of Korea.

Methods: Secondary data from relevant databases and reports, including the electronic State Party Self-Assessment Annual Reporting mechanism and global health security index, were used to assess health security in these countries. Descriptive statistics summarized the basic features of the scores, and a strengths, weaknesses, opportunities, and threats (SWOT) analysis was subsequently performed to identify factors affecting health security scores while highlighting key similarities and differences between countries.

Results: Early warning and event management emerged as the primary strength in most countries. Common opportunities included international commitments and immunization programs. In contrast, many countries shared weaknesses related to the policy, legal, and normative frameworks for IHR implementation, as well as challenges in human resources, chemical event management, and radiation emergency preparedness. Recurring threats involved issues such as biosafety, biosecurity, dual-use research and the culture of responsible science, infection control practices, coordination between public health and security authorities, laboratory supply chain vulnerabilities, and communication with healthcare workers during public health emergencies.

Conclusion: In order to counter future global health threats, countries should prioritize enhancing surveillance capacity (early warning and event management) as well as the immunization indicator (vaccination rates for human and animal diseases, including the national vaccine delivery system).

Keywords: Global health; Immunization; One Health; Surveillance

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Introduction

Health security and preparedness are crucial for nations to effectively prevent, detect, and respond to a wide range of global health threats—including infectious disease epidemics, disasters, and bioterrorism—in today's interconnected world [1,2]. In this context, the electronic State Party Self-Assessment Annual Reporting mechanism (e-SPAR) and the global health security (GHS) index provide comprehensive frameworks that enable systematic evaluation and comparison of countries' capabilities in these critical areas [3,4].

The International Health Regulation (IHR) 2005 is a legal instrument developed by the World Health Organization (WHO) to enhance the ability of signatory states to manage public health risks. States Parties are required to establish minimum capacities for surveillance and response to public health events, and the effectiveness of the IHR depends on full adherence and compliance by all signatories. Implementation is reported by the States Parties and reviewed by the Director-General of the World Health Assembly. Countries use the e-SPAR tool for annual self-assessment reporting, which covers 35 indicators across 15 IHR capacities, each evaluated using 1 to 3 specific indicators and further detailed by additional attributes. Following the World Health Assembly each year, the e-SPAR questionnaire is distributed to facilitate multisectoral self-assessment and comprehensive data collection [5].

The GHS index assesses health security capabilities in 195 nations. It enhances global preparedness for epidemics by providing objective data that holds governments accountable for pandemic readiness investments, supports evidence-based policymaking for resource allocation, and establishes benchmarks for biosecurity and pandemic preparedness. The 2021 GHS index evaluated countries across 6 categories, 37 indicators, and 171 questions using publicly available data. By contextualizing health security within broader factors such as political stability, the Joint External Evaluation, and health system robustness the index promotes transparency regarding national deficiencies in outbreak response [6].

In developing countries, health security is a multifaceted issue that encompasses food security, global health threats, and the need for robust health systems [7,8]. These interrelated factors significantly influence both health outcomes and overall security. Although Indonesia, Cambodia, Vietnam, the Dominican Republic, and Ghana differ in geographic, economic, and sociopolitical contexts, they face similar challenges in strengthening their health security systems. In contrast, the Republic of Korea is recognized for its robust surveillance system and overall preparedness [9]. This study aimed to evaluate and compare the health security and preparedness of Indonesia, Vietnam, the Dominican Republic, Cambodia, Ghana, and the Republic of Korea using e-SPAR and GHS index scores, with the goal of identifying key strengths and weaknesses and offering targeted recommendations to strengthen national preparedness and promote international collaboration for future health threats.

HIGHLIGHTS

- World Health Organization International Health Regulations capacities were generally low, with particular concerns about preparedness for chemical disasters, food safety, and cross-border infectious disease transmission.
- The study emphasized that surveillance capacity—as an internal factor (early warning and event management)—and the immunization indicator—as an external factor (vaccination rates for human and animal diseases, including the national vaccine delivery system)—are priority strategies for strengthening future prevention and detection systems.
- To effectively respond to global health threats, countries must focus on improving 2 technical areas (early warning and event management, and national vaccine access and delivery) using a One Health approach.

Materials and Methods

This study employed a comparative case study approach that integrated quantitative and qualitative analyses. Secondary data from e-SPAR (internal evaluation) scores and the GHS index (external evaluation) were used to assess health security and preparedness in 6 selected countries. The 2023 e-SPAR database was obtained from the WHO website [5] and filtered to include reports from 5 low- and middle-income countries (LMICs)—3 Southeast Asian countries (Indonesia, Cambodia, and Vietnam), 1 Latin American country (the Dominican Republic), and 1 African country (Ghana). The selection criteria focused on countries with a strategic partnership with the Republic of Korea in terms of Official Development Assistance and on those represented by students in the Yonsei University School of Medicine's Global Health Security Research Group. The Republic of Korea was included to represent a developed country, having achieved the No. 1 ranking in Bloomberg's final tally for coronavirus disease 2019 (COVID-19) resilience.

Average scores for each country were summarized using descriptive statistics, with the lowest scores based on capacities and indicators identified. The GHS index scores for the 6 countries were obtained from the 2021 GHS index report [6]. Descriptive statistics were then used to compare each country's scores in various categories against the global average.

A strengths, weaknesses, opportunities, and threats (SWOT) analysis was conducted for each of the 5 LMICs (Indonesia, Cambodia, Vietnam, the Dominican Republic, and Ghana) to assess their current status in health security and preparedness. Strengths and weaknesses were sourced directly from the WHO e-SPAR database (2023). Opportunities were identified by selecting indicators with a minimum score of 75 (reflecting the range of the country with the highest overall health security index score) from the 2021 GHS index report, while threats were determined by identifying indicators with a score of 0 (mirroring the range of the country with the lowest score). Common features present in at least 3 countries were then highlighted through a collective SWOT analysis. Finally, the characteristics of the developing countries were compared with those of the Republic of Korea, and recommended strategies were proposed based on this analysis.

Results

The study examined 6 countries: 4 from Asia, 1 from Africa, and 1 from Latin America (Table 1). Politically, the sample included 1 constitutional monarchy (parliamentary cabinet system), 4 republics (presidential systems), and 1 socialist republic (communist party system). Four countries had a gross domestic product per capita below 5,000 United States dollars (USD), 1 had approximately 10,000 USD, and 1 had around 30,000 USD. Four countries had populations under 50 million, 1 had about 100 million, and 1 had approximately 300 million. Technically, the 2024 global innovation index information and communications technology scores were 95 in the Republic of Korea, 76.7 in Indonesia, 70.6 in Vietnam, 59.3 in the Dominican Republic, 51.4 in Ghana, and 49.9 in Cambodia.

The overall average scores for the 15 IHR implementation capacities in 2023 were 99, 75, 68, 56, 54, and 52 for the Republic of Korea, Indonesia, Cambodia, Ghana, Vietnam, and the Dominican Republic, respectively (Figure 1). Compared with the global average of 64, the scores for Indonesia, Cambodia, and the Republic of Korea were above average, whereas the other 3 countries remained below this threshold.

According to the 2021 GHS index report, the Republic of Korea, Indonesia, Vietnam, the Dominican Republic, Ghana, and Cambodia ranked 9th, 45th, 65th, 103rd, 104th, and 126th, respectively. Figure 2 details the overall average scores and the 6 pillars of health security (prevent, detect, respond, health, norms, risks) for these countries. Indonesia's overall score was 50.4, with the lowest score in the prevention category. The overall scores for Cambodia, Vietnam, the Dominican Republic, and Ghana were 31.1, 42.9, 34.5, and 34.3, respectively, with particularly low scores noted in the health system category.

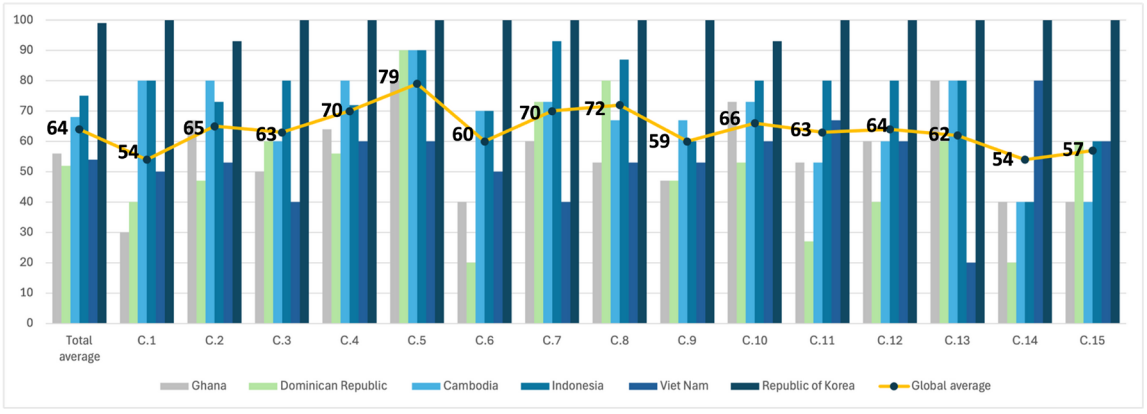
Each country was analyzed individually using the SWOT framework, with the e-SPAR and GHS index data used to identify internal factors (strengths and weaknesses) and external factors (opportunities and threats) as shown in Figure 3. Common features observed in at least 3 countries

Table 1. PEST analysis of 6 countries

Country	Cambodia	Indonesia	Vietnam	Ghana	Dominican Republic	Republic of Korea
Politics	Constitutional monarchy/ parliamentary cabinet system	Republic/ presidential system	Socialist Republic/ communist party	Republic/ presidential system	Republic/ presidential system	Republic/ presidential system
Economy (GDP per capita, USD/ economic growth)	2,744 USD/5.5% (2024 IMF)	4,920 USD/5.0% (2023 IMF)	4,649.1 USD/6.1% (2024 IMF)	2,270 USD/4.7% (2022/2021 IMF)	10,581 USD/4.9% (2022 IMF)	33,121 USD/2.5% (2023/2024 IMF)
Society (population/main religion/climate)	17,180,000/ Buddhism/ Tropical Monsoon	278,700,000/Islam/ Tropical Monsoon	100,770,000/ Buddhism/ Tropical and Subtropical Monsoon	32,400,000/ Christianity/ Tropical	10,630,000 (2022 IMF)/Roman Catholicism/ Tropical	51,680,000 (2024 IMF)/Christianity/ four-season mid-latitude temperate
Technology (2024 GII ICT scores)	49.9	76.7	70.6	51.4	59.3	95.0

PEST, politics, economy, society, technology; GDP, gross domestic product; USD, United States dollar; IMF, International Monetary Fund; GII, global innovation index; ICT, information and communications technology.

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Capacity	Title
C.1	Policy, legal and normative instruments to implement IHR
C.2	IHR Coordination, National IHR Focal Point functions and advocacy
C.3	Financing
C.4	Laboratory
C.5	Surveillance
C.6	Human resources
C.7	Health emergency management
C.8	Health services provision
C.9	Infection prevention and control
C.10	Risk communication and community engagement
C.11	Points of entry and border health
C.12	Zoonotic diseases
C.13	Food safety
C.14	Chemical events
C.15	Radiation emergencies

Figure 1. The International Health Regulations (IHR) electronic State Party Self-Assessment Annual Reporting mechanism scores for each capacity in 6 selected countries.

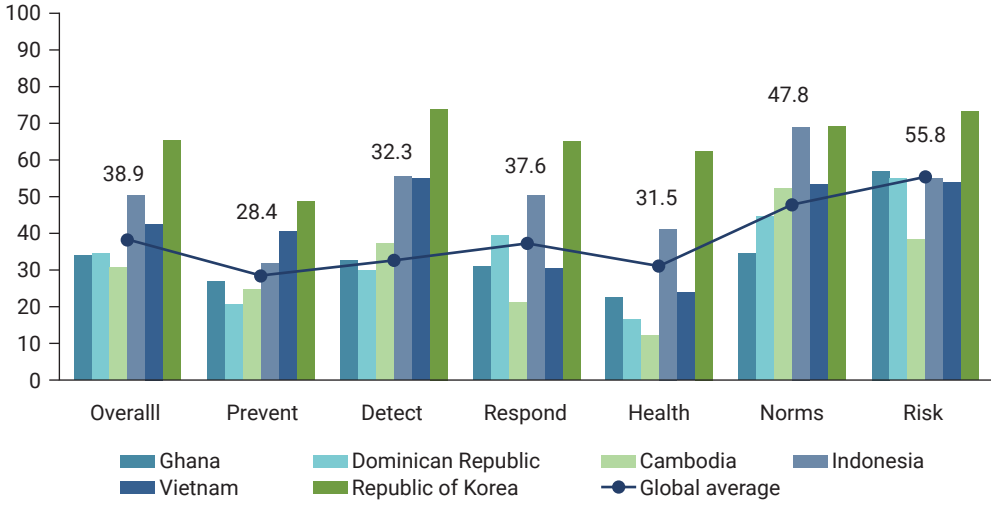


Figure 2. The global health security index scores of 6 selected countries.

were then highlighted in a collective SWOT analysis. Surveillance (early warning and event management) emerged as the primary strength across most countries. Common opportunities included international commitments and robust immunization programs. In contrast, many countries exhibited weaknesses related to policy, legal, and normative frameworks for IHR implementation, as well as challenges in human resources, chemical event management, and radiation emergency preparedness. Recurring threats involved biosafety, biosecurity, dual-use research and the culture of responsible science, infection control practices, coordination between public health and security authorities, vulnerabilities in laboratory supply chains, and communication issues with healthcare workers during public health emergencies (Figure 4).

Discussion

Figure 4 illustrates the main challenges and main strengths in every member state that submitted e-SPAR information to the WHO. The SWOT analysis of 6 countries found that common challenges in LMICs were policy, legal, and normative instruments to implement IHR, human resources, chemical events, and radiation emergencies, while common strengths were surveillance (early warning and event management). The GHS index (2021) was also analyzed for opportunities and threat analysis.

Based on the SWOT analysis, recommended strategies were developed to enhance GHS (Figure 5). Among these, strengthening surveillance (i.e., early warning systems and event management, which includes verification, investigation,

Indonesia

Strengths	Weaknesses
- C7 Health emergency management - C5 Surveillance - C8 Health services provision - C1 Policy, legal and normative instruments to implement IHR	- C14 Chemical events - C9 IPC - C15 Radiation emergencies - C6 Human resources
Opportunities	**Threats**
- AMR - Laboratory system, strength, and quality - Real-time surveillance and reporting - Linking public health and security authorities - IHR reporting compliance and disaster risk reduction - International commitments	- Biosafety - Dual-use research and culture of responsible science - Infection control practices

Cambodia

Strengths	Weaknesses
- C5 Surveillance - C1 Policy, legal and normative instruments to implement IHR - C2 IHR coordination, national IHR focal point function and advocacy - C4 Laboratory	- C14 Chemical events - C15 Radiation emergencies - C11 PoEs and border health - C3 Financing
Opportunities	**Threats**
- Immunization - International commitments	- Biosecurity - Biosafety - Dual-use research and culture of responsible science - Laboratory supply chain - Case-based investigation - Linking public health and security authorities - Trade and travel restrictions - Supply chain for health system and healthcare workers - Medical countermeasures and personnel development - Communication with healthcare workers during the public health emergencies - Infection control practices

Vietnam

Strengths	Weaknesses
- C14 Chemical events - C11 PoEs and border health - C3 Financing - C5 Surveillance	- C13 Food safety - C3 Financing - C7 Health emergency management - C1 Policy, legal and normative instruments to implement IHR
Opportunities	**Threats**
- Immunization - Laboratory system, strength, and quality - Epidemiology workforce - International commitments	- Dual-use research and culture of responsible science - Laboratory supply chain - Linking public health and security authorities - Trade and travel restrictions - Communication with healthcare workers during the public health emergencies - Infection control practices

Dominican Republic

Strengths	Weaknesses
- C5 Surveillance - C8 Health services provision - C7 Health emergency management - C3 Financing	- C6 Human resources - C14 Chemical events - C11 PoEs and border health - C1 Policy, legal and normative instruments to implement IHR
Opportunities	**Threats**
- Epidemiology workforce - Risk communication	- Biosecurity - Dual-use research and culture of responsible science - Laboratory supply chain - Exercising response plans - Linking public health and security authorities - Supply chain for health system and healthcare workers - Medical countermeasures and personnel development - Communication with healthcare workers during the public health emergencies - Infection control practices - JEE and PVS

Ghana

Strengths	Weaknesses
- C5 Surveillance - C13 Food safety - C10 RCCE - C2 IHR Coordination, National IHR Focal Point functions and advocacy	- C1 Policy, legal and normative instruments to implement IHR - C6 Human resources - C14 Chemical events - C15 Radiation emergencies
Opportunities	**Threats**
- AMR - Immunization	- Biosecurity - Biosafety - Dual-use research and culture of responsible science - Laboratory supply chain - Emergency preparedness and response planning - Linking public health and security authorities - Communication with healthcare workers during the public health emergencies - Infection control practices - Cross-border agreements on public and health emergency response

Figure 3. SWOT analysis of health security in 5 selected low- and middle-income countries using e-SPAR and GHS index.
IHR, International Health Regulations; IPC, infection prevention and control; PoE, point of entry; JEE, Joint External Evaluation; PVS, Performance Veterinary Service; SWOT, strengths, weaknesses, opportunities, and threats; e-SPAR, electronic State Party Self-Assessment Annual Reporting mechanism; GHS, global health security.

