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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

Integrating life-course determinants, infectious disease risks, and digital innovation in health care: a systems perspective in contemporary public health

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This issue of *Osong Public Health and Research Perspectives* presents a coherent cross-section of contemporary public health challenges and opportunities, spanning life-course determinants, infectious disease risks, health system performance, and emerging digital innovations. Collectively, these studies underscore a central theme: the need for integrated, systems-oriented approaches that connect upstream determinants with downstream clinical and policy responses.

As this issue coincides with World Immunization Week 2026 (the last week of April) [1], it is both timely and contextually relevant to reflect on vaccination through the lens of the Republic of Korea's public health experience. The nationwide measles outbreak in 2000–2001 was brought under control through a government-led catch-up campaign, the institutionalization of a 2-dose vaccination schedule, and strengthened school-entry verification, all supported by universal health coverage that ensured equitable access. These combined efforts enabled the Republic of Korea to interrupt endemic transmission and subsequently sustain elimination status through high vaccination coverage, sensitive surveillance, and rapid outbreak response. At a time when several countries have experienced measles resurgence and even lost elimination status, the Republic of Korea's experience underscores that elimination is not a 1-time achievement, but a system-level outcome that must be continuously maintained. In this context, World Immunization Week is not merely commemorative, but a reminder that vaccination is a system-level achievement requiring sustained policy commitment, equitable delivery, and continuous health system performance. This commitment is also reflected in the Republic of Korea through commemorative initiatives, including an immunization award and ceremony organized in collaboration with the International Vaccine Institute and its partners to recognize contributions to advancing vaccination as a global public good [2]. Marking the 50th anniversary of the Expanded Programme on Immunization, which is estimated to have prevented more than 154 million deaths globally since 1974 [3], this moment calls for renewed commitment to sustaining and strengthening immunization systems worldwide.

At the population level, two studies highlight the importance of early-life and lifestyle determinants in shaping long-term health outcomes. A systematic review and meta-analysis on perinatal factors demonstrates that maternal conditions—including pre-pregnancy obesity, excessive gestational weight gain, cesarean delivery, and early-life exposures—significantly increase the risk of childhood obesity, while breastfeeding offers a protective effect. These findings

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reinforce the concept that prevention must begin before birth, aligning with a life-course approach to noncommunicable disease control. Complementing this, a cross-sectional study on dietary fat intake and sleep quality reveals complex associations between both the quantity and type of fat consumed and multiple dimensions of sleep. Together, these studies highlight that health systems must extend beyond clinical services to address upstream determinants that shape population health trajectories.

Moving from determinants to disease outcomes, several studies in this issue address infectious disease severity and transmission dynamics in clinical settings. A retrospective study from Vietnam identified cardiometabolic comorbidities, particularly hyperlipidemia and combinations of hypertension and cardiovascular disease, as significant predictors of severe dengue. This finding underscores the growing intersection between noncommunicable diseases and infectious disease outcomes and highlights the need for integrated risk stratification at the point of care. Similarly, a prospective cohort study among hemodialysis patients in India reported notable rates of hepatitis B and C seroconversion, with risk factors including multiple facility visits and dialyzer reuse. These findings point to persistent vulnerabilities in infection prevention and control practices among high-risk clinical populations.

A study conducted in the Republic of Korea further provides molecular and epidemiological evidence of nosocomial transmission of severe fever with thrombocytopenia syndrome, with secondary infections occurring during high-risk procedures such as cardiopulmonary resuscitation in the absence of adequate personal protective equipment. This finding highlights the continuing importance of infection prevention and control as a core health system function, particularly in the context of emerging pathogens.

Beyond individual patient outcomes, this issue also addresses health system performance, particularly with respect to continuity of care. An analysis of tuberculosis surveillance data from Indonesia revealed that nearly 1 in 5 patients with drug-sensitive tuberculosis were lost to follow-up. The study identified multiple contributing factors, including non-standard treatment, human immunodeficiency virus co-infection, and gaps in referral systems. These findings illustrate systemic weaknesses in care delivery and emphasize the need for patient-centered interventions, stronger coordination, and robust monitoring systems to improve treatment adherence and outcomes.

Looking ahead, 2 articles explore the transformative potential of digital technologies in health care. A comprehensive review of artificial intelligence applications highlights its expanding role in diagnostics, predictive analytics, precision medicine, and health system efficiency, while also identifying persistent challenges related to data integration, algorithmic bias, and ethical governance. In parallel, a perspective on virtual reality outlines its potential to enhance medical education and patient engagement through immersive, interactive environments. These innovations signal a shift toward more adaptive, technology-enabled health systems while underscoring the importance of equitable access and responsible implementation.

In summary, this issue reflects the evolving public health landscape, in which traditional boundaries between communicable and noncommunicable diseases, prevention and care, and human and technological systems are increasingly blurred. Collectively, the studies call for a more integrated framework that combines life-course prevention, risk stratification, resilient health systems, and responsible innovation. As illustrated by the experience of immunization and measles elimination, achieving and sustaining population health gains ultimately depends on the continuous performance of health systems grounded in equity, evidence, and global cooperation.

Notes

Ethics Approval
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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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Perspective

Scoping insights into the application of virtual reality in patient care and clinical practice

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Virtual reality (VR) describes the use of a 3-dimensional, computer-generated, interactive, immersive simulation environment. Through headsets and sensory feedback, VR aims to create a sense of presence within a virtual environment, in which the user feels mentally immersed, interacts with the simulation, and becomes part of that environment. Interactivity and multisensory integration—visual, tactile, auditory, and olfactory—are fundamental concepts in VR. Users can manipulate objects, complete sequences of actions, and interact with virtual characters in a realistic manner while fully engaged in this virtual world [1,2]. VR environments can support the personalization of learning to individual needs and make complex topics more approachable. Evidence indicates that the use of visual aids makes risk information easier to understand and recall, particularly among vulnerable groups such as older adults, high-risk patients, and individuals with limited medical knowledge. Furthermore, VR content can be made available in multiple languages, which may help individuals who face literacy and language barriers [3–5].

In healthcare settings, VR holds considerable promise for transforming clinical practice. It can serve as a useful tool for facilitating in-depth learning in medical education and training for health professionals. Earlier studies have reported significant improvements in skills and satisfaction, as well as more favorable knowledge outcomes. These findings support the incorporation of VR into a range of healthcare education activities and highlight its potential to provide patients with complex medical conditions with a deeper understanding and more engaging learning experiences [6,7]. Similarly, VR enables immersive, interactive patient education experiences that may engage users more effectively than passive approaches. It is increasingly used in patient education to expand knowledge, enhance patient satisfaction and engagement, and reduce anxiety and discomfort. Prior studies have shown that VR can improve patient experiences by providing immersive and interactive environments for learning and practice. In these applications, the benefits of VR in patient education extend beyond knowledge gains to include improved patient satisfaction and emotional well-being [7,8]. Consequently, VR can promote patients' active participation in their care while also opening new possibilities for educational provision. One benefit of VR is the ability to provide personalized explanations of a diagnosis or treatment course. It allows patients to virtually experience the hospital setting and anticipated length of stay and enables them to revisit and discuss this experience with family members or relatives at home as needed [3,9].

Additionally, VR-based approaches can improve cancer patients' preparation for radiotherapy

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(RT), which is expected to be administered to more than half of all cancer patients during the course of treatment. Patients' concerns about therapy may increase due to this complex therapy. VR used in educational sessions may address patients' information needs regarding the RT procedure by providing a realistic treatment experience, including exposure to the auditory conditions they may encounter during radiation. In this way, patients can engage with the environment, become familiar with RT equipment, and experience what will occur during therapy, thereby improving understanding and reducing anxiety [10–12].

An important aspect of obtaining informed consent for surgery is the patient's understanding of the operation. For consent to be informed, a thorough discussion of the risks, potential adverse effects, and surgical alternatives is necessary. VR has been found to lessen the influence of the patient's surroundings while providing a subjectively immersive experience and a sense of physical presence in a virtual world. In this regard, VR technology can be considered a promising pain control strategy for various pain conditions and may serve as an adjunct or alternative approach to pain management. Earlier studies have demonstrated successful applications of VR in pain-related settings, with promising outcomes including reduced procedure duration, anxiety, and procedure-related pain during difficult interventions, including perioperative and periprocedural surgical procedures, as well as chronic pain during cancer therapy [13–15].

Meanwhile, VR appears useful in treating acute or chronic pain related to a range of physical and mental conditions and during procedures such as wound dressing changes, intravenous cannulation, and dental procedures. It has also been applied in pain associated with injuries, cancer, diabetic neuropathy, migraine headaches, and pruritus. Pain perception is believed to depend in part on a patient's ability to direct cognitive attention to painful stimuli, and many explanations attribute VR's benefits to simple distraction. Through direct or indirect changes to neural signaling pathways involving attention, focus, memory, emotion, and sensory processing (sight, hearing, and touch), VR may reduce perceived pain [16–18]. By diverting the patient's attention away from pain, the immersive and engaging nature of VR may lessen anxiety, discomfort, and unpleasantness. VR can serve as a distraction by occupying visual, auditory, and proprioceptive input, thereby reducing the patient's capacity to process painful sensations [17]. Furthermore, VR has also been shown to be useful for relaxation. Because virtual environments can be calming and stress-relieving, they are often used to address stress-related physical disorders that cause pain. These conditions, including postherpetic neuralgia, neuropathic pain, and fibromyalgia, are highly prevalent in primary care settings. Neuroimaging studies have supported patient self-reports of reduced anxiety, time spent thinking about pain, and pain intensity after VR treatment. Compared with conventional treatments, VR has been associated with significant improvements in functional impairment among patients with fibromyalgia [17–19].

Moreover, VR exposure therapy offers a treatment strategy that may help address anxiety in ways that medication alone may not. VR exposure therapy has been used to treat agoraphobia, arachnophobia, claustrophobia, panic disorder, obsessive-compulsive disorder, generalized anxiety disorder, social anxiety disorder, and post-traumatic stress disorder. It has also been used in conjunction with medications for the treatment of anxiety and phobias [17,20]. In addition, VR has been used in the treatment of autism spectrum disorder because it can provide a controlled environment in which individuals can learn new skills. Two systematic reviews support the use of VR to help individuals with autism practice communication and imitation skills, which may help them manage social situations [21,22].

Nevertheless, during in-depth interviews conducted to inform the development of VR education tools, patients identified several potential limitations and challenges that should be considered. VR interventions vary in their technical applications and implementation settings. In this context, evaluation is critical for assessing the use of VR in clinical practice, which may be influenced by a range of factors. These include the need for individualized information; the role of immersive and/or experiential learning; the need to create a realistic environment; the presence of a moderator to guide the VR experience and facilitate individual- or group-based education sessions; motion sickness; a reduced sense of presence; eye strain; and potentially inappropriate responses in the real world. Some patients find the technology confusing, uncomfortable, or difficult to use, and some perceive the

HIGHLIGHTS

- Virtual reality (VR) is increasingly being employed in patient education and is also opening new avenues for educational provision.
- VR technology has demonstrated promising outcomes in modulating emotional processes during the treatment of major diseases.
- Patients considered VR education beneficial and effective because it improved understanding, communication with healthcare providers, and adherence to therapy.

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benefits of VR experiences as unclear. Furthermore, younger patients may be more willing and able to use VR than older patients [23,24].

This scoping review highlighted that numerous healthcare disciplines, including patient education, rehabilitation, and emotional regulation, have used this promising technology. The increasing use of VR in clinical settings is helping to change how patients learn about illnesses and therapies by promoting active participation in their care while also creating new possibilities for educational provision to improve patient outcomes. VR can expand knowledge and enhance patient satisfaction and engagement in disease management. Therefore, this technology may encourage patients to participate more actively in their care, supporting improved disease management and quality of life.

Notes

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The author has no conflicts of interest to declare.

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Review Article

Collaborative networks, trends, and comparative analysis of artificial intelligence techniques in healthcare research: a narrative review

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ABSTRACT

Objectives: Artificial intelligence (AI) is reshaping healthcare by improving diagnosis and treatment planning, increasing operational efficiency, and streamlining administrative workflows. This paper integrates findings from an extensive PubMed search (2015–2025) with bibliometric analysis using RStudio and VOSviewer to investigate the comparative applications of AI methods in healthcare, collaborative networks, and emerging trends.

Methods: A total of 1,243 records were identified through the PubMed search, and after removal of 143 duplicates, 1,100 records were screened. Following full-text assessment and exclusion of ineligible studies, 986 articles were included in the final bibliometric analysis.

Results: The main research areas included robotic-assisted surgery, predictive analytics, diagnostic imaging, and precision medicine, with particular emphasis on the prevalence of machine learning and deep learning in imaging and the increasing application of natural language processing to unstructured medical information.

Conclusion: The review emphasizes the need for greater budgetary allocation to scalable and pragmatic AI technologies and for interdisciplinary cooperation among researchers, industry, and healthcare providers. Despite this growth, challenges such as algorithmic bias, data integration, and ethical concerns persist. The paper also highlights the importance of equitable collaboration, accountable AI, and multinational partnerships in ensuring that AI can be used ethically and efficiently in healthcare over the long term to improve patient care and biomedical innovation. It does so by mapping international and regional trends, identifying the most influential authors, institutions, and funding sources, and evaluating methodological approaches.

Keywords: Artificial intelligence; Biomedical innovation; Collaborative networks; Healthcare artificial intelligence; Research Trends

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Introduction

Artificial intelligence (AI) has become a transformative force in modern healthcare, reshaping clinical practice, biomedical research, and healthcare administration. Through machine learning (ML), deep learning (DL), and natural language processing (NLP), AI systems can improve diagnostic accuracy, support predictive analytics [1–3], personalise treatment planning, and increase efficiency within healthcare systems. Notable applications include diagnostic imaging, predictive disease modelling, precision medicine, robotic-assisted surgery, and clinical decision support. Recent research indicates that AI-based models often outperform conventional algorithms in radiology and diagnostic imaging, enabling more accurate detection of lung, breast, and cardiovascular diseases. ML systems are widely used for disease-risk prediction and outcome prediction in chronic conditions, including diabetes and cardiovascular disease, whereas DL methods support automated feature extraction from medical images and genomic data in precision healthcare. At the same time, NLP approaches enable analysis of unstructured clinical data contained in electronic health records (EHRs) and the medical literature, thereby improving patient stratification and knowledge discovery. Applications of AI in surgery, particularly through surgical robotics, further demonstrate its clinical relevance by improving procedural precision and shortening recovery time. Alongside these developments, ethical and regulatory frameworks have received increasing attention in response to concerns regarding transparency, fairness, accountability, and patient safety in clinical AI [4,5]. This progress has been driven by the rapid expansion of biomedical data, increasing computational power, and the global shift toward digital health systems, all of which have accelerated AI adoption in healthcare over the past decade. Despite these advances, important limitations remain, including data-integration challenges, algorithmic bias, limited explainability of complex models, and inequitable access to AI technologies worldwide [6]. Although previous reviews have examined individual AI methods or single clinical applications, relatively little research has integrated large-scale bibliometric mapping with comparative narrative synthesis to critically evaluate research patterns, collaboration networks, and methodological developments across AI methods in healthcare. In this paper, the authors present a comprehensive bibliometric and narrative review of 986 peer-reviewed articles published between 2015 and 2025 to address this gap. By combining quantitative bibliometric indicators with qualitative synthesis, this review identifies publication trends, global and institutional collaboration networks, prevalent and emerging AI methods, and major application areas in healthcare. It also examines AI-driven innovation in relation to ethical principles, sustainability, and global health equity, while outlining barriers and opportunities for the future development of responsible and scalable AI integration [7]. These findings may inform researchers, policymakers, and healthcare stakeholders seeking to promote the effective, safe, and equitable implementation of AI in healthcare. Despite the rapid growth of AI-based healthcare research, existing reviews have focused primarily on individual methods, single applications, or qualitative overviews. Few studies have combined large-scale bibliometric mapping with comparative analysis of ML, DL, and NLP while also examining global collaboration networks and sustainability-related alignment. This review seeks to address that gap by integrating quantitative bibliometric analysis of 986 publications with guided narrative synthesis and by providing a reproducible, comparative, and policy-relevant overview of AI techniques in healthcare.

HIGHLIGHTS

- Examines global research trends in artificial intelligence (AI) applications in healthcare.
- Identifies key collaborative networks among institutions and researchers.
- Compares major AI techniques used in healthcare research and clinical applications.
- Highlights emerging opportunities and challenges in AI-driven healthcare systems.
- Provides insights for future interdisciplinary research and innovation.

Contribution & Novelty

(1) Combines bibliometric mapping and narrative synthesis to provide a comprehensive evaluation. (2) Uses a comparative lens to assess ML, DL, and NLP across diagnostic imaging, predictive medicine, precision healthcare, and robotics. (3) Emphasizes collaboration by mapping global co-authorship and institutional networks and highlighting synergies among academia, industry, and healthcare. (4) Examines how AI in healthcare aligns with the United Nations Sustainable Development Goals (SDGs), with particular attention to fairness, ethics, and global health impact. (5) Proposes a future roadmap by identifying emerging areas for responsible adoption, including federated learning,

explainable AI, and bias reduction (Figure 1).

Objectives and Scope of the Study

This study aims to provide a comprehensive and comparative assessment of AI applications in healthcare between 2015 and 2025 using an integrated bibliometric and narrative synthesis approach. Specifically, it seeks to: (1) analyze publication growth, geographic distribution, and collaborative research networks; (2) compare major AI techniques—ML, DL, and NLP—across key healthcare applications, including diagnostic imaging, predictive medicine, precision healthcare, and robotic surgery; (3) identify emerging themes, ethical challenges, and sustainability-aligned innovations; and (4) propose data-driven future research directions to support responsible, equitable, and scalable AI adoption in healthcare systems.

Significance

AI techniques have the potential to transform healthcare by improving diagnostic performance, personalizing treatment plans, and increasing operational efficiency. Numerous studies have examined the impact of AI technologies in healthcare [8]. AI-driven tools may improve prognosis, diagnosis, and treatment planning. In the future, AI is likely to become an increasingly important component of healthcare services and to influence a wide range of treatments. AI refers to computer-based systems, including software and hardware, that can perform certain tasks, solve problems, and make decisions without direct human involvement [9,10]. AI encompasses a wide range of approaches and applications, including genetic algorithms, neural networks, ML, and pattern recognition [11]. The significance of this research lies in the following:

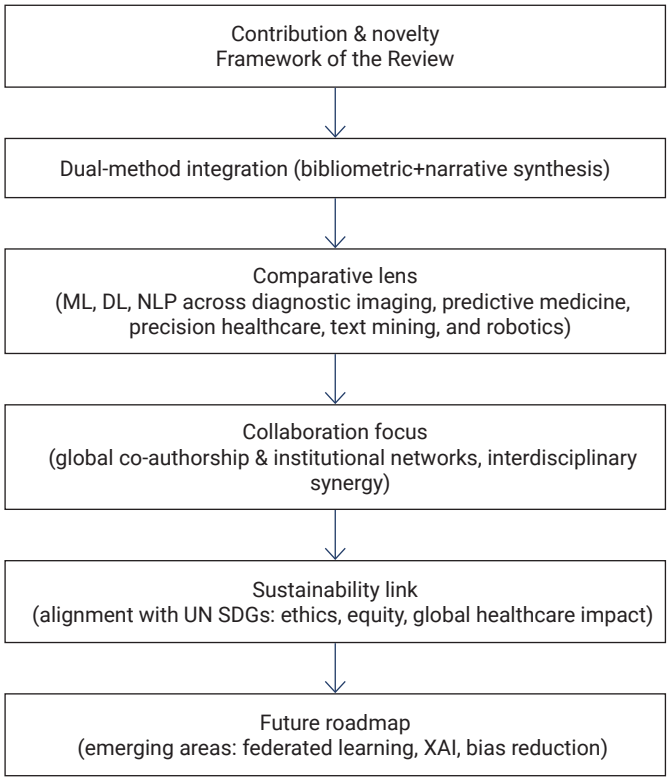


Figure 1. Conceptual framework of the review.
ML, machine learning; DL, deep learning; NLP, natural language processing; UN SDG, United Nations Sustainable Development Goals; XAI, explainable artificial intelligence.

Improved Patient Outcomes

AI can be applied in healthcare to predict risks and provide recommendations. The use of big data and AI may improve patient health, diagnostic performance, and predictive capacity [12]. Because AI can rapidly and accurately process and analyse complex medical data, it may support earlier diagnosis, stronger predictive analytics, and more effective therapeutic interventions, thereby improving patient care and outcomes.

Advances in Innovation

AI-related technologies may transform patient care and outcomes through their application in multiple areas of cancer care, including drug research and development, early diagnosis and screening, and drug discovery [13]. This study examines how AI can advance medical imaging, drug discovery, and robotic-assisted practice, thereby promoting medical innovation.

Collaborative Synergy

AI has introduced new opportunities in healthcare and has transformed the delivery of medical activities and patient care. This paper examines the interactive relationship between AI and healthcare, with particular attention to the disruptive potential of AI technologies in the medical sector [14,15]. By mapping multidisciplinary relationships among academia, industry, and healthcare providers, the study highlights collaboration and resource sharing as important mechanisms for addressing global healthcare challenges and workforce shortages.

Ethical and Technical Challenges

This research contributes to the literature by synthesizing evidence on AI applications in healthcare. It also provides a detailed description of the ethical and governance issues that stakeholders seeking to implement AI in healthcare should consider. According to the review, ethical concerns,

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algorithmic bias, and data-integration challenges must be addressed to ensure that AI applications in healthcare are fair, transparent, and sustainable.

Future Directions

The paper provides stakeholders with a roadmap for realizing the promise of AI in healthcare by identifying emerging trends and opportunities and by addressing related sociotechnical barriers.

Advancing the Field of AI Techniques in Healthcare

AI techniques in healthcare hold considerable promise. Advancing the field will require a broad strategy that both realizes this potential and addresses the associated challenges. Key priorities for improved data integration include interoperability, real-time analytics, and scalable infrastructure [16,17]. Algorithmic development is increasingly focused on personalized medicine, bias reduction, and model explainability in order to improve accuracy and trust. Important clinical advances include more sophisticated diagnostic imaging, predictive analytics, and robotic surgery. Stronger collaboration among academia, industry, and healthcare (Table 1) providers promotes innovation and resource sharing, whereas global and public-private partnerships help address system-level challenges [18,19]. Responsible AI deployment also depends on ethical and regulatory considerations, including transparent governance, patient privacy, and equitable access. Ongoing clinician education, awareness-building, and corrective feedback mechanisms may further support acceptance and continuous improvement, thereby advancing AI-based healthcare systems. Pharmaceutical companies have long faced challenges in developing new treatments that are not only faster and less costly to produce, but also high in quality, safety, and performance. Advances in AI and computing have strengthened researchers' ability to accelerate drug discovery and development. AI is the science and engineering of intelligent machines [20,21]. More recent disease-specific applications also illustrate the translational utility of AI-based personalized medicine. For example, the literature suggests that AI may improve human immunodeficiency virus (HIV) management through predictive analytics, monitoring of treatment adherence, and optimization of individualized therapy [22]. These findings indicate that AI-enabled personalization may improve treatment processes and support long-term disease management, reinforcing the relevance of disease-centered AI solutions within broader healthcare innovation trends.

Methodology

Materials and Methods

This research used an integrated bibliometric and narrative review approach to examine studies on AI in healthcare published between 2015 and 2025. PubMed was selected as the primary data source because it provides broad coverage of peer-reviewed biomedical and healthcare literature. Table 1 presents the detailed search strings used in the structured search, which combined keywords such as artificial intelligence, machine learning, deep learning, natural language processing, healthcare, diagnostic imaging, predictive analytics, precision medicine, and robotic surgery. Peer-reviewed English-language articles involving empirical, modeling, or systematic analysis of AI applications in healthcare were included. Excluded articles comprised of non-healthcare AI studies, editorials, commentaries, conference abstracts, and non-English

Table 1. Keyword clusters and research themes in AI-driven healthcare (2015–2025)

Cluster	Primary theme	Representative keywords	Interpretation
1	Diagnostic imaging	Machine learning, deep learning, CNN, MRI, CT	Reflects dominance of DL-based imaging diagnostics and radiology automation.
2	Predictive medicine	Predictive analytics, risk prediction, big data, diabetes	Focuses on AI models forecasting patient risk and chronic disease progression.
3	Precision healthcare	Genomics, personalized treatment, molecular data	Integration of AI with genomics for tailored therapeutic pathways.
4	Clinical text mining	NLP, EHR, BERT, unstructured data	Highlights the rise of NLP in extracting clinical insights from text-heavy datasets.
5	Surgical innovation	Robotics, automation, minimally invasive surgery	Centers on robotic-assisted precision interventions.
6	Collaborative networks	Digital ecosystems, older-adult care, and healthcare innovation	Emphasizes multi-sector partnerships fostering healthcare innovation.