Common features of the 5 LMICs

Strengths	Weaknesses
- C5 Surveillance	- C1 Policy, legal and normative instruments to implement IHR - C6 Human resources - C14 Chemical events - C15 Radiation emergencies
Opportunities	**Threats**
- Immunization - International commitments	- Biosafety - Biosecurity - Dual-use research and culture of responsible science - Infection control practices - Linking public health and security authorities - Laboratory supply chain - Communication with healthcare workers during the public health emergencies

Republic of Korea

Strengths	Weaknesses
- C1 Policy, legal and normative instruments to implement IHR - C3 Financing - C4 Laboratory - C5 Surveillance	
Opportunities	**Threats**
- AMR - Real-time surveillance and reporting - Surveillance data accessibility and transparency - Epidemiology workforce - Emergency preparedness and response planning - Linking public health and security authorities - Risk communication - Access to communications infrastructure - Health capacity in clinics, hospitals, and community care centers - Infection control practices - Capacity to test and approve new medical countermeasures - IHR reporting compliance and disaster risk reduction - International commitments - Financing - Socio-economic resilience - Infrastructure adequacy - Public health vulnerability	- Dual-use research and culture of responsible science - Trade and travel restrictions

Figure 4. SWOT analysis of health security in low- and middle-income countries and Republic of Korea.
LMIC, low- and middle-income country; IHR, International Health Regulations; AMR, antimicrobial resistance; SWOT, strengths, weaknesses, opportunities, and threats.

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Internal / External	Strengths	Weaknesses
Opportunities	**SO strategy** **1. Surveillance through global cooperation** • S: C5 Surveillance • O: International commitments	**WO strategies** **1. Policy and legal frameworks through international commitments** • W: C1 Policy, legal and normat ve instruments to implement IHR • O: International commitments **2. Human resources with international support** • W: C6 Human resources • O: International commitments
Threats	**ST strategies** **1. Surveillance to support biosafety and biosecurity** • S: C5 Surveillance • T: Biosafety; Biosecurity **2. Supporting infection control practices through surveillance** • S: C5 Surveillance • T: Infection control practices	**WT strategies** **1. Human resources for infection control and communication** • W: C6 Human resources • T: Infection control practices; Communication with healthcare workers during the public health emergencies **2. Policies for biosecurity and biosafety** • W: C1 Policy, legal and normative instruments to implement IHR • T: Biosecurity; Biosafety; Dual-use research and culture of responsible science **3. Emergency preparedness to address chemical and radiation threats** • W: C14 Chemical events; C15 Radiation emergencies • T: Biosecurity; Biosafety; Dual-use research and culture of responsible science **4. Coordination between public health and security authorities through policies** • W: C1 Policy, legal and normative instruments to implement IHR • T: Linking public health and security authorities

Figure 5. Recommended strategies based on SWOT analysis. SWOT, strengths, weaknesses, opportunities, and threats.

analysis and dissemination of information) through global collaboration emerged as the most promising strength-opportunity strategy for the 5 LMICs. This strategy is critical for managing transboundary diseases that affect human, animal, and environmental health. Integrating surveillance efforts across borders can lead to more efficient resource use, improved preparedness, and a robust response to emerging threats. Nevertheless, implementing such cooperative strategies poses challenges, including the uneven distribution of costs and benefits among participating countries. Global cooperative surveillance can optimize efficiency and resource allocation, with international partnerships enhancing the capacity to detect and respond to health events [10]. Moreover, global surveillance networks—such as the Global Public Health Intelligence Network and HealthMap—play crucial roles in informing both national and transnational practices [11]. Organizations like Connecting Organizations for Regional Disease Surveillance also highlight the importance of trust-based networks for sharing best practices and innovations in disease surveillance [12]. Enhanced surveillance supports biosafety, biosecurity, and infection control by providing early detection, situational awareness, and data-driven decision-making. Integrating advanced technologies and methodologies is essential to confront the growing challenges posed by emerging infectious diseases, bioterrorism, and the global movement of people and goods.

Surveillance was found to be a main strength in the Republic of Korea, as shown by a perfect score from e-SPAR capacity and a high score in the Detecting and Reporting category of the GHS index. This performance is particularly notable in real-time One Health surveillance, reporting indicators, and data accessibility and transparency. The Republic of Korea's health surveillance system, which is an advanced framework designed to monitor and manage public health threats effectively, integrates traditional surveillance methods with cutting-edge digital tools to enhance its capabilities in disease detection, monitoring, and response. For instance, its sentinel surveillance system for Hand, Foot, and Mouth Disease (HFMD), operational since 2009 in approximately 100 pediatric clinics nationwide, is crucial for tracking incidence trends and informing public health planning [13]. Additionally, the Korean National Healthcare-associated Infections Surveillance System has significantly reduced central line-associated bloodstream infection rates across intensive care units, demonstrating the system's effectiveness in infection control [14]. During the COVID-19 pandemic, the Epidemiological Investigation Support System leveraged big data from cellular base stations, credit card transactions, and QR codes to track infected individuals, enhancing the speed and accuracy of epidemiological investigations [15]. The National Health Insurance Claims-based Surveillance further complements conventional

methods by using claims data to monitor disease incidence, thereby providing a stable measure of disease trends with fewer limitations than traditional reporting systems [16]. The Republic of Korea's comprehensive surveillance system represents a best practice that developing countries could adopt to improve their One Health approach.

Some limitations of this study should be acknowledged. Although e-SPAR provides the most recent official data reported directly to WHO headquarters to describe internal factors, and the GHS index offers current external evaluations, both data sources may not fully capture the present situation. Moreover, due to the challenges of assessing all 195 countries, the SWOT analysis based on these 6 countries may not be generalizable worldwide. Future studies should also investigate the underlying causes of the identified weaknesses and threats.

Conclusion

The SWOT analysis, based on e-SPAR and GHS index scores for Indonesia, Cambodia, Vietnam, the Dominican Republic, and Ghana, indicates that countries should prioritize enhancing surveillance capacity (including early warning functions and event management encompassing verification, investigation, analysis, and information dissemination) as an internal success factor, and improving the immunization indicator (encompassing vaccination rates for human and animal diseases and the national vaccine delivery system) as an external success factor. Consequently, nations should concentrate on 2 technical areas: early warning and event management, and national vaccine access and delivery.

Global collaboration—through building trust-based networks with developed countries such as the Republic of Korea, which possesses a comprehensive government surveillance system and immunization ecosystem that includes the International Vaccine Institute—can facilitate the sharing of best practices.

Notes

Ethics Approval
The informed consent was waived because of the retrospective nature of this study.

Conflicts of Interest
Chaeshin Chu has been the managing editor of *Osong Public Health and Research Perspectives* since October 2011. The other authors have no conflicts of interest to declare.

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None.

Availability of Data
The datasets generated and/or analyzed during the current study are available in the WHO repository, https://extranet.who.int/e-spar/ and the GHS index repository, https://ghsindex.org.

Authors' Contributions
Conceptualization: MY, NF, OKA; Data curation: NF, TLNN, DIJB; Formal analysis: all authors; Investigation: all authors; Methodology: MY, NF, OKA; Project administration: NF, VP; Supervision: MY, CC; Validation: CC; Visualization: NF, MY; Writing–original draft: NF, MY; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

The first report of antibiotic resistance and virulence factor profiles in multidrug-resistant clinical isolates of *Klebsiella pneumoniae* from Pontianak, Indonesia

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ABSTRACT

Objectives: *Klebsiella pneumoniae* is known as one of the most common causes of hospital-acquired infections. Its prevalence poses substantial challenges to both hospital and public health systems, particularly due to the rise of multidrug-resistant strains. Understanding the epidemiology and resistance properties of *K. pneumoniae* can inform antimicrobial stewardship and infection control programs. A cross-sectional study was employed from November 2021 to November 2023.

Methods: A total of 24 isolates underwent antimicrobial susceptibility testing using the disk diffusion method, an extended-spectrum beta-lactamase (ESBL) production test, and molecular gene detection.

Results: The study found that 95.8% of clinical isolates were classified as multidrug-resistant. All isolates were resistant to ampicillin (100%). A high percentage of isolates were resistant to cefazolin (91.7%), ceftriaxone (87.5%), cefotaxime (87.5%), cefepime (87.5%), ciprofloxacin (83.3%), and sulfamethoxazole-trimethoprim (83.3%). Of the 24 isolates, 87.5% harbored ESBL genes, while the frequencies for GES, NDM, SIM, and OXA-48 were 16.7%, 20.8%, 8.3%, and 41.7%, respectively. Notably, the OXA-23 and OXA-51 genes, which are typically associated with *Acinetobacter baumannii*, were detected in 16.7% and 20.8% of isolates, respectively. Moreover, the prevalence of virulence genes rmpA, acrAB, and tolC was 0%, 95.8%, and 87.5%, respectively.

Conclusion: This study demonstrated a high level of antibiotic resistance and a significant presence of virulence genes among *K. pneumoniae* isolates. Consequently, these findings represent a critical public health issue that requires heightened awareness among all stakeholders, including health workers.

Keywords: Antibiotic resistance; Carbapenemase; Extended-spectrum beta-lactamase; Gene detection; *Klebsiella pneumoniae*

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Introduction

Klebsiella pneumoniae is an opportunistic pathogen found in the blood, respiratory, and urinary tracts and is a common cause of bloodstream infections, pneumonia, and urinary tract infections; it is also considered a frequent cause of healthcare-associated infections [1,2]. The emergence of hypervirulent *K. pneumoniae* infections has been on the rise and has been associated with invasive diseases and increasing mortality over the past 3 decades [3]. The prevalence of *K. pneumoniae* infections ranges from 18% to 87.7% in Asian countries, whereas in Western countries it varies from 5% to 35% [2,4]. The mortality rate for bloodstream infections caused by *K. pneumoniae* is approximately 43.0% [5]. Indonesian surveillance data on hospital antibiotic resistance indicate that *K. pneumoniae* is the most frequently isolated bacterium from blood and sputum samples, and the second most frequently isolated from urine specimens, with an infection incidence of 14% [6].

Susceptible strains of *K. pneumoniae* are commonly eradicated by broad-spectrum β-lactams (with the exception of ampicillin and ticarcillin), carbapenems, trimethoprim-sulfamethoxazole, tetracycline, aminoglycosides, and fluoroquinolones [7]. However, treatment becomes more challenging due to plasmid-mediated antimicrobial resistance [8,9]. According to the Global Antimicrobial Resistance and Surveillance System on Emerging Antimicrobial Resistance Reporting data from 2024, hypervirulent, carbapenem-resistant *K. pneumoniae* is on the rise [10]. European countries have reported an increasing detection of hypervirulent *K. pneumoniae* that combines antibiotic resistance, with some isolates being extensively drug-resistant (XDR) [11]. Surveillance in South and Southeast Asia has revealed that 47% of isolates are extended-spectrum beta-lactamase (ESBL) producers and 17% are carbapenemase producers [12]. Additionally, reports from Baghdad indicate that quinolone resistance in *K. pneumoniae* is high [13]. *K. pneumoniae* has thus emerged as a significant challenge in hospital settings and public health, primarily due to the increasing incidence of infections caused by multidrug-resistant (MDR) strains. However, the prevalence of antibiotic resistance and virulence genes among pathogenic *K. pneumoniae* has yet to be investigated in West Kalimantan, Indonesia. Therefore, this study aimed to evaluate the incidence of *K. pneumoniae* infections and their antibiotic resistance properties, including virulence genes, in Pontianak, Indonesia.

HIGHLIGHTS

- Multidrug-resistant *Klebsiella pneumoniae* infections have been on the rise.
- *K. pneumoniae* has emerged as a significant challenge in hospital settings and public health.
- Multidrug-resistant *K. pneumoniae* has been associated with invasive diseases and increasing mortality for the last 3 decades.
- Antibiotic stewardship should be implemented to curb the increase in antibiotic-resistant strains.

Materials and Methods

Study Population

A cross-sectional study was conducted from November 2021 to November 2023. A total of 154 clinical specimens from patients diagnosed with infections at 5 hospitals in Pontianak, West Kalimantan, Indonesia, were examined. Twenty-5 isolates confirmed as *K. pneumoniae* were initially collected; however, 24 isolates were ultimately included in the final analysis.

Specimens

Specimens were collected from feces, urine, sputum, pus, wound swabs, vitreous humor, ear/nose secretions, and bronchoalveolar lavage (BAL) according to the participants' diagnoses. All specimens were stored in sterile containers and transported to the laboratory at 4 °C. Samples were processed within 2 hours of collection.

Phenotypic Identification

Specimens were inoculated on blood agar (Merck, USA) and MacConkey agar (Merck, USA), and then incubated at 37 °C for 18 hours. Single colonies from both media were subjected to Gram staining to determine bacterial shape and Gram reaction. Gram-negative rods were further identified to the species level using an oxidase test (Merck, USA) and API 20E (Biomerieux). A 0.5 McFarland bacterial suspension was prepared and used in accordance with the API 20E protocol, followed by incubation at 37 °C for 18 hours. Identification results were validated using https://apiweb.biomerieux.com, and only *K. pneumoniae* isolates with an identification percentage of ≥ 80% were included in the study.

Antibiotic Susceptibility Test by Disk Diffusion Method

A 0.5 McFarland bacterial suspension was prepared and

inoculated onto Mueller Hinton agar (Merck, USA) using a sterile cotton swab for the antibiotic susceptibility test by the disk diffusion method. Fourteen representative antibiotics from different classes were tested, including ampicillin (AMP, 10 µg; Oxoid), cefazolin (KZ, 30 µg; Oxoid), gentamicin (CN, 10 µg; Oxoid), tobramycin (NN, 10 µg; BD BBL), amikacin (AK, 30 µg; Oxoid), amoxicillin-clavulanate (AMC, 30 µg; Oxoid), cefepime (FEP, 30 µg; Oxoid), ceftriaxone (CRO, 30 µg; Oxoid), ciprofloxacin (CIP, 5 µg; Oxoid), levofloxacin (LEV, 5 µg; Oxoid), meropenem (MEM, 10 µg; Oxoid), sulfamethoxazole-trimethoprim (SXT, 25 µg; Oxoid), aztreonam (ATM, 30 µg; Oxoid), ceftazidime (CAZ, 30 µg; Oxoid), cefotaxime (CTX, 30 µg; Oxoid), tetracycline (TE, 30 µg; Oxoid), chloramphenicol (C, 30 µg; Oxoid), and azithromycin (AZM, 15 µg; Oxoid). Plates were incubated at 37 °C for 18 hours. The inhibition zones were interpreted according to the Clinical and Laboratory Standard Institute (CLSI) guidelines [14]. The results were then used to classify the bacteria as MDR, XDR, or pan-drug-resistant (PDR) [15].

Screening and Confirmation of ESBL-Producing Isolates

Phenotypic detection of ESBL-producing isolates was performed using the disk diffusion method with amoxicillin-clavulanate (AMC, 30 µg; Oxoid) in conjunction with cefotaxime (CTX, 30 µg; Oxoid) and ceftazidime (CAZ, 30 µg; Oxoid). A 0.5 McFarland isolate suspension was inoculated onto Mueller Hinton agar (Merck, Germany) using a sterile cotton swab. The cefotaxime and ceftazidime disks were placed side by side with the amoxicillin-clavulanate disk, at a distance of 20 mm from the disk center. Plates were then incubated at 37 °C for 16 to 18 hours. An increase in the inhibition zone diameter of more than 5 mm towards the amoxicillin-clavulanate disk compared to the zones for cefotaxime and/or ceftazidime was considered indicative of ESBL production [14,16].

Bacterial DNA Extraction and Identification

A single colony from each bacterial isolate was suspended in 1 mL of nuclease-free water (NFW) and then centrifuged at 13,000 rpm for 10 minutes. The resulting pellet was resuspended in 200 µL of NFW, and DNA was extracted according to the manufacturer's protocol (Presto Mini gDNA bacteria kit; GeneAid). Molecular identification of *K. pneumoniae* was performed using the khe gene, which also serves as a housekeeping gene in virulence gene detection. Identification via the khe gene was conducted using real-time polymerase chain reaction (PCR) on an Applied Biosystems Quant Studio 5 Real-Time PCR System. The PCR reaction was carried out in a total volume of 20 µL, consisting of 2X Fast Q-PCR Master Mix (SMOBIO Technology), 0.6 µL (10 µM) of each primer, 2 µL of DNA template, and NFW. The PCR conditions were as follows: an initial denaturation at 94 °C for 5 minutes, followed by 33 cycles of 1 minute at 94 °C for denaturation, 30 seconds at 55 °C for annealing, and 60 seconds for extension, with a final extension at 72 °C for 10 minutes. The primers for the khe gene are listed in Table 1 [16–19].

Antibiotic Resistance Gene Detection

Antibiotic resistance gene detection was performed using the Antimicrobial Resistance (AMR) Direct Flow Chip Kit (Vitro, Spain). A DNA template of 80 µL was used in the AMR Direct Sepsis Flow Chip Kit PCR protocol. Thermal cycling was carried out on a Classic KF960 Thermal Cycler (Heal Force) with an initial step at 25 °C for 10 minutes, followed by 95 °C for 3 minutes, and then 40 amplification cycles at 95 °C for 15 seconds, 55 °C for 45 seconds, and 72 °C for 1 minute, with a final elongation at 72 °C for 7 minutes. The PCR products were then subjected to a hybridization process on the HybriSpot 12 system (Vitro) following the manufacturer's protocol. After hybridization, the results were captured and analyzed using HybriSoft software ver. HSHS 2.2.0.R11. Resistance genes with a spot thickness of ≥4 were considered positive. The probes targeted for *K. pneumoniae* included SHV, CTX-M, KPC, SME, NMC/IMI, GES, VIM, GIM, SPM, NDM, SIM, IMP, OXA-23, OXA-24, OXA-48, OXA-51, and OXA-58 [18].

Virulence Gene Detection

Identification of the rmpA, acrAB, and tolC genes was performed using real-time PCR on an Applied Biosystems Quant Studio 5 Real-Time PCR System. The PCR reaction was carried out in a total volume of 20 µL, which included 2X Fast Q-PCR Master Mix, 0.6 µL (10 µM) of each primer, 2 µL of DNA template, and NFW. The PCR conditions were as follows: an initial denaturation at 94 °C for 5 minutes, followed by 33 cycles of 1 minute at 94°C for denaturation, 30 seconds for annealing (with specific temperatures: rmpA at 55 °C, acrAB at 53 °C, and tolC at 51 °C), and 60 seconds for extension, with a final extension at 72 °C for 10 minutes. The primers used for virulence gene detection are listed in Table 1 [19,20].

Data Analysis

Data were entered into Microsoft Excel for analysis, and the results were presented in tabular form.

Ethics Statement

The study protocol was approved by the Health Research Ethics Committee of the Faculty of Medicine at Universitas Tanjungpura, Pontianak, Indonesia (approval number:

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Table 1. The target genes of the housekeeping gene, carbapenemase, and primer sequences of the target genes

Target gene	Allelic variation/primer sequence (5′ to 3′)	Reference
Housekeeping gene		
khe	F TGATTGCATTCGCCACTGG	[16]
Hemolysin gene	R GGTCAACCCAACGATCCTGG	
Carbapenemase genes		[17]
ges	Alleles 1–26	
Class A GES carbapenemase		
sme	Alleles 1–5	
Class A SME carbapenemase		
kpc	Alleles 1–23	
Class A KPC carbapenemase		
nmc/imi	Alleles 1–29	
Class A NMC/IMI carbapenemase		
sim	Sim	
Class B SIM carbapenemase		
gim	Alleles 1–2	
Class B GIM carbapenemase		
Spm	Spm	
Class B SPM carbapenemase		
ndm	Alleles 1–16	
Class B NDM carbapenemase		
Vim	Alleles 1–46	
Class B VIM carbapenemase		
imp	Alleles 1–3, 5–6, 8–11, 15, 19–21, 24–25, 28–30, 40–42, and 47	
Class B IMP carbapenemase		
OXA-23	Alleles 23, 27, 49, 73, 133, 146, 165–171, and 225	
Class D OXA23_like carbapenemase		
OXA-24	Alleles 24–26, 40, 72, 139, and 160	
Class D OXA24_like carbapenemase		
OXA-48	Alleles 48, 162, 163, and 181	
Class D OXA48_like carbapenemase		
OXA-51	Alleles 51, 60, 65–70, 75–80, 82–84, 88–99, 106–117, 128, 130–132, 138, 144, 148–150, 172–180, 194–197, 200–206, 208, and 223	
Class D OXA51_like carbapenemase		
OXA-58	Alleles 58, 96, 97, and 164	
Class D OXA58_like carbapenemase		
Virulence genes		
rmpA	F ACTGGGCTACCTCTGCTTCA	[18]
Regulator of mucoid phenotype gene	R CTTGCATGAGCCATCTTTCA	
acrAB	F ATCAGCGGCCGGATTGGTAAA	[19]
multidrug efflux pump gene	R CGGGTTCGGGAAAATAGCGCG	
tolC	F ATCAGCAACCCCGATCTGCGT	[19]
multidrug efflux pump gene	R CCGGTGACTTGACGCAGTCCT	

5949/UN22.9/PG/2021).

Results

A total of 24 clinical samples of *K. pneumoniae* were obtained from 154 patients with clinically diagnosed infections. The most common sources of specimens were sputum (80%), followed by BAL fluid (9%), urine (5%), wound swabs/discharge (4%), and feces (2%).

Phenotypic Detection of Antibiotic Resistance Characteristic

This study found that 23 out of 24 (95.8%) clinical isolates were classified as MDR, while 1 out of 24 (4.2%) exhibited PDR;

no XDR isolates were identified (Table 2). The antimicrobial resistance profiles of the isolates, as classified based on their antibiotic resistance results, are presented in Table 2. All isolates were resistant to ampicillin (100%, 24/24). Furthermore, a high percentage of isolates were resistant to cefazolin (91.7%, 22/24), ceftriaxone (87.5%, 21/24), cefotaxime (87.5%, 21/24), cefepime (87.5%, 21/24), ciprofloxacin (83.3%, 20/24), and sulfamethoxazole-trimethoprim (83.3%, 20/24).

Table 2. Resistance pattern of *Klebsiella pneumoniae* clinical isolates according to the disk diffusion method ($n = 24$)

	Resistance frequency (*n*, %)
Antibiotics	
Penicillin	
Ampicillin	24 (100.0)
Cephalosporin (first generation)	
Cefazolin	22 (91.7)
Cephalosporin (third generation)	
Ceftriaxone	21 (87.5)
Cefotaxime	21 (87.5)
Ceftazidime	18 (75.0)
Cephalosporin (fourth generation)	
Cefepime	21 (87.5)
Carbapenem	
Meropenem	10 (41.7)
Monobactam	
Aztreonam	19 (79.2)
Beta-lactam and anti-beta-lactamase	
Amoxicillin-clavulanate	13 (54.2)
Tetracycline (30S)	
Tetracycline	12 (50.0)
Fluoroquinolone	
Ciprofloxacin	20 (83.3)
Levofloxacin	17 (70.8)
Sulfonamide and dihydrofolate reductase inhibitors	
Sulfamethoxazole-trimethoprim	20 (83.3)
Nitrofurantoin	
Nitrofurantoin	15 (62.5)
Phenicol (50S)	
Chloramphenicol	16 (66.7)
Aminoglycoside (30S)	
Gentamicin	9 (37.5)
Tobramycin	8 (33.3)
Amikacin	2 (8.3)
Macrolide (50S)	
Azithromycin	15 (62.5)
Drug resistance classification	
Multidrug-resistant	23 (95.8)
Extensively drug-resistant	0 (0)
Pan-drug-resistant	1 (4.2)

30S, ribosomal protein 30S; 50S, ribosomal protein 50S.

Among the 24 isolates, 5 (20.8%) were classified as ESBL-producing *K. pneumoniae* based on the phenotypic ESBL test. Fifteen isolates (62.5%) demonstrated resistance to ceftazidime, amoxicillin-clavulanate, and cefotaxime, which resulted in the absence of any distortion or increase in the inhibition zone towards the amoxicillin-clavulanate disk. ESBL-producing *K. pneumoniae*, as identified by the ESBL test, are illustrated in Figure 1.

Molecular Detection of Antibiotic Resistance and Virulence Associated Genes

Molecular detection for ESBL genes, specifically CTX-M and SHV, demonstrated that 14 (58.3%) clinical isolates were positive for these ESBL genes, while 3 (12.5%) isolates were negative. The majority of isolates (41.7%) harbored the OXA-48 gene. Notably, the less common resistance genes, OXA-23 and OXA-51, were detected in 4 (16.7%) and 5 (20.8%) isolates, respectively. These genes encode carbapenemases that confer decreased susceptibility to carbapenems, notably meropenem and imipenem [21]. Additionally, all isolates predominantly harbored the virulence genes acrAB and tolC at rates of 95.8% and 87.5%, respectively. Detailed data are

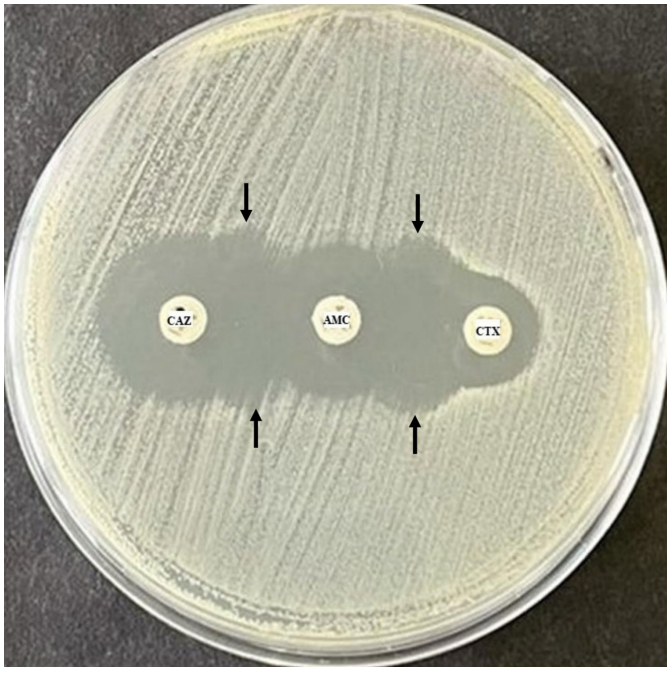


Figure 1. Positive finding extended-spectrum beta-lactamase production in *Klebsiella pneumoniae* screening by the disk diffusion test. Left to right: CAZ–AMC–CTX.
CAZ, ceftazidime; AMC, amoxicillin-clavulanate; CTX, cefotaxime. Black arrow: increase diameter in the zone inhibition towards the disk of amoxicillin-clavulanate.

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presented in Table 3.

Discussion

This is the first report describing the detection of MDR and PDR *K. pneumoniae* in Pontianak, Indonesia. Our findings demonstrated that the majority (95.8%, 23/24) of *K. pneumoniae* isolates collected from 5 different specimen types were MDR strains (Table 2). A similar pattern has been observed in studies from Iran, Saudi Arabia, and China, indicating a significant global issue with MDR *K. pneumoniae* [22–24]. According to the first meta-analysis on nosocomial MDR *K. pneumoniae*, its emergence is expected to increase globally, highlighting the urgent need to improve and evaluate the use of appropriate antibiotics [25]. Infections associated with MDR *K. pneumoniae* can complicate treatment, prolong hospitalization, and increase medical costs, as well as mortality and morbidity rates [23]. Moreover, infections caused by MDR *K. pneumoniae* are linked to 22% to 72% mortality in hospitalized and immunocompromised patients [26]. Unfortunately, our study did not assess the association between MDR *K. pneumoniae* infections and morbidity, which is a limitation of this report.

Data presented in Table 1 indicate that most *K. pneumoniae* strains are MDR and PDR, with more than 75% of the 24 isolates resistant to all beta-lactam antibiotics tested, although 54.2% of isolates were susceptible to meropenem. A previous study reached a similar conclusion, noting that MDR *K. pneumoniae* exhibited good sensitivity only to meropenem [27]. Additionally, all isolates were resistant to ampicillin, which is consistent with a study from China that reported the majority of MDR *K. pneumoniae* (>90%) were resistant to penicillin G [28].

The treatment options for MDR *K. pneumoniae* are not well optimized [9]. However, aminoglycosides are frequently used in combination with other antibiotic classes to combat these MDR strains [9], which is consistent with our results showing that 83% of isolates were sensitive to amikacin, followed by gentamicin and tobramycin (Table 2). Our findings also confirm that the isolates exhibited high resistance to sulfamethoxazole-trimethoprim (83.3%, 20/24) and amoxicillin-clavulanate (54.2%, 13/24). This contrasts with 2 clinical studies where these antibiotics appeared promising for treating infections caused by carbapenemase- and ESBL-producing *K. pneumoniae* [29,30]. Tigecycline and colistin are recognized as highly effective against PDR *K. pneumoniae* infections; tigecycline is considered first-line therapy for PDR *K. pneumoniae*, while colistin serves as the last resort [31].

K. pneumoniae exhibits resistance to beta-lactam antibiotics through several mechanisms, including the enzymatic hydrolysis

Table 3. Detection of antibiotic-resistant and virulence genes in *Klebsiella pneumoniae* (*n* = 24)

ESBL				ESBL-producing test		Carbapenemase												Virulencegene		
ESBL gene						Class A			Class B					Class D						
CTX-M alone	SHV alone	CTX-M and SHV	Not detected	ESBL	Non-ESBL	KPC	SME	NMC/IMI	GES	VIM	GIM	SPM	NDM	SIM	IMP	OXA-23	OXA-24	OXA-48	OXA-51	OXA-58	rmpA	acrAB	tolC
6 (25.0)	1 (4.2)	14 (58.3)	3 (12.5)	5 (20.8)	19 (79.2)	0 (0)	0 (0)	0 (0)	4 (16.7)	0 (0)	0 (0)	0 (0)	5 (20.8)	2 (8.3)	0 (0)	4 (16.7)	0 (0)	10 (41.7)	5 (20.8)	0 (0)	0 (0)	23 (95.8)	21 (87.5)

Data are presented as *n* (%).
ESBL, extended-spectrum beta-lactamase.

of carbapenems and beta-lactams by carbapenemases and ESBLs [8]. Our results indicated that 87.5% of isolates expressed ESBL genes (including CTX-M and SHV), with these genes absent in 3 of the 24 isolates (Table 3). This finding is consistent with the results reported by Beena et al. [32], who found that 84% of 250 *K. pneumoniae* isolates were ESBL producers. Similarly, Sheikh and colleagues reported that 65% of 120 clinical isolates were ESBL producers [33].

ESBLs can be inhibited by beta-lactamase inhibitors such as clavulanic acid. Phenotypic identification of ESBL production is typically performed using the disk diffusion method with a cephalosporin combined with a beta-lactamase inhibitor, such as ceftazidime-clavulanate or cefotaxime-clavulanate, as recommended by the CLSI guidelines. However, the phenotypic test is prone to false-negative results. Therefore, molecular gene detection is recommended as a primary method for identifying antibiotic resistance [14,34]. In Indonesia, access to the combination disks is limited; hence, amoxicillin-clavulanate was used in this study. Consequently, 19 out of 24 isolates were identified as non-ESBL producers by phenotypic testing, whereas molecular detection yielded positive results for 17 of these 19 phenotypically negative isolates. Based on our findings, the phenotypic test produced false negatives at a rate of 89.5%.