AI, artificial intelligence; CNN, convolutional neural network; MRI, magnetic resonance imaging; CT, computed tomography; DL, deep learning; NLP, natural language processing; EHR, electronic health record; BERT, Bidirectional Encoder Representations from Transformers.

publications. Article selection adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table 2). It included duplicate removal, title and abstract screening, and full-text evaluation, yielding a final dataset of 986 articles. R ver. 4.3.2 (R Foundation for Statistical Computing), RStudio (Posit PBC), and VOSviewer (Centre for Science and Technology Studies) were used to analyze publication patterns, citation trends, keyword co-occurrence, collaboration networks, and thematic clustering; the analytical tools and their functions are summarized in Table 3.

Data Summary

A total of 986 articles on AI in healthcare published between 2015 and 2025 were reviewed across 399 journals and other academic sources. The dataset included 9,655 contributing authors, with an average of 12 co-authors per document and an international collaboration rate of 37.83%, indicating a highly multidisciplinary and globally connected research community (Table 4). The annual publication growth rate was 8.1%, and the median document age was 4.47 years. Bibliometric analysis identified 4,453 keywords representing diverse research topics, with ML, DL, NLP appearing frequently in studies related to diagnostic imaging, predictive analytics, precision medicine, and robotic-assisted surgery. Publication distribution, co-authorship networks, and topic clusters were identified through visualization and network mapping using R ver. 4.3.2, RStudio, and VOSviewer, whereas narrative synthesis clarified patterns in the effects of AI on patient care, biomedical innovation, and operational efficiency. Challenges related to algorithmic bias, data integration, transparency, and patient privacy were also examined. The findings were further contextualized through cross-referencing with World Health Organization (WHO) and Food and Drug Administration (FDA) reports and with expert peer-reviewed literature, suggesting that AI in healthcare is a growing, collaborative, and multidisciplinary research field with both substantial opportunities and important ethical and practical challenges. The study selection process followed the PRISMA 2020 guidelines. The initial PubMed search identified 1,243 records published between 2015 and 2025. After removal of 143 duplicate

Table 3. Bibliometric tools and analytical functions

Tool	Version	Purpose
R	4.3.2	Data cleaning, descriptive statistics, and trend analysis
RStudio	IDE	Script execution and visualization
VOSviewer	Latest	Keyword co-occurrence, citation mapping, collaboration networks, clustering

IDE, integrated development environment.

Table 4. Data extracted using R ver. 4.3.2 and RStudio

Description	Results
Main information	
Timespan (year)	2015:2025
Sources (journals, books, etc.)	399
Documents	986
Annual growth rate (%)	8.1
Document average age (y)	4.47
Average citations per document	0
References	1
Document contents	
Keywords plus (ID)	4,453
Author's keywords (DE)	4,453
Authors	
Authors	9,655
Authors of single-authored documents	3
Author collaboration	
Single-authored documents	12
Co-authors per document	12
International co-authorships (%)	37.83

Table 2. PRISMA flow diagram for article selection (2015–2025)

Stage	Description	Records (*n*)
Identification	PubMed search (2015–2025) using keywords: "artificial intelligence," "machine learning," "deep learning," "natural language processing," "healthcare," "precision medicine," "diagnostic imaging," "predictive analytics," "robotic surgery"	1,243
Screening	Duplicate and irrelevant titles/abstracts removed	257 Excluded
Eligibility	Full-text evaluation for relevance, methodology clarity, and healthcare focus	986
Excluded (full text)	Editorials, commentaries, or non-healthcare AI applications	68 Excluded
Included in bibliometric+ narrative analysis	Peer-reviewed articles meeting the inclusion criteria	918
Final datasets analyzed (including cross-validation & reference checks)	Added validated high-impact papers via reference cross-checks (WHO, FDA, and peer-reviewed sources)	986

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AI, artificial intelligence; WHO, World Health Organization; FDA, Food and Drug Administration.

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records, 1,100 articles remained for title and abstract screening. During screening, 114 records were excluded for not meeting the study scope. Subsequently, 986 full-text articles were assessed for eligibility. All studies satisfied the inclusion criteria, resulting in a final dataset of 986 publications included in the bibliometric and narrative analyses.

Transparency in Analysis

This paper aims to maintain transparency by clearly presenting the methodology used to examine AI in healthcare, including bibliometric analysis, case-based evidence, and comparative analysis. The data sources are identified and include bibliometric records, published literature, and applied case examples. Collaborative networks were mapped using VOSviewer and Gephi (Gephi Consortium), and key AI techniques, including ML, DL, and NLP, were examined comparatively. Major areas of analysis, such as collaboration, AI applications, and ethical concerns, are clearly delineated. These findings were supported through cross-referencing with credible sources, including WHO and FDA materials, and through consideration of peer-reviewed literature. Ethical issues are explicitly addressed, and future opportunities for equitable AI collaboration are discussed. Overall, the study presents a clear, comprehensive, and structured analysis. The article-selection and screening procedure followed PRISMA principles to support transparency and reproducibility. Initially, 1,243 records were identified through a comprehensive PubMed search covering the years 2015 to 2025 using keywords including artificial intelligence, machine learning, deep learning, natural language processing, healthcare, precision medicine, predictive analytics, and robotic surgery. After duplicate removal and initial title and abstract screening, 257 articles were excluded because of duplication or lack of relevance. The remaining records underwent full-text review, and 986 papers were determined to meet the inclusion criteria. Sixty-eight articles were excluded because they were editorials, were unrelated to healthcare AI, or lacked sufficient methodological clarity.

Results

Bibliometric Parameters and Analytical Settings

To extract and analyze publication trends, collaboration networks, and topic structures, the bibliometric analysis was conducted using R ver. 4.3.2, RStudio, and VOSviewer. PubMed served as the primary data source, and the study parameters included authorship, institutional affiliations, year of publication, country of origin, citation counts, and author keywords. To improve analytical rigor, the minimum keyword-occurrence threshold was set at 5, and the minimum co-authorship link strength was set at 3. Documents with fewer than 10 citations were excluded from citation mapping. Theme clusters were identified using the VOSviewer modularity-based clustering algorithm (Louvain method), which applied association-strength normalization to balance links between frequently and infrequently occurring terms. Keywords were standardized through synonym merging (e.g., AI and artificial intelligence), removal of stop words, and lemmatization to improve comparability across studies. The resulting visualizations included keyword co-occurrence networks, author collaboration networks, and a topic-progression heatmap, providing an overall view of the research landscape from 2015 onward.

Bibliometric Findings

AI has advanced personalized healthcare applications, and research activity in this field has expanded alongside the growing volume and diversity of health-related data [22]. This study used visual analytics, and bibliometric visualizations were generated in RStudio ver. 4.3.2 with VOSviewer. The visual elements used to improve the clarity and depth of the findings included the following. Table 5 summarizes the descriptive characteristics of the final dataset comprising 986 included studies, consistent with the PRISMA selection process.

Co-authorship networks

To demonstrate interdisciplinary and cross-national research connections, particular attention was given to the international collaboration rate of 37.83%.

Citation maps

Citation mapping helped identify influential authors and their networks, including clusters centered on LeCun (DL), Esteva (medical imaging), and Topol (AI ethics).

Table 5. Descriptive characteristics of the final dataset

Stage	Count
Records identified	1,243
Duplicates removed	143
Records screened	1,100
Records excluded	114
Full-text assessed	986
Studies included	986

Thematic cluster visualization

Figure 2 presents 6 major domains—diagnostic imaging, predictive medicine, precision healthcare, clinical text mining, surgical innovation, and collaborative networks—thereby adding interpretive depth to the findings. The inclusion of such graphical representations is important because it makes the bibliometric and comparative analyses not only statistically supported but also visually interpretable.

Geographical Distribution

The United States, China, and the European Union accounted for the highest levels of research output, supported by strong funding programs and policy initiatives. India, Republic of Korea, and the Middle East also emerged as growing contributors with increasing global engagement.

Institutional and Author Networks

Co-authorship and institutional analyses showed that major universities, hospitals, and research institutes were actively engaged in collaborative activity with commercial partners. Prominent funding bodies included the National Institutes of Health (US), the National Natural Science Foundation of China, and Horizon Europe.

Keyword Co-occurrence and Clustering

Bibliometric analysis identified 6 clusters of research activity (Table 1). These clusters reflect major thematic orientations in healthcare AI and illustrate developments at the frontiers of research.

Citation Metrics

Highly cited publications included studies on convolutional neural networks (CNNs) for imaging, NLP for EHR mining, and surgical robotics. Many of the most highly cited papers were published in journals focused on medical informatics, biomedical engineering, and applied AI across disciplines.

Consolidation and interpretation of topic clusters

VOSviewer was used to perform thematic clustering based on keyword co-occurrence analysis, generating

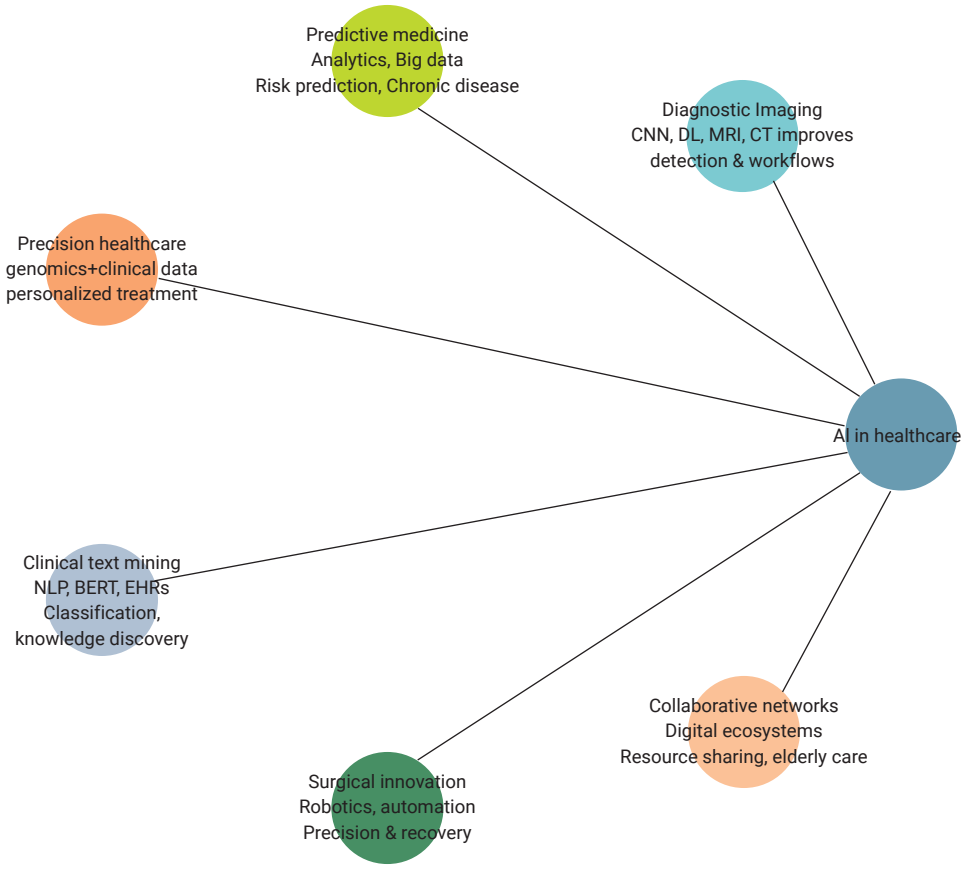


Figure 2. Thematic clusters of artificial intelligence (AI) applications in healthcare (2015–2025).
CNN, convolutional neural network; DL, deep learning; MRI, magnetic resonance imaging; CT, computed tomography; NLP, natural language processing; BERT, Bidirectional Encoder Representations from Transformer; EHR, electronic health record.

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6 aggregated clusters representing distinct but related areas of AI application in healthcare. These clusters were identified on the basis of semantic similarity and keyword co-occurrence frequency and were considered to represent the thematic structure of the field appropriately. The 6 main clusters were as follows: (1) diagnostic imaging, focused on the application of DL and CNNs to radiological interpretation; (2) predictive medicine, focused on big-data-driven models for chronic disease-risk prediction; (3) precision healthcare, (4) clinical text mining, dominated largely by NLP models such as Bidirectional Encoder Representations from Transformers (BERT) for processing unstructured EHRs; and (5) surgical innovation, focused on automation and robotics (Table 1). These clusters were then interpreted through a combination of bibliometric strength indicators, including link weight and centrality, and narrative synthesis, showing how AI methods interact with both the clinical and operational dimensions of contemporary healthcare.

Bibliometric indicators supporting the analysis

The impact, structure, and collaborative dynamics of AI research in healthcare were evaluated using a range of bibliometric indicators. The total corpus had an h-index of 67, indicating substantial and sustained citation impact. Intellectual visibility was also high, with an average citation rate of 12.3 citations per item. Co-citation analysis identified foundational authors such as LeCun (DL), Esteva (medical imaging), and Topol (AI ethics) as central to the field's intellectual structure. Cluster-centrality analysis identified diagnostic imaging and predictive medicine as particularly influential research areas, as both showed high betweenness centrality and served as bridges between technical and clinical domains. The collaboration index, calculated as the average number of co-authors per article, was 12.0, reflecting strong multidisciplinary participation. In addition, 37.83% of all included articles involved international co-authorship, underscoring the global and collaborative nature of healthcare AI research. Together, these metrics support the maturity, connectedness, and resilience of the field over the study period.

Trends in AI applications in healthcare

According to the Institute of Medicine (IOM) of the National Academies of Sciences, preventable healthcare errors result in 44,000 to 98,000 deaths annually in the United States. The IOM has criticized the healthcare sector for its inability to adopt new technologies in a consistently safe and effective manner [23,24]. In recent years, AI has shown considerable potential for improving the quality and efficiency of diagnosis, predicting patient outcomes, and personalizing treatment plans [25]. AI applications in healthcare have advanced substantially, particularly in diagnosis, treatment planning, and healthcare management. ML algorithms may support faster and more accurate diagnosis, whereas AI systems may also help tailor treatment strategies to individual patients and improve clinical outcomes. Healthcare management has similarly benefited from AI through improvements in resource allocation and process optimization. Interest in this field has been reflected in the rapid increase in publications and patents related to AI in healthcare. Emerging applications are also beginning to influence areas such as mental health diagnostics, rural healthcare accessibility, and early-stage disease prediction, suggesting broadening use across healthcare domains.

Enhanced comparative analysis through ML, DL, and NLP

A comparative analysis of ML, DL, and NLP highlights their distinct yet complementary roles in healthcare. ML is widely used in predictive modeling and patient-risk assessment because of its interpretability for structured data, although it is less effective for highly complex or unstructured information. DL dominates diagnostic imaging, robotics, and radiomics because of its high accuracy and automated feature extraction, despite limitations related to data requirements and limited transparency. NLP is essential for analyzing unstructured clinical material, such as EHRs and the medical literature, because it enables extraction of meaningful insights despite challenges related to linguistic variation and data quality. Collectively, these approaches suggest that integrated or hybrid AI models combining DL's analytical power, ML's interpretability, and NLP's language-processing capabilities may provide a more comprehensive framework for healthcare innovation (Table 6).

Thematic clusters

AI is now widely used to support diagnosis and administration in healthcare. Since the coronavirus disease 2019 (COVID-19) pandemic, interest has increased in the deployment of AI and robotics to protect healthcare personnel from exposure during patient care [26]. The clustering analysis identified 6 major research themes: (1) Diagnostic imaging: AI models, including CNNs and other DL methods, are used to analyze magnetic resonance imaging and computed tomography scans to improve disease detection and radiological workflows. (2) Predictive medicine: Predictive analytics and big-data approaches are improving risk prediction, particularly for chronic diseases such as diabetes. (3) Precision healthcare: Integration of genetic and clinical data supports tailored therapy and precision medicine. (4) Clinical text mining:

NLP approaches, including BERT-based models, can analyze unstructured EHRs and medical literature to improve patient classification and knowledge discovery. (5) Surgical innovation: Robotics and automation improve surgical precision and recovery. (6) Collaborative networks: Research on digital healthcare ecosystems highlights resource sharing, distributed decision-making, and innovation in older-adult care.

Trends, comparative analysis, and biomedical innovation

The evolution of AI research in healthcare shows a progression from early emphasis on diagnostic imaging and predictive analytics (2015–2018), to greater use of NLP and robotics during the COVID-19 period (2019–2021), and more recently (2022–2025) to areas such as mental health, rural care, and rare-disease diagnosis (Figure 2). DL has outperformed traditional ML in many imaging tasks, NLP remains essential for analysis of unstructured clinical data, and hybrid models are increasingly being developed for more comprehensive analysis. These technologies are driving biomedical innovation by accelerating drug development, supporting genomics-based personalized medicine, and improving surgical precision through adaptive robotics. AI may also improve epidemic prediction and resource allocation in healthcare, whereas partnerships among academia, industry, and healthcare organizations remain important for translating innovation into practice. The bibliometric findings also contribute substantially to comparative analysis of AI applications involving ML, DL, and NLP. The dataset comprised 986 peer-reviewed articles published between 2015 and 2025 across 399 academic sources, with an annual growth rate of 8.1% and a mean of 12 co-authors per paper, indicating strong global research collaboration. Of the 6 identified thematic clusters, diagnostic imaging and predictive medicine showed the highest betweenness centrality, consistent with the dominant roles of DL in imaging and ML in predictive analytics. The field's intellectual maturity is further reflected in an h-index of 67 (Table 7) and a mean citation rate of 12.3 citations per document. In addition, publications related to NLP increased markedly in 2020, likely reflecting rising interest in EHR mining and data analytics during the pandemic. These numerical findings support the complementary roles of ML, DL, and NLP in healthcare innovation. Recent articles also

Table 6. Comparative overview of AI techniques in healthcare

AI technique	Primary applications	Strengths	Limitations	Representative studies/trends (2015–2025)
Machine learning	Risk prediction, classification, patient stratification	Simple models, interpretable, useful for structured data	Limited scalability; less effective for complex unstructured data	Used extensively in predictive medicine, e.g., diabetes and cardiovascular models
Deep learning	Diagnostic imaging, radiomics, robotics	High accuracy for image-based diagnosis; automated feature learning	Data-hungry; low interpretability; prone to bias	Rapid growth post-2019; CNN-based radiology and robotic surgery papers dominate citations
Natural language processing	Clinical text mining, EHR data, literature mining	Enables understanding of unstructured clinical notes; supports decision-making	Requires linguistic diversity; sensitive to data noise	Post-COVID-19 expansion into EHR interoperability, mental health monitoring, and documentation automation

AI, artificial intelligence; CNN, convolutional neural network; EHR, electronic health record; COVID-19, coronavirus disease 2019.

Table 7. Key bibliometric performance and structural indicators of AI research in healthcare (2015–2025)

Indicator	Definition/purpose	Findings
h-index	Assesses research impact within AI–healthcare publications.	Overall dataset h-index = 67 (indicating consistent citation influence).
Average citations per document	Measures engagement level of the research corpus.	12.3 citations per document (after excluding 2025 in-progress items).
Co-citation analysis	Determines intellectual base via frequently co-cited authors.	Identified clusters around LeCun (DL), Esteva (medical imaging), Topol (AI ethics).
Cluster centrality	Evaluates importance of themes within keyword networks.	Diagnostic imaging (Cluster 1) and predictive medicine (Cluster 2) showed highest betweenness centrality, linking technical and clinical subfields.
Collaboration index	Mean co-authors per paper.	12.0, indicating strong interdisciplinary work.
International collaboration rate	% of multi-country co-authorships.	37.83%, reflecting high global participation.

AI, artificial intelligence; DL, deep learning.

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provide practical examples of advanced AI models such as federated learning and explainable AI. Federated learning has emerged as a privacy-preserving approach for training models across multiple healthcare institutions while maintaining data protection and improving the robustness of diagnostic systems. For example, studies [27,28] reported that federated learning improved breast cancer prediction and supported multicenter collaboration without direct data exchange. In contrast, explainable AI has been proposed to enhance clinical trust and decision transparency, particularly in radiology and precision medicine, by making algorithmic reasoning more interpretable to clinicians and patients. These examples illustrate the practical relevance and ethical promise of AI in real-world healthcare settings. Beyond summarizing trends, the review also emphasizes methodological rigor, generalizability, and therapeutic relevance through critical analysis of high-impact studies. The included research was evaluated in relation to dataset diversity, external validation, reporting transparency, and real-world testing outcomes. Although some studies were methodologically innovative, many still require further validation and clinical testing. The review therefore categorizes the literature into 3 stages of maturity—basic methodological studies, translational pilots, and scalable deployments—with common strengths including rigorous validation and transparency, and common limitations including sample bias and limited clinical-trial evidence. This critical perspective underscores the importance of fairness audits, future-oriented analysis, and implementation-focused research in moving AI in healthcare beyond experimental success toward evidence-based clinical practice.

Future directions and opportunities

Future developments in healthcare AI should emphasize emerging applications such as mental health diagnosis and rare-disease detection. AI may also substantially improve personalized medicine through integration of imaging, genetic, and clinical data to identify individualized risks, optimize treatments, and support patient monitoring. Infectious diseases such as HIV have also become targets for AI-enabled prediction of treatment outcomes, detection of adherence risks, and identification of resistance mutations to guide therapy selection. These applications may enable more precise treatment, earlier intervention, and better-targeted public health strategies. However, additional efforts in clinical validation, data diversity, and equity remain necessary to ensure that these benefits are distributed fairly across populations (Table 3). AI-based personalized treatment planning may support advances in these areas. Research in these domains may improve early detection, patient outcomes, and the capacity of healthcare systems to address existing gaps. Emerging approaches such as federated learning also enable privacy-preserving AI training by allowing institutions to collaborate without disclosing sensitive patient data, thereby improving model performance while protecting confidentiality. In addition, explainable AI may play an essential role in strengthening confidence in AI-driven healthcare decisions by making model outputs more visible and interpretable to both clinicians and patients. To promote equitable AI-based healthcare solutions globally, future strategies must include broader access to AI technologies in under-resourced settings, mitigation of bias through more diverse data representation, and the development of global partnerships for ethical AI systems. Governments, technology companies, and healthcare institutions should work together to reduce disparities and promote health equity worldwide.

The implications of AI breakthroughs in healthcare are substantial because they may help address fundamental challenges, improve patient outcomes, and stimulate progress in medical practice. AI algorithms emulate aspects of human learning, synthesis, analysis, generalization, and problem-solving and include approaches such as NLP, ML, DL, and large language models [29]. The performance of an AI system depends heavily on both data volume and data quality. To evaluate the full potential of AI algorithms, large and diverse datasets drawn from multiple healthcare systems are needed [30]. The significance of these findings can be summarized as follows: (1) Improved patient care: AI may support earlier disease detection, more personalized treatment, and better outcomes for patients with rare diseases. (2) Bridging healthcare gaps: AI may improve healthcare access in underserved areas through mobile health technologies and federated learning while maintaining data confidentiality. (3) Trust and ethical AI: Explainable AI may improve transparency and reduce bias, thereby supporting more equitable decision-making across populations. (4) Public health and crisis preparedness: AI may strengthen health-system resilience, improve preparedness, and support epidemic detection through more effective use of healthcare resources. (5) Global AI standardization: International collaboration may support ethical AI, regulatory alignment, and more equitable healthcare solutions worldwide.

How AI in Healthcare Aligns with Sustainability Goals

Bibliometric evidence suggests that healthcare AI research has increasingly converged on sustainability-oriented themes, particularly after 2020, as reflected by growing keyword

co-occurrence with terms such as ethics, equity, privacy, and global health access. Applications of AI in healthcare, including medical imaging analysis, predictive modeling, and personalized medicine, Patient-Reported Outcomes & Value Evidence, may improve healthcare delivery, expand access to high-quality care (Figure 3), and reduce inequities [31,32]. Direct AI applications in healthcare may also support several United Nations SDGs, including improved access to quality healthcare, equitable treatment, and more efficient resource use. Emerging bibliometric clusters also indicate growing interest in federated learning, reflecting an emphasis on privacy-preserving model training. Federated learning may help address major concerns related to patient privacy and data security because it avoids direct data exchange across institutions while allowing decentralized learning, thereby supporting ethical AI use and aligning with SDG 3, which emphasizes safe, inclusive, and high-quality healthcare. The increasing frequency of keywords related to NLP likewise suggests growing interest in text-based clinical intelligence and patient communication. However, the relatively limited use of NLP in mental health research points to a valuable avenue for future work, particularly the development of more accessible and scalable tools for early psychological screening, patient engagement, and support in digitally underserved populations. The following points connect these findings to global sustainability goals.

AI for universal health coverage

AI may strengthen universal health coverage by supporting early diagnosis, personalized treatment, and improved patient outcomes. It may also help address gaps in mental health and rare-disease care while enhancing population-health surveillance for epidemic prevention and health-system resilience.