Our findings indicate that 66.67% of *K. pneumoniae* isolates were resistant to meropenem as determined by the disk diffusion test. Among the carbapenemase gene-resistant strains, all were ESBL-positive (13/24). In our study, 41.7% of isolates harbored the OXA-48 gene and 20.8% harbored the NDM gene. OXA-48 and NDM are well known as major contributors to carbapenem resistance in *K. pneumoniae*, as reported in studies from India and Ukraine [35,36]. Notably, our study detected the OXA-23 and OXA-51 genes in 16.7% and 20.8% of isolates, respectively (Table 3). These class D carbapenemases, typically found in *Acinetobacter baumannii*, were initially identified in *A. baumannii*, with OXA-23 being the first OXA enzyme detected that exhibited carbapenemase activity. Both genes can be encoded on plasmids and chromosomes [37,38]. A study from Iran reported similar findings, with OXA-51 found more frequently (30%) than OXA-23 (2.6%) [39].

OXA-23 and OXA-51 are commonly associated with ISAba1-based transposons, specifically found in AbaR4-type resistance islands and in transposons such as Tn2006, Tn2008, and Tn2009 for OXA-23 [40]. Through ISAba1-mediated transposition, these elements can be inserted into plasmids or integrated into chromosomes [40,41]. Antimicrobial resistance genes can transfer across different pathogen species or between strains via mobile genetic elements such as insertion sequences, integrons, and transposons [40]. Thus, horizontal gene transfer is considered a key mechanism in the emergence of OXA-23 and OXA-51 in *K. pneumoniae*. Carbapenems are widely regarded as reliable and effective antibiotics for treating severe nosocomial infections that are resistant to cephalosporins [42]. This situation warrants global attention, as it could contribute to the rise of antibiotic-resistant microorganisms and limit the availability of effective antibiotics.

Our study also examined the presence of virulence-encoding genes acrAB, tolC, and rmpA, with prevalence rates of 95.8%, 87.5%, and 0%, respectively (Table 3). The acrAB and tolC genes encode major resistance-nodulation-division (RND) efflux pumps, which are unique to Gram-negative bacteria and play a significant role in treatment outcomes. These efflux pumps are crucial for antibiotic export and contribute to the intrinsic resistance of Gram-negative bacteria. Additionally, acrAB and tolC are involved in biofilm formation, pathogenicity, and adaptation to environmental stresses [43]. These RND efflux pumps can export a wide range of substrates, including various antibiotics, bile salts, detergents, dyes, and biocides [43–45]. In contrast, rmpA is recognized as a marker gene for hypervirulent *K. pneumoniae* strains, which are capable of causing community-acquired infections and pose a global concern due to their ability to infect healthy individuals and cause infections at multiple sites [46].

The prevalence of the acrAB and tolC genes was high in our study (Table 3), and together they constitute the primary RND efflux pump in Enterobacterales. Other studies have reported a lower prevalence of acrAB and tolC (41% and 33%, respectively) [20]. The active acrAB-tolC efflux pump can export several antibiotics, including beta-lactams, macrolides, fluoroquinolones, and tetracycline [47]. This is consistent with our findings, which show that the majority of *K. pneumoniae* isolates exhibited high levels of resistance to these antibiotics (Table 2). Notably, the rmpA gene was not detected in any of the *K. pneumoniae* isolates in this study. Since rmpA plays a crucial role in the hypervirulence of *K. pneumoniae* by inducing capsule production [46], its absence suggests that all the isolates in our study were non-hypervirulent strains.

Conclusion

To the best of our knowledge, this is the first report of *K. pneumoniae* data from Pontianak, Indonesia. This finding should raise awareness among health workers about the threat of antibiotic resistance in West Kalimantan. Despite the limited number of isolates in the study, the high prevalence of resistance genes among *K. pneumoniae* isolates signals a global threat that warrants attention from all stakeholders,

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including health workers. The responsible use of antibiotics, regular monitoring, and strict infection control practices are essential for reducing the spread of MDR bacteria and protecting public health. Additionally, comprehensive studies with larger sample sizes are necessary to elucidate the local epidemiology of *K. pneumoniae* and to inform the development of targeted interventions to combat antibiotic resistance in the region.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Faculty of Medicine of Universitas Tanjungpura, Pontianak, Indonesia (approval number: 5949/UN22.9/PG/2021) and performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained for publication of this study and accompanying images.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

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

Authors' Contributions

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

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Original Article

Multilevel analysis of individual, household, and community factors influencing COVID-19 vaccination intention: evidence from the 2021 Korea Community Health Survey

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ABSTRACT

Objectives: This study aimed to investigate the combined effects of individual, household, and community-level factors on coronavirus disease 2019 (COVID-19) vaccination intention using a multilevel analysis.

Methods: This cross-sectional study analyzed raw data from the 2021 Korea Community Health Survey and regional statistics from 255 health centers, with a final sample of 229,216 individuals. Multilevel analysis was conducted, focusing on individual, household, and community-level factors. Individual-level factors included demographics, health status, and COVID-19 concerns; household-level factors included income and marital status; and community-level factors included city type and vaccination rates.

Results: At the individual level, significant differences were observed across all variables. At the household level, higher vaccination intention was associated with households of 4 or more members and a monthly income of 4 million Korean won or more. At the community level, higher flu vaccination rates, greater concern about COVID-19 infection, and higher COVID-19 vaccination rates were linked to increased vaccination intention.

Conclusion: This study highlights that COVID-19 vaccination intention is influenced by factors at the individual, household, and community levels. Vaccination strategies that integrate household and community-level approaches may be more effective. Policymakers should consider both individual and social health factors when designing vaccination policies.

Keywords: COVID-19; Intention; Multilevel analysis; Vaccination

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Introduction

Nearly 5 years have passed since the World Health Organization (WHO) declared the severe acute respiratory syndrome coronavirus 2 virus an international public health emergency, yet the burden of the coronavirus disease 2019 (COVID-19) pandemic continues to have uneven impacts at the population level. On January 30, 2020, the WHO declared COVID-19 the sixth Public Health Emergency of International Concern (PHEIC) in history. Since then, the world, including the Republic of Korea, has grappled with the pandemic. In May 2023, the WHO officially announced the end of the COVID-19 PHEIC, transitioning from an emergency response to a long-term management framework [1].

The COVID-19 vaccine, introduced in 2021, was expected to be a key strategy for mitigating the pandemic's impact and reducing its spread [2]. However, achieving this goal requires a sufficient vaccination rate [3]. Unfortunately, widespread vaccine hesitancy or rejection has emerged due to distrust in vaccine effectiveness and concerns about potential side effects. This hesitancy has also fueled resentment toward government policies, leading to social conflict during the early stages of vaccine rollout [4]. Consequently, numerous studies have been conducted on vaccine safety and strategies to promote vaccination [5,6].

Systematic reviews from other countries have identified factors associated with vaccine hesitancy or rejection, including younger age, lower education levels, and lower socioeconomic status. However, individuals exist within complex social contexts where interactions between personal and environmental factors shape behavior [7]. Vaccine-related knowledge, attitudes, and perceptions can vary significantly based on individual characteristics and the social environment [8,9].

In the Republic of Korea, dozens of studies have explored factors influencing vaccination, but most focus solely on individual-level factors. To date, no study has examined how both individual and community characteristics affect COVID-19 vaccination intentions. This study aims to fill this gap by investigating the individual, household, and community-level factors influencing COVID-19 vaccination intentions among the general population in the Republic of Korea. Using multilevel analysis, we assess the combined impact of these factors on vaccination intentions. By doing so, we aim to contribute to strengthening the Republic of Korea's public health emergency response system and provide foundational data for developing effective vaccination policies against COVID-19 and future emerging infectious diseases.

HIGHLIGHTS

- A multilevel analysis was conducted to identify individual, household, and community-level factors influencing individuals' intentions to receive the coronavirus disease 2019 (COVID-19) vaccine.
- At the household level, individuals with 4 or more household members and a monthly household income exceeding 4 million Korean won showed a higher intention to get vaccinated.
- At the community level, higher flu vaccination rates, greater concern about COVID-19 infection, and higher COVID-19 vaccination rates were associated with increased vaccination intention.

Materials and Methods

Study Population and Datasets

This study employed a cross-sectional design and defined communities for multilevel analysis using administrative units divided into 255 Public Health Center (PHC) districts nationwide. The analysis utilized raw data from the 2021 Korea Community Health Survey (KCHS) and publicly available statistics for the 255 PHCs, provided by national agencies such as Statistics Korea. The public statistics were based on data as of the end of 2021 and were obtained online through the national statistics portal of Statistics Korea (http://kostat.go.kr), the KCHS website (http://chs.kdca.go.kr), and the Republic of Korea's COVID-19 Dashboard (http://ncov.kdca.go.kr). The KCHS is a nationwide health survey conducted by the Korea Disease Control and Prevention Agency since 2008. It aims to produce representative health statistics for all local governments, specifically all PHC districts. The KCHS uses a stratified 2-stage cluster sampling method, with residential areas and households serving as sequential sampling units for each local government [10]. The 2021 KCHS was conducted from August 16 to October 31, 2021, and a total of 229,242 individuals completed the survey. Of these, 229,216 were included in the analysis after excluding 26 individuals who did not respond to the question regarding COVID-19 vaccination intention.

Variables

All individual- and household-level variables, excluding community-level variables, were analyzed using raw data from the 2021 KCHS. Survey items in the KCHS were validated for validity and reliability by expert members of the Korea Disease Control and Prevention Agency's Indicators Division. The outcome variable, COVID-19 vaccination intention, was

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categorized into 2 groups: those who intended to receive the vaccine, and those who did not. This categorization was based on responses to 2 questions in the KCHS: (1) "Have you been vaccinated against COVID-19?" (yes/no) and (2) "Are you willing to be vaccinated against COVID-19?" (very likely, likely, not likely, very unlikely). Responses of "very likely" and "likely" were categorized as likely to get vaccinated. At the time of the survey, vaccination opportunities were provided according to government policy priorities. Vaccination intention was defined as including individuals who had already been vaccinated or intended to get vaccinated in the future, while non-intention included those who had not been vaccinated and had no intention of doing so.

The following individual- and household-level factors influencing vaccination intention were selected based on a literature review and additional variables of interest to the researchers [2–6]: Individual-level factors included sociodemographic variables (age, sex, social assistance recipients, education level, economic activity status, attitude toward social assets, understanding of health information), health-related variables (subjective health level, subjective obesity level, history of annual flu vaccination, health exam history in the past 2 years), and COVID-19-related variables (staying home when sick, concern about COVID-19 infection, subjective score of COVID-19's impact on daily life, and income change due to COVID-19). Age was categorized into 3 groups: 19–49, 50–64, and ≥65. Education level was divided into middle school or less, high school, and bachelor's degree or higher. Attitudes toward social assets were classified into quartiles by summing the scores of 7 items: trust in neighbors, help from neighbors, youth safety level, natural environment, living environment, public transportation status, and medical facility status. Each item was measured on a dichotomous scale (1=dissatisfaction, 2=satisfaction). Understanding of health information was categorized as very difficult, difficult, easy, and very easy. Subjective health level was categorized as poor, average, and good. Subjective obesity level was divided into obese, normal weight, and thin. Concern about COVID-19 infection was divided into not concerned, somewhat concerned, and concerned. The subjective score of COVID-19's impact on daily life was measured in 10-point increments out of 100 and classified into ≤30 points, 40–60 points, and ≥70 points. Household-level factors included monthly household income, marital status, children living together, spouse living together, and number of household members. Marital status was categorized as married, divorced or widowed, and unmarried.

Community-level factors included residential city type, population density, proportion of the elderly, flu vaccination rate, cumulative number of confirmed COVID-19 cases, cumulative number of COVID-19 deaths, concern rate for COVID-19 infection, practice rate for social distancing, COVID-19 vaccination rate, and number of COVID-19 vaccination centers. Residential city type was divided into 3 categories: metropolitan city, small or medium-sized city, and rural county. Other community-level factors, except for residential city type, were classified into quartiles based on the distribution of the 255 PHCs.

Data Analysis

Data analysis was conducted using STATA/SE ver. 17 (StataCorp.) while accounting for the complex sample design. Associations between individual-, household-, and community-level factors and vaccination intention were analyzed using the chi-square test. To identify factors influencing vaccination intention at the individual, household, and community levels, multilevel analysis was employed using a random intercept model that did not consider the variance of the regression coefficient. First, the need for multilevel analysis was confirmed by checking whether the community-level variance was significant through the null model (empty model). Next, the effect of individual-level variables on vaccination intention was examined using the individual-level model (model 1), and the effect of household-level variables was verified using the individual-household-level model (model 2). Finally, the effect of community-level variables was assessed in the individual-household-community-level model (model 3) while controlling for individual- and household-level variables. The explanatory variables included in each model were selected based on the results of univariate analysis, a review of previous research, and consideration of multicollinearity between variables. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) were obtained for all predictors retained in each model. Statistical significance was determined at a p-value of <0.05.

The Institutional Review Board (IRB) of Kyungpook National University Hospital approved the study protocol and waived the requirement for informed consent (IRB No. 2023-01-013).

Results

Individual, Household and Community Factors Affecting Intention for COVID-19 Vaccination

Individual factors

By age group, the intention to receive the COVID-19 vaccine was highest among individuals aged 50 to 64 (98.0%), followed by those aged 65 and older (97.1%) and those aged 19 to 49 (94.6%). Vaccine intention was higher among individuals who were not social assistance recipients (96.1%) and those with active economic activity status (96.7%) ($p<0.001$). Regarding education level, the highest intention was

observed among those with a middle school education or less (96.9%), followed by those with a bachelor's degree or higher (96.2%) and high school graduates (95.6%). In terms of understanding health information, the highest intention was among those who found it easy (96.2%), followed by those who found it difficult (95.9%), very easy (95.7%), and very difficult (92.6%). For attitudes toward social assets, higher quartiles were associated with a higher proportion of individuals with vaccination intention ($p < 0.001$). In terms of subjective health level, the proportion of individuals with vaccination intention was highest among those with an average health level (96.4%), followed by those with a good health level (96.2%) and a poor health level (93.5%). For subjective obesity level, the proportion was highest among those who were thin (96.4%), followed by those with a normal weight (96.2%) and those who were obese (94.2%) ($p < 0.001$). The proportion of individuals with vaccination intention was higher among those with a history of annual flu vaccination (97.9%) and those who had a health exam in the past 2 years (97.0%) ($p < 0.001$). Concern about COVID-19 infection was higher among those who were somewhat concerned (96.3%) and concerned (96.3%) compared to those who were not concerned (93.8%). Additionally, a higher subjective score of COVID-19's impact on daily life was associated with a higher proportion of individuals with vaccination intention ($p < 0.001$) (Table 1).

Household factors

For monthly household income, the proportion of individuals with vaccination intention was highest among those with an income of 2–2.99 million Korean won (KRW) (97.3%), followed by those with an income of 4 million KRW or more (96.6%), 1–1.99 million KRW (96.1%), 3–3.99 million KRW (95.8%), and less than 1 million KRW (95.4%) ($p < 0.001$). By marital status, the proportion was highest among married individuals (96.8%), followed by those who were divorced or widowed (96.3%) and unmarried (93.9%) ($p < 0.001$). The proportion of individuals with vaccination intention was also higher among those living with a spouse (96.7%) ($p < 0.001$) (Table 2).

Community factors

The proportion of individuals with vaccination intention was generally higher with increased rates of practicing social distancing (Q4, 96.4%; Q2, 96.1%; Q3, 96.0%; Q1, 95.4%) ($p = 0.004$), while other variables did not show significant differences (Table 3).

Factors Affecting Intention to Receive the COVID-19 Vaccine

To identify individual, household, and community-level factors influencing the intention to receive the COVID-19 vaccine, multilevel analysis was conducted, with the results presented in Tables 4 and 5. First, in the null model, which did not include explanatory variables, the variance in vaccination intention between communities was estimated to determine whether differences existed across communities. The results showed statistically significant variances at both the household and community levels, indicating the presence of group-level variability. This suggests that community-level effects on vaccination intention exist, highlighting the need to estimate these effects through multilevel analysis.

In model 1, the community-level intraclass correlation coefficient (ICC) was 0.019, and the household residual ICC was 0.149, showing no change compared to the null model. However, in model 2, the community ICC decreased to 0.013, and in model 3, it further decreased to 0.007, while the household ICC decreased to 0.143. This indicates that including individual, household, and community-level variables explained additional variability in vaccination intention across communities and households.

At the individual level, all variables showed significant differences. The intention to receive the COVID-19 vaccine was higher among older individuals, specifically those aged 65 and older (aOR, 3.21; 95% CI, 2.92–3.53) and those aged 50 to 64 years (aOR, 2.53; 95% CI, 2.35–2.73). It was also higher among individuals with an active economic activity status (aOR, 1.80; 95% CI, 1.70–1.89) and those who found understanding health information easy (aOR, 1.93; 95% CI, 1.72–2.17), very easy (aOR, 1.85; 95% CI, 1.63–2.10), or difficult (aOR, 1.76; 95% CI, 1.56–1.99) compared to those who found it very difficult. Attitudes toward social assets were positively associated with higher quartiles (Q4: aOR, 1.58; 95% CI, 1.47–1.69; Q3: aOR, 1.37; 95% CI, 1.28–1.47; Q2: aOR, 1.22; 95% CI, 1.14–1.30).

Regarding the subjective health level, higher vaccination intention was found for those with good (aOR, 2.24; 95% CI, 2.09–2.41) or average health (aOR, 2.11; 95% CI, 1.97–2.35) compared to poor health. Subjective obesity level showed higher intention among those who were thin (aOR, 1.62; 95% CI, 1.52–1.74) or of normal weight (aOR, 1.33; 95% CI, 1.25–1.42) compared to those who were obese. Vaccination intention was also higher among individuals who had a health exam history in the past 2 years (aOR, 2.11; 95% CI, 2.00–2.22) and increased with higher subjective scores of COVID-19's impact on daily life (≥70 points: aOR, 1.28; 95% CI, 1.20–1.37; 40–60 points: aOR, 1.25; 95% CI, 1.18–1.33). Concern about COVID-19 infection was associated with higher vaccination intention among those who were concerned (aOR, 1.99; 95% CI, 1.87–2.12) or somewhat concerned (aOR, 1.74; 95% CI, 1.62–1.87) compared to those who were not concerned. At

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Table 1. Individual characteristics of study subjects

Variable	Category	Vaccination non-intention	Vaccination intention	Total	p[a]
Total		7,874 (4.0)	221,342 (96.0)	229,216	
Age (y)	19–49	4,471 (5.4)	81,479 (94.6)	85,950	<0.001
	50–64	1,399 (2.0)	67,384 (98.0)	68,783	
	≥65	2,004 (2.9)	72,479 (97.1)	74,483	
Sex	Female	4,231 (4.1)	120,492 (95.9)	124,723	0.0736
	Male	3,643 (3.9)	100,850 (96.1)	104,493	
Social assistance recipient	No	7,250 (3.9)	212,406 (96.1)	219,656	<0.001
	Yes	624 (6.4)	8,936 (93.6)	9,560	
Education level	Middle school or less	2,077 (3.1)	73,406 (96.9)	75,483	<0.001
	High school	3,775 (4.4)	96,122 (95.6)	99,897	
	Bachelor's degree or higher	2,022 (3.8)	51,814 (96.2)	53,836	
Economic activity status	None	4,160 (5.3)	81,585 (94.7)	85,745	<0.001
	Active	3,714 (3.3)	139,757 (96.7)	143,471	
Attitudes toward social assets	Q1	2,779 (5.5)	53,614 (94.5)	56,393	<0.001
	Q2	1,920 (4.2)	50,055 (95.8)	51,975	
	Q3	1,675 (3.2)	53,984 (96.8)	55,659	
	Q4	1,499 (2.5)	63,689 (97.5)	65,188	
Understanding health information	Very difficult	422 (7.4)	5,457 (92.6)	5,879	<0.001
	Difficult	1,626 (4.1)	44,734 (95.9)	46,360	
	Easy	4,090 (3.8)	122,995 (96.2)	127,085	
	Very easy	1,736 (4.3)	48,156 (95.7)	49,892	
Subjective health level	Poor	2,139 (6.5)	36,666 (93.5)	38,805	<0.001
	Average	2,797 (3.6)	94,583 (96.4)	97,380	
	Good	2,938 (3.8)	90,093 (96.2)	93,031	
Subjective obesity level	Obese	1,885 (5.8)	37,203 (94.2)	39,088	<0.001
	Normal weight	3,327 (3.8)	100,717 (96.2)	104,044	
	Thin	2,662 (3.6)	83,422 (96.4)	86,084	
History of annual flu vaccination	No	5,539 (6.0)	87,476 (94.0)	93,015	<0.001
	Yes	2,335 (2.1)	133,866 (97.9)	136,201	
Heath exam history in the past 2 years	No	3,776 (6.7)	53,828 (93.3)	57,604	<0.001
	Yes	4,098 (3.0)	167,514 (97.0)	171,612	
Ability to stay home when sick	Possible	7,563 (4.0)	213,588 (96.0)	221,151	0.287
	Impossible	311 (4.3)	7,754 (95.7)	8,065	
Concern about COVID-19 infection	Not concerned	1,856 (6.2)	30,985 (93.8)	32,841	<0.001
	Somewhat concerned	1,785 (3.7)	50,067 (96.3)	51,852	
	Concerned	4,233 (3.7)	140,290 (96.3)	144,523	
Subjective score of COVID-19's impact on daily life	≤30 Point	1,741 (5.2)	37,432 (94.7)	39,173	<0.001
	40–60 Point	3,292 (3.9)	98,641 (96.1)	101,933	
	≥70 Point	2,841 (3.4)	85,269 (96.5)	88,110	
Income change due to COVID-19	No	5,055 (3.9)	143,502 (96.1)	148,557	0.0873
	Yes	2,819 (4.2)	77,840 (95.8)	80,659	

Data are presented as *n* (weighted %).
[a]*p*-value was calculated using the Pearson chi-square test with the svy command.

the household level, the intention to receive the vaccine was higher in households with 4 or more members compared to those with only one member (aOR, 1.16; 95% CI, 1.05–1.28). It was also higher among those with a monthly household income of 4 million KRW or more compared to those with an income below 1 million KRW (aOR, 1.22; 95% CI, 1.11–1.35). No significant associations were found for other variables.

At the community level, higher vaccination intention was associated with a higher flu vaccination rate in Q4 compared to Q1 (aOR, 1.13; 95% CI, 1.01–1.26), greater concern about COVID-19 infection (Q4 compared to Q1: aOR, 1.13; 95% CI, 1.01–1.25; Q3: aOR, 1.11; 95% CI, 1.01–1.25), and higher COVID-19

Table 2. Household-level characteristics of the study subjects

Variable	Category	Vaccination non-intention	Vaccination intention	Total	p[a]
Total		7,874 (4.0)	221,342 (96.0)	229,216	
Monthly household income (10,000 KRW)	<100	1,355 (4.6)	32,556 (95.4)	33,911	<0.001
	100–199	1,183 (4.9)	23,248 (96.1)	24,431	
	200–299	1,209 (4.7)	33,239 (97.3)	34,448	
	300–399	1,198 (4.2)	50,517 (95.8)	51,715	
	≥400	2,929 (3.4)	90,782 (96.6)	93,711	
Marital status	Married	4,128 (3.2)	147,364 (96.8)	151,492	<0.001
	Divorced or widowed	1,367 (3.7)	36,803 (96.3)	38,170	
	Unmarried	2,379 (6.1)	17,175 (93.9)	39,554	
Children living together	No	6,119 (4.0)	177,986 (96.0)	184,105	0.8986
	Yes	1,764 (4.0)	43,356 (96.0)	45,120	
Spouse living together	No	3,979 (5.2)	81,143 (94.8)	85,122	<0.001
	Yes	3,895 (3.3)	140,199 (96.7)	144,094	
No. of household members	1 Person	1,582 (4.5)	38,372 (95.5)	39,954	0.0551
	2–3 Persons	4,356 (4.0)	130,683 (96.0)	135,039	
	≥4 Persons	1,936 (3.8)	52,287 (96.2)	54,223	

Data are presented as *n* (weighted %).
KRW, Korean won.
[a]*p*-value is calculated using the Pearson chi-square test with the svy command.

vaccination rates (Q3 compared to Q1: aOR, 1.33; 95% CI, 1.21–1.45; Q4: aOR, 1.18; 95% CI, 1.06–1.32; Q2: aOR, 1.12; 95% CI, 1.02–1.23).

Discussion

This study aimed to comprehensively examine how individual, household, and community characteristics influence individuals' intention to receive the COVID-19 vaccine through multilevel analysis. While previous studies have primarily focused on individual factors, this study is unique in its simultaneous analysis of various factors, including household and community characteristics, that impact vaccine intention. The results confirm that not only individual characteristics but also household and community characteristics play significant roles in shaping vaccination intentions. This finding suggests that the decision to get vaccinated is not determined solely by individual factors but is also influenced by the social context of the household and community in which the individual resides. Therefore, when developing vaccination recommendation policies and campaigns, it is essential to adopt a socio-ecological approach that considers not only individual characteristics but also household- and community-level factors. This study provides valuable foundational data for creating more effective and comprehensive vaccination policies.

Individual characteristics, including age, sex, education level, understanding of health information, social assistance recipient status, economic activity status, attitudes toward social assets, subjective health level, subjective obesity level, health exam history, concern about COVID-19 infection, and subjective scores of COVID-19's impact on daily life, showed significant associations with vaccination intention.

The observation that vaccination intention increases with age is consistent with previous studies [11–13] and can be explained by several factors. Initially, vaccination policies targeted older adults [11], and outreach efforts and public health messages specifically aimed at this population have further emphasized the importance of vaccinations [14]. Furthermore, the risk of severe illness and death from COVID-19 infection is reported to be higher in older adults [15]. Therefore, older adults have demonstrated a higher willingness to be vaccinated against COVID-19, driven by their heightened perception of the threat of severe illness [16].

It was also observed that individuals with lower understanding of health information were less likely to intend to get vaccinated, which aligns with existing research linking lower understanding of health information to reduced vaccination intention [17]. Since understanding of health information generally correlates with educational attainment, it may seems counterintuitive that individuals with higher education levels exhibit lower vaccination intention. Howeve, this discrepancy could stem from factors such as differing perceptions of vaccine safety and necessity among highly educated individuals. Previous studies have shown that higher education is typically linked with greater COVID-19 vaccination intention, while older adults are more likely to have lower education levels. This suggests that lower-educated older adults, who were mandated to

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Table 3. Community level characteristics for study subjects

Variable	Category	Vaccination non-intention	Vaccination intention	Total	p[a)]
Total		7,874 (4.0)	221,342 (96.0)	229,216	
Residential city type	Metropolitan city	2,654 (4.1)	65,758 (95.9)	68,412	0.1703
	Small/medium-sized city	3,228 (3.9)	86,139 (96.1)	89,367	
	Rural county	1,992 (3.2)	69,445 (96.8)	71,437	
Population density	Q1	1,845 (4.2)	55,719 (95.8)	57,564	0.8111
	Q2	1,951 (3.9)	59,403 (96.1)	61,354	
	Q3	2,039 (4.1)	52,647 (95.9)	54,686	
	Q4	2,039 (4.0)	53,573 (96.0)	55,612	
Proportion of older adults	Q1	2,134 (3.9)	58,803 (96.1)	60,937	0.635
	Q2	2,139 (4.2)	55,582 (95.8)	57,721	
	Q3	1,885 (3.8)	54,397 (96.2)	56,282	
	Q4	1,616 (4.0)	52,560 (96.0)	54,176	
Vaccination rate for flu	Q1	2,270 (4.1)	56,401 (95.9)	58,671	0.1621
	Q2	2,189 (4.0)	55,033 (96.0)	57,222	
	Q3	1,891 (3.7)	54,700 (96.3)	56,591	
	Q4	1,524 (3.2)	55,208 (96.8)	56,732	
No. of cumulative confirmed COVID-19 cases	Q1	1,573 (3.0)	55,793 (97.0)	57,366	0.2297
	Q2	1,973 (3.7)	55,399 (96.3)	57,372	
	Q3	2,158 (4.0)	55,144 (96.0)	57,302	
	Q4	2,154 (4.0)	54,154 (96.0)	56,308	
No. of cumulative COVID-19 deaths	Q1	1,629 (3.4)	55,781 (96.6)	57,410	0.2297
	Q2	1,915 (3.6)	55,490 (96.4)	57,405	
	Q3	2,114 (4.1)	54,913 (95.9)	57,027	
	Q4	2,200 (4.0)	54,306 (96.0)	56,506	
Proportion of individuals concerned about COVID-19 infection	Q1	2,294 (4.3)	57,857 (95.7)	60,151	0.1601
	Q2	1,967 (4.0)	53,835 (96.0)	55,802	
	Q3	1,921 (3.8)	55,817 (96.2)	57,738	
	Q4	1,692 (3.7)	53,833 (96.3)	55,525	
Rate of practicing social distancing	Q1	2,217 (4.6)	55,220 (95.4)	57,437	0.004
	Q2	1,914 (3.9)	57,124 (96.1)	59,038	
	Q3	2,116 (4.0)	57,546 (96.0)	59,662	
	Q4	1,692 (3.6)	51,452 (96.4)	53,144	
COVID-19 vaccination rate	Q1	3,059 (4.3)	74,029 (95.7)	77,088	0.085
	Q2	1,832 (4.0)	50,482 (96.0)	52,314	
	Q3	1,706 (3.8)	52,611 (96.2)	54,317	
	Q4	1,277 (3.5)	44,220 (96.5)	45,497	
No. of COVID-19 vaccination centers	Q1	2,099 (4.2)	58,827 (95.8)	60,926	0.447
	Q2	2,196 (4.0)	59,545 (96.0)	61,741	
	Q3	2,155 (4.0)	62,508 (96.0)	64,663	
	Q4	1,424 (3.8)	40,462 (96.2)	41,886	

Data are presented as *n* (weighted %).
[a)]*p*-value is calculated using the Pearson chi-square test with the svy command.

be vaccinated at the time of the survey, may have already been vaccinated regardless of their personal intentions. Consequently, these groups may have been classified as having vaccination intention according to the study's operational definition, or it may be due to the fact that higher education levels correspond to a more accurate understanding of information [18]. Therefore, from an educational standpoint, it is essential to enhance accessibility by providing clear and straightforward information about the effectiveness, safety, and administration of vaccines to vulnerable populations.

The finding that individuals with no economic activity status or those receiving social assistance have lower vaccination intentions aligns with previous research indicating that socially disadvantaged groups tend to have lower vaccination

Table 4. Factors affecting COVID-19 vaccination intention according to multilevel analysis-1

Variable	Category	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Level 1. Individual factors					
Age (y)	50-64 (ref: 19–49)		2.45 (2.29–2.63)	2.53 (2.35–2.76)	2.53 (2.35–2.73)
	≥65 (ref: 19–49)		2.98 (2.74–3.26)	3.26 (2.98–3.57)	3.21 (2.92–3.53)
Sex	Male (ref: female)		0.94 (0.89–0.99)	0.95 (0.91–0.99)	0.95 (0.90–0.99)
Social assistance recipient	Yes (ref: no)		0.70 (0.64–0.78)	0.75 (0.68–0.83)	0.76 (0.68–0.84)
Education level	High school (ref: middle school or less)		0.94 (0.87–1.02)	0.91 (0.84–0.99)	0.92 (0.85–0.99)
	Bachelor's degree or higher (ref: middle school or less)		0.85 (0.80–0.94)	0.81 (0.74–0.89)	0.82 (0.75–0.90)
Economic activity status	Active (ref: none)		1.83 (1.73–1.92)	1.80 (1.71–1.90)	1.80 (1.70–1.89)
Understanding health information	Difficult (ref: very difficult)		1.74 (1.54–1.96)	1.75 (1.55–1.98)	1.76 (1.56–1.99)
	Easy (ref: very difficult)		1.90 (1.69–2.14)	1.91 (1.70–2.16)	1.93 (1.72–2.17)
	Very easy (ref: very difficult)		1.85 (1.63–2.10)	1.86 (1.64–2.11)	1.85 (1.63–2.10)
Attitudes toward social assets	Q2 (ref: Q1)		1.23 (1.15–1.31)	1.26 (1.14–1.30)	1.22 (1.14–1.30)
	Q3 (ref: Q1)		1.39 (1.30–1.49)	1.37 (1.28–1.46)	1.37 (1.28–1.47)
	Q4 (ref: Q1)		1.61 (1.50–1.73)	1.59 (1.48–1.71)	1.58 (1.47–1.69)
Subjective health level	Average (ref: poor)		2.13 (1.99–2.27)	2.10 (1.97–2.25)	2.11 (1.97–2.25)
	Good (ref: poor)		2.28 (2.12–2.45)	2.24 (2.09–2.40)	2.24 (2.09–2.41)
Subjective obesity level	Normal weight (ref: obese)		1.34 (1.25–1.42)	1.33 (1.25–1.42)	1.33 (1.25–1.42)
	Thin (ref: obese)		1.63 (1.52–1.74)	1.62 (1.52–1.73)	1.62 (1.52–1.74)
Heath exam history in the past 2 years	Yes (ref: no)		2.13 (2.02–2.24)	2.10 (1.71–1.90)	2.11 (2.00–2.22)
Subjective score of COVID-19's impact on daily life	40–60 Points (ref: ≤30 points)		1.27 (1.19–1.35)	1.26 (1.18–1.34)	1.25 (1.18–1.33)
	≥70 Points (ref: ≤30 points)		1.30 (1.22–1.39)	1.29 (1.21–1.38)	1.28 (1.20–1.37)
Concern about COVID-19 infection	Somewhat concerned (ref: not concerned)		1.75 (1.63–1.88)	1.74 (1.62–1.87)	1.74 (1.62–1.87)
	Concerned (ref: not concerned)		2.01 (1.89–2.14)	1.99 (1.87–2.12)	1.99 (1.87–2.12)

Data are presented as adjusted odds ratio (95% confidence interval).
COVID-19, coronavirus disease 2019; ref, reference.
[a]Null model, [b]individual model, [c]individual-household model (2-level), [d]individual-household-community model (3-level).

intentions [19,20]. The disparity in vaccination intentions from a socioeconomic perspective leads to differential outcomes in the practice of infection prevention measures, subsequently increasing the risk of COVID-19 infection among different groups [21]. As noted in previous research, socioeconomically vulnerable groups face higher COVID-19 infection risks, lower medical accessibility, and increased risk of severe illness and death. Consequently, lower socioeconomic conditions contribute to disproportionately negative effects on infection risk, treatment, and mortality, exacerbating the burden on vulnerable groups and leading to increased health inequities [19,22]. Therefore, it is crucial to strengthen safety nets for socially vulnerable groups during crises like COVID-19, ensuring that these populations are better protected and supported to mitigate the heightened risks they face.