Federated learning and ethical AI

Federated learning and ethical AI frameworks may support secure AI research by protecting patient information and promoting compliance with legal and regulatory requirements [33]. Explainable AI may also improve reliability and transparency in medical decision-making, thereby increasing trust in AI-based care. In addition, AI-informed policies may strengthen healthcare governance and security while promoting ethical and responsible AI use.

AI for equitable

AI may improve equitable healthcare access through telemedicine and mobile applications that extend care to underserved communities. Reducing bias in AI systems may also promote fairer treatment across diverse populations and help reduce disparities in healthcare delivery.

AI for resource efficiency and climate

Predictive AI may improve sustainability by strengthening allocation and supply-chain management of medical resources. AI-based disease surveillance may also improve preparedness for health emergencies. In addition, remote AI-enabled healthcare may reduce emissions and environmental burden by decreasing unnecessary travel and resource waste [34].

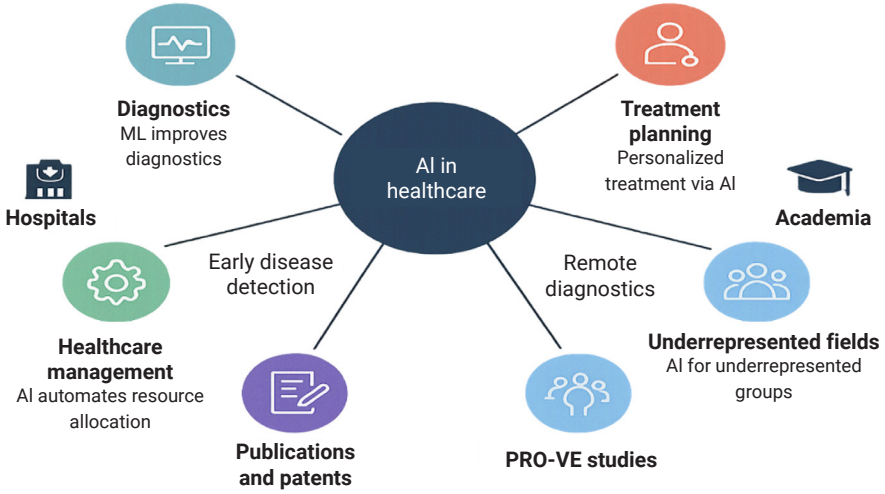


Figure 3. Artificial intelligence (AI) healthcare: a structured view. ML, machine learning; PRO-VE, Patient-Reported Outcomes & Value Evidence.

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Discussion

The adoption of AI in healthcare may support sustainability by improving patient care, increasing resource efficiency, and reducing inequities in access. Through predictive analytics, personalized medicine, and AI-based diagnostics, earlier disease detection and more targeted treatment planning may improve patient outcomes while supporting more efficient use of medical resources. Federated learning and ethical AI approaches may also strengthen data privacy, transparency, and trust in decision-making. Mobile health solutions and telemedicine may help reduce healthcare disparities while also decreasing the environmental burden associated with unnecessary travel and inefficient resource use. Together, these developments suggest that AI may contribute to a more sustainable, efficient, and inclusive global healthcare system. The potential of AI to address major healthcare challenges and support sustainable development across multiple domains is substantial. AI may improve healthcare delivery through earlier diagnosis, personalized treatment strategies, and predictive analytics for population-health programs [29]. Although AI research and healthcare research have traditionally differed in structure and emphasis, the 2 fields are becoming increasingly interconnected. AI research focuses primarily on scalable algorithms, computational models, and automated analytical methods such as ML, DL, and NLP. In contrast, healthcare research remains patient-centered and grounded in clinical trials, epidemiology, and evidence-based treatment, with strict ethical and regulatory requirements. The use of AI in healthcare bridges these domains by enabling data-driven innovation without abandoning the human-centered principles of care. Manual administrative practices in hospitals may also hinder efficient decision-making in healthcare systems. AI technologies have therefore been introduced into healthcare not only to address existing operational challenges, but also to create new opportunities through improved data processing and analysis [32,33]. From a sustainability perspective, AI may support universal health coverage by enabling earlier diagnosis, personalized medicine, and remote healthcare access in underserved settings. Ethical frameworks, federated learning, and explainable AI may help ensure that implementation is secure, transparent, and equitable, thereby strengthening stakeholder confidence. AI-supported optimization of medical supply chains and predictive analytics may also improve system efficiency and climate resilience. Taken together, these findings underscore the potentially transformative role of AI in promoting sustainable and equitable healthcare worldwide.

Ethical and Practical Challenges in AI-Driven Healthcare

The use of AI in healthcare raises major ethical and practical challenges, including algorithmic bias, data privacy concerns, limited transparency, legal ambiguity, and infrastructural constraints. Bias often arises from unrepresentative datasets and may lead to unequal outcomes across populations. In addition, fragmented EHR systems and nonstandardized data formats make model training and validation more difficult. Clinician trust depends heavily on both competence and accountability, making interpretable and clinician-in-the-loop systems especially important. Practical implementation is further hindered by regulatory uncertainty and limited computing resources. To address these challenges, global standards such as Institute of Electrical and Electronics Engineers (IEEE) and WHO guidance recommend privacy-preserving approaches, including federated learning, fairness audits, transparent reporting, and structured governance. Emerging best practices emphasize diverse

Table 8. Future directions and expected impact of AI in healthcare

Area	Key directions	Expected impact
Mental health	NLP for early symptoms, behavioral analysis, and digital health integration	Early detection, personalized care, continuous monitoring
Rare diseases	Genomic analysis, advanced imaging, predictive modeling	Faster and more accurate diagnosis, tailored treatment, and new drug discovery
Personalized treatment	Predictive analytics, real-time monitoring, drug response optimization	Targeted therapies, fewer side effects, individualized care
Federated learning	Privacy-focused AI training, improved models, and regulatory compliance	Secure data use, improved accuracy, aligned with regulations
Explainable AI	Transparent models, trust-building, compliance	Credibility, adoption, and responsible innovation
Low-resource settings	Affordable AI, scalable solutions, wider access	Inclusive care, bridging gaps, community outreach
Bias reduction	Fair and reliable AI models	Equity, accuracy, inclusiveness
Global collaboration	Shared ethics and regulations, cross-border AI work	Harmonized standards, fair access, stronger partnerships

AI, artificial intelligence; NLP, natural language processing.

data inclusion, clinician engagement, interoperable data standards, and scalable infrastructure to support AI in healthcare that is more ethical, transparent, and sustainable. Several reviewed studies also highlighted concrete ethical concerns. For example, DL models for imaging that were trained primarily on Western datasets showed lower diagnostic accuracy in underrepresented populations, raising concerns about algorithmic bias. NLP-based EHR-mining studies also reported privacy risks associated with potential re-identification, especially when multi-institutional datasets were used. In addition, black-box DL systems in radiology were reported to undermine clinician trust because of limited explainability, prompting calls for more robust explainable-AI frameworks in clinical decision support.

Future Research Directions

According to the bibliometric patterns observed in this review, the future of AI in healthcare may shift away from an exclusive focus on imaging-based applications and place greater emphasis on less represented areas such as mental health, where AI-based screening, monitoring, and intervention tools remain underused despite increasing demand. Greater geographic diversification is also needed, because current research output remains concentrated in high-income settings; stronger participation from low- and middle-income countries is necessary, particularly through resource-efficient and context-sensitive AI solutions. In addition, although many highly cited studies are methodologically innovative, an important gap remains in large-scale clinical validation, highlighting the need for real-world implementation studies and longitudinal analysis. Privacy-preserving strategies such as federated learning should be expanded to support cross-institutional collaboration without compromising patient confidentiality, thereby enabling more ethical and scalable healthcare AI systems (Table 8). At the same time, integration of explainable AI is essential, particularly in high-risk settings such as oncology and radiology, to improve transparency, trust, and clinical uptake. Taken together, these priorities emphasize the need to align technological progress with ethical governance, international equity, and long-term healthcare sustainability.

Notes

Ethics Approval

Not applicable.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

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

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Review Article

Evidence for a perinatal origin of childhood obesity: a systematic review and meta-analysis of risk and protective factors

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ABSTRACT

Objectives: This systematic review aimed to identify perinatal risk factors associated with obesity in children aged ≤5 years.

Methods: This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Medline (via PubMed), Embase, and Cochrane CENTRAL were searched from inception, without language or date restrictions. In addition, gray literature sources, including LILACS and CNKI, were screened for comprehensive evidence synthesis. Meta-analyses were conducted to estimate pooled risk ratios. Study quality was independently assessed by 2 reviewers using the Joanna Briggs Institute critical appraisal tool.

Results: A total of 24,643 articles were screened, and 39 cohort studies were included in the final analysis. Sample sizes ranged from 169 to 333,353 participants. Meta-analysis results indicated that high gestational weight gain (adjusted risk ratio [aRR], 1.46; 95% confidence interval [CI], 1.17–1.82), history of cesarean section (aRR, 1.25; 95% CI, 1.17–1.33), macrosomia (aRR, 1.88; 95% CI, 1.55–2.27), antibiotic use (aRR, 1.31; 95% CI, 1.14–1.51), pre-pregnancy obesity (aRR, 1.82; 95% CI, 1.21–2.73), and female sex (aRR, 1.46; 95% CI, 1.32–1.61) were associated with an increased risk of obesity in children aged ≤5 years. Exclusive breastfeeding (aRR, 0.74; 95% CI, 0.64–0.85) was identified as a protective factor.

Conclusion: Perinatal factors and pre-pregnancy obesity played important roles in increasing the risk of obesity in children aged ≤5 years. Breastfeeding was associated with a protective effect against childhood obesity. Therefore, obesity prevention efforts should begin during pregnancy, and maintaining appropriate maternal weight before conception is equally essential.

Keywords: Breast feeding; Child; Obesity; Risk factors

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Introduction

Over the past 2 decades, the prevalence of overweight and obesity among children aged ≤5 years has shown a gradual yet consistent increase, rising from 5.4% in 2000 to 5.7% in 2022. Currently, 72 million children and adolescents aged 5–19 years are either overweight or obese, and this number is projected to increase to 101 million by 2035 [1]. Several studies have shown that approximately 25% of children with obesity and up to 80% of children aged 10–14 years with obesity remain obese into adulthood [2,3]. The increasing incidence of childhood overweight and obesity has been linked to a wide range of adverse health outcomes, including metabolic syndrome, cardiovascular disease, type 2 diabetes mellitus, respiratory symptoms, malignancies, and behavioral problems [4–6]. Each year, obesity is estimated to cause 4.72 million deaths worldwide, a figure comparable to the number of deaths attributed to air pollution [7].

The increasing incidence of childhood obesity is likely driven by a complex interaction of genetic factors, lifestyle behaviors, environmental exposures, dietary patterns, and socioeconomic conditions. Maternal factors, including high pre-pregnancy body mass index (BMI), excessive gestational weight gain, gestational diabetes mellitus, and maternal perinatal depression, have been associated with obesity in children aged 5 and 9 years [8,9]. In addition, nonexclusive breastfeeding, macrosomia, mode of delivery, and antibiotic use have been identified as risk factors for childhood obesity [10,11]. Antibiotic exposure and cesarean delivery may disrupt the composition of the gut microbiota, resulting in dysbiosis. The gut microbiota plays a critical role in energy extraction from food, appetite regulation, and maintenance of intestinal barrier function [12].

Several systematic reviews and umbrella reviews have examined early-life determinants of childhood obesity [13–16]. However, the available evidence remains inconsistent. For example, Weng et al. [15] reported a 15% protective effect of breastfeeding, whereas Woo et al. [13] concluded that the association between breastfeeding and obesity prevention is inconsistent across studies. These discrepancies are partly attributable to variations in follow-up duration, as many studies only monitor outcomes during the first few months of life, thereby limiting conclusions regarding long-term effects [13]. Conversely, studies with follow-up periods extending from conception to 18 or 26 years of age may be too prolonged to isolate early-life factors specific to childhood obesity [13,16]. In addition, the limited number of studies evaluating specific exposures, such as cesarean delivery, gestational weight gain, or infant temperament, restricts the ability to draw robust conclusions regarding these factors [15].

HIGHLIGHTS

- High gestational weight gain, pre-pregnancy obesity, sex, cesarean delivery, macrosomia, and early antibiotic exposure were identified as risk factors for obesity in children aged ≤5 years.
- Exclusive breastfeeding was identified as a protective factor against obesity in children aged ≤5 years.
- These findings highlight the perinatal period as a critical window for the implementation of obesity prevention strategies.

The heterogeneity of findings across previous reviews, along with variability in follow-up duration, underscores the need for a more comprehensive and up-to-date synthesis of the evidence. Such an evaluation is essential for identifying perinatal risk factors that remain relevant in the context of current childhood obesity trends. Focusing on children aged ≤5 years is particularly important, as this period represents a critical window for metabolic programming and the establishment of early dietary and sedentary behavior patterns. Accordingly, this systematic review and meta-analysis aimed to identify perinatal risk factors for childhood obesity in children aged ≤5 years. By concentrating on this sensitive developmental period, this study seeks to inform global policy frameworks and early intervention strategies designed to mitigate the long-term health consequences of childhood obesity.

Materials and Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered with PROSPERO (CRD42024513913).

Eligibility Criteria

We included cohort studies in this meta-analysis based on the population, exposure, comparison, and outcome (PECO) framework. Population: Perinatal or early infancy cohorts followed longitudinally. Specifically, we included prospective studies in which participants were recruited during the pre-pregnancy period or infancy and followed until age ≤5 years. Exposure: Early-life determinants, including preconception, prenatal, perinatal, and postnatal factors. There was no restricted time window for these

exposures, which encompassed the entire developmental trajectory prior to the assessment of obesity status. Comparison: children not exposed to the specified risk factors. Outcome: obesity.

To minimize publication and language bias, no language or date restrictions were applied, and the search was expanded to include gray literature sources, such as Latin American and Caribbean Health Sciences Literature (LILACS) and China National Knowledge Infrastructure (CNKI). All identified non-English studies were assessed for eligibility using translation services when necessary. A priori exclusion criteria included non-cohort study designs, studies in which the final obesity assessment occurred after age 5 years, failure to assess obesity as a primary or secondary outcome, and studies focused on specific clinical populations.

Information Sources

Medline (via PubMed), Embase, Cochrane CENTRAL, LILACS, and CNKI were searched for articles relevant to the study objectives. These databases were searched from their inception (1973 for Medline, 1996 for Embase, 1990 for Cochrane CENTRAL, 1981 for LILACS, and 1994 for CNKI) through December 18, 2025.

Search Strategy

Keywords and related synonyms were applied by combining Medical Subject Headings (MeSH) and free text terms, as follows: (("child"[MeSH Terms] OR "infant"[MeSH Terms] OR "child, preschool"[MeSH Terms] OR "infant*"[Title/Abstract] OR "toddler*"[Title/Abstract] OR "preschool*"[Title/Abstract] OR "under five*"[Title/Abstract]) AND ("determinant*"[Title/Abstract] OR "risk factor*"[Title/Abstract] OR "protective factor*"[Title/Abstract] OR "predictor*"[Title/Abstract]) AND ("obesity"[MeSH Terms] OR "overweight"[MeSH Terms] OR "body mass index"[MeSH Terms] OR "obes*"[Title/Abstract] OR "overweight"[Title/Abstract] OR "BMI"[Title/Abstract] OR "weight-for-length"[Title/Abstract] OR "weight-for-height"[Title/Abstract] OR "z score*"[Title/Abstract] OR "WHZ"[Title/Abstract] OR "WFL"[Title/Abstract])).

Selection Process

The outcomes evaluated were the incidence of obesity in children aged ≤5 years and associated risk factors. After exporting records from the 5 databases into Mendeley, duplicate records were removed. Based on the eligibility criteria, 2 researchers (A.R.S. and J.O.R.) independently screened the titles and abstracts to identify studies relevant to the objectives of this review. Following this initial screening, full-text articles were retrieved and reviewed in detail to determine final eligibility. In cases of disagreement, 2 additional reviewers (N.N. and M.I.K.) were consulted to reach consensus.

Data Collection Process

Two researchers (A.R.S. and J.O.R.) independently extracted data into Microsoft Excel using a structured data extraction template. Extracted information included authors and year of publication, country, study design, sample size, exposure variables, operational definition of obesity (e.g., World Health Organization [WHO], Centers for Disease Control and Prevention [CDC], or International Obesity Task Force [IOTF]), timing of obesity assessment (reported in years), covariate adjustment, and adjusted risk ratios (aRRs) for obesity outcomes.

Data Items

The main outcome of interest in this study was obesity in children aged ≤5 years. Recognizing that included studies used different growth reference standards, outcome definitions were harmonized to ensure clinical and statistical comparability. Obesity was defined as a BMI-for-age z-score ≥+2 standard deviations according to the WHO Child Growth Standards, which is clinically equivalent to the ≥95th percentile on the CDC growth charts and the age- and sex-specific cut-offs defined by the IOTF. Overweight status was not analyzed, as this review focused exclusively on obesity. To ensure consistency across studies, a standardized harmonization protocol was applied to all exposure variables. For each determinant, minimum thresholds or binary classifications were defined based on clinical relevance. Mode of delivery was categorized as cesarean section or vaginal delivery. Antibiotic exposure was assessed based on the child's history of antibiotic use (yes/no), rather than maternal antibiotic use during pregnancy. When studies reported multiple exposure levels (e.g., dosage or frequency), data corresponding to the highest exposure level were extracted. Macrosomia was defined as birth weight >4,000 g. Gestational weight gain was classified as excessive when it exceeded the upper recommended limit and as normal when it fell within recommended ranges according to the Institute of Medicine guidelines. Exclusive breastfeeding was defined as feeding with breast milk only, without formula, other milk, or complementary foods, until 6 months of age. Studies that did not align with these classifications were excluded from the meta-analysis to preserve statistical homogeneity but were retained in the study characteristics table for qualitative descriptive purposes.

Study Risk of Bias Assessment

Study quality was independently assessed by 2 reviewers

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(A.R.S. and J.O.R.) using the Joanna Briggs Institute (JBI) checklist for cohort studies [17]. This checklist comprises 11 criteria, including population similarity, consistency and validity of exposure measurement, identification and management of confounding factors, confirmation that participants were outcome-free at baseline, validity and reliability of outcome measurement, adequacy of follow-up duration and completeness, strategies for addressing incomplete follow-up, and appropriateness of statistical analyses. All included studies met the predefined quality threshold of ≥7 points, ensuring that only high-quality evidence contributed to the meta-analysis.

Effect Measures

The primary effect measure was the pooled aRR, representing the association between exposure and childhood obesity risk. When studies reported odds ratios (ORs), these were considered equivalent to aRRs when outcome incidence was low (<10%). Otherwise, ORs were converted to aRRs using the following formula: $aRR = OR/[(1-P_0)+(P_0 \times OR)]$, where P_0 represents the incidence of the outcome in the unexposed group [18]. Review Manager (RevMan) version 5.3 software (The Cochrane Collaboration) was used to conduct meta-analyses. Statistical heterogeneity was assessed using the I^2 statistic. A fixed-effects model was applied when $I^2 < 50\%$, whereas a random-effects model was used when $I^2 \geq 50\%$.

Synthesis Methods

Studies meeting the inclusion criteria were grouped according to the perinatal risk factors evaluated. Only studies reporting obesity in children aged ≤5 years as an outcome were included in the quantitative synthesis. When ORs were reported, these were converted to aRRs using baseline risk estimates from the comparison group. Studies defining obesity using the 95th percentile were adjusted to align with the WHO definition. When summary data were incomplete, such as missing confidence intervals (CIs), calculations were derived from raw data when available. All quantitative analyses were performed using RevMan version 5.3 software, and results are presented using forest plots. Meta-analyses were conducted using a random-effects model to account for between-study variability. Statistical heterogeneity was evaluated using the I^2 statistic, with values ≥50% indicating substantial heterogeneity. To assess the robustness of pooled estimates and determine whether any single study exerted disproportionate influence, a leave-one-out sensitivity analysis was conducted by sequentially excluding each study.

Results

Study Selection

Database searches identified 24,890 records (13,971 from Medline via PubMed, 726 from Cochrane CENTRAL, 8,852 from Embase, 1,210 from LILACS, and 131 from CNKI). After removing 247 duplicate records, 24,643 records remained for title and abstract screening. Of these, 24,591 records were excluded because they did not meet the inclusion criteria. The full texts of 52 articles were assessed for eligibility. Twelve articles were excluded for the following reasons: obesity was measured beyond 5 years of age ($n=3$), the study design was not a cohort study ($n=3$), or results were not stratified for obesity outcomes ($n=6$). The complete process of study identification, screening, and inclusion is presented in Figure 1.

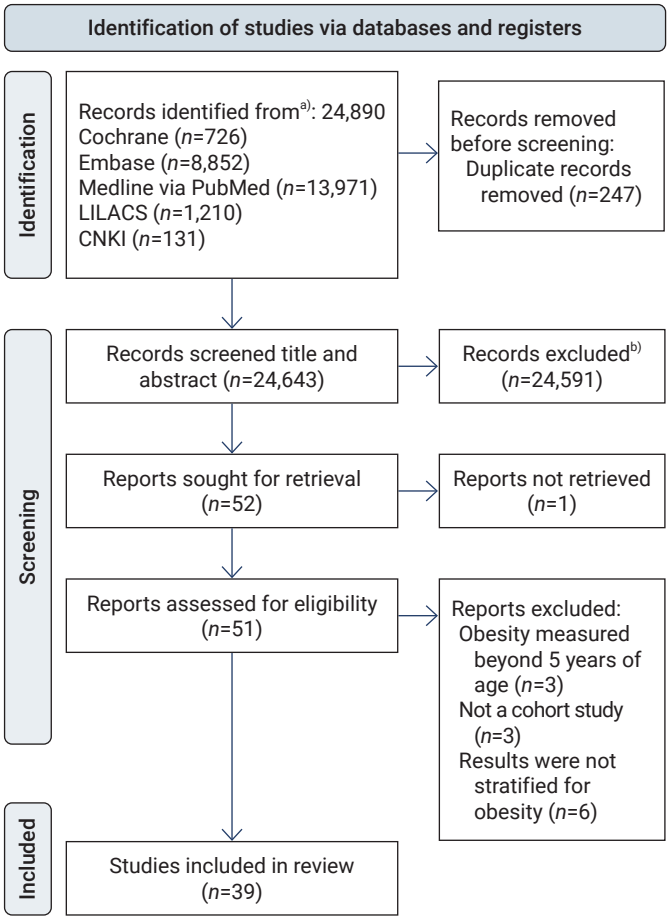


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study identification and selection. [a]Databases searched include Cochrane, Embase, Medline (via PubMed), LILACS, and CNKI. [b]Records excluded after title and abstract screening due to irrelevance or not meeting inclusion criteria.

Study Characteristics

A total of 39 studies were included in this review. The included studies were conducted across diverse geographical regions, including China [19–22], Ireland [23–25], the United States [11,26–41], Japan [42], England [43–47], the Netherlands [48], Korea [10,49], Germany [50], Hawaii [51], Australia [52] and New Zealand [12,53,54]. Sample sizes ranged from 169 to 333,353 participants, with study populations generally comprising children aged ≤ 5 years. The detailed characteristics of the included studies are summarized in Table 1.