It was found that a more positive attitude toward social assets was associated with a greater intention to get vaccinated. Although no studies have directly examined the relationship between social assets and vaccination intention, existing research indicates that social assets are linked to positive changes in health status [23,24]. Therefore, it can be interpreted that a more positive attitude toward social assets positively influences vaccination intention. Furthermore, strengthening social assets and building trust in everyday life can help communities respond more effectively to infectious disease crises. A strong foundation of social trust and support networks enhances cooperation and compliance with public health measures, contributing to a more resilient and coordinated response during pandemics. These efforts not only improve crisis management but also support higher vaccination rates, as individuals in trusted and well-connected communities are more likely to accept and participate in vaccination programs.

The finding that higher subjective health levels are associated with greater vaccination intention is consistent with previous research [25]. A likely explanation for this association is that individuals with very poor health may have concerns about the safety of the COVID-19 vaccine and potential side effects [26].

Therefore, it is necessary to provide reliable information about the effectiveness and safety of vaccination to groups in need of health management. Additionally, there is a need for intervention strategies and practical support systems

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Table 5. Factors affecting COVID-19 vaccination intention by multilevel analysis-2

Variable	Category	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
Level 2. Household factors					
Spouse living together	Yes (ref: no)			1.03 (0.97–1.10)	1.03 (0.97–1.10)
Children living together	Yes (ref: no)			0.95 (0.88–1.02)	0.95 (0.88–1.02)
No. of household members	2–3 Persons (ref: 1 person)			0.97 (0.90–1.04)	0.97 (0.90–1.05)
	≥4 Persons (ref: 1 person)			1.16 (1.05–1.27)	1.16 (1.05–1.28)
Monthly household income (unit. 10,000 KRW)	100–199 (ref: <100)			1.00 (0.91–1.10)	1.00 (0.91–1.10)
	200–299 (ref: <100)			1.01 (0.91–1.11)	1.01 (0.92–1.12)
	300–399 (ref: <100)			1.03 (0.93–1.14)	1.03 (0.93–1.15)
	≥400 (ref: <100)			1.22 (1.11–1.35)	1.22 (1.11–1.35)
Level 3. Community factors					
Vaccination rate for flu	Q2 (ref: Q1)				0.95 (0.87–1.05)
	Q3 (ref: Q1)				1.04 (0.95–1.15)
	Q4 (ref: Q1)				1.13 (1.01–1.26)
Proportion of individuals concerned about COVID-19 infection	Q2 (ref: Q1)				1.05 (0.95–1.15)
	Q3 (ref: Q1)				1.11 (1.01–1.23)
	Q4 (ref: Q1)				1.13 (1.01–1.25)
Practice rate for social distancing	Q2 (ref: Q1)				1.09 (0.99–1.21)
	Q3 (ref: Q1)				1.06 (0.96–1.17)
	Q4 (ref: Q1)				1.07 (0.96–1.19)
COVID-19 vaccination rate	Q2 (ref: Q1)				1.12 (1.02–1.23)
	Q3 (ref: Q1)				1.33 (1.21–1.45)
	Q4 (ref: Q1)				1.18 (1.06–1.32)
Variance (community)		0.074±0.011	0051±0.009	0.051±0.009	0.028±0.007
Variance (household)		0.497±0.034	0.530±0.037	0.525±0.037	0.523±0.037
Chi-square		617.0	504.8	500.2	414.86
p-value		<0.001	<0.001	<0.001	<0.001
Residual ICC[e] (community)		0.019	0.019	0.013	0.007
Residual ICC (household)		0.149	0.149	0.149	0.143

Data are presented as adjusted odds ratio (95% confidence interval) or mean±standard deviation.
COVID-19, coronavirus disease 2019; ref, reference; KRW, Korean won.
[a]Null model, [b]individual model, [c]individual-household model (2-level), [d]individual-household-community model (3-level), [e]Intraclass correlation coefficient.

that can facilitate actual vaccination. Implementing clear support measures to address potential side effects following vaccination would also be beneficial.

The finding that individuals who perceive themselves as thin had higher vaccination intentions than those who perceived themselves as obese is inconsistent with some previous studies examining the relationship between body mass index and vaccination intention [27]. This discrepancy may be due to differences between perceived obesity and actual obesity levels, as identified in prior research [27]. It is also possible that those who perceive themselves as obese are more concerned about vaccine side effects, which may lead them to avoid vaccination. Further research is needed to explore these possibilities.

The observation that individuals who have undergone a health exam in the past 2 years have higher vaccination intentions suggests that a general interest in one's health status can influence vaccination practices [28]. Providing opportunities for individuals to assess their basic health status and fostering an environment that encourages ongoing health management can help promote vaccination.

The finding that individuals who were concerned or somewhat concerned about COVID-19 infection had higher vaccination intentions than those who were not concerned is consistent with previous research [20]. Risk perception is a crucial factor influencing risk behavior, and individuals with lower risk perception tend to engage in riskier behaviors or reduce preventive actions [29]. A lack of awareness about the risk of COVID-19 infection can lead to vaccine refusal, so educational interventions to improve risk perception are necessary. However, overstating the risk of infection can lead to fear and anxiety, potentially causing individuals to disengage from public health measures or distrust health information [30]. Therefore, it is essential to provide accurate and balanced information about the risks of infection, emphasizing realistic threats without causing unnecessary

alarm. Clear and factual communication can help improve public understanding, support informed decision-making, and promote vaccination.

The finding that a higher subjective COVID-19 daily life impact score was associated with greater vaccination intention aligns with previous research, which suggests that individuals who view COVID-19 as a serious threat are more likely to get vaccinated [11]. Shmueli [31] defined perceived severity as an individual's belief about the difficulties a disease may cause medically and socially, such as pain or missed workdays. In this context, the subjective COVID-19 daily life impact score can be considered an important predictor of COVID-19 vaccination intention.

In terms of household characteristics, monthly household income and the number of household members showed a significant association with vaccination intention. Individuals from households with 4 or more members were found to have a higher likelihood of vaccination, suggesting that family members may influence the decision to get vaccinated [32]. Previous research indicates that fear or anxiety related to new infectious diseases often arises from concerns about the risk of infection for oneself or family members [33,34]. Additionally, the worry of being a potential transmission route to other family members can increase vaccination intention, as individuals may feel responsible for protecting those around them. This may explain the association between having a larger number of family members and a higher level of vaccination intention. Promoting vaccination through family-oriented strategies could thus be an effective approach.

It was found that individuals with a monthly household income of 4 million KRW or more were more likely to intend to get vaccinated compared to those with an income below 1 million KRW, but no significant results were observed in other income groups. A possible explanation for this may be that socioeconomic factors affect an individual's ability to engage in health-promoting and disease-preventing behaviors and to effectively utilize healthcare services [22]. Higher household income not only reflects better economic status, but may also indicate a greater number of economically active individuals within the household. Therefore, the combined impact of household income and concerns about infection among economically active members might exert a complex influence on vaccination intention.

In terms of community factors, higher COVID-19 and influenza vaccine coverage rates in an area, along with greater concerns about COVID-19 infection, were associated with an increased likelihood of vaccination. This is largely due to the formation of a distinct social identity within vaccination groups, where individuals align their attitudes and behaviors with those of the group [35]. Studies have demonstrated a positive correlation between the intention to vaccinate and the vaccination rates among friends and family, underscoring the significant role of social influence in shaping vaccination behaviors [36]. Observing community members getting vaccinated without experiencing adverse effects diminishes personal hesitations and motivates others to do the same. Higher community vaccination rates enhance the perception of safety and reinforce social norms, making individuals feel more comfortable and supported in their decision to vaccinate [37]. Networking with others who accept the COVID-19 vaccine is a strong predictor of vaccination intention, as it reinforces the perception of vaccination as a normative and safe behavior [38]. Conversely, the public goods dilemma occurs when some individuals opt out of vaccination, relying on the high vaccination rates of others to provide sufficient herd immunity [39]. This behavior reflects a tendency to avoid perceived costs, such as side effects, while still benefiting from community protection. This underscores the importance of fostering positive social influence and engaging the community to promote higher vaccination rates, particularly among hesitant populations. Encouraging community involvement and addressing concerns with accurate information can help mitigate hesitancy and ensure broader vaccine uptake.

This study has several limitations. First, a substantial number of participants were already vaccinated in accordance with government policies at the time of the survey. This precludes a uniform assessment of vaccination intentions across all participants, potentially limiting the generalizability of the study results. Second, there is a time discrepancy of up to 5 months in the measurement of individual, household, and some community factors. The KCHS, which provided data on individual and household factors, was conducted from August to October 2021, while demographic factors such as the aging rate and population density were measured in December 2021. Third, the study did not consider factors such as knowledge and attitudes toward COVID-19 or vaccines, which could influence vaccination intention. Fourth, common issues associated with survey-based research, such as non-response bias and social desirability bias, cannot be ruled out, and thus the results should be interpreted with caution. Finally, since the data were collected in 2021, the results may not fully reflect subsequent changes in the COVID-19 situation or related policies. Nevertheless, we believe the findings remain significant as they capture the patterns of vaccination intention during the early stages of the COVID-19 vaccine rollout.

Despite these limitations, this study's strength lies in its

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multilevel analysis of individual, household, and community-level factors, which distinguishes it from previous research that focused solely on individual factors affecting COVID-19 vaccination intention. The results suggest that promoting COVID-19 vaccination requires a social-ecological approach that considers not just individual factors but also household and community networks. Additionally, in pandemic crisis situations, it is crucial to develop tailored policies for high-risk groups identified through this study to protect the health rights of socially vulnerable populations.

Conclusion

The multilevel analysis of this study demonstrated that variables at the individual, household, and community levels affected the intention to receive the COVID-19 vaccine. Therefore, strategies for encouraging individual COVID-19 vaccination are likely to be more effective when combined with household and community-level approaches. It is essential to integrate both individual and social health factors into vaccination policies to reflect these interconnected elements.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Kyungpook National University Hospital (No. 2023-01-013) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Availability of Data

The datasets analyzed during the current study are available on the websites of Community Health Survey (https://chs.kdca.go.kr).

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Original Article

Factors influencing satisfaction with medical services in medically underserved populations: an analytical cross-sectional study at a free medical clinic in the Republic of Korea

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ABSTRACT

Objectives: This study aimed to explore factors influencing satisfaction with medical services among medically underserved populations at the free medical clinic, providing data to improve free medical services for these populations.

Methods: We employed a descriptive correlational study design involving 112 individuals (aged 19 years and older) from medically underserved populations who visited the clinic. Data were collected through face-to-face surveys from September to October 2023, and statistical analyses (t-tests, analysis of variance, Pearson correlation, and hierarchical multiple regression) were used to identify key predictors of satisfaction.

Results: Perceived support from healthcare providers emerged as the strongest predictor of satisfaction with medical services, demonstrating a significant positive association. While social support was positively correlated with perceived support from healthcare providers, it did not independently predict satisfaction.

Conclusion: These findings underscore the importance of healthcare provider and social support in increasing satisfaction with medical services among medically underserved populations. Developing tailored healthcare programs and specialized healthcare provider training are essential strategies to improve healthcare access and outcomes for these vulnerable groups.

Keywords: Health services; Ill-housed persons; Patient satisfaction; Primary health care; Professional-patient relations

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Introduction

The late 1990s economic crisis in the Republic of Korea precipitated widespread unemployment, dramatically increasing the number of individuals experiencing homelessness and contributing to the expansion of the urban poor, collectively described as medically underserved populations [1]. Economic instability and growing socioeconomic inequality further exacerbated labor market polarization, leading to an increase in the impoverished population [2]. Although the Republic of Korea's social welfare system provides shelters and meal assistance, healthcare services remain inadequate. Many individuals experiencing homelessness lack the necessary documentation or stable residency required for coverage under the National Health Insurance program, restricting their ability to obtain essential medical care [3].

Despite a 21% decline in the number of people experiencing homelessness in the Republic of Korea from 2016 to 2021, substantial challenges persist. Urban centers such as Seoul, where access to healthcare remains a major issue, are particularly affected [4]. Internationally, similar barriers exist, with those experiencing homelessness facing economic hardship, stigma, and systemic inefficiencies that impede healthcare utilization [5]. Even in countries with universal healthcare systems, administrative hurdles and discrimination restrict access [6,7].

The coronavirus disease 2019 (COVID-19) pandemic exacerbated healthcare disparities, increasing the proportion of individuals avoiding medical care despite being ill [4]. Many public hospitals were repurposed for the COVID-19 response, further limiting healthcare access for marginalized groups [3]. Studies have highlighted financial instability, stigma, and negative healthcare experiences as key barriers to medical service utilization, which result in delayed treatments and preventable hospitalizations [5,6,8,9].

Traditional healthcare systems are designed for populations with stable residency and health insurance, which creates barriers for people experiencing homelessness [10,11]. Non-governmental organizations help bridge these gaps by providing healthcare outreach services that facilitate access and reduce emergency department visits [12,13]. Research indicates that integrating community-based programs with formal healthcare systems significantly improves health outcomes [12].

Consequently, the Republic of Korea has developed community-based initiatives to improve healthcare access for individuals experiencing homelessness. The free medical clinic, established in 1997, has consistently provided free healthcare services, including mobile outreach initiatives and regional support. Since March 2021, it has offered weekly free medical services in Seoul, establishing it as one of the few clinics to continuously serve medically underserved populations [4].

This study aims to analyze factors influencing satisfaction with medical services at the free medical clinic, as well as to provide foundational data to support free healthcare services for medically underserved populations. By identifying key determinants of patient satisfaction, this research seeks to improve healthcare accessibility and quality for marginalized groups and to offer insights for policymakers and healthcare providers.

HIGHLIGHTS

- Support from healthcare providers emerged as the strongest predictor of satisfaction with medical services among people experiencing homelessness and the urban poor.
- Social support and perceived support from healthcare providers demonstrated significant positive correlations with overall satisfaction.
- High satisfaction levels were reported for medical services, emphasizing the importance of tailored healthcare programs and provider training.
- Expanding free clinic services to include dental and ophthalmology specialties could increase accessibility and satisfaction.
- Integrated educational programs on chronic disease and oral health management are essential to address unmet needs and improve health outcomes.

Materials and Methods

Study Design

This analytical cross-sectional study examines factors influencing patient satisfaction with medical services at the free medical clinic.

Setting and Sample

This study targeted men and women aged 19 years and older who had visited the free medical clinic at least once and who had no communication difficulties. Participants who voluntarily provided written consent were surveyed face-to-face. A convenience sampling method was used based on the accessibility and availability of participants at the clinic.

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Using G*Power 3.1 (University of Düsseldorf), the sample size was determined for the multiple linear regression analysis of factors influencing patient satisfaction. Assuming an effect size of 0.15, a significance level of 0.05, and a power of 0.90, the minimum required sample size was calculated to be 99 participants [14]. Considering a potential 20% dropout rate, 124 participants were initially selected. However, challenges in participant recruitment and incomplete responses led to the exclusion of 12 surveys, yielding a final dataset of 112 participants.

Measurements/Instruments

The survey included 16 items on general characteristics, 10 items from the Mini-Mental State Examination [15], 20 items on social support, 8 items on perceived medical support [16], and 29 items on satisfaction with medical services [17]. The last of these categories was subdivided into 6 questions about facility and environment, 6 on medical skills and expertise, 4 on staff friendliness, 7 on patient care and service, 4 on procedure convenience, and 2 on other relevant aspects. The survey also contained 2 questions on educational needs, 9 on satisfaction with medical or pharmacy services, and 1 on additional medical services desired.

Demographic characteristics

Demographic and other factors collected from participants included gender, age, marital status, highest level of education, religion, regular monthly income, permanent residence status, temporary accommodations, permanent residence location, family cohabitation, subjective health status, smoking and alcohol consumption, and current health issues. Additionally, respondents were asked about the most favorable aspect of visiting the Raphael Free Clinic.

Mini-Mental State Examination

The Mini-Mental State Examination comprises 10 items [15], each scored 0 for an incorrect response and 1 for a correct one. Higher scores indicate better cognitive function. In this study, all 112 participants scored 9 or above [15], and data from all participants were included in the final analysis.

Social support

Social support was measured using 20 items [15] on a 4-point scale, where higher scores indicate a higher level of support. Item 15, which pertained to children, was excluded as it was generally not applicable to participants. Thus, 19 items were ultimately included in the analysis. The reliability of the instrument in this study, as determined by the Cronbach α, was 0.93.

Perceived support from medical personnel

Perceived support from medical professionals was assessed using 8 items from the 16-item social support scale developed by Tae [16]. This scale consists of 2 sections: family support and medical personnel support. Each item is rated on a 5-point scale, with higher scores reflecting greater perceived support. Item 8, concerning inpatients, was removed, leaving 7 items for analysis. The reliability of the instrument, as measured by the Cronbach α, was 0.84.

Satisfaction with medical services

Satisfaction with medical services was assessed using a modified questionnaire originally created by Cho [17], adapted to suit the context of the Raphael Clinic. The questionnaire comprises 24 items across 6 categories: facilities and environment, medical skills and expertise, staff friendliness, patient care and services, procedure convenience, and 2 additional items concerning reuse and recommendation. Each item is rated on a 5-point scale, with higher scores indicating greater satisfaction. The reliability of the questionnaire in this study, as measured by Cronbach α values, was 0.87 for facilities and environment, 0.87 for medical skills and expertise, 0.91 for staff friendliness, 0.90 for patient care and services, 0.72 for procedure convenience, 0.60 for reuse and recommendation, and 0.94 for overall satisfaction.

Educational needs

Educational needs were evaluated using 2 items: one regarding education on the chronic disease management of diabetes and hypertension, and another pertaining to education on oral health management. Each item was measured on an 11-point scale, ranging from 0 (“not needed at all”) to 10 (“very much needed”), with higher scores thus indicating greater educational needs.

Satisfaction with clinic or pharmacy services

Satisfaction with clinic or pharmacy services was assessed using 9 items, each measuring satisfaction with specific services: pharmacy, reception, pre-examination room, general consultation, internal/family medicine consultation, orthopedic (rehabilitation) consultation, urology consultation, dermatology consultation, and neurosurgery consultation. Each item was rated on an 11-point scale, ranging from 0 (“not satisfied at all”) to 10 (“very satisfied”), with higher scores thus indicating greater satisfaction.

Additional medical services desired

Participants were surveyed regarding additional medical services they desired, encompassing obstetrics and gynecology, ophthalmology, otolaryngology, dentistry, neuropsychiatry,

neurology, and surgery.

For items not directly derived from previously validated instruments, expert consultation was sought with public health and healthcare professionals to refine the content validity. Following expert feedback, modifications were made to the "satisfaction with clinic/pharmacy services" section to better clarify the evaluation criteria, such as friendliness, the clarity of medical explanations, and wait times.

A pilot test was conducted with a small cohort of participants outside the principal study sample to ensure the clarity and appropriateness of the survey items. Based on the results, additional instructions were integrated to aid respondents in assessing clinical service satisfaction. Additionally, a directive was added to the question regarding additional medical services desired, indicating that multiple selections were permitted.

As satisfaction and needs for additional services were gauged using simple rating scales that reflected subjective evaluations, formal reliability testing was deemed unnecessary. These adjustments ensured that the questionnaire was comprehensible, user-friendly, and relevant to the study population.

Data Collection/Procedure

Data were collected from September 1, 2023, to October 27, 2023. After approval was obtained from the director of the free medical clinic, participants were enlisted through a notice posted on the bulletin board inside Myeong-dong Cathedral. Surveys were distributed in written form, and data collection occurred in the reception area on the first floor of the clinic.

The researcher outlined the survey procedure to participants and remained available to address any queries regarding the items. To minimize potential bias, however, participants completed the survey independently without external assistance. The survey required approximately 10 to 15 minutes to complete, and participants received a modest token of appreciation upon submission.

Data Analysis

The collected data were analyzed using IBM SPSS for Windows ver. 25.0 (IBM Corp.). Descriptive statistics, including frequency, mean, and standard deviation, were computed for all study variables. Independent t-tests and one-way analysis of variance (ANOVA) were applied to assess differences in participants' mental states, levels of social support, perceived support from medical personnel, and satisfaction with medical services. The Scheffe test was utilized for *post-hoc* comparisons.

Pearson correlation analysis was applied to investigate relationships between key study variables. Hierarchical multiple linear regression analysis was employed to delineate factors influencing satisfaction with medical services, with the total satisfaction score serving as the continuous dependent variable. Dummy coding was applied to nominal-scale variables, designating the category with higher satisfaction levels as the reference.

Ethical Considerations

This study was approved by the Kangwon National University Institutional Review Board (KWNUIRB-2023-05-001-004). Participant recruitment was managed by independent research staff with no direct clinical relationship to the respondents, thereby minimizing undue influence. The recruiters were trained research personnel, not clinic staff or healthcare providers. Informed consent was obtained after researchers detailed the study's purpose, procedures, potential risks and benefits, voluntary nature of participation, withdrawal options, and data protection measures. Participants were given 10 to 15 minutes to review the consent form before signing to ensure a thorough understanding.

Eligibility was confirmed using de-identified clinic records to verify prior visits. These records were accessed solely for verification purposes, and no identifiable personal data were included in the study dataset. The demographic information collected included gender, age, marital status, education level, religion, income, housing status, and temporary housing, along with general residential location (e.g., city or district) to ensure anonymity. A designated member of the research team, trained in data protection protocols, anonymized the personal data. This process ensured the complete removal of all personal identifiers before analysis began. Strict confidentiality protocols were enforced, and clinical data were accessed only for eligibility verification, without the inclusion of personal identifiers. All anonymized data were securely stored and used exclusively for research purposes.

Results

General Characteristics of the Study Population

The study included 112 participants: 93 men (83.0%) and 19 women (17.0%), with an average age of 74.0 years. The majority were married (62 participants, 55.4%). Among the participants, 47 (42.0%) had completed high school, and 49 (43.8%) reported no religious affiliation, while 34 (30.4%) identified as Christian. Thirty-five participants (31.3%) reported having a source of income, with an average monthly income of 800,000 Korean won (approximately

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US$553.29 as of February 5, 2025). Most participants (103, 92.0%) had permanent residences, with 83 (74.1%) living in Seoul and 20 (17.9%) in Gyeonggi Province. Of those without permanent residences, 1 participant (11.1%) was experiencing homelessness, 5 (4.5%) lived in a small room (*jjokbang*), and 3 (2.7%) had other temporary accommodations, such as staying with relatives or in a *goshiwon* (a small, affordable dormitory). Fifty-five participants (49.1%) lived with their families, and the average subjective health status was 3.25±1.00 out of 5, indicating moderate perceived health. Most respondents were non-smokers (106 participants, 94.6%) and abstained from alcohol (83 participants, 74.1%). Common health issues included hypertension (61 participants, 58.7%), arthritis (47 participants, 45.2%), benign prostatic hyperplasia (39 participants, 37.5%), diabetes (29 participants, 27.9%), sciatica (23 participants, 22.1%), hyperlipidemia (22 participants, 21.2%), and eye diseases (15 participants, 14.4%) (Table 1).

Social Support, Support from Medical Professionals, and Satisfaction with Medical Services

The average score for social support was 32.63±11.10 out of 76 points, while for support from medical professionals, the average score was 22.15±7.08 out of 35 points. Satisfaction with medical services was rated as follows: facilities and environment, 19.78±3.57 out of 25 points; medical skills and professionalism, 19.95±3.56 out of 25 points; staff kindness, 13.01±2.01 out of 15 points; patient care and services, 24.82±3.84 out of 30 points; procedure convenience, 10.83±2.85 out of 15 points; and intention to reuse and recommend to others, 8.14±1.70 out of 10 points. Overall, satisfaction with medical services received a mean score of 96.53±13.64 out of 120 points (Table 2).

Differences in Social Support, Perceived Support from Healthcare Providers, and Satisfaction with Medical Services According to General Characteristics

One-way ANOVA results indicated statistically significant differences in social support based on marital status ($F=2.90$, $p=0.025$), residence status ($F=2.02$, $p=0.046$), and family cohabitation ($F=3.51$, $p=0.001$). However, the Scheffe *post-hoc* test revealed no statistically significant differences among specific groups, potentially due to its conservative nature in controlling for multiple comparisons and reduced sensitivity in smaller sample sizes. A significant disparity was observed regarding satisfaction with medical services by gender ($t=-2.59$, $p=0.011$), with female participants reporting a higher mean satisfaction score (103.74±10.90)

Table 1. General characteristics ($n=112$)

Characteristic	Category	Value
Sex	Male	93 (83.0)
	Female	19 (17.0)
Age (y)	<70	24 (21.4)
	70–79	59 (52.7)
	≥80	29 (25.9)
	Mean±SD	73.96±8.36
Marital status	Unmarried	13 (11.6)
	Married	62 (55.4)
	Separated	6 (5.4)
	Widowed	15 (13.4)
	Divorced	16 (14.3)
Education	No formal education	3 (2.7)
	Elementary school graduate	21 (18.8)
	Middle school graduate	30 (26.8)
	High school graduate	47 (42.0)
	College graduate	3 (2.7)
	University graduate or higher	8 (7.1)
Religion	None	49 (43.8)
	Christian	34 (30.4)
	Buddhist	12 (10.7)
	Catholic	16 (14.3)
	No response	1 (0.9)
Income	Yes	35 (31.3)
	No	77 (68.8)
If yes, income amount (unit 10,000 KRW)	Mean±SD	79.52±47.01
Residence	Yes	103 (92.0)
	No	9 (8.0)
Temporary shelter	Street	1 (11.1)
	Gjok room	5 (4.5)
	Others	3 (2.7)
Residential area	Gyeonggi-do	20 (17.9)
	Seoul	83 (74.1)
	Others	2 (1.8)
	No response	7 (6.3)
Cohabitation with family	Yes	55 (49.1)
	No	57 (50.9)
Perceived health status	Mean±SD	3.25±1.00
Smoking	Yes	6 (5.4)
	No	106 (94.6)
Alcohol consumption	Yes	29 (25.9)
	No	83 (74.1)
Health issues[a)]	Hypertension	61 (58.7)
	Diabetes mellitus	29 (27.9)
	Arthritis	47 (45.2)
	Hyperlipidemia	22 (21.2)
	Cardiac disease	5 (4.8)
	Cerebrovascular accident	5 (4.8)
	Osteoporosis	12 (11.5)
	Ophthalmic disorders	15 (14.4)
	Sciatica	23 (22.1)
	Benign prostatic hyperplasia	39 (37.5)
	Cancer	3 (2.9)
	Others	21 (20.2)

Data are presented as *n* (%) unless otherwise stated.
SD, standard deviation; KRW, Korean won.
[a)]Multiple responses were permitted.

Table 2. Social support, support from medical professionals, and satisfaction with medical services (n = 112)

Variable	Minimum	Maximum	Mean ± SD
Social support	19	76	32.63 ± 11.10
Support from medical professionals	7	35	22.15 ± 7.08
Satisfaction with medical services	52	120	96.53 ± 13.64
Facilities and environment	11	25	19.78 ± 3.57
Medical technology and expertise	10	25	19.95 ± 3.56
Staff friendliness	5	15	13.01 ± 2.01
Interest in patient engagement and service quality	15	30	24.82 ± 3.84
Procedure convenience	6	15	10.83 ± 2.29
Willingness to reuse and recommend to others	2	10	8.14 ± 1.70

SD, standard deviation.

than male respondents (95.05 ± 13.72) (Table 3).

Correlations between Variables

Correlation analysis of the main variables revealed a positive relationship between social support and perceived support from healthcare providers (r = 0.34, p < 0.001). Additionally, perceived support from healthcare providers was positively correlated with satisfaction with medical services (r = 0.37, p < 0.001) (Table 4).

Factors Influencing Satisfaction with Medical Services

To identify the factors affecting satisfaction with medical services, multiple regression analysis was applied (Table 5). Dummy variables were generated for nominal-scale variables, using the category with higher satisfaction as the reference. The reference categories were female gender, presence of income, living in a residence, and cohabitation with family. The Durbin-Watson statistic was 2.03, confirming the assumption of independence. Tolerance values ranged from 0.76 to 0.96, well above the threshold of 0.1, while variation inflation factor values ranged from 1.05 to 1.31, all below the critical value of 10. These findings indicated the absence of multicollinearity issues and confirmed the analysis's suitability. The analysis identified perceived support from healthcare providers (β = 0.35, p = 0.001) as a significant predictor of satisfaction with medical services. The regression model displayed statistical significance (F = 3.39, p = 0.003) and accounted for 13.4% of the variance in satisfaction with medical services (Table 5).

Additional Analysis

Satisfaction by department

Satisfaction levels across various departments and pharmacy services were measured on a 10-point scale. The highest satisfaction was reported for internal/family medicine services, with an average score of 7.82 ± 1.86. Pharmacy services received the lowest satisfaction rating, with an average score of 7.22 ± 2.39. The other departments' satisfaction scores were as follows: urology, 7.70 ± 2.11; overall clinic services, 7.66 ± 2.07; dermatology, 7.64 ± 2.19; neurosurgery, 7.63 ± 2.43; preliminary examination, 7.59 ± 2.20; reception, 7.51 ± 2.22; and orthopedic (rehabilitation), 7.44 ± 2.10. Regarding additional services, 38 participants (53.5%) expressed a preference for dental services, while 33 participants (46.5%) preferred ophthalmology services.

Educational needs

Educational needs were assessed on a 10-point scale. The mean score for education on the management of chronic diseases, such as diabetes and hypertension, was 6.36 ± 2.98. The need for oral health education was marginally higher, with an average score of 6.58 ± 3.25.

Discussion

This study investigated factors influencing patient satisfaction with medical services among individuals experiencing homelessness and the urban poor at the free medical clinic, providing foundational data to improve the services offered by such clinics. It examined various elements affecting medical service experiences, including general characteristics, social support, and healthcare provider support. Notably, the study explored economic, social, and psychological barriers to healthcare access and proposed strategies to increase satisfaction. By identifying essential support measures, the research underscores the key role of free clinics in improving healthcare access and quality of life for medically underserved populations.