Table 1. Descriptive summary of the studies

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Anderson et al. [34]	2020	USA	Cohort	260,935	Sex-specific BMI 95th percentile for age	4	Children's age, sex, race/ethnicity, family income	Breastfeeding (female) Breastfeeding (male)	0.67 0.78
Awujoola et al. [26]	2024	USA	Retrospective cohort	1,447	Sex-specific BMI 95th percentile for age	5	Maternal age at delivery, ethnicity, pregravid maternal weight, mode of delivery, intrapartum prophylaxis against group B streptococcal disease, birth weight, neonatal sex, type of feeding, mother and child comorbidities	Neonatal antibiotic	1.27[a]
Badon et al. [35]	2020	USA	Cohort	96,289	Sex-specific BMI 95th percentile for age	3	Maternal age, race/ethnicity, parity, education, insurance, smoking	High gestational weight gain	1.30
Bailey et al. [36]	2014	USA	Cohort	65,480	Sex-specific BMI 95th percentile for age	2–5	Gender, race, ethnicity, age at first primary care visit, location at first visit, insurance, clinical diagnoses, steroid use, antireflux medication use	Antibiotic use	1.11
Butler et al. [54]	2021	New Zealand	Cohort	1,731	Sex-specific BMI 95th percentile for age	4–5	Paternal BMI, maternal smoking, infant weight gain	Birth weight	3.81
Chaparro et al. [37]	2020	USA	Cohort	9,129	Sex-specific BMI 95th percentile for age	4	Child sex, race/ethnicity, family poverty, maternal education	Breastfeeding (female) Breastfeeding (male)	1.10 1.00
Chiasson et al. [39]	2016	USA	Cohort	50,589	Sex-specific BMI 95th percentile for age	3	Race, residence, birth weight, breastfeeding package, screen time, healthy food daily, fruit and vegetable consumption	Macrosomia Exclusive breastfeeding Screen time >2 h daily	1.66[a] 0.55[a] 1.15[a]
Choi et al. [10]	2022	Korea	Cohort	26,047	Sex-specific BMI 95th percentile for age	5	Birth weight, breastfeeding, income level, dietary behaviors, physical activity	Macrosomia Female Maternal BMI Middle income Good appetite Heavy intake of sweet food	1.42[a] 1.44[a] 2.02[a] 1.15[a] 1.51[a] 1.24[a]

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Table 1. Continued

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Diesel et al. [38]	2015	USA	Cohort	609	Sex-specific BMI 95th percentile for age	3	Race, marital status, employment status, household income, education, parity, mental health, smoking, alcohol, pre-pregnancy BMI, breastfed status	High gestational weight gain	2.20
Gaillard et al. [48]	2013	The Netherlands	Cohort	4,571	IOTF cut-offs for BMI, which are age and sex-specific	4	Maternal age, education, ethnicity, parity, folic acid supplementation, smoking habit, alcohol consumption	High gestational weight gain	0.93
Hawkins et al. [11]	2019	USA	Cohort	55,058	Sex-specific BMI 95th percentile for age	5	Child sex, race/ethnicity, maternal education, maternal age, marital status, sibling order, child year of birth	Cesarean section Breastfeeding Smoking during pregnancy	1.26 0.80 1.54
Hu et al. [40]	2019	USA	Cohort	1,425	Sex-specific BMI 95th percentile for age	4	Maternal age, race, marital status, education, insurance, energy intake during pregnancy, alcohol, tobacco use, parity, child sex, birth weight, gestational age, breastfed status	High gestational weight gain Pre-pregnancy obesity Gestational diabetes	1.46 2.24 2.14
Kelly et al. [24]	2019	Ireland	Cohort	8,186	Sex-specific BMI 98th percentile for age	5	Gender, creche, breastfed, food energy intake, level of exercise, having chronic illness, maternal BMI, birth weight of child, social class of household, maternal smoking, maternal education, and ethnicity	Antibiotics use	1.60
Malihi et al. [53]	2021	New Zealand	Cohort	5,598	IOTF cut-offs for BMI, which are age and sex-specific	4.5	Child sex, ethnicity, birth weight, household income, maternal age, maternal education	Macrosomia Lower food security during infancy Screen time >1 h/d Shorter sleep duration Weekly to daily consumption soft drink Female	1.40 1.32 1.22 1.30 1.25 1.26
Masukume et al. [25]	2018	Ireland	Cohort	11,134	IOTF cut-offs for BMI, which are age and sex-specific	3	Maternal age, education, ethnicity, marital status, region, infant sex, gestational age, pre-eclampsia, gestational diabetes, parity, birth weight	Cesarean section (elective)	1.32

(Continued to the next page)

Table 1. Continued

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Masukume et al. [12]	2019	New Zealand	Cohort	6,599	IOTF cut-offs for BMI, which are age and sex-specific	2–4.5	Maternal age, maternal ethnicity, education, marital status, pre-pregnancy BMI, maternal smoking during pregnancy, infant sex, gestational age at delivery, birth weight, parity, diabetes mellitus.	Cesarean section (planned)	1.42
Pan et al. [19]	2019	China	Cohort	1,767	Sex-specific BMI 95th percentile for age	3	Maternal age, gestational age, parity, infant sex, education, anemia at first antenatal visit, pre-pregnancy BMI, gestational weight gain, breastfeeding	Macrosomia	2.40[a)]
Pei et al. [50]	2014	Germany	Cohort	1,734	Sex-specific BMI 95th percentile for age	2	Parental education, birth weight, duration of gestation, head circumference, maternal age, maternal pre-pregnancy BMI, maternal smoking	Cesarean section	1.59[a)]
Ralphs et al. [46]	2021	UK	Cohort	6,410	Sex-specific BMI 95th percentile for age	4–5	Maternal age, maternal BMI, maternal education, alcohol consumption, maternal smoking, parity, gestational diabetes, child sex, birth weight, gestational period, maternal job status, maternal house tenure	Cesarean section	0.98[a)]
Stark et al. [41]	2019	USA	Retrospective Cohort	333,353	Sex-specific BMI 95th percentile for age	2	Maternal smoking, parental relationship, mode of delivery, birth weight, birth length.	Antibiotics use Cesarean section	1.42 1.26
Terashita et al. [42]	2023	Japan	Cohort	60,769	IOTF cut-offs for BMI, which are age and sex-specific	3	Maternal age, pre-pregnancy BMI, education, household income, history of smoking, alcohol consumption, pregnancy complication, parity, child sex, birth term, birth weight	Cesarean section	1.16
Ziauddeen et al. [43]	2022	UK	Cohort	4,789	Sex-specific BMI 95th percentile for age	4–5	Maternal age, maternal education, smoking, employment status, gestational diabetes, birth weight, gestational age, breastfeeding	High gestational weight gain	1.87

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Table 1. Continued

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Anderson et al. [27]	2011	USA	Cohort	6,650	Sex-specific BMI 95th percentile for age	4.5	Parenting practices, maternal BMI, sociodemographic characteristics, the quality of mother-child interaction	Insecure attachment	1.24[a]
Taveras et al. [28]	2010	USA	Cohort prospective	826	Sex-specific BMI 95th percentile for age	4	Maternal age, education, parity, household income, pre-pregnancy BMI, paternal BMI	Higher rates of maternal depression	1.51
								Infancy rapid weight gain	2.27
								Introduce solid food before 4 months of age	2.14
								Higher rates of maternal restrictive feeding practice	2.99
								Television in bedroom	2.00
								Higher intake of sugar-sweetened beverages	4.58
								Higher intake of fast food	2.00
Yang et al. [21]	2025	China	Cohort prospective	8,201	BMI for age ≥+2 SD	3	Parental sociodemographic characteristics (education, occupation, household size, and household income); maternal health factors (delivery mode and gestational illness); and child-level variables (birth year, birth weight, gestational age, sex, anemia, breastfeeding, and primary caregiver)	Low economic status	2.15
								Mother work in agriculture	2.30
								Small for gestational age	1.63
Okihiro et al. [51]	2012	Hawaii	Retrospective cohort	389	Sex-specific BMI 95th percentile for age	4–5	Ethnicity, cohort and sex	Severe rapid gain from 12 to 23 months	2.64[a]

(Continued to the next page)

Table 1. Continued

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Brophy et al. [47]	2009	UK	Cohort prospective	17,561	IOTF cut-offs for BMI, which are age and sex-specific	5	Socioeconomic status	Ethnic group Asian	1.6
								Ethnic group African	2.5
								Watch more time 3 hours of TV a day	1.3
								Solid food before 3 months	1.2
								Smoking near child	1.3
								Mothers pre-pregnancy weight	1.9
Goodwin et al. [44]	2025	UK	Cohort prospective	10,446	BMI z-score ≥ 95th percentile	4–5	Gestational diabetes, socioeconomic position, smoking during pregnancy, maternal pre-pregnancy obesity, low birth weight, prenatal antibiotic use	Early life antibiotic use	1.36
Janjua et al. [29]	2012	USA	Cohort prospective	740	BMI for age and sex ≥ 95th percentile	5	Maternal pre-pregnancy BMI, birth weight, number of children at home, sex, smoking during pregnancy	Maternal pre-pregnancy BMI (obese)	2.53
								Birth weight	2.04
								Number of children at home (< 2)	1.64
								Sex (female)	1.67
								Smoking during pregnancy (1–12 cigarette)	1.42

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Table 1. Continued

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Lee et al. [49]	2024	Korea	Cohort	16,866	BMI for age and sex ≥95th percentile	3–5	Prematurity, prolonged breastfeeding, late complementary food, sugar-sweetened beverages	At 3 years, meat in complementary food	1.27
								Prolonged breastfeeding	1.14
								Consumption of sweetened beverages	1.37
								At 4 years, meat in complementary food	1.24
								Consumption of sweetened beverages	1.58
								At 5 years, meat in complementary food	1.16
								Consumption of sweetened beverages	1.514
Wojcicki et al. [30]	2015	USA	Retrospective	833	BMI for age and sex ≥95th percentile	3	Maternal and family sociodemographic, prenatal and postnatal health, infant delivery and feeding, maternal and child psychosocial, child dietary and lifestyle	Low income	3.94
								Maternal pre-pregnancy obesity	1.77
								Longer duration of breastfeeding	0.95
Sun et al. [22]	2017	China	Cohort	1,949	BAZ >+2	2	Gender, delivery mode, maternal age, birth weight, duration of breastfeeding and sleeping	Higher BMI magnitude	2.69
								Later timing of infant BMI peak	1.35
Zhang et al. [20]	2013	China	Cohort	1,098	BMI for age and sex ≥95th percentile	2	Child sex, delivery type, gestational age, number of siblings, and parental social demographic and economic	Birth weight	1.85
								Pre-pregnancy maternal BMI	1.09
								Paternal BMI	1.06
								Exclusive breastfeeding	0.53
								Bottle emptying by encouragement	1.35
Verstraete et al. [31]	2014	USA	Cohort	169	BMI for age and sex ≥95th percentile	4	Maternal obesity, maternal marriage status, maternal education, maternal country of origin, years mother has lived in the United States	Breastfeeding	0.29

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Table 1. Continued

Study	Year	Country	Study design	Sample size	Obesity definition (standard)	Timing of obesity assessment (y)	Adjusted variables	Factors	aRR
Peacock-Chambers et al. [33]	2017	USA	Cohort	5,750	BMI for age and sex ≥95th percentile	4	Child race, birth weight, maternal age, maternal pre-pregnancy weight, maternal education, child gestational age, parent marital status, maternal employment, smoking in pregnancy.	Infants with ITSC scores ≥6	1.25[a]
Goisis et al. [45]	2016	UK	Cohort prospective	11,965	IOTF cut-offs for BMI, which are age and sex-specific	5	child's sex, mother smoking during pregnancy, length of breastfeeding, introduction to solid foods before months, frequency of sport per week, frequency of active playing with a parent per week, frequency of TV, watching, frequency of PC use, bed time, frequency child is taken to the playground, fruit portion per day, eating breakfast every day, maternal BMI and sweet drinks consumption	Bottom income quintile	1.3
Huh et al. [32]	2012	USA	Cohort prospective	1,255	BMI for age and sex ≥95th percentile	3	Maternal age, maternal education, race/ethnicity, child age, sex, maternal pre-pregnancy BMI, birth weight	Cesarean delivery	2.10
Layte et al. [23]	2014	Ireland	Cohort prospective	9,057	IOTF cut-offs for BMI, which are age and sex-specific	3	Maternal age, child sex, gestation, birth weight, birth order, weight gain in pregnancy and multiple status	Female Birth weight Breastfeeding (6+mo) Smoking in pregnancy (6–10 daily) Maternal obesity	1.44 1.75 0.51 1.93 2.83
O'Callaghan et al. [52]	1997	Australia	Cohort	4,062	BMI for age and sex ≥95th percentile	5		Birth weight (≥95 percentiles) Female Maternal BMI (≥95 percentiles) Maternal education (primary) Income (5 y) Paternal BMI (≥95 percentiles)	1.70 1.40 3.90 1.90 1.20 2.00

aRR, adjusted risk ratio; BMI, body mass index; IOTF, International Obesity Task Force; TSC, Infant–Toddler Social and Emotional Assessment.
[a]aRR converted from odds ratio.

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Risk of Bias in Studies

All studies included in the analysis demonstrated a low risk of bias, with quality assessment scores ≥7 (Tables 2, 3). Despite the overall high methodological quality, several studies did not report the number of participants lost to follow-up or the reasons for attrition. In addition, explicit strategies for addressing incomplete follow-up in the statistical analysis were often lacking. Another common limitation across the majority of studies was insufficient adjustment for potential confounding variables, particularly lifestyle-related factors such as diet, screen time, and physical activity.

Results of Syntheses

The synthesis of early-life determinants of childhood obesity (≤5 years) is visually summarized in Figure 2. Meta-analyses were performed for 7 key variables, as described below.

High gestational weight gain

The meta-analysis of 5 studies examining the association between excessive gestational weight gain and childhood obesity demonstrated a significantly increased risk. The pooled aRR was 1.46 (95% CI, 1.17–1.82; I^2=52%), indicating that children born to mothers with excessive gestational weight gain had a 46% higher risk of obesity compared with those born to mothers with adequate gestational weight gain. Heterogeneity across studies was moderate (I^2=52%, χ^2=8.31, degrees of freedom [df]=4, p=0.08). Detailed results are presented in Figure 3.

Cesarean section

Cesarean section was associated with a 25% increased risk of obesity in children aged ≤5 years (Figure 4), with a pooled aRR of 1.25 (95% CI, 1.17–1.33; I^2=55%). Most studies reported positive associations, although 2 studies did not observe statistically significant results. Despite this variability, the overall pooled effect remained highly significant,

Table 2. Risk of bias assessment of each study included in the systematic review (Joanna Briggs Institute)

	A1	A2	B1	B2	B3	C1	C2	C3	D	G	H1	H2	K	M1	M2	M3	P1	P2	R	S	T	Z
Were the 2 groups similar and recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were confounding factors identified?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	No	No	?	Yes	No	No	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Were strategies to address incomplete follow-up utilized?	No	No	?	Yes	No	No	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Was appropriate statistical analysis used	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Score	9	9	9	9	9	9	11	9	10	9	9	9	9	9	10	11	11	11	11	8	8	11

A1=Anderson 2020, B3=Butler 2021, D=Diesel 2015, K=Kelly 2019, P1=Pan 2019, T=Terashita 2022, A2=Awujoola 2023, C1=Chappar o 2019, G=Gaillard 2013, M1=Malihi 2021, P2=Pei 2014, Z=Ziauddeen 2022, B1=Badon 2020, C2=Chiasson 2016, H1=Hawkins 2019, M2=Masukume 2018, R=Ralphs 2021, B2=Bailey 2024, C3=Choi 2022, H2=Hu 2019, M3=Masukume 2019, S=Stark 2018. Quality assessment was rated as yes, no, unclear (indicated by ?), or not applicable.

Table 3. Risk of bias assessment of each study included in the systematic review (Joanna Briggs Institute) continued

	A1	A2	B1	B2	B3	C1	C2	C3	D	G	H1	H2	K	M1	M2	M3
Were the 2 groups similar and recruited from the same population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure measured in a valid and reliable way?	Yes	?	?	Yes	?	?	?	Yes	Yes	?	Yes	?	Yes	Yes	Yes	?
Were confounding factors identified?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were strategies to deal with confounding factors stated?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the outcomes measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the follow-up time reported and sufficient to be long enough for outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was follow-up complete, and if not, were the reasons to loss to follow-up described and explored?	?	?	?	?	No	?	?	?	?	?	?	?	Yes	No	Yes	?
Were strategies to address incomplete follow-up utilized?	No	No	No	?	No	No	No	No	No	No	No	No	No	No	Yes	No
Was appropriate statistical analysis used	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Score	9	8	8	7	8	8	8	9	9	8	9	8	10	9	11	8

A1 = Anderson 2011, B3 = Brophy 2009, D = Wojicicki 2015, K = Peacock-Chambers 2017, A2 = Taveras 2010, C1 = Goodwin 2025, G = Sun 2017, M1 = Hu 2012, B1 = Yang 2025, C2 = Janjua 2012, H1 = Zhang 2013, M2 = Layte 2014, B2 = Okihiro 2012, C3 = Lee 2024, H2 = Verstaete 2014, M = O'Callaghan.
Quality assessment was rated as yes, no, unclear (indicated by ?), or not applicable.

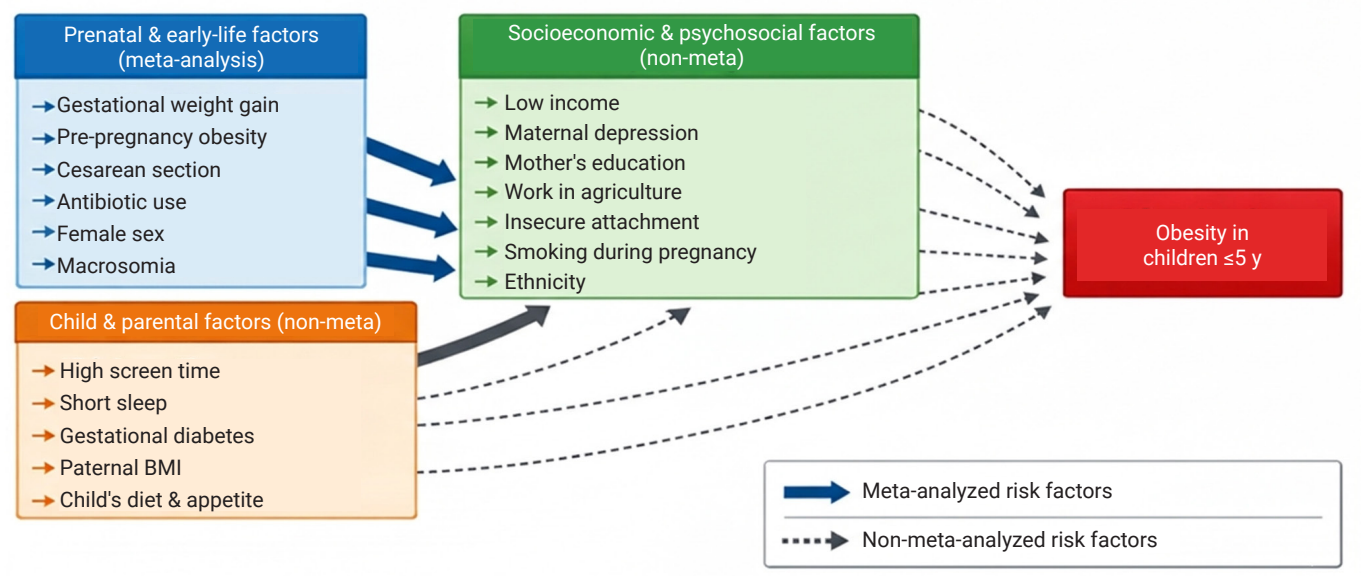


Figure 2. Conceptual framework of perinatal/early determinants of childhood obesity. BMI, body mass index.

supporting cesarean delivery as a risk factor for childhood obesity.

Macrosomia

Children with a birth weight greater than 4,000 g demonstrated an increased risk of obesity, with a pooled aRR of 1.88 (95% CI, 1.55–2.27; I^2 = 76%). All included studies reported positive associations, with effect sizes ranging from moderate to strong (Figure 5).

Antibiotic use

The pooled aRR for antibiotic exposure was 1.31 (95% CI, 1.14–1.51; Z = 3.75, p < 0.00001), indicating that children exposed to antibiotics had a 31% higher risk of developing obesity compared with those without antibiotic exposure. Heterogeneity across studies was very high (I^2 = 86%; χ^2 = 33.08, df = 4, p < 0.00001), reflecting substantial variability among studies. Despite this heterogeneity, all included studies consistently demonstrated a positive association between antibiotic exposure and childhood obesity (Figure 6).

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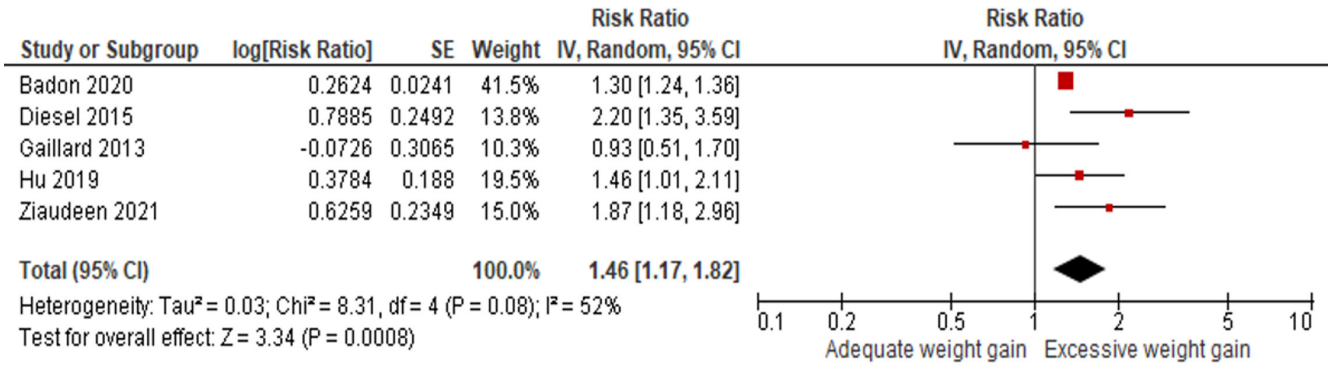


Figure 3. Forest plot of the association between high gestational weight gain and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

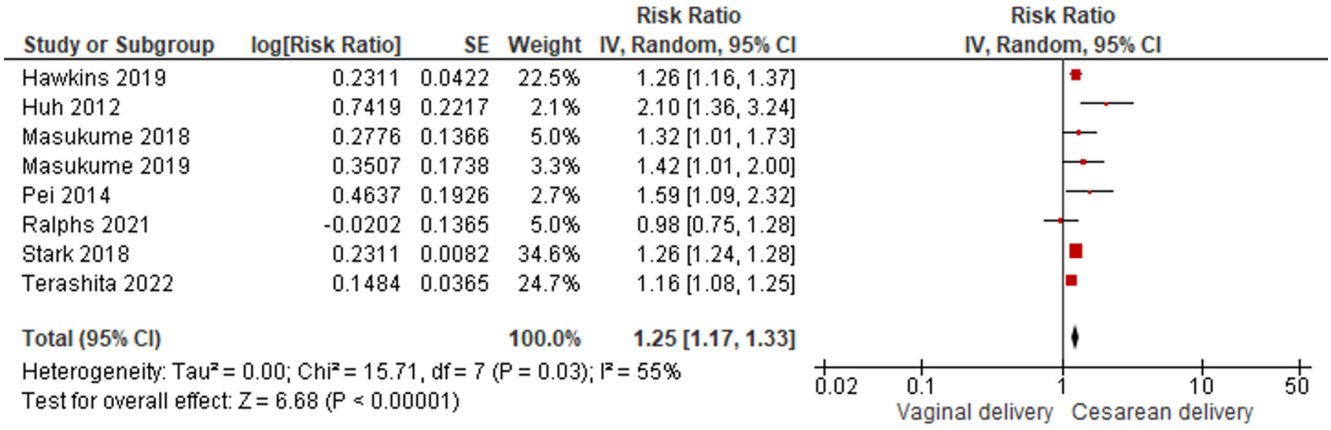


Figure 4. Forest plot of the association between cesarean section and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

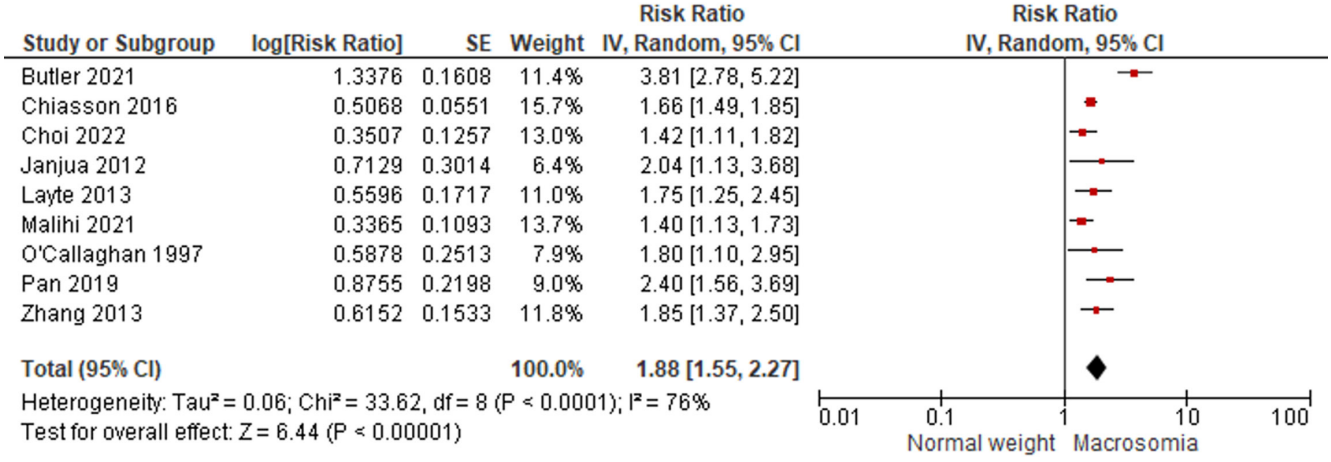


Figure 5. Forest plot of the association between macrosomia and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

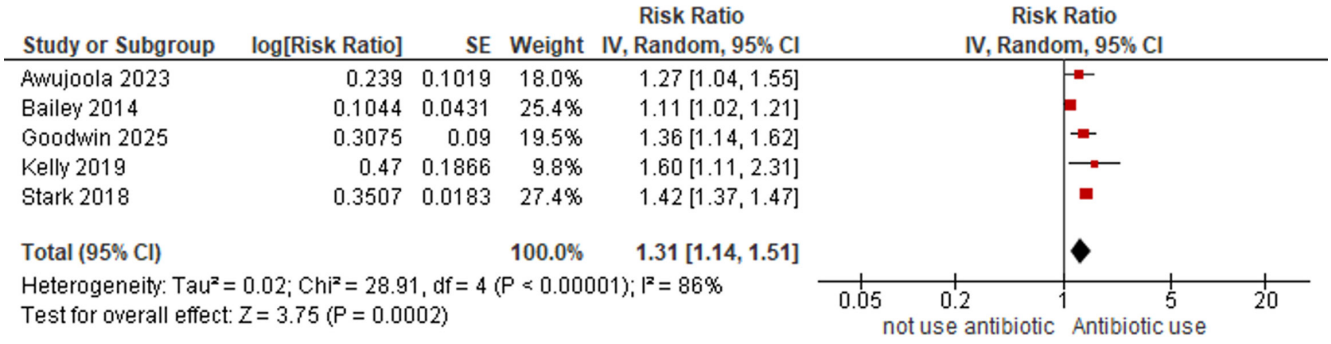


Figure 6. Forest plot of the association between antibiotic use and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

Exclusive breastfeeding

Exclusive breastfeeding was associated with a 26% reduction in the risk of childhood obesity among children aged ≤5 years, with a pooled aRR of 0.74 (95% CI, 0.64–0.85; I^2=90%). Heterogeneity among studies was very high (I^2=90%, χ^2=80.27, df=8, p<0.00001). Despite this variability, the overall pooled effect consistently indicated that exclusive breastfeeding acts as a protective factor against childhood obesity (Figure 7). Subgroup analysis revealed that age at obesity assessment was a significant source of heterogeneity (p=0.02). In the subgroup of children aged ≤3 years, heterogeneity was completely eliminated (I^2=0%).