The primary health issues among participants were hypertension, arthritis, benign prostatic hyperplasia, diabetes, sciatica, hyperlipidemia, and eye diseases. These findings align with those reported by Han and Yoon [9], who documented similar health conditions among residents of

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Table 3. Differences in social support, support from medical professionals, and satisfaction with medical services by general characteristics (n = 112)

Characteristic	Support from social networks		Support from medical professionals		Satisfaction with medical services	
	Mean ± SD	t or F (p) Scheffe	Mean ± SD	t or F (p) Scheffe	Mean ± SD	t or F (p) Scheffe
Sex		−0.63 (0.528)		−1.91 (0.059)		−2.59 (0.011)
Male	32.33 ± 11.14		21.58 ± 6.89		95.05 ± 13.72	
Female	34.11 ± 11.09		24.95 ± 7.52		103.74 ± 10.90	
Age (y)		0.51 (0.605)		0.19 (0.829)		0.27 (0.767)
< 70	32.17 ± 14.10		21.63 ± 7.44		95.08 ± 16.45	
70–79	33.58 ± 10.82		22.05 ± 6.92		97.37 ± 13.60	
≥ 80	31.10 ± 8.83		22.79 ± 7.32		96.00 ± 11.36	
Marital status		2.90 (0.025)		0.41 (0.801)		0.23 (0.920)
Unmarried	35.54 ± 17.21		21.08 ± 9.07		93.54 ± 19.75	
Married	34.58 ± 10.16		22.73 ± 6.68		96.48 ± 12.80	
Separated	23.17 ± 6.40		21.50 ± 7.18		97.17 ± 15.16	
Widowed	31.40 ± 10.11		20.47 ± 7.81		98.40 ± 12.68	
Divorced	27.44 ± 7.55		22.63 ± 6.64		97.13 ± 12.69	
Education		1.38 (0.239)		0.35 (0.880)		0.09 (0.994)
No formal education	27.67 ± 11.59		19.00 ± 5.57		94.33 ± 22.19	
Elementary school graduate	30.62 ± 9.73		21.33 ± 7.68		96.24 ± 12.79	
Middle school graduate	31.73 ± 10.23		21.73 ± 8.24		97.60 ± 12.88	
High school graduate	35.53 ± 12.32		22.81 ± 6.67		96.32 ± 15.05	
College graduate	26.33 ± 7.10		21.00 ± 6.25		93.33 ± 4.51	
University graduate or above	28.50 ± 8.99		23.63 ± 4.53		96.50 ± 12.25	
Religion		1.51 (0.217)		0.72 (0.544)		0.92 (0.432)
None	31.29 ± 12.10		22.00 ± 7.70		96.22 ± 13.78	
Christian	34.03 ± 10.29		21.53 ± 7.35		97.32 ± 13.86	
Buddhism	29.67 ± 8.99		21.17 ± 7.10		99.83 ± 10.60	
Catholic	36.88 ± 10.10		24.44 ± 4.21		91.81 ± 13.90	
Income		0.44 (0.664)		−1.96 (0.052)		0.41 (0.682)
Yes	33.31 ± 10.84		20.23 ± 6.94		97.31 ± 14.72	
No	32.32 ± 11.28		23.03 ± 7.02		96.17 ± 13.21	
Residence		2.02 (0.046)		0.41 (0.683)		−0.29 (0.776)
Yes	33.25 ± 11.20		22.23 ± 6.91		96.42 ± 13.92	
No	25.56 ± 6.93		21.22 ± 9.26		97.78 ± 10.41	
Cohabitation with family		3.51 (0.001)		0.90 (0.372)		−0.33 (0.741)
Yes	33.25 ± 11.20		22.23 ± 6.91		96.42 ± 13.92	
No	25.56 ± 6.93		21.22 ± 9.26		97.78 ± 10.41	

SD, standard deviation.

Table 4. Correlations between variables (n = 112)

Variable	Social support		Support from medical professionals		Age		Satisfaction with medical services	
	r	p	r	p	r	p	r	p
Social support	1							
Support from medical professionals	0.34	< 0.001	1					
Age	−0.08	0.385	0.04	0.656	1			
Satisfaction with medical services	0.13	0.173	0.37	< 0.001	0.11	0.238	1	

Table 5. Factors affecting satisfaction with medical services ($n = 112$)

Variable	B	SE	β	*t*	*p*	VIF
(Constant)	70.36	12.67		5.56	< 0.001	
Sex						
Male	5.83	3.30	0.16	1.76	0.081	1.06
Age	0.14	0.15	0.09	0.94	0.350	1.05
Income						
No	−2.76	2.71	−0.09	−1.02	0.312	1.10
Residence						
No	2.96	4.71	0.06	0.63	0.532	1.14
Cohabitation with family						
No	1.13	2.67	0.04	0.42	0.674	1.23
Social support	0.04	0.12	0.03	0.30	0.765	1.05
Support from medical professionals	0.67	0.19	0.35	3.54	0.001	1.23

Adjusted $R^2 = 0.13$, $F = 3.39$, $p = 0.003$.
SE, standard error; VIF, variation inflation factor.

homeless shelters, including high rates of alcohol-related diseases, hypertension, diabetes, gastrointestinal disorders, dental problems, tuberculosis, and musculoskeletal disorders. They also noted the inadequacy of medical services and low satisfaction with community healthcare. Persistent health challenges and barriers to accessing medical care remain prevalent among those experiencing homelessness [18]. Wiens et al. [19] demonstrated that inadequate diabetes management in this population contributes to increased complications. This study reaffirms that chronic conditions such as hypertension, arthritis, and diabetes are of paramount concern, emphasizing the need for strategies that improve access and ensure sustained care.

This study revealed that social support among individuals experiencing homelessness and the urban poor was low, with an average score of 32.63 ± 11.10 out of a potential 76, consistent with previous findings [20]. Limited social networks, economic poverty, stigma, and mental distress adversely affect the health and quality of life of these individuals [20]. Furthermore, the absence of social connections hinders their ability to obtain necessary support [20]. Therefore, providing financial assistance and stable housing is crucial for improving healthcare satisfaction and overall well-being [21]. In addition to healthcare access programs, policies that promote economic stability are essential.

Support from healthcare providers was quantified at 22.15 ± 7.08 out of 35, underscoring its beneficial effect on healthcare satisfaction. Hauff and Secor-Turner [18] affirmed that support from providers improves access to healthcare among those experiencing homelessness. Similarly, Park and Kim [1] emphasized the significance of self-efficacy and emotional support, advocating for psychosocial interventions within healthcare programs. This study supports these conclusions by demonstrating that trust and support from healthcare providers are essential for increasing satisfaction with healthcare services among individuals experiencing homelessness and the urban poor. However, since the score for healthcare provider support was not as high as desired, there is room for further improvement. In addition to social and provider support, emotional support and programs that boost self-efficacy are vital for improving the health of this demographic.

Satisfaction with healthcare services was high across all evaluated categories, including facilities, staff friendliness, medical expertise, and convenience. The overall satisfaction score at the free medical clinic averaged 96.53 ± 13.64 out of 120, reflecting a positive evaluation. Individuals experiencing homelessness and the urban poor face substantial economic and social barriers that impede their access to healthcare [18]. Economic instability remains a significant challenge, emphasizing the need for systematic support. Improvements in healthcare quality and the development of a comprehensive management system are key to satisfaction and health outcomes. Developing programs that facilitate easier access and address the specific needs of these populations will markedly improve their healthcare experiences [18].

Social support varied considerably based on marital status, housing stability, and cohabitation with family members, corroborating Lee and Kim [2]'s findings that familial relationships significantly influence social support. The presence of family members in the home positively impacted psychological stability and health. Individuals experiencing homelessness and the urban poor often struggle to meet basic needs, which in turn limits their access to healthcare and social services [22].

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Healthcare satisfaction varied by gender, with male respondents reporting lower satisfaction, possibly due to more severe health issues and weaker social networks. Barriers to healthcare access include unstable housing, economic hardship, limited health literacy, and stigma [23]. Additionally, healthcare providers face challenges such as resource shortages and systemic obstacles, including transportation difficulties and overloaded systems [24]. These barriers hinder many individuals from effectively utilizing healthcare services [23]. Nevertheless, access to medical services and community support significantly increases overall satisfaction [25], highlighting the need for structured programs that provide continuous and accessible healthcare support for medically underserved populations.

Correlation analysis revealed that social support was positively associated with healthcare provider support; however, in the regression model, it did not directly affect satisfaction with medical services. Instead, support from healthcare providers was identified as the primary determinant of satisfaction, emphasizing its pivotal role in enhancing healthcare utilization. This finding suggests that although social support may augment the perception of provider support, its influence on satisfaction is likely indirect.

Lee and Kim [2] observed that individuals with prolonged homelessness and repeated job loss exhibited reduced self-efficacy, which was positively correlated with healthcare satisfaction. These results indicate that psychosocial factors, particularly social support, are vital for engaging with healthcare services. Future studies should investigate whether social support moderates or mediates the relationship between provider support and satisfaction, using additional statistical analyses such as mediation or interaction modeling.

Interventions that strengthen both social and provider support could improve the healthcare experiences of individuals experiencing homelessness and the urban poor. However, because this study did not include interaction terms in the regression analysis, further research is needed to determine whether social support modifies the relationship between provider support and satisfaction.

Analysis of factors influencing satisfaction with healthcare services revealed that support from healthcare providers had the strongest impact ($\beta = 0.35$, $p = 0.001$). Consistent with the findings of Hauff and Secor-Turner [18], this result underscores the vital role of provider support in enhancing healthcare access and satisfaction among those experiencing homelessness. The regression model ($F = 3.39$, $p = 0.003$) accounted for 13.4% of the variance in service satisfaction, highlighting the need to strengthen provider-patient relationships. Miller et al. [26] identified "accessibility," "person-centered care," and "respect and empathy" as key priorities in healthcare services for individuals experiencing homelessness, corroborating our finding that perceived provider support substantially influences satisfaction. Moreover, studies by Clark et al. [27] and Perna et al. [28] suggest that continuous care, multidisciplinary approaches, and person-centered services improve overall well-being. A study by Bell et al. [29] further corroborates the role of accessible healthcare in meeting the needs of vulnerable populations. Increasing healthcare provider support and expanding patient-centered programs are crucial for addressing systemic barriers and improving health outcomes for people experiencing homelessness and the urban poor. Policies and programs that foster respect, empathy, and continuous care should increase satisfaction with healthcare services and yield long-term health benefits [3].

Satisfaction with medical and pharmacy services varied in this study. Internal/family medicine received the highest score (7.82 ± 1.86 out of 10), while pharmacy services scored the lowest (7.22 ± 2.39). Research by Farmer et al. [30] stressed the essential role of pharmacists in supporting medication adherence among individuals experiencing homelessness, who frequently face challenges in understanding their prescriptions. Proper counseling on usage, side effects, and drug interactions can improve adherence and treatment outcomes. By modifying packaging or simplifying medication regimens, pharmacists can further support patient compliance. Increased pharmacist involvement is anticipated to improve both health management and overall satisfaction with healthcare services for people experiencing homelessness and the urban poor.

Developing targeted strategies for those experiencing homelessness is essential. Expanding dental and ophthalmology services in free or mobile clinics through collaborations with specialists and volunteer recruitment can increase access to care. Strategic clinic placement and mobile medical units can further improve accessibility for these individuals [31]. Additionally, continuous assessment of healthcare needs and integration of patient feedback into service enhancements are imperative. These measures will ensure timely medical care, leading to improved health outcomes and overall well-being for individuals experiencing homelessness and the urban poor.

Educational needs regarding the management of chronic diseases, such as diabetes and hypertension, received a mean rating of 6.36 ± 2.98 out of 10. The need for oral health management scored slightly higher, at 6.58 ± 3.25. Farmer et al. [30] observed that individuals experiencing homelessness could effectively manage their health when provided with

both practical and emotional support, underscoring the indispensable role of such support in program efficacy. Thorndike et al. [32] highlighted the necessity of trust-building and patient-centered educational programs, arguing that tailored education could significantly increase engagement with healthcare services. The study advocates for comprehensive educational programs that incorporate both practical and emotional support [24], emphasizing chronic disease and oral health management through audiovisual resources and hands-on practice. Programs should prioritize accessibility and sustainability, while also incorporating healthcare professionals, social workers, and psychological counselors in a multidisciplinary approach. Regular feedback and support for voluntary participation can increase program effectiveness, ultimately empowering those experiencing homelessness and the urban poor to manage their health and improve their quality of life.

This study systematically examined the barriers that prevent people experiencing homelessness and the urban poor from accessing healthcare services, identifying key economic, social, and legal constraints. These findings provide insights for developing practical interventions to enhance healthcare access. By analyzing the factors affecting satisfaction with a free clinic, the study provides foundational data for improving medical services tailored to medically underserved populations. Future research should focus on developing customized support programs and healthcare provider training to support both service quality and patient satisfaction. Moreover, additional studies across various regions and populations are essential to refine interventions that increase healthcare accessibility and effectiveness for people experiencing homelessness and the urban poor.

Conclusion

The findings of this study indicate that support from healthcare providers, financial assistance, and accessible healthcare services are vital in improving satisfaction with healthcare services among people experiencing homelessness and the urban poor. In particular, the study underscores that support from healthcare providers plays a significant role in influencing satisfaction levels, emphasizing the need for providers to recognize the unique circumstances of this population and offer tailored support.

Future research should further investigate these factors, especially in the development of customized support programs for people experiencing homelessness and the urban poor, as well as in training initiatives targeting healthcare providers to improve service quality and patient satisfaction. Expanding free clinic services to include additional specialties such as dental and ophthalmology care, alongside educational programs on chronic disease and oral health management, can help address unmet healthcare needs and yield better overall health outcomes.

By augmenting targeted support programs and providing specialized training for healthcare providers, healthcare services can be made more accessible and responsive to the needs of people experiencing homelessness and the urban poor. Ultimately, these measures may improve their access to healthcare, enhance their quality of life, and contribute to better health outcomes, thereby supporting reintegration into society.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of Kangwon National University (No: KWNUIRB-2023-05-001-004) and performed in accordance with the principles of the Declaration of Helsinki.

Conflicts of Interest

Curie Ahn 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 authors have no conflicts of interest to declare.

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Availability of Data

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

Authors' Contributions

Conceptualization: JHK, YJH; Data curation: all authors; Formal analysis: all authors; Funding acquisition: JBK, SP, JSL; Investigation: all authors; Methodology: JHK, YJH; Project administration: JHK; Resources: all authors; Software: all authors; Supervision: JHK; Validation: all authors; Visualization: all authors; Writing–original draft: JHK, YJH; 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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SUBMISSION & PEER REVIEW PROCESS

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MANUSCRIPT PREPARATION

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- All pages should be paginated consecutively.
- All numbers should be written in Arabic numerals throughout the manuscript except for the first word of the sentence. Texts should be justified on both sides and not hyphenated and headings should be in bold letters, aligned in the center. If possible, avoid using abbreviated words at the beginning of sentences.
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- **Correspondence** is a comment from readers regarding a published article with a reply from the authors of the article. Manuscript limitations are 500 words, 2 tables/figures, and 5 references.
- **Book reviews** may be published. Please dispatch a book to the editorial office if you think the book is essential to public health personnel.

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

Table 1. Key features and limits of articles

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

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

Title Page

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

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

Highlights

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

Main Body

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

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

References

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

- References are presented with [ ] following a surname in the main text, such as Kim [1] and Kim et al. [2]. When a reference is cited within the content, it is shown as [3] or [4,5] at the end. References should be searchable online.
- The last names and initials of all the authors (up to 3) should be included. For articles with more than 3 authors, list the first 3 authors only followed by "et al."
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- Do not cite abstracts unless they are the only available reference to an important concept.
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- Other types of references not described below should follow the ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).

Please refer to the following examples.

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

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Tables should be simple, self-explanatory, and supplemental, and should not duplicate the text or figures. Each table must be on a separate page, not exceeding 1 page when printed, and have a concise and informative title. The tables should be numbered with Arabic numerals in consecutive order. Each column should be appropriately headed with units in parentheses if numerical measures are given. All units of measurements and concentrations must be indicated. Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table ([a], [b], [c],

[d]...), and notes on level of probability (*, **, *** for *p*).

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

Figures that are drawn or photographed professionally should be sent as JPG or PPT files. However, if an article receives approval for publication, files must be submitted as .tiff or .pdf. Each figure must have a caption explaining the figure. The preferred size of the images is 8 × 8 cm but 16.5 cm in width × 8 cm in length is also acceptable. It is authors' full responsibility to submit images of sufficient quality for accurate reproduction and to approve the final color galley proof. All images must be correctly exposed, sharply focused, and prepared in files of 500 dpi or more.

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

Appendix and Supplemental Data

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

FINAL PREPARATION FOR PUBLICATION

Final Version

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