Sex

Female sex was associated with a higher risk of obesity, with a pooled aRR of 1.46 (95% CI, 1.32–1.61; I^2=0%). These results are illustrated in Figure 8.

Pre-pregnancy obesity

Figure 9 presents the pooled analysis of maternal pre-pregnancy obesity. Children born to mothers with obesity prior to pregnancy were 1.82 times more likely to develop obesity. Maternal pre-pregnancy obesity was significantly associated with an increased risk of childhood obesity (aRR, 1.82; 95% CI, 1.21–2.73; I^2=94%). Age at obesity assessment significantly explained between-study variability (p=0.02 for subgroup differences). After stratification, heterogeneity was substantially reduced: the subgroup aged ≤3 years showed an I^2 of 49%, whereas the subgroup aged >3 years demonstrated low heterogeneity (I^2=17%).

Discussion

Our findings indicate that several perinatal and early-life factors are significantly associated with the risk of obesity in children aged ≤5 years. Specifically, high gestational weight gain, sex, pre-pregnancy obesity, history of cesarean section, macrosomia, and early-life antibiotic exposure were associated with an increased risk of obesity, whereas exclusive breastfeeding demonstrated a protective effect. Excessive maternal weight gain during pregnancy was associated with a 46% higher risk of obesity in offspring. Eating behavior–related factors and genetic predispositions that contribute to excessive weight gain during pregnancy are likely to be transmitted to children who develop obesity early in life [10,43,53]. Children born to mothers who experienced high gestational weight gain during their first pregnancy remained at increased risk of obesity, even when maternal pre-pregnancy BMI was within the normal range [43,48]. Similarly, children of mothers who experienced excessive weight gain during both the first and second pregnancies were at increased risk of overweight, regardless of whether the mother was normal weight or obese prior to pregnancy [43,48]. These findings underscore the importance of weight control during pregnancy, as gestational weight gain may exert long-term effects on child obesity risk.

Our results were consistent with findings from a study conducted in Japan, which reported that excessive gestational weight gain increased the risk of offspring overweight by 20% to 27% at age 3 years [24]. Similarly, Voerman et al. [55], using pooled data from more than 160,000 mother–child dyads in an individual participant data meta-analysis, demonstrated that excessive gestational weight gain was associated with an increased risk of childhood overweight. A dysmetabolic intrauterine environment resulting from excessive gestational weight gain, particularly during the first trimester, may expose the fetus to excess energy substrates, reflecting increased maternal fat accumulation [53]. Excessive gestational weight gain may therefore represent nutritional overload and altered maternal metabolism, leading to elevated fetal exposure to glucose and lipids. This exposure may stimulate increased fetal insulin production, thereby promoting greater infant adiposity [40,53].

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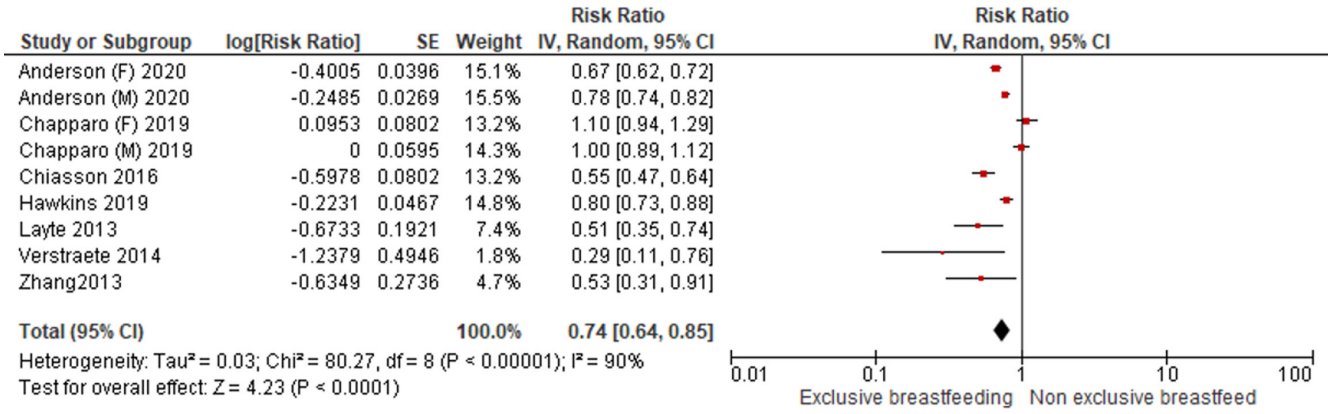


Figure 7. Forest plot of the association between exclusive breastfeeding and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

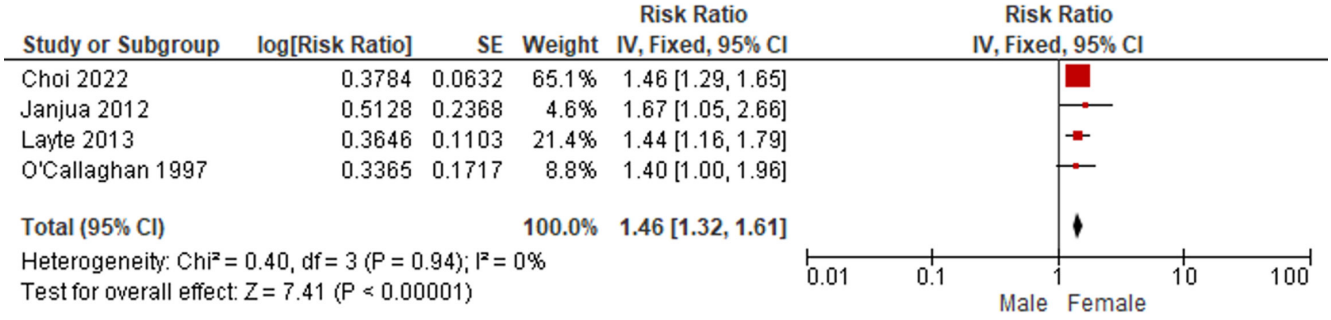


Figure 8. Forest plot of the association between female sex and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

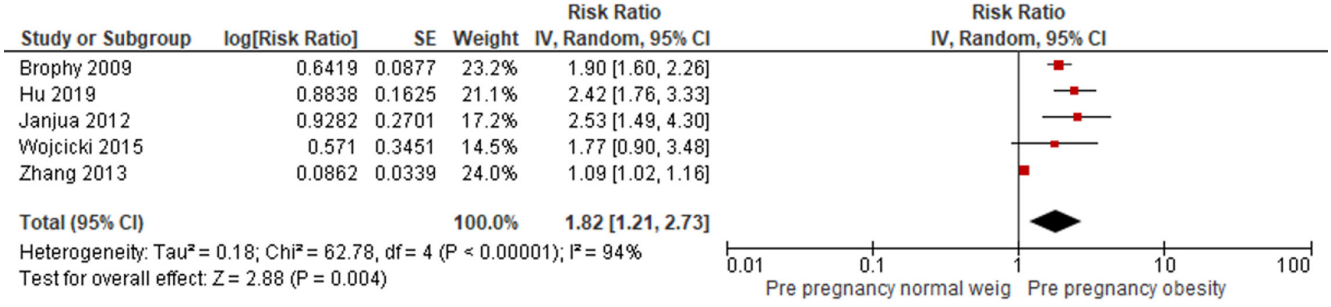


Figure 9. Forest plot of the association between pre-pregnancy obesity and the risk of childhood obesity.
SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

Cesarean section was associated with a 25% increased risk of obesity in children aged ≤5 years. Cesarean delivery limits neonatal exposure to maternal vaginal microbiota, which is a primary source of early gut colonization in newborns [25]. Alterations in gut microbiota composition may affect energy metabolism, as microbial fermentation of indigestible carbohydrates contributes to additional energy extraction. Moreover, the gut microbiota plays a role in regulating circulating lipopolysaccharide levels, which are implicated in long-term systemic inflammation and metabolic dysregulation, including obesity and diabetes [12]. Zhang et al. [56] conducted a meta-analysis of 9 studies and reported that cesarean delivery was associated with a 10% increased risk of obesity, particularly among children aged 3–18 years. In contrast, the present study focused exclusively on children aged ≤5 years and identified a comparable effect size, reinforcing the relevance of cesarean-related microbial alterations during early childhood.

Cesarean delivery has been associated with reduced abundance of Bacteroidetes and increased abundance of

Firmicutes, microbial patterns frequently observed in obese children. These bacterial groups can extract energy from indigestible colonic polysaccharides, thereby increasing caloric availability [12,57]. In addition, pregnancy- or early childhood–related antibiotic exposure has been shown to increase obesity risk. Previous studies reported a 4% increased risk of obesity in children aged 5 years following antibiotic exposure, whereas our meta-analysis identified a substantially higher pooled risk. This difference likely reflects the heightened vulnerability of children aged ≤5 years to disruptions of gut microbiota during critical periods of development. Antibiotics exert broad-spectrum antibacterial effects that can substantially alter the composition and diversity of the child's intestinal microbiota [58].

High birth weight (>4,000 g) was associated with nearly double the risk of childhood obesity. Macrosomia emerged as a key perinatal factor, corroborating findings from prior studies. For example, previous research reported that children with macrosomia at birth had a 70%–130% higher likelihood of being overweight or obese [48]. A survey by Adebile et al. [59] similarly demonstrated that macrosomia (birth weight ≥4,000 g) significantly increased the risk of childhood obesity. Our findings align with this literature, emphasizing birth weight as a strong predictor of early childhood obesity. Potential mechanisms underlying the association between macrosomia and childhood obesity include shared genetic predispositions and intrauterine programming effects that influence early hormonal responses and energy balance regulation [35]. Maternal hyperglycemia is a central contributor to the development of macrosomia. Elevated levels of pregnancy-related hormones, such as cortisol, human placental lactogen, and prolactin, particularly during the second trimester, increase maternal insulin resistance. Enhanced placental glucose transfer results in fetal hyperglycemia, leading to increased fetal insulin secretion and excessive fetal growth [11,35]. In this meta-analysis, macrosomia—particularly in Asian populations—appeared to be strongly influenced by maternal obesity prior to pregnancy, suggesting a genetic and metabolic predisposition to obesity in offspring. In addition, behavioral factors such as food preferences and early eating patterns increasingly influence obesity risk by age 5 years. These postnatal behavioral influences may attenuate the effect of macrosomia on obesity at age 5, although its impact remains more pronounced at younger ages.

Exclusive breastfeeding demonstrated a protective effect against childhood obesity. Subgroup analysis indicated that the age at obesity assessment significantly influenced result consistency. Among children assessed at ≤3 years of age, the protective effect of breastfeeding was highly consistent. As children grow older (>3 years), exposure to increasingly diverse obesogenic environments intensifies. Variations in complementary feeding practices, consumption of sugar-sweetened beverages, and physical activity levels accumulate over time. These external influences vary substantially across study populations and geographical regions, likely contributing to the persistently high heterogeneity observed in older age groups. In contrast, among children aged ≤3 years, the direct biological effects of breastfeeding—such as modulation of gut microbiota, insulin responses, and leptin regulation—appear to remain the dominant determinants of weight status. At this early developmental stage, the influence of external environmental factors is relatively limited.

Breastfeeding influences infant gut microbiota development and may mitigate the effects of antibiotic exposure and cesarean delivery [26,50]. Multiple reviews have reported a protective association between exclusive breastfeeding and obesity. For instance, Horta et al. [60] estimated a 26% reduction in obesity risk among breastfed individuals aged 1–9 years. Breast milk serves as the primary source of infant nutrition and contains numerous bioactive components that support early gut microbial balance and protect against pathogenic bacteria [37,61]. Human milk oligosaccharides promote the growth of Bifidobacteria and Bacteroidetes, microbial groups that are typically reduced in obese children [57]. Consistent with this, Wang et al. [57] reported reduced Bacteroidetes abundance in obese children, whereas other studies have demonstrated increased Firmicutes abundance in obese children and adults [62]. These microbial shifts enhance energy extraction from indigestible polysaccharides in the colon, thereby increasing caloric availability [63]. Collectively, these findings highlight breastfeeding as a critical postnatal factor in shaping early gut microbial colonization and reducing obesity risk. The results of the present meta-analysis are consistent with previous evidence supporting the protective role of breastfeeding against childhood obesity.

Beyond the factors included in the meta-analysis, several additional determinants were identified in the systematic review but could not be quantitatively synthesized because of the limited number of available studies. These determinants spanned a broad range of sociodemographic, maternal, behavioral, and psychosocial domains, including maternal education, sedentary behaviors, smoking during pregnancy, feeding practices, insecure attachment, and infant temperament.

The interplay between family socioeconomic status and childhood obesity operates through multiple complex mechanisms, ranging from nutritional access to environmental

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stressors. Household income and food security serve as primary determinants; families with low income often face limited access to nutrient-dense foods and may rely disproportionately on energy-dense, low-cost processed foods that increase obesity risk. Moreover, children living in food-insecure households are paradoxically more vulnerable to obesity due to the hunger–obesity cycle, in which irregular food availability promotes overeating when food becomes accessible [26]. Maternal education and related characteristics also play a pivotal role in shaping child health outcomes. Lower maternal educational attainment is frequently associated with limited nutritional literacy, which may contribute to suboptimal complementary feeding practices following the cessation of exclusive breastfeeding [21].

With respect to maternal pre-pregnancy obesity, our meta-analysis demonstrated substantial heterogeneity. However, subgroup analyses stratified by age at obesity assessment markedly reduced statistical inconsistency, particularly in older children. The influence of the intrauterine environment and maternal metabolic status may follow a sleeper effect or a progressive trajectory. Although infant growth (≤3 years) is highly dynamic and sensitive to rapid changes in feeding practices, epigenetic programming associated with maternal obesity may become increasingly evident and stable as the child's physiological systems mature.

Maternal pre-pregnancy obesity functions as both a biological and environmental predictor, as elevated maternal BMI is often associated with higher child BMI at age 5 through a combination of genetic susceptibility and shared household lifestyle patterns [52]. Emerging evidence further indicates that maternal overweight and obesity pre-pregnancy are independent risk factors for congenital heart defects (CHDs) in offspring, with risk increasing in proportion to the severity of maternal adiposity [64]. The underlying mechanisms likely involve chronic inflammation, oxidative stress, and disrupted glucose metabolism, which collectively interfere with molecular signaling essential for normal cardiac development during the first trimester. Severe CHD phenotypes, including tetralogy of Fallot, pulmonary valve stenosis, and atrial septal defects, have been reported more frequently among offspring of mothers with severe obesity, with odds of major malformations up to 1.8-fold higher in this group [64]. These findings highlight maternal pre-pregnancy weight as a critical and modifiable risk factor that warrants prioritization in preconception counseling to improve neonatal cardiovascular outcomes. As highlighted in recent prediction models, early identification of high-risk infants through maternal and neonatal data is crucial for timely and effective obesity prevention strategies. Specifically, the integration of factors such as maternal pre-pregnancy BMI, paternal BMI, and infant birth weight into screening protocols allows for more precise risk stratification during the first years of life, which is a critical window for mitigating long-term metabolic and cardiovascular complications [54].

Family structure and geographical context further modulate obesity risk in early childhood. In some regions, larger household size may strain financial resources, potentially diminishing the quality of individual caregiving and dietary intake [21]. Certain occupation-related risks have also been reported; for example, in rural Shaanxi, children of mothers employed in agriculture exhibited a higher risk of obesity, possibly reflecting differences in childcare arrangements or daily physical activity patterns [21]. Social disadvantage and ethnic background frequently intersect with healthcare access. Children from socially disadvantaged or underserved communities, such as those residing in the South Bronx in New York City, experience cumulative exposures to environmental stressors and reduced access to preventive healthcare services [26]. Similarly, in the Korean context, children from lower-income groups within the national health insurance system showed a significantly higher prevalence of obesity by age 5, underscoring economic stability as a consistent protective factor against early childhood weight gain [10].

The development of childhood obesity is increasingly understood to involve early emotional and behavioral regulation processes, beginning with the security of mother–child attachment [27]. Insecure attachment has been hypothesized to elevate obesity risk by disrupting stress-response systems, leading to maladaptive physiological and behavioral reactions to psychological stress. Children with insecure attachment may have diminished capacity for emotional regulation, increasing susceptibility to behaviors such as eating in the absence of hunger as a coping mechanism. Infant temperament and appetite-related traits also serve as early precursors shaping long-term weight trajectories [10]. Innate characteristics, such as heightened food responsiveness or strong appetite signals identified through temperament assessments, may result in excessive energy intake when responsive feeding practices are lacking. Behavioral patterns established as early as age 3, including rapid eating and preferences for energy-dense, sweet, or oily foods, have been identified as significant predictors of obesity by age 5 [10,27].

A key strength of this systematic review is the exclusive inclusion of cohort studies, ensuring that exposure preceded obesity outcomes. Additionally, ORs were converted to

aRRs to minimize overestimation or underestimation of associations. Nevertheless, several limitations should be acknowledged. The included studies exhibited considerable methodological heterogeneity, particularly in variable definitions and measurement approaches across populations. This limitation was addressed by applying a random-effects model and conducting leave-one-out sensitivity analyses, which demonstrated that pooled estimates remained stable and statistically significant despite study-level variability. Furthermore, many studies provided limited adjustment for important confounding factors, including maternal BMI, socioeconomic status, and postnatal lifestyle behaviors such as child diet, physical activity, and screen time. As a result, residual confounding may contribute to variability in findings and restrict causal interpretation; thus, observed relationships should be interpreted as statistically significant associations rather than definitive causal effects. In addition, although antibiotic exposure was evaluated, variations in dosage and clinical indications could not be assessed and may have influenced the observed associations.

Another limitation is the exclusion of 12 studies during the full-text assessment due to methodological inconsistencies, such as the use of combined 'overweight/obesity' categories, ineligible study designs (cross-sectional or case-control), and outcome definitions that did not align with our inclusion criteria [65–76]. Detailed justifications for each excluded study are systematically documented in Table S1 [65–76].

These findings have several implications. For practice, promoting appropriate gestational weight gain, encouraging exclusive breastfeeding, and using antibiotics cautiously in early life may help reduce obesity risk. At the policy level, public health strategies should prioritize maternal nutrition, safe delivery practices, and early-life interventions targeting modifiable risk factors. Future research should further investigate the biological mechanisms linking perinatal exposures to childhood obesity and evaluate intervention effectiveness across diverse populations to strengthen causal inference.

Conclusion

Excessive gestational weight gain, pre-pregnancy obesity, female sex, cesarean section, macrosomia, and early-life antibiotic exposure were associated with an increased risk of obesity in children aged ≤ 5 years. In contrast, exclusive breastfeeding demonstrated a protective effect against early childhood obesity. Accordingly, promoting and supporting exclusive breastfeeding is particularly important for children at elevated risk of obesity. At the same time, it is essential to recognize that these perinatal factors do not operate in isolation but interact dynamically with postnatal environmental influences and lifestyle behaviors. Obesity prevention should therefore be conceptualized as a continuum that begins before conception. Maintaining optimal maternal weight prior to pregnancy is a critical component of this continuum, as it provides a foundational benefit for offspring growth, metabolic regulation, and long-term health.

Supplementary Material

Table S1. List of studies excluded during full-text screening with reasons for exclusion. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0351.

Notes

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Not applicable.

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. Other data may be requested through the corresponding author.

Authors' Contributions
Conceptualization: ARS, NN, MIK, SBM; Data curation: ARS, MIK, JOR; Formal analysis: ARS, MIK, JOR; Funding acquisition: None; Investigation: all authors; Methodology: ARS, NN, MIK, JOR; Project administration: all authors; Resources: all authors; Software: all authors; Supervision: NN, MIK, SBM; Validation: ARS, SBM, JOR; Visualization: ARS, NN, MIK; Writing–original draft: ARS; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Original Article

Metabolic and cardiovascular comorbidities as predictors of severe dengue in Vietnamese adults: a retrospective study, 2022–2024

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ABSTRACT

Objectives: This study aimed to determine the prevalence of severe dengue and examine the associations between pre-existing comorbidities and disease severity.
Methods: This retrospective study examined patients with dengue fever who received inpatient treatment at a hospital in northern Vietnam between January 1, 2022, and December 30, 2024. Patients were categorized into 2 groups—severe dengue and non-severe dengue—based on the 2009 World Health Organization criteria. Multivariable logistic regression was performed to assess factors associated with severe dengue.
Results: Among 3,692 patients, the prevalence of severe dengue was 1.5%. Patients with any pre-existing comorbidity had higher odds of severe dengue compared to those without comorbidities (adjusted odds ratio [aOR], 2.06; 95% confidence interval [CI], 1.20–3.53). Having 2 or more comorbidities was also associated with higher odds of severe dengue (aOR, 2.26; 95% CI, 1.18–4.33). Among individual conditions, hyperlipidemia was associated with severe dengue (aOR, 2.32; 95% CI, 1.17–4.81). Certain combinations of comorbidities, including hypertension with hyperlipidemia (aOR, 2.88; 95% CI, 1.39–5.97), hypertension with cardiac disease (aOR, 4.39; 95% CI, 1.30–14.79), and hyperlipidemia with cardiac disease (aOR, 4.02; 95% CI, 1.19–13.53), were also associated with higher odds of severe dengue.
Conclusion: Pre-existing comorbidities, particularly cardiometabolic conditions, were associated with higher odds of severe dengue. Considering comorbidity profiles at hospital admission may help identify patients who require closer clinical monitoring.

Keywords: Dengue; Severe dengue; Vietnam

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Introduction

Dengue fever is an acute infectious disease caused by the dengue virus and is primarily transmitted

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by *Aedes* mosquitoes. It is prevalent in tropical and subtropical regions [1]. In recent years, dengue outbreaks have increased, becoming a serious global public health concern. The number of reported cases increased from over 500,000 in 2000 to more than 6.5 million in 2023 [2,3]. In Vietnam, dengue fever exhibits seasonal patterns with unpredictable fluctuations, typically peaking during the rainy months from June to October each year. The incidence rate per 100,000 population increased from 120 in 2009 (105,370 cases) to 194 in 2017 (184,000 cases) [4].

In 2009, the World Health Organization (WHO) introduced a new classification system for dengue cases, replacing the previous terms "dengue fever" and "dengue shock syndrome" with the categories "dengue with or without warning signs" and "severe dengue" [5]. Severe dengue is characterized by significant plasma leakage leading to shock and/or fluid accumulation with respiratory distress; severe bleeding; and severe organ involvement, including hepatic, renal, neurological, and cardiovascular dysfunction [5]. While most symptomatic cases range from mild to moderate, approximately 5% of patients may progress to severe disease [6].

Numerous studies have demonstrated that pre-existing comorbidities—such as diabetes [7–9], hypertension [8–10], cardiovascular disease [7–9], chronic kidney disease [7,9,11], obesity [8,12], and chronic respiratory disease [7,9,11]—are associated with a higher risk of severe dengue. Individuals with these conditions are more likely to require hospitalization and have a higher risk of complications, longer treatment duration, and increased mortality [7,9,11]. Notably, patients with 2 or more comorbidities may face a 2- to 3-fold increased risk of severe dengue [7,11]. The underlying mechanisms are thought to involve immune dysregulation, endothelial dysfunction, and multi-organ injury. A weakened or dysregulated immune response reduces the body's ability to control the dengue virus, leading to inefficient viral clearance and an increased risk of progression to severe dengue [13,14]. Dengue infection also causes vascular endothelial dysfunction, increasing vascular permeability and resulting in plasma leakage—the fundamental mechanism underlying dengue shock syndrome. This process may be exacerbated in patients with pre-existing endothelial damage due to hypertension, diabetes, or cardiovascular disease [15–17]. In addition, the dengue virus can affect multiple organs, including the heart, kidneys, liver, and nervous system—particularly in individuals with pre-existing chronic conditions—thereby increasing the risk of severe complications and mortality [6].

HIGHLIGHTS

- The prevalence of severe dengue among hospitalized patients at a facility in northern Vietnam was 1.5%.
- The presence of pre-existing comorbidities or 2 or more co-occurring conditions was significantly associated with greater odds of severe dengue.
- Hyperlipidemia and certain combinations of comorbidities (such as hypertension and hyperlipidemia, hypertension and cardiac disease, and hyperlipidemia and cardiac disease) were strongly associated with higher odds of severe dengue.

Objectives

In Vietnam, data on the impact of pre-existing comorbidities on severe dengue in adults remain limited. Therefore, this study was conducted to determine the prevalence of severe dengue and to examine the association between pre-existing comorbidities and severe dengue among hospitalized adults in northern Vietnam from 2022 to 2024. The findings may provide useful evidence to support clinical risk assessment and severity stratification at hospital admission.

Materials and Methods

Study Design and Setting

This retrospective study included patients diagnosed with dengue who were hospitalized at Haiphong Medical University Hospital, a 300-bed healthcare facility in northern Vietnam, approximately 120 km from Hanoi, the capital city.

Participants

Inclusion criteria: Eligible participants were adults aged 18 years and older who presented with fever and at least 2 clinical signs or symptoms suggestive of dengue, such as nausea/vomiting, skin rash, musculoskeletal pain, or a positive tourniquet test, or who tested positive by at least 1 diagnostic method, according to the 2009 WHO guidelines. Exclusion criteria: Patients with incomplete data on demographics, comorbidities, clinical manifestations, or laboratory findings were excluded. Between January 2022 and December 2024, 3,692 patients met the inclusion criteria and were included in the final analysis.

Data Collection Form

Data were extracted from the hospital management software using a pre-designed data collection form. The extraction

was performed by an information technology engineer who had received basic training in medical data to support accurate interpretation and handling of clinical information. To verify the accuracy of the extracted data, 10% of cases were randomly selected and cross-checked against the corresponding paper-based medical records. This validation step was performed to ensure the reliability and consistency of the collected data. The data collection form consisted of 3 sections.

Demographic characteristics

Sex (male or female), age (years), place of residence (urban or suburban), weight (kg), height (cm), and length of hospital stay (days). Nutritional status was classified as "non-overweight/obese" (including underweight and normal weight; body mass index [BMI] <23 kg/m^2) or "overweight/obese" (BMI ≥23 kg/m^2) [18].

Pre-existing comorbidities

Hypertension, hyperlipidemia, diabetes, lung disease, liver disease, kidney disease, cardiac disease, heart failure, and asthma. Based on a previous study, lung disease included pleural effusion, bronchitis, pneumonia, pulmonary tuberculosis, and chronic obstructive pulmonary disease. Liver disease included viral hepatitis, cirrhosis, acute hepatitis, acute liver failure, and fatty liver disease. Kidney disease included chronic kidney disease, kidney stones, glomerulonephritis, and other renal conditions. Cardiac disease included ischemic heart disease, myocardial infarction, ventricular extrasystoles, and other heart conditions, excluding heart failure and peripheral vascular disease [7].

Clinical manifestations and laboratory features

All symptoms and test results were recorded at hospital admission. Laboratory parameters included red blood cell count (×10^{12}/L), platelet count (×10^9/L), white blood cell count (×10^9/L), hemoglobin (g/L), hematocrit (%), aspartate aminotransferase (AST; U/L), and alanine aminotransferase (ALT; U/L). Hematological tests were performed using the DxH 690T analyzer (Beckman Coulter), and biochemical tests were conducted with the AU480 chemistry analyzer (Beckman Coulter).

Dengue Diagnosis and Severity

All collected plasma samples were tested for dengue nonstructural protein 1 (NS1) antigen using the BIOLINE Dengue Duo rapid diagnostic test (Abbott Diagnostics Korea Inc.). Anti-dengue virus (DENV) immunoglobulin M (Ig) M and IgG antibodies were detected using enzyme-linked immunosorbent assay (ELISA). Dengue was diagnosed based on clinical criteria consistent with the 2009 WHO guidelines and was confirmed by either a positive NS1 antigen result during the early febrile phase (days 1–5 of illness) or IgM/IgG antibody detection by ELISA from day 5 onward [5].

Severe dengue was diagnosed when at least 1 of the following criteria was present: plasma leakage (clinical fluid accumulation or a hematocrit increase of ≥20%) accompanied by shock—defined by at least 1 of the following signs: tachycardia (heart rate >100 beats/min), hypotension (systolic blood pressure <90 mmHg), or narrow pulse pressure (<20 mmHg)—or respiratory distress; severe bleeding defined as WHO grade 2 or higher, such as hematemesis, melena, menorrhagia, or clinically significant hemoglobin decrease requiring blood transfusion (whole blood or packed red blood cells); or severe organ involvement, including liver injury (AST or ALT >1,000 IU/L), kidney injury (acute kidney injury stage 2, defined as a ≥100% increase in serum creatinine from baseline), or heart failure [5].

Statistical Methods

Data were extracted from the hospital management software and imported into Excel for Microsoft 365 (Microsoft Corp.), then analyzed using IBM SPSS ver. 25.0 (IBM Corp.). Only patients with complete data for all study variables were included in the analysis. Records with missing information for any variable were excluded, and no data imputation was performed.

Categorical variables were presented as frequencies and percentages. Continuous variables were summarized as mean and standard deviation for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Variables were compared between the severe and non-severe dengue groups using the chi-square test or Fisher exact test, as appropriate. Between-group differences in continuous variables were assessed using the independent-samples *t*-test for normally distributed data or the Mann-Whitney U-test for non-normally distributed data.

Univariable logistic regression was performed to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with severe dengue. Multivariable logistic regression models were then fitted to estimate adjusted ORs (aORs). Covariates included in the multivariable models were selected *a priori* based on clinical relevance and the previous literature. All models were adjusted for key potential confounders, including age group, sex, place of residence, and overweight/obesity status. Potential multicollinearity among covariates was assessed using variance inflation factors. Model fit was

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evaluated using the Hosmer-Lemeshow goodness-of-fit test. A 2-sided *p*-value less than 0.05 was considered to indicate statistical significance.

Ethics Statement

The study protocol was approved by the Scientific Committee of Haiphong University of Medicine and Pharmacy, Haiphong, Vietnam (No. 2004/QĐ-YDHP; code: HPMU.ĐTCS.2024.123; dated September 30, 2024) and was authorized by the leadership of Haiphong Medical University Hospital. All data were anonymized and collected retrospectively; therefore, the requirement for informed consent was waived.

Results

The prevalence of severe dengue was 1.5% (56 cases). No significant differences were observed between the severe and non-severe groups in sex, age, place of residence, or overweight/obesity status (all $p > 0.05$). However, patients with severe dengue were more likely to have any pre-existing condition (57.1% vs. 39.4%, $p = 0.007$) and to have 2 or more comorbidities (28.6% vs. 18.1%, $p = 0.024$). Hypertension (28.6% vs. 18.1%, $p = 0.045$), hyperlipidemia (28.6% vs. 13.5%, $p = 0.001$), and cardiac disease (8.9% vs. 3.3%, $p = 0.022$) were significantly more common in the severe group. The length of hospital stay was slightly longer among patients with severe dengue, but the difference was not statistically significant (6.79 days vs. 6.45 days, $p = 0.289$) (Table 1).

All patients presented with fever (100%). Fatigue was significantly less frequent in the severe dengue group (76.8%) than in the non-severe group (90.7%, $p < 0.001$). In contrast, headache (78.6% vs. 63.6%, $p = 0.020$), cough (16.1% vs. 4.8%, $p < 0.001$), skin rash (12.5% vs. 2.9%, $p < 0.001$), pruritic rash (8.9% vs. 2.6%, $p = 0.004$), hemorrhage (12.5% vs. 2.4%, $p < 0.001$), dizziness (5.4% vs. 0.8%, $p < 0.001$), and myalgia (3.6% vs. 0.6%, $p = 0.004$) were significantly more common among severe dengue cases. Regarding laboratory parameters, AST levels were significantly higher in the severe dengue group (median, 48.80 U/L; IQR, 26.80–132.33) than in the non-severe group (median, 33.90 U/L; IQR, 23.63–71.53; $p = 0.021$), suggesting greater hepatic involvement in severe cases. ALT levels were also higher among patients with severe dengue, although this difference was not statistically significant ($p = 0.058$) (Table 2).

Patients with any pre-existing condition had higher odds of severe dengue than those without comorbidities (aOR, 2.06; 95% CI, 1.20–3.53). Patients with 2 or more pre-existing conditions also had higher odds of severe dengue (aOR, 2.26; 95% CI, 1.18–4.33). Among individual comorbidities, hyperlipidemia remained significantly associated with severe dengue (aOR, 2.32; 95% CI, 1.17–4.81). In exploratory analyses, certain combinations of cardiometabolic conditions—hypertension with hyperlipidemia (aOR, 2.88; 95% CI, 1.39–5.97), hypertension with cardiac disease (aOR, 4.39; 95% CI, 1.30–14.79), and hyperlipidemia with cardiac disease (aOR, 4.02; 95% CI, 1.19–13.53)—were also associated with greater odds of severe dengue (Table 3).

Discussion

This retrospective study, conducted over 3 years (2022–2024) at a hospital in northern Vietnam, found a relatively low prevalence of severe dengue (1.5%). This estimate is lower than that reported in prior studies from tertiary hospitals in Vietnam, including studies conducted in both northern and southern settings [19,20]. It is also lower than figures reported in other Asian outbreaks, such as those in Bangladesh and China [21,22]. Several factors may explain the differences in severe dengue rates across studies. First, local epidemiological characteristics likely play a key role. The rate of severe dengue depends largely on circulating virus serotypes, population immunity, and regional transmission patterns. Areas where less virulent strains predominate or cross-immunity is common often report lower rates of severe dengue complications [23,24]. Second, diagnostic criteria and sampling methods vary. Differences in the definition of "severe dengue," admission criteria, and diagnostic approaches across studies can substantially influence reported rates. Studies applying stricter criteria or enrolling patients from tertiary referral hospitals often report higher rates of severe dengue [24,25]. Third, healthcare access and early intervention may affect outcomes. Early medical care, greater community awareness, prompt detection, and timely treatment can help reduce the incidence of severe dengue [25,26].

Notably, our findings indicate that patients with pre-existing comorbidities had higher odds of developing severe dengue than those without underlying conditions. Moreover, the likelihood of severe dengue increased with the number of comorbidities, with patients presenting with 2 or more chronic conditions appearing particularly vulnerable. These results are consistent with evidence from systematic reviews and studies across diverse populations, which have identified comorbidities as important factors associated with severe dengue outcomes [7,9,11,27–30].

Among specific conditions, hyperlipidemia remained significantly associated with severe dengue in our study. This association may be partly explained by interactions

Table 1. Comparison of demographic characteristics and disease history between severe dengue and non-severe dengue

Characteristic	Total (*n* = 3,692)	Severe dengue		*p*
		Yes (*n* = 56)	No (*n* = 3,636)	
Sex				0.555
Male	1,527 (41.4)	21 (37.5)	1,506 (41.4)	
Female	2,165 (58.6)	35 (62.5)	2,130 (58.6)	
Age (y)	46.33 ± 16.38	46.07 ± 16.48	46.34 ± 16.38	0.904
18–30	691 (18.7)	11 (19.6)	680 (18.7)	0.992
30–39	685 (18.6)	9 (16.1)	676 (18.6)	
40–49	670 (18.1)	10 (17.9)	660 (18.2)	
50–59	623 (16.9)	10 (17.9)	613 (16.9)	
60–78	1,023 (27.7)	16 (28.6)	1,007 (27.7)	
Place of residence				0.267
Urban	3,215 (87.1)	46 (82.1)	3,169 (87.2)	
Suburban	477 (12.9)	10 (17.9)	467 (12.8)	
Body mass index (kg/m^2)	21.59 ± 1.57	21.78 ± 1.66	21.58 ± 1.56	0.366
Overweight/obesity				0.123
No	3,110 (84.2)	43 (76.8)	3,067 (84.4)	
Yes	582 (15.8)	13 (23.2)	569 (15.6)	
Any pre-existing illness				0.007
No	2,206 (59.8)	24 (42.9)	2,202 (60.6)	
Yes	1,486 (40.2)	32 (57.1)	1,434 (39.4)	
No. of pre-existing illnesses				0.024
0	2,226 (60.3)	24 (42.8)	2,202 (60.6)	
1	789 (21.4)	16 (28.6)	773 (21.3)	
≥ 2	677 (18.3)	16 (28.6)	661 (18.2)	
Hypertension	675 (18.3)	16 (28.6)	659 (18.1)	0.045
Hyperlipidemia	506 (13.7)	16 (28.6)	490 (13.5)	0.001
Diabetes	372 (10.1)	5 (8.9)	367 (10.1)	0.774
Lung disease	349 (9.5)	7 (12.5)	342 (9.4)	0.432
Liver disease	204 (5.5)	5 (8.9)	199 (5.5)	0.261[a)]
Kidney disease	144 (3.9)	1 (1.8)	143 (3.9)	0.410[a)]
Cardiac disease	126 (3.4)	5 (8.9)	121 (3.3)	0.022[a)]
Heart failure	21 (0.6)	0 (0)	21 (0.6)	NA
Asthma	5 (0.1)	0 (0)	5 (0.1)	NA
Length of stay (d)	6.45 ± 2.36	6.79 ± 2.38	6.45 ± 2.36	0.289
1–3	365 (9.9)	2 (3.6)	363 (10.0)	0.275
4–6	1,519 (41.1)	24 (42.9)	1,495 (41.1)	
> 6	1,808 (49.0)	30 (53.6)	1,778 (48.9)	

Data are presented as *n* (%) or mean ± standard deviation. *p*-values were calculated using the chi-square test or Fisher's exact test (when ≥ 25% of expected cell counts were < 5) for categorical variables and the Independent-samples t-test for continuous variables.
NA, statistical test not applicable.
[a)]By Fisher exact test.

between dengue infection and host lipid metabolism. Dengue virus replication relies on host lipid pathways, and systemic inflammation and hepatic involvement may further disrupt lipid homeostasis. Prior studies have described characteristic alterations in lipid profiles with increasing dengue severity, suggesting that lipid abnormalities may reflect inflammatory and endothelial changes that contribute to plasma leakage in severe dengue [31,32]. These findings support closer monitoring of patients with dyslipidemia at admission.

Exploratory analyses suggested that certain comorbidity combinations—such as hypertension with hyperlipidemia or cardiac disorders—were associated with higher odds of severe dengue. Similar observations have been reported in other settings, indicating that the burden and clustering of chronic diseases may influence dengue progression

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Table 2. Comparison of clinical manifestations and laboratory features between severe dengue and non-severe dengue

Variable	Total (n = 3,692)	Severe dengue		p[a]
		Yes (n = 56)	No (n = 3,636)	
Clinical manifestation				
Fever	3,692 (100.0)	56 (100.0)	3,636 (100.0)	NA
Fatigue	3,341 (90.5)	43 (76.8)	3,298 (90.7)	< 0.001
Body aches	2,684 (72.7)	42 (75.0)	2,642 (72.7)	0.697
Headache	2,355 (63.8)	44 (78.6)	2,311 (63.6)	0.020
Anorexia	574 (15.5)	6 (10.7)	568 (15.6)	0.315
Vomiting/nausea	541 (14.7)	12 (21.4)	529 (14.5)	0.149
Chest pain	188 (5.1)	0 (0)	188 (5.2)	NA
Cough	182 (4.9)	9 (16.1)	173 (4.8)	< 0.001[b]
Palpitations	171 (4.6)	4 (7.1)	167 (4.6)	0.368[b]
Skin rash	112 (3.0)	7 (12.5)	105 (2.9)	< 0.001[b]
Pruritic rash	99 (2.7)	5 (8.9)	94 (2.6)	0.004[b]
Hemorrhage	94 (2.5)	7 (12.5)	87 (2.4)	< 0.001[b]
Dizziness	31 (0.8)	3 (5.4)	28 (0.8)	< 0.001[b]
Myalgia	22 (0.6)	2 (3.6)	20 (0.6)	0.004[b]
Retro-orbital pain	13 (0.4)	1 (1.8)	12 (0.3)	0.068[b]
Clinical laboratory features				
RBC ($\times 10^{12}$/L)	4.65 ± 0.57	4.61 ± 0.61	4.65 ± 0.57	0.597
WBC ($\times 10^{9}$/L)	4.62 ± 2.36	4.22 ± 1.91	4.63 ± 2.36	0.200
PLT ($\times 10^{9}$/L)	84.68 ± 63.80	88.77 ± 42.47	84.62 ± 64.08	0.475
Hb (g/L)	146.82 ± 13.64	147.02 ± 14.19	146.81 ± 13.64	0.909
Hct (%)	40.46 ± 4.90	40.39 ± 4.70	40.46 ± 4.90	0.912
AST (U/L)	33.95 (23.73–73.05)	48.80 (26.80–132.33)	33.90 (23.63–71.53)	0.021
ALT (U/L)	27.80 (17.80–52.53)	35.40 (17.65–79.93)	27.75 (17.80–51.80)	0.058

Data are presented as n (%), mean ± standard deviation, or median (interquartile range).
RBC, red blood cell; WBC, white blood cell; PLT, platelet; Hb, hemoglobin; Hct, hematocrit; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NA, statistical test not applicable.
[a]p-values were calculated using the chi-square test or Fisher exact test (when ≥ 25% of expected cell counts were < 5) for categorical variables and the independent-samples t-test or Mann-Whitney U-test for continuous variables. [b]By Fisher exact test.

[11,24,27]. These associations may reflect shared underlying pathways, including endothelial dysfunction, chronic inflammation, and altered immune responses, which could contribute to plasma leakage and systemic complications during acute infection [14,16,33,34]. However, these findings should be interpreted cautiously, given the limited number of severe dengue cases.

Overall, our findings reinforce current clinical recommendations, highlighting the importance of early risk stratification and close monitoring of patients with dengue and multiple cardiometabolic comorbidities. Targeted attention to these high-risk groups at hospital admission may help optimize management and reduce severe outcomes and dengue-related mortality [35–37].

Strengths and Limitations

This study has several strengths. First, the large sample size enhances the statistical power and reliability of the findings. Second, the use of the 2009 WHO classification criteria for severe and non-severe dengue ensures standardized disease categorization and comparability with other studies. Finally, the findings have clear clinical relevance, as identifying comorbidities associated with severe dengue can support early risk stratification and prioritization of close monitoring for hospitalized patients.

However, several limitations should be acknowledged. First, the retrospective cross-sectional design precludes causal inference regarding the relationship between comorbidities and severe dengue. Second, restricting the analysis to patients with complete data across all variables, without imputation for missing values, may have introduced selection bias. Third, several potential confounders, including smoking, alcohol use, socioeconomic status, and healthcare access, were not collected and therefore could not be adjusted for. Fourth, the study did not assess the severity or degree of control of underlying comorbidities, which may influence clinical outcomes. Finally, because the data were obtained from a single hospital in northern

Table 3. Association between pre-existing illnesses and severe dengue (*n* = 3,692)

Variable	Severe dengue (*n*, %)		OR (95% CI)	*p*	aOR (95% CI)	*p*
	Yes (*n* = 56)	No (*n* = 3,636)				
Model 1. Any pre-existing illness						
No	24 (1.1)	2,202 (98.9)	1		1	
Yes	32 (2.2)	1,434 (97.8)	2.05 (1.20–3.49)	0.008	2.06 (1.20–3.53)	0.009
Model 2. Number of pre-existing illnesses						
0	24 (1.1)	2,202 (98.9)	1		1	
1	16 (2.0)	773 (98.0)	1.90 (1.00–3.59)	0.049	1.89 (0.99–3.60)	0.051
≥ 2	16 (2.4)	661 (97.6)	2.22 (1.17–4.21)	0.014	2.26 (1.18–4.33)	0.014
Model 3. Pre-existing illnesses						
Hypertension	16 (2.4)	659 (97.6)	1.81 (1.01–3.25)	0.048	1.36 (0.68–2.73)	0.385
Hyperlipidemia	16 (3.2)	490 (96.8)	2.57 (1.43–4.62)	0.002	2.32 (1.17–4.81)	0.024
Diabetes	5 (1.3)	367 (98.7)	0.87 (0.35–2.20)	0.774	0.58 (0.22–1.54)	0.277
Lung disease	7 (2.0)	342 (98.0)	1.38 (0.62–3.06)	0.434	1.23 (0.55–2.79)	0.615
Liver disease	5 (2.5)	199 (97.5)	1.69 (0.67–4.29)	0.267	1.92 (0.75–4.90)	0.173
Kidney disease	1 (0.7)	143 (99.3)	0.44 (0.06–3.23)	0.423	0.44 (0.06–3.22)	0.416
Cardiac disease	5 (4.0)	121 (96.0)	2.85 (1.12–7.26)	0.028	1.95 (0.72–5.29)	0.187
Heart failure	0 (0)	21 (100)	NA	NA	NA	NA
Asthma	0 (0)	5 (100)	NA	NA	NA	NA
Model 4. Hypertension, hyperlipidemia						
No HT, no HL	34 (1.2)	2,773 (98.8)	1		1	
HT, no HL	6 (1.6)	373 (98.4)	1.31 (0.55–3.15)	0.543	1.33 (0.55–3.21)	0.525
No HT, HL	6 (2.9)	204 (97.1)	2.40 (0.99–5.78)	0.051	2.47 (1.01–6.03)	0.047
HT and HL	10 (3.4)	286 (96.6)	2.85 (1.39–5.83)	0.004	2.88 (1.39–5.97)	0.005
Model 5. Hypertension, cardiac disease						
No HT, no CD	38 (1.3)	2,909 (98.7)	1		1	
HT, no CD	13 (2.1)	606 (97.9)	1.64 (0.87–3.10)	0.126	1.64 (0.86–3.12)	0.134
No HT, CD	2 (2.9)	68 (97.1)	2.25 (0.53–9.52)	0.270	2.25 (0.53–9.54)	0.273
HT and CD	3 (5.4)	53 (94.6)	4.33 (1.30–14.48)	0.017	4.39 (1.30–14.79)	0.017
Model 6. Hyperlipidemia, cardiac disease						
No HL, no CD	38 (1.2)	3,087 (98.8)	1		1	
HL, no CD	13 (2.9)	428 (97.1)	2.47 (1.30–4.67)	0.006	2.50 (1.31–4.79)	0.006
No HL, CD	2 (3.3)	59 (96.7)	2.75 (0.65–11.68)	0.169	2.77 (0.65–11.82)	0.169
HL and CD	3 (4.6)	62 (95.4)	3.93 (1.18–13.08)	0.026	4.02 (1.19–13.53)	0.025

All models were adjusted for sex, age group, place of residence, and overweight/obesity. Percentages are presented as row percentages to illustrate the proportion of severe dengue within each category of pre-existing conditions.
OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; HT, hypertension; HL, hyperlipidemia; CD, cardiac disease; NA, Variable not included in the model due to zero event.

Vietnam, the generalizability of the findings to other settings or healthcare systems may be limited.

Conclusion

The proportion of patients with severe dengue in our study was relatively low. Nevertheless, pre-existing comorbidities were significantly associated with higher odds of severe dengue, particularly among individuals with multiple chronic conditions and those with hyperlipidemia. Exploratory analyses also suggested that certain cardiometabolic comorbidity clusters, such as hypertension combined with hyperlipidemia or cardiac disease, may be associated with increased odds of severe outcomes. These findings highlight the importance of early risk stratification and careful clinical monitoring of patients with dengue and underlying chronic diseases. Greater attention to patients with cardiometabolic comorbidities at admission may facilitate timely recognition of warning signs and supportive management, potentially reducing the risk of complications. In addition, improving awareness among individuals living with chronic conditions about the potential for progression to severe dengue may encourage earlier care-seeking and prompt intervention.

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Notes

Ethics Approval
The study protocol was approved by the Scientific Committee of Haiphong University of Medicine and Pharmacy, Haiphong, Vietnam (No. 2004/QĐ-YDHP; code: HPMU.ĐTCS.2024.123; dated September 30, 2024) and was authorized by the leadership of Haiphong Medical University Hospital. All data were anonymized and collected retrospectively; therefore, the requirement for informed consent was waived.

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.

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Original Article

Barriers to treatment completion among drug-sensitive tuberculosis patients: evidence from Indonesia's tuberculosis surveillance system

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ABSTRACT

Objectives: This study aimed to estimate the prevalence of loss to follow-up (LTFU) among tuberculosis (TB) patients in Indonesia and to identify associated factors.

Methods: This study analyzed data from the 2022 Tuberculosis Information System in Indonesia. A total of 71,665 drug-sensitive TB patients were included in the analysis. Age, sex, employment status, diagnosis type, human immunodeficiency virus (HIV) status, diabetes mellitus, TB type, mode of treatment, treatment standard, referral status, and type of residence. Categorical variables were analyzed using chi-square tests, followed by multivariable logistic regression to identify confounder-adjusted independent predictors of LTFU.

Results: The prevalence of LTFU was 18.4%. A higher likelihood of LTFU was observed among older adults aged ≥65 years (adjusted-prevalence-odds-ratio [aPOR], 1.862), men (aPOR, 1.187), unemployed individuals (aPOR, 1.136), non-referred patients (aPOR, 1.547), patients with HIV (aPOR, 3.712), and those obtaining TB drugs out of pocket (aPOR, 4.998). The strongest predictor was receipt of non-standard treatment, which was associated with a markedly increased likelihood of LTFU (aPOR, 26.912). In contrast, rural residence demonstrated a protective association (aPOR, 0.610). All associations were statistically significant ($p < 0.001$).

Conclusion: This study highlights a substantial burden of LTFU among TB patients in Indonesia, with nearly one in five patients discontinuing treatment. Multiple sociodemographic and clinical factors—particularly non-standard treatment, non-referral status, and HIV co-infection—were strongly associated with LTFU, underscoring gaps in the TB care continuum. These findings emphasize the need for targeted, patient-centered interventions, strengthened referral pathways, improved communication, and enhanced care coordination to reduce LTFU in high-risk groups.

Keywords: Health services accessibility; Lost to follow-up; Treatment outcome

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Introduction

Tuberculosis (TB) remains a major global infectious disease, with an estimated 10.6 million cases and 1.25 million deaths reported in 2023. It continues to pose a substantial public health burden, particularly in high-incidence countries such as Indonesia [1]. Indonesia ranks second globally in TB incidence, with 820,789 reported cases out of an estimated 1,060,000 in 2023. The disease remains a leading cause of mortality in the country, contributing to approximately 150,000 deaths annually [2]. Despite national and global efforts to control TB, Indonesia's treatment success rate in 2022 was 82%, well below the national target of 90% [2]. Successful TB treatment requires strict adherence to a minimum 6-month regimen; however, many patients face challenges in completing therapy, resulting in loss to follow-up (LTFU). LTFU is defined as discontinuation of treatment for 2 or more consecutive months and is a key contributor to Indonesia's suboptimal treatment success rate [1].

According to the Indonesian Ministry of Health, the LTFU rate has increased in recent years, rising from 4% in 2021 to 7.4% in 2022 and further to 7.7% in 2023 [2]. The consequences of LTFU in TB treatment are substantial, contributing to higher rates of treatment failure, drug resistance, and ongoing community transmission, thereby exacerbating the public health burden [3]. Patients who discontinue treatment are at increased risk of developing multidrug-resistant TB, which requires longer, more complex, and more costly therapy [1]. Furthermore, untreated TB patients may continue to transmit the disease within their communities, perpetuating the cycle of infection. Several studies have demonstrated the adverse impact of LTFU on treatment outcomes and mortality. A cohort study involving 24,265 TB patients reported an LTFU prevalence of 12.51%, which was associated with reduced treatment adherence and increased mortality [4]. Similarly, a study conducted in Kenya found that 6.3% of TB patients who were lost to follow-up experienced heightened risks of relapse and death [5].

LTFU is influenced by a complex interplay of individual, health system, and environmental factors. Individuals aged 15–64 years may face work-related barriers to adherence, whereas older adults may be more vulnerable because of age-related frailty and adverse drug effects [6,7]. Sex-based differences have also been reported; men are more likely to discontinue treatment because of work demands and stigma, whereas women generally demonstrate better adherence [8]. Comorbidities such as human immunodeficiency virus (HIV) and diabetes mellitus further increase the likelihood of LTFU because of complex treatment regimens and medication-related adverse effects [5,9]. Diagnostic certainty also plays an important role. Patients with bacteriological confirmation (e.g., sputum microscopy or GeneXpert) tend to adhere more consistently than those who are clinically diagnosed based solely on symptoms [5,9].

Health system factors also shape treatment continuity. Patients who obtain anti-TB drugs through out-of-pocket payment may face financial barriers and variable drug quality, which can increase the likelihood of treatment discontinuation [10,11]. In contrast, the national Directly Observed Treatment, Short-course (DOTS) program provides free, standardized anti-TB drugs, supporting improved adherence. Patients entering care through formal referral pathways typically access services earlier and receive clearer guidance, whereas non-referred individuals may be more prone to delayed treatment initiation and LTFU [12]. Moreover, patients receiving non-standard TB regimens have a substantially higher risk of discontinuation—26% versus 8% among those receiving standard protocols [4].

HIGHLIGHTS

- Standard treatment emerged as the most influential factor; patients receiving non-standard treatment had a significantly higher likelihood of loss to follow-up (LTFU).
- Older age (≥65 years), male sex, unemployment, receipt of out-of-pocket tuberculosis (TB) drugs, non-referral status, clinical diagnosis, TB–human immunodeficiency virus co-infection, and extrapulmonary TB were all significantly associated with an increased risk of LTFU.
- In contrast, rural residence was significantly associated with a lower likelihood of LTFU, suggesting a potential protective effect that may support continued engagement in TB care.
- Given the strong association between non-standard treatment and LTFU, greater emphasis should be placed on strengthening drug distribution monitoring and expanding access to standardized TB treatment programs. Although Indonesia's national TB program provides free treatment through public health facilities, limited integration of private providers into the national surveillance and supply system remains a challenge. Strengthening public–private mix strategies, improving reporting through the Tuberculosis Information System, and enforcing stricter regulation of anti-TB drug sales are essential to reduce treatment fragmentation.

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Environmental and socioeconomic factors, including unstable employment, rural residence, and geographic barriers to care, may further contribute to LTFU. Individuals in informal employment may prioritize immediate income over health needs, whereas rural residents may face long travel distances, limited transportation, and fewer healthcare facilities [13,14].

The Tuberculosis Information System in Indonesia (*Sistem Informasi Tuberculosis*, *SITB*) is the national TB surveillance platform that captures data on TB cases, treatment adherence, and outcomes. Although SITB plays an important role in monitoring and evaluating TB control efforts, few studies have used these data to examine nationwide determinants of LTFU. Most existing research is hospital- or region-based, leaving a critical gap in understanding the national epidemiology of LTFU. Given projections that reducing LTFU could decrease TB re-treatment needs by 10%–20% [15], a comprehensive national analysis is needed. Identifying and addressing factors associated with LTFU is essential to improving treatment outcomes and advancing Indonesia's TB control goals. This study aimed to examine the recent rate of LTFU among TB patients in Indonesia and associated determinants.

Materials and Methods

Study Design and Setting

This study was conducted as a secondary data analysis using surveillance data from the Tuberculosis Information System (SITB), managed by the Directorate of Disease Prevention and Control, Ministry of Health, Republic of Indonesia. The dataset included all patients registered in SITB between January 1, 2022, and December 31, 2022. Patient data were derived from TB-03, a standardized registry used by healthcare facilities, including community health centers, hospitals, clinics, and laboratories. TB-03 records include demographic information; TB type; diagnostic methods; laboratory results (sputum, GeneXpert/Xpert MTB/RIF, culture); treatment category and regimen; HIV testing and linkage; and treatment outcomes [16].

Participants

The study sample consisted of all drug-sensitive TB patients (n = 637,554) recorded in SITB. Records meeting the eligibility criteria were included in the analysis. Inclusion criteria for the final analytical sample were: (1) a final treatment outcome recorded as either "recovery/cured" or "LTFU," and (2) complete data for all variables under investigation. Patients were excluded if the recorded treatment outcome was death or treatment failure. Additional exclusions were applied for duplicate records and entries with missing data for key variables. Figure 1 presents the participant selection process.

Variables

Patients classified as LTFU were defined as having discontinued TB treatment for 2 or more consecutive months (8 weeks) for any reason without medical consent. The independent variables extracted from SITB were age, sex, employment status, diagnosis type (clinical or bacteriological), HIV status, diabetes mellitus, TB type (extrapulmonary or pulmonary), mode of treatment (government program vs. out of pocket, including private health insurance), treatment standard (standardized vs. non-standard according to the National Clinical Practice Guidelines for Tuberculosis Management), referral status (non-referral vs. referral), and type of residence (urban vs. rural, based on administrative

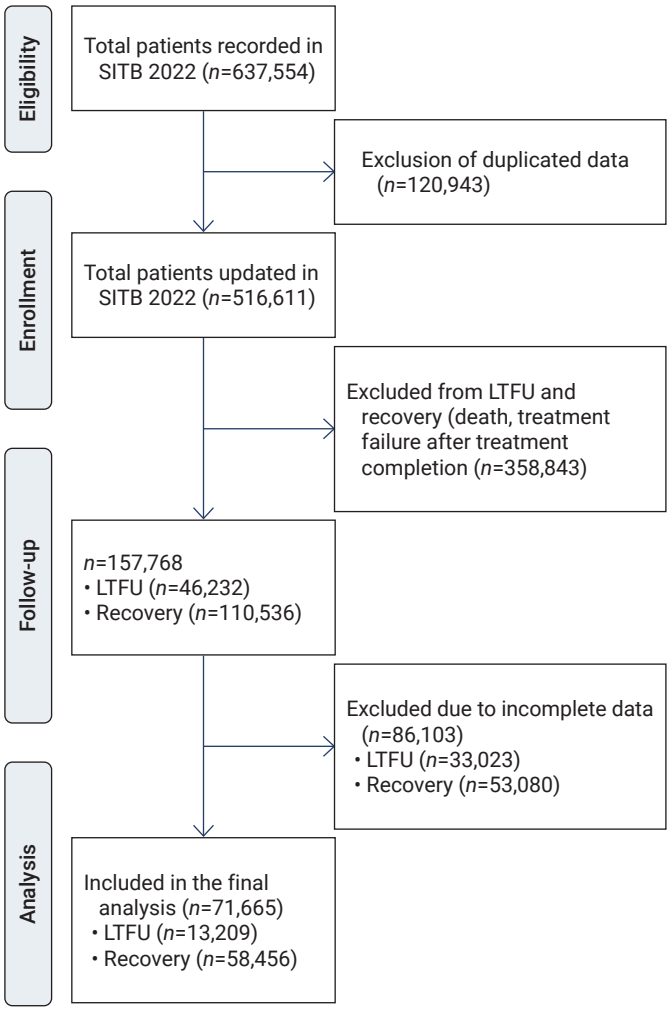


Figure 1. Recruitment flow.
SITB, Tuberculosis Information System; LTFU, loss to follow-up.

area codes). Non-standard treatment included prescriptions issued by private practitioners or facilities not integrated into the DOTS program; regimens that did not comply with the fixed-dose combination supplied by the program; incomplete treatment monitoring; or the absence of standardized follow-up sputum examinations.

Bias

To minimize selection bias, this study used data from the national SITB. Although underreporting may still occur—particularly among private providers—SITB remains the most comprehensive national source of notified TB case data and provides broad geographic coverage of drug-sensitive TB patients across Indonesia.

Inclusion and exclusion criteria were applied systematically to reduce the risk of arbitrary sample selection. Information bias was addressed through data cleaning, including the removal of duplicate records and the exclusion of incomplete entries to improve data reliability. Confounding was addressed using multivariable logistic regression, enabling estimation of the independent association between each variable and LTFU while adjusting for other covariates.

Statistical Methods

Analyses began with univariate summaries to describe the frequency and percentage of each variable. Bivariate associations between independent variables and LTFU were assessed using chi-square tests, with statistical significance set at $p<0.05$. Associations were quantified using prevalence odds ratios (PORs) with 95% confidence intervals (CIs); a POR >1 indicated higher odds of LTFU, whereas a POR <1 indicated lower odds (protective association). Variables associated with LTFU in bivariate analyses were entered into a multivariable logistic regression model to identify the most relevant determinants while adjusting for other covariates.

Ethics Statement

This study received ethical approval from the Ethics Committee of the Faculty of Medicine, Universitas Negeri Semarang (No. 933/KEPK/FK/KLE/2025).

Results

(1) The prevalence of LTFU in the analytical sample was 18.4%. (2) Standard treatment emerged as the most influential factor; patients receiving non-standard treatment showed a substantially higher likelihood of LTFU. (3) Older age (≥65 years), male sex, unemployment, receipt of out-of-pocket TB drugs, non-referral status, clinical diagnosis, TB–HIV co-infection, extrapulmonary TB, and receipt of non-standard treatment were all significantly associated with an increased likelihood of LTFU. (4) In contrast, rural residence was significantly associated with a lower likelihood of LTFU, suggesting a potential protective association that may support continued engagement in TB care.

A total of 71,665 patients were included in the final analysis. As shown in Table 1, the prevalence of LTFU in the

Table 1. Characteristics of the final analytical sample from the Indonesian Tuberculosis Information System, 2022 ($n=71,665$)

Characteristic	Value
Age (y)	
≥65	8,569 (12.0)
15–64	63,069 (88.0)
Sex	
Male	43,311 (60.4)
Female	28,354 (39.6)
Employment status	
Unemployed	28,331 (39.5)
Employed	43,334 (60.5)
Mode of treatment	
Out of pocket	1,059 (1.5)
Government program	70,606 (98.5)
Referral status	
Non-referral	57,554 (80.3)
Referral	14,111 19.7
Type of residence	
Rural	48,605 (67.8)
Urban	23,060 (32.2)
Diagnosis type	
Clinical	6,393 (8.9)
Bacteriological	65,272 (91.1)
HIV infection	
Yes	1,815 (2.5)
No	69,850 (97.5)
Diabetes mellitus	
Yes	14,599 (20.4)
No	57,066 (79.6)
Type of tuberculosis	
Extrapulmonary	1,152 (1.6)
Pulmonary	70,513 (98.4)
Treatment standard	
Non-standard	345 (0.5)
Standard	71,320 (99.5)
Treatment outcome	
Loss to follow-up	13,209 (18.4)
Recovery	58,456 (81.6)

Data are presented as *n* (%).
HIV, human immunodeficiency virus.

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analytical sample was 18.4%, and 81.6% were reported as recovered. Participants aged 15–64 years accounted for 88.0% of the sample, and men comprised 60.4%. Employed individuals accounted for 60.5% of the sample, and 98.5% received medication through the government program. Non-referral cases were the most prevalent (80.3%), and 67.8% of participants resided in rural areas. Bacteriological diagnosis was most common (91.1%); most participants were HIV-negative (97.5%) and without diabetes mellitus (79.6%). Pulmonary TB accounted for 98.4% of cases, and nearly all patients (99.5%) received standardized treatment.

Table 2 summarizes bivariate associations between participant characteristics and LTFU. Age was strongly associated with LTFU: participants aged ≥65 years had higher LTFU prevalence (27.0%) than those aged 15–64 years (17.3%), corresponding to a POR of 1.566 (95% CI, 1.506–1.627; $p < 0.001$). Men had a slightly higher LTFU prevalence (19.3%) than women (17.1%) (POR, 1.124; 95% CI, 1.088–1.160; $p < 0.001$). Unemployed participants also had higher LTFU prevalence (19.2%) than employed participants (18.0%) (POR, 1.067; 95% CI, 1.035–1.101; $p < 0.001$). Mode of treatment showed one of the strongest associations: participants

Table 2. Treatment outcome based on subjects' characteristics from the Indonesian Tuberculosis Information System, 2022

Variable	Treatment outcome (*n*, %)		POR (95% CI)	*P**
	LTFU	Recovery		
Age (y)			1.566 (1.506–1.627)	<0.001
≥65	2,323 (27.0)	6,273 (73.0)		
15–64	10,886 (17.3)	52,183 (82.7)		
Sex			1.124 (1.088–1.160)	<0.001
Male	8,347 (19.3)	34,964 (80.7)		
Female	4,862 (17.1)	23,492 (82.9)		
Employment status			1.067 (1.035–1.102)	<0.001
Unemployed	5,429 (19.2)	22,902 (80.8)		
Employed	7,780 (18.0)	35,554 (82.0)		
Mode of treatment			3.001 (2.832–2.181)	<0.001
Out of pocket	569 (53.7)	490 (46.3)		
Government program	12,640 (17.9)	57,966 (82.1)		
Referral status			1.446 (1.383–1.512)	<0.001
Non-referral	11,294 (19.6)	42,620 (80.4)		
Referral	1,915 (13.6)	12,196 (86.4)		
Type of residence			0.673 (0.653–0.694)	<0.001
Rural	7,749 (15.9)	40,856 (84.1)		
Urban	5,460 (23.7)	17,600 (76.3)		
Diagnosis type			9.576 (9.364–9.794)	<0.001
Clinical	6,393 (100.0)	0 (0)		
Bacteriological	6,816 (10.4)	58,456 (89.6)		
HIV infection			2.501 (2.370–2.639)	<0.001
Yes	806 (44.4)	1,009 (55.6)		
No	12,403 (17.6)	57,447 (82.2)		
Diabetes mellitus			0.822 (0.789–0.857)	<0.001
Yes	2,296 (15.7)	12,303 (84.3)		
No	10,913 (19.1)	46,153 (80.9)		
Type of tuberculosis			5.848 (5.754–5.944)	<0.001
Extrapulmonary	1,152 (100.0)	0 (0)		
Pulmonary	12,057 (17.1)	58,456 (82.9)		
Treatment standard			4.821 (4.616–5.034)	<0.001
Non-standard	301 (87.2)	44 (12.8)		
Standard	12,908 (18.1)	58,412 (81.9)		

LTFU, loss to follow-up; POR, prevalence odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.
*$p < 0.05$ (statistically significant).

obtaining drugs through out-of-pocket payment had substantially higher LTFU prevalence (53.7%) than those receiving drugs through the government program (17.9%) (POR, 3.001; 95% CI, 2.832–3.181; $p < 0.001$). Non-referral participants had higher LTFU prevalence (19.6%) than referral participants (13.6%) (POR, 1.446; 95% CI, 1.383–1.512; $p < 0.001$). Urban residents were more likely to be LTFU (23.7%) than rural residents (15.9%), with rural residence demonstrating a protective association (POR, 0.673; 95% CI, 0.653–0.694; $p < 0.001$). Diagnosis type was strongly associated with LTFU: clinically diagnosed participants had 100.0% LTFU versus 10.4% among bacteriologically confirmed participants (POR, 9.576; 95% CI, 9.364–9.794; $p < 0.001$). HIV-positive participants had higher LTFU prevalence (44.4%) than HIV-negative participants (17.6%) (POR, 2.501; 95% CI, 2.370–2.639; $p < 0.001$). Participants with diabetes mellitus had lower LTFU prevalence (15.7%) than those without diabetes (19.1%), indicating a protective association (POR, 0.822; 95% CI, 0.789–0.857; $p < 0.001$). Finally, extrapulmonary TB cases had 100.0% LTFU compared with 17.1% among pulmonary TB cases (POR, 5.848; 95% CI, 5.754–5.944; $p < 0.001$).

In the multivariable analysis presented in Table 3, several factors were significantly associated with LTFU. Higher likelihood of LTFU was observed among participants aged ≥65 years (adjusted POR [aPOR], 1.862; 95% CI, 1.765–1.965), men (aPOR, 1.187; 95% CI, 1.133–1.244), and unemployed participants (aPOR, 1.136; 95% CI, 1.084–1.189). LTFU was also more likely among those obtaining drugs through out-of-pocket treatment (aPOR, 4.998; 95% CI, 4.404–5.672), non-referral participants (aPOR, 1.547; 95% CI, 1.466–1.632), and HIV-positive participants (aPOR, 3.712; 95% CI, 3.367–4.092). In contrast, rural residence was associated with a lower likelihood of LTFU (aPOR, 0.610; 95% CI, 0.586–0.635). The strongest association was observed for receipt of non-standard treatment (aPOR, 26.912; 95% CI, 19.500–37.141). All associations were statistically significant ($p < 0.001$).

Discussion

The national TB program, including DOTS, provides free, standardized, quality-assured medications along with structured follow-up, education, and adherence support. A primary objective of this model is to reduce LTFU among TB patients. Indonesia supports TB surveillance and case reporting through SITB. Despite these systemic efforts, this study identified several factors significantly associated with LTFU in Indonesia, including receipt of non-standard treatment, obtaining TB drugs out of pocket, TB–HIV co-infection, older age (≥65 years), non-referral status, male sex, unemployment, and rural residence. Among these factors, receipt of non-standard treatment showed the strongest association, with patients being 26.9 times more likely to experience LTFU. Adherence to standard TB treatment, typically a 6-month DOTS-based course, is essential for treatment success and prevention of drug resistance [17]. Standard protocols include counseling, follow-up, and support that can promote adherence, particularly when tailored to patient needs [18]. In contrast, patients receiving non-standard TB regimens may have longer treatment durations, less familiar or less tolerated medications, and non-standard dosing or monitoring, which may increase uncertainty and hinder continuation. This finding is consistent with a previous study reporting higher LTFU rates among patients receiving non-standard regimens [4]. The World Health Organization also emphasizes that non-standard or second-line regimens require additional support, including enhanced counseling and monitoring, to reduce patient burden [19].

Another important determinant was mode of treatment: participants obtaining anti-TB drugs through out-of-pocket payment had a 4.9-times higher likelihood of LTFU than those receiving drugs through the TB program, consistent with studies in Indonesia and China [12,20].

Table 3. Multivariate analysis with binary logistic regression of the sample from the Indonesian Tuberculosis Information System, 2022

Variable	B	Wald	*p*	aPOR (95% CI)
Aged ≥65 y	0.622	511.970	<0.001	1.862 (1.765–1.965)
Male	0.172	51.813	<0.001	1.187 (1.133–1.244)
Unemployed	0.127	28.979	<0.001	1.136 (1.084–1.189)
Out-of-pocket treatment	1.609	621.387	<0.001	4.998 (4.404–5.672)
Non-referral	0.436	253.254	<0.001	1.547 (1.466–1.632)
Rural residence	−0.494	584.016	<0.001	0.610 (0.586–0.635)
Non-standard treatment	3.293	401.269	<0.001	26.912 (19.500–37.141)
HIV	1.311	694.757	<0.001	3.712 (3.367–4.092)
Constant	−5.203	788.320	<0.001	

aPOR, adjusted prevalence odds ratio; CI, confidence interval; HIV, human immunodeficiency virus.

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The national TB program, including DOTS, provides free, standardized, quality-assured drugs along with structured follow-up, education, and adherence support, and has been associated with improved adherence rates (from 79% to 94%) [21]. Prior evidence also suggests that access through national programs can reduce socioeconomic barriers and support adherence [18]. In contrast, patients using private pharmacies or non-government providers may lack adherence support and face high drug costs, variable drug quality, and limited supervision, all of which may contribute to LTFU [10,22]. Uncoordinated care, adverse effects, and patient confusion may further hinder treatment continuation [11]. Some individuals may choose non-program sources because of stigma, distrust, or a desire for privacy—particularly in urban areas—although this may be associated with poorer outcomes. This pattern is consistent with findings from Vietnam, where default rates were higher among patients treated outside formal programs [23].

HIV status was also strongly associated with LTFU, with TB–HIV co-infected patients being 3.7 times more likely to be LTFU. The immune system plays a central role in TB pathogenesis, with macrophages, dendritic cells, and neutrophils contributing to control of *Mycobacterium tuberculosis*. TB can disrupt these immune responses, and in HIV co-infection, CD4+ T-cell depletion further impairs both innate and adaptive immunity. This can increase disease severity, complicate diagnosis and treatment, and contribute to immune reconstitution inflammatory syndrome after initiation of antiretroviral therapy [24,25]. This finding is consistent with global evidence; a study in Kenya reported lower treatment completion and a higher risk of LTFU among HIV-positive TB patients [5]. Contributing factors may include medication adverse effects and pill burden from antiretroviral (and anti-TB drug combinations, complex regimens, frequent clinic visits, and psychological distress [26]. Social stigma may also contribute, as fear of discrimination and unintended disclosure can discourage sustained engagement in care. A previous study reported that stigma, depression, and limited social support were major drivers of LTFU among co-infected individuals [27].

In addition, age was significantly associated with LTFU in TB treatment. This study observed higher odds of LTFU among non-working-age groups, including teenagers and older adults, which may reflect biological, behavioral, and socioeconomic factors. Older adults may misattribute TB symptoms to normal aging, reducing perceived need for treatment [28]. Frailty, comorbidities, and mobility limitations may further contribute to treatment interruption [6,29]. In contrast, working-age individuals may be more likely to complete treatment because of greater health literacy, autonomy, and perceived responsibility [30]. In children, adherence often depends on caregivers; when caregivers face financial or logistical barriers, treatment interruption may be more likely. Prior studies have noted that pediatric TB is frequently underdiagnosed and may be suboptimally managed because children rely on adult supervision for diagnosis, follow-up, and medication administration [31].

Referral status was significantly associated with LTFU, with non-referral patients demonstrating a higher likelihood of LTFU than referral patients. This finding is consistent with prior work identifying referral status as a determinant of LTFU in the context of public–private mix implementation [20]. Formal referrals may facilitate earlier diagnosis, integration into national systems, and access to monitoring and support services [12]. In contrast, self-presenting (non-referred) patients may experience delays, have less understanding of the treatment process, and receive weaker adherence support [13]. Referral status may also reflect clinical oversight and perceived urgency, which can promote treatment continuation. The World Health Organization highlights referral systems as important for timely diagnosis, treatment initiation, and continuity across levels of care [19]. Prior evidence also suggests that patients lost between facilities may miss key steps in care, such as drug initiation and sputum monitoring, underscoring the need for robust referral networks in TB programs [32].

Sex was also significantly associated with LTFU, with men showing a higher likelihood of LTFU than women (aPOR, approximately 1.1). This disparity is consistent with prior literature describing sex-based differences in TB care. For example, evidence from South Africa suggests that men may delay care-seeking and are more likely to discontinue therapy because of work-related responsibilities, traditional gender norms, and stigma [33]. This finding is also consistent with studies in Indonesia reporting higher non-adherence among men and with findings from Selangor, Malaysia, where missed follow-up was more common among men and was attributed to financial constraints, work priorities, and limited family support [6,34]. In contrast, women may be more likely to seek initial care at private facilities and may report higher trust in healthcare providers, which can support treatment adherence [8].

These sex-based differences in LTFU may intersect with socioeconomic factors, including employment status. In this study, unemployment was associated with a higher likelihood of LTFU compared with employment, consistent with prior studies [35,36]. Unemployment may contribute to financial hardship, transportation barriers,

lower health literacy, and reduced social support, which can hinder completion of TB treatment. In contrast, formal employment may support adherence by providing structure, routine, and access to resources, including stable income and workplace support [37]. Similarly, individuals working in informal sectors may prioritize daily income over health needs, increasing vulnerability to treatment interruption [36]. Consistent with this explanation, 1 study reported that civil construction workers—who often experience precarious employment—were more likely to be LTFU [14].

Finally, the type of residence was significantly associated with LTFU, with rural residents showing a lower likelihood of LTFU than urban residents. This finding is consistent with evidence from India highlighting strengths of community-based TB programs in rural settings, including social cohesion, family involvement, and structured primary care [38]. These factors may support supervision and accountability, thereby promoting adherence. However, this result contrasts with several studies reporting poorer TB outcomes among rural populations. Research from Ethiopia, India, and Indonesia has documented access barriers in rural areas, including long travel distances, limited transportation, and constrained health infrastructure. For example, rural TB patients in Ethiopia were nearly twice as likely to be lost to follow-up [29]. Another study reported similar challenges in rural Indonesian districts, potentially related to delayed diagnosis and socioeconomic hardship [39]. These differences may reflect context-specific factors, including variation in local health system capacity, primary care investment, and urban barriers to continuity of care. Despite geographic proximity to health services, urban patients—particularly those living in informal settlements—may experience high mobility, work constraints, stigma, limited social support, and fragmented care, which can increase the likelihood of LTFU [40,41].

These findings have important implications for achieving Sustainable Development Goal 3 (Good Health and Well-Being), particularly by reducing LTFU in support of the End TB Strategy. Strengthening adherence support through standardized regimens, coordinated referral systems, and integrated care for TB–HIV and TB–diabetes mellitus comorbidities may improve treatment completion and reduce transmission. Expanding outreach and adherence support in urban settings for high-risk patients may also be important. Overall, addressing LTFU likely requires integrated, multi-level approaches that combine patient-centered support with health system strengthening.

Generalizability

This study has high generalizability to drug-sensitive TB patients in Indonesia because it used a large, nationwide dataset from SITB and reflects routine programmatic data. However, caution is warranted when applying these findings to other countries because determinants of LTFU are context-specific. The findings are limited to drug-sensitive TB and may not apply to drug-resistant TB populations. In addition, restricting the analysis to a single year (2022) and excluding records with missing data may affect representativeness and introduce selection bias.

We did not perform subgroup analyses; therefore, potential interactions between variables may remain unexamined. However, we conducted a multivariable analysis in which all relevant variables were entered simultaneously, yielding aPORs. Potential effect modification by biologically plausible factors (e.g., HIV status) could not be evaluated because of the small number of HIV-positive cases (n=806), which represented 6.10% of the 13,209 participants classified as LTFU.

Limitations

This study has several limitations. First, reliance on secondary data from the 2022 SITB restricted the analysis to variables available in the surveillance system and did not capture psychosocial, behavioral, or environmental factors that may influence adherence. Second, the use of routine surveillance data may introduce bias because of inaccuracies, misclassification, or inconsistencies in data entry. Third, the analysis may not fully address complex inter-variable relationships; although associations observed in bivariate analyses remained similar after multivariable adjustment, this does not preclude residual confounding or effect modification.

Conclusion

This analysis identified several factors significantly associated with LTFU among drug-sensitive TB patients in Indonesia. Older age, male sex, unemployment, non-referral status, HIV co-infection, and obtaining drugs outside the national program were all associated with a higher likelihood of LTFU. Notably, receipt of non-standard treatment showed the strongest association, whereas rural residence was associated with a lower likelihood of LTFU. Overall, nearly 1 in 5 TB patients discontinued treatment, indicating a substantial burden of LTFU. Multiple sociodemographic and clinical factors—particularly non-standard treatment, non-referral status, and HIV co-infection—were strongly associated with LTFU, suggesting important gaps in the

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care continuum. These findings underscore the need for targeted, patient-centered interventions, improved care coordination and communication, strengthened referral pathways, and strategies to reduce use of non-standard treatment to support adherence and reduce LTFU in high-risk groups.

Notes

Ethics Approval

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Negeri Semarang (Approval number 933/KEPK/FK/KLE/2025).

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: MaA, LH; Data curation: LH, MuA; Formal analysis: all author; Funding acquisition: MaA, SSA, AIF; Investigation: AFK, MaA; Methodology: AIF, SSA, MaA; Project administration: LH, AIF; Resources: MaA, AIF; Software: LH; Supervision: MuA, AFK, MY; Validation: MY, MaA; Visualization: MIK, SSA, LH; Writing–original draft: LH; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

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Original Article

Secondary transmission of severe fever with thrombocytopenia syndrome in a hospital setting in Republic of Korea: a retrospective observational study of personal protective equipment use and infection risk factors

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ABSTRACT

Objectives: This study investigated a cluster of secondary human-to-human transmission of severe fever with thrombocytopenia syndrome (SFTS) in a hospital setting, focusing on infection risk factors and the role of personal protective equipment (PPE).

Methods: A descriptive epidemiological investigation was conducted following the death of an index patient with laboratory-confirmed SFTS. A total of 27 close contacts, including healthcare workers and a funeral director, were monitored for symptoms. Suspected cases underwent real-time reverse transcription polymerase chain reaction testing. Clinical features, PPE use, and exposure histories were analyzed. The Fisher exact test was used to assess associations between PPE use and infection. Viral genotyping and sequence analyses were performed to evaluate transmission routes.

Results: The index patient deteriorated rapidly and died after repeated cardiopulmonary resuscitation (CPR), during which 8 secondary cases occurred. Most infections were identified among individuals involved in CPR or postmortem care without adequate PPE. Although not statistically significant, infection rates were higher among those who did not wear masks or who used low-filtration masks. Proper use of gloves, gowns, and goggles was associated with lower infection rates. Cycle threshold values in secondary cases (range, 34–39) were higher than in the index case (14.07), suggesting lower viral loads. Sequence analysis demonstrated 99.6%–100% homology between the index and secondary cases; all isolates were genotype B, indicating direct transmission.

Conclusion: This study provides molecular and epidemiological evidence of nosocomial SFTS transmission. Inadequate PPE use during aerosol-generating procedures likely facilitated infection, underscoring the importance of strict adherence to PPE protocols and reinforced infection control practices.

Keywords: Cross infection; Infection control; Personal protective equipment; Severe fever with thrombocytopenia syndrome

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Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is a zoonotic disease caused by SFTS virus (SFTSV), an RNA virus in the genus *Bandavirus* and the family *Phenuiviridae*. It is transmitted by ticks, including *Haemaphysalis longicornis*, *Amblyomma testudinarium*, *Ixodes nipponensis*, and *Rhipicephalus microplus* [1].

SFTS was first clinically identified in China in 2009 and was officially reported as a novel tick-borne viral disease in 2011. It is now endemic in several regions of China, with SFTSV infection reported in 1%–3% of the population [2]. Recent studies suggest that Japan may have been the earliest endemic region for SFTSV and that migratory bird routes likely facilitated its initial spread, followed by dissemination throughout East Asia [3]. Key factors contributing to its spread across East Asia include migratory bird movements and tick-borne transmission among wild animals [3–5]. In Japan, the first patient was identified in Yamaguchi Prefecture in the fall of 2012, and numerous cases have since been reported, primarily in western Japan [6]. In the Republic of Korea, SFTS was designated a Class 4 Notifiable Infectious Disease and has been under surveillance since the first patient was identified in May 2013. Following the 2020 amendment to the Act on the Prevention and Control of Infectious Diseases, it was reclassified as a Class 3 Notifiable Infectious Disease.

The primary route of SFTS transmission is through tick bites. According to a meta-analysis by Woo et al. [7], tick bites increase the risk of SFTS infection approximately 6-fold. However, person-to-person transmission has also been reported, primarily through contact with blood or body fluids from infected patients [7]. Furthermore, human infections following contact with SFTS-infected dogs and cats have increasingly been described, representing an additional transmission route [8,9]. SFTS can lead to severe complications, including central nervous system involvement, multiple organ failure, and hemophagocytic lymphohistiocytosis [10–12]. Delayed diagnosis has been associated with an increased risk of death, whereas high initial viral load and elevated inflammatory markers are associated with progression to severe disease [13].

Several cases of human-to-human transmission of SFTS have been reported. Among these, exposure to blood or conjunctival secretions has been linked to an increased risk of infection, underscoring the importance of wearing goggles in addition to standard protective equipment [14]. Some secondary infections have been asymptomatic; others have followed brief contact with blood or secretions from patients with SFTS [14,15]. Secondary infections have generally been reported to be clinically milder than primary infections [16]. Between 1996 and 2019, secondary transmission cases identified in China and the Republic of Korea showed secondary attack rates ranging from 1.72% to 55%, and the basic reproduction number (R0) averaged 0.13 [16]. In the Republic of Korea, cluster infections have occurred in hospitals treating patients with SFTS, primarily among healthcare workers performing cardiopulmonary resuscitation (CPR) and exposed to blood, body fluids, or contaminated gowns [17,18].

This study investigated cases involving healthcare workers and a funeral director who were secondarily infected by a patient who died of SFTS in a healthcare facility. The patient presented in early June 2025 with typical SFTS symptoms, including high fever, thrombocytopenia, and leukopenia. Seven healthcare workers and 1 funeral director were presumed to have been secondarily infected following exposure to blood and body fluids during emergency procedures, including CPR, performed after cardiac arrest during hospitalization. All 8 individuals were laboratory-confirmed to have SFTS. Symptoms, including fever and vomiting, developed between June 17 and June 21. Accordingly, this study analyzed the epidemiological characteristics of these secondary human-to-human SFTS infections and examined the association between personal protective equipment (PPE) use and infection risk to clarify potential transmission patterns.

HIGHLIGHTS

- We analyzed a cluster of secondary human-to-human transmission of severe fever with thrombocytopenia syndrome involving 8 healthcare workers following high-risk procedures, including cardiopulmonary resuscitation.
- Inadequate or absent use of personal protective equipment, especially low-filtration masks, was associated with an increased risk of infection, although statistical significance was limited by the small sample size.
- Viral sequencing identified genotype B with 99.6%–100% homology between the index and secondary cases, providing molecular evidence of direct nosocomial transmission and emphasizing the urgent need for strengthened infection control measures.

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Materials and Methods

Index Case

The index patient was admitted to Hospital A on June 5, 2025, with pancytopenia of unknown etiology and was transferred to Hospital B on June 9, 2025, because of clinical deterioration.

Her clinical condition subsequently deteriorated, and she was transferred to the intensive care unit around midnight on June 11. She died of multiple organ failure at 9:58 AM on June 11. CPR was performed 5 to 6 times over approximately 5 hours prior to her death, and a total of 22 medical personnel participated in the emergency response. Of these, 9 individuals who developed symptoms, including fever, vomiting, and diarrhea, were tested for SFTS; 7 tested positive. After death, the body was transported from Hospital B to Hospital A for funeral arrangements. Among the 4 funeral directors involved in this process, 1 was confirmed to have SFTS.

The index patient was a woman in her 60s whose initial symptom was fever (maximum temperature, 39.2 °C) beginning on June 2, 2025. She had no history of overseas travel but frequently tended her front garden. The site of the suspected tick bite was unclear, and no eschar was observed. She was admitted to Hospital A on June 5, 2025. At admission, laboratory testing showed a white blood cell (WBC) count of 1.03×10³/μL (reference range, 4.0–10.0×10³/μL) and a platelet count of 86×10³/μL (reference range, 150–450×10³/μL), consistent with leukopenia and thrombocytopenia. After the outbreak was recognized, 1 asymptomatic funeral director who had transported the body was identified as a contact. Subsequently, 4 additional funeral directors who participated in the funeral at Hospital A were traced. One of these individuals presented with fever of unknown origin and thrombocytopenia and was admitted to Hospital B in Cheongju, North Chungcheong Province, where SFTS was confirmed by polymerase chain reaction (PCR) testing on July 1, 2025. In total, 27 individuals were identified as having had contact with the index patient, including 4 at Hospital A and 23 at Hospital B; 8 of these individuals tested positive.

Case Definition

A case was defined as an individual who had close contact with the index patient during high-risk procedures, such as CPR or body handling, and who subsequently developed clinical symptoms consistent with SFTS or had laboratory-confirmed SFTSV infection.

Epidemiological Investigation

A total of 27 contacts were investigated. Among these, 10 individuals at Hospital B who developed symptoms such as fever, myalgia, or gastrointestinal disturbances.

Nine of them underwent testing for SFTSV infection using real-time reverse transcription PCR (RT-PCR), while one refused testing. In addition, 4 funeral directors who handled the body at Hospital A were also tested using RT-PCR. Clinical specimens (serum or throat swabs) were collected, and RT-PCR assays targeting the M and S segments of the SFTSV genome were performed. Cycle threshold (Ct) values for both segments were recorded as indirect indicators of viral load. In addition, epidemiological data—including demographic characteristics, clinical features, exposure sites, and PPE use—were collected for all 27 contacts at Hospitals A and B and were analyzed descriptively.

Statistical Analysis

The infection rate among SFTS contacts and the association between PPE use and infection were analyzed using R ver. 4.4.1 (R Foundation for Statistical Computing). For each type of PPE (gloves, gown, mask, and goggles/face shield), the infection rate was calculated as the proportion of confirmed cases among individuals who used that specific PPE. Infection rate distributions by type of PPE were visualized using the ggplot2 package. The Fisher exact test was used to compare infection rates according to PPE use, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

$$\text{Infection rate} = \frac{\text{Number of confirmed cases under a specific condition}}{\text{Total number of individuals under the same condition}} \times 100$$

Laboratory Analysis

Nine positive serum samples, including that of the index patient, were collected from this SFTS cluster and subjected to SFTSV genotyping and sequence homology analysis.

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of the Korea Disease Control and Prevention Agency (IRB No: 2025-08-03-PE-01).

Results

Clinical Characteristics

The index patient developed symptoms on June 2, was admitted to Hospital A on June 5, and was transferred to Hospital B on June 9.

Due to clinical deterioration, she was transferred to the intensive care unit on June 11. Despite repeated CPR, she died later that day. A total of 27 individuals were identified as having had contact with the patient before or after her

death. Of these, 13 developed symptoms suggestive of SFTS and underwent real-time RT-PCR testing. Eight healthcare workers and funeral directors involved in patient care or body handling were confirmed to have contracted the virus (Figure 1).

Between 5:00 AM and 10:00 AM on June 11, 2025, CPR was performed 5 to 6 times, including central venous catheter insertion, urinary catheter placement, endotracheal intubation, and mechanical ventilation. Repeated sputum suctioning and manual ventilation using an Ambu bag were performed, and blood was observed in the endotracheal tube. Sputum suctioning generated large amounts of bloody secretions, which likely increased the risk of skin and mucosal exposure. In addition, substantial aerosol generation likely occurred during manual ventilation, creating a high-risk exposure environment for healthcare workers.

All secondary cases developed symptoms between June 17 and June 21 and shared a history of high-risk exposure (e.g., CPR, contact with blood or body fluids, and body handling) around the time of the index patient's death. The 8 confirmed cases included 2 physicians, 5 nurses, and 1 funeral director (Figure 1). None reported a history of tick bites, and the epidemiological findings strongly supported human-to-human transmission. These observations suggest that close contact with blood and body fluids during CPR was a major factor associated with increased SFTS transmission risk. Specifically, improper or inconsistent PPE use during emergency treatment or postmortem care likely contributed to infection.

The index patient exhibited marked leukopenia (WBC, 3.27×10^3/μL) and thrombocytopenia (platelet count [PLT], 27×10^3/μL), with an absolute neutrophil count of 2.13×10^3/μL (reference range, 1.5–8.0×10^3/μL). Liver enzyme levels were markedly elevated, with aspartate aminotransferase (AST) at 3,040 IU/L (reference range, 10–40 IU/L); lactate dehydrogenase (LDH) was also high at 24,690 IU/L (reference range, 140–280 IU/L). High-sensitivity C-reactive protein was mildly elevated at 0.55 mg/dL (<1.0 mg/dL, low risk). The Ct value for the M segment on RT-PCR was 14.07, indicating a high viral load.

In contrast, the 8 confirmed secondary cases showed mild decreases in WBC and PLT along with modest elevations in AST and LDH, although these abnormalities were less pronounced than in the index patient. The M segment Ct values ranged from 34 to 39, indicating markedly higher Ct values—and therefore lower viral loads—than in the index patient. The index patient was 69 years old, whereas the secondary cases were younger, with a median age of 34 years (range, 26–55 years). The demographic and clinical characteristics of the index and secondary cases are summarized in Table 1.

Wearing PPE

To examine the association between PPE use and secondary SFTS infection, the 27 close contacts were categorized according to PPE use. Mask type was classified into 4 categories: no mask, dental mask, KF94 mask, and N95

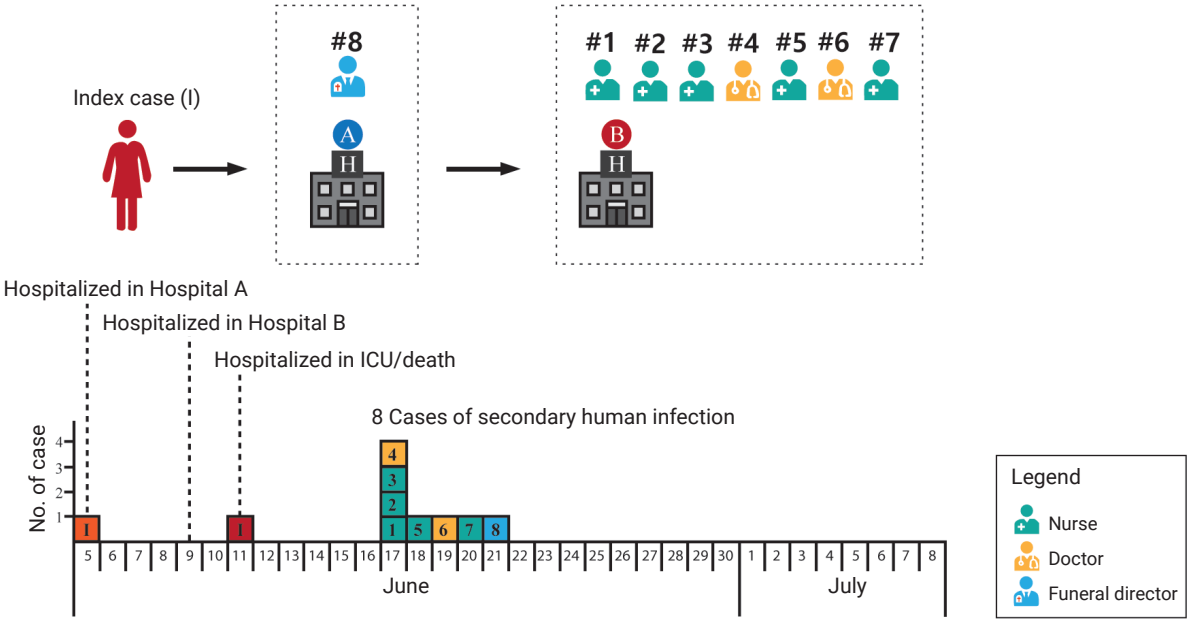


Figure 1. Epidemic curve and transmission linkage of the index case and 8 secondary human severe fever with thrombocytopenia syndrome infections.

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Table 1. Demographic and clinical-epidemiological characteristics of the index case and secondary SFTS infections

Characteristic	Index case	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7	Patient #8
Sex	Female	Female	Male	Male	Female	Female	Male	Female	Male
Age (y)	69	26	30	29	49	28	38	40	55
Occupation	Unemployed	Nurse	Nurse	Nurse	Doctor	Nurse	Doctor	Nurse	Funeral director
Date of onset	June 2, 2025	June 17, 2025	June 17, 2025	June 17, 2025	June 17, 2025	June 18, 2025	June 19, 2025	June 20, 2025	June 21, 2025
Temperature (°C)	39.2	38.0	38.1	39.3	38.0	38.0	38.0	38.0	37.7
Clinical symptoms	Fever	Fever, myalgia	Fever, headache	Fever, myalgia	Fever, myalgia, rash	Fever, myalgia	Fever, diarrhea	Fever, myalgia	Fever, chills, myalgia, vomiting
Underlying disease	No	VPB	Hyperlipidemia	Gout, kidney donor	IDA, carcinoma of the uterine cervix, Tis	No	No	Asthma	No
WBC (CBC) (×10³/μL)	3.27	2.79	3.06	2.23	1.76	2.00	4.49	2.05	1.61
PLT (×10³/μL)	27	126	151	155	108	135	155	160	60
ANC (×10³/μL)	2.13	2.05	1.65	1.01	1.17	1.28	0.69	1.11	1.11
Creatinine (mg/dL)	0.70	0.73	1.33	0.89	0.57	0.67	0.99	0.50	1.09
AST (IU/L)	3,040	21	25	28	34	58	47	26	179
ALT (IU/L)	510	13	20	18	25	69	54	20	85
hs-CRP (mg/dL)	0.55	0.22	0.14	0.07	0.28	0.07	0.08	0.04	-
LDH (serum) (IU/L)	24,690	366	375	492	307	309	600	643	-
PT (INR)	1.48	1.04	1.07	1.01	0.96	0.99	0.97	1.03	1.00
Ct (M segment)	14.07	37.59	38.96	37.78	34.79	34.65	35.48	36.6	34.86
Ct (S segment)	12.87	38.94	38.45	35.95	34.5	33.62	35.11	37.48	35.45
Outcome	Death	Discharge	Discharge	Admitted and discharged	Discharge	Discharge	Admitted and discharged	Discharge	Discharge

SFTS, severe fever with thrombocytopenia syndrome; IDA, iron deficiency anemia; Tis, carcinoma in situ; VPB, ventricular premature beat; WBC, white blood cell; CBC, complete blood count; PLT, platelet count; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; hs-CRP, high-sensitivity C-reactive protein; LDH, lactate dehydrogenase; PT (INR), prothrombin time international normalized ratio; Ct, cycle threshold value (M and S segments, real-time reverse transcription polymerase chain reaction).

respirator. Individuals who did not wear masks or who wore lower-filtration masks tended to have higher infection rates.

Specifically, the odds of SFTS infection were higher among individuals who did not wear masks compared with those who wore higher-grade masks (OR, 4.80; 95% CI, 0.62–36.8). Similarly, individuals who did not use eye protection had higher odds of infection than those who did (OR, 5.20; 95% CI, 0.57–47.2). However, the CIs were wide and included 1, reflecting statistical uncertainty due to the small sample size.

No statistically significant association was observed between PPE type and SFTS infection ($p > 0.05$). Nevertheless, infections occurred more frequently among individuals who did not wear masks or gloves properly (Table 2; Figure 2). Individual-level exposure characteristics, procedures performed, and PPE use are summarized in Table S1 for all 27 contacts, with stratified presentation for infected and non-infected individuals. Aggregate-level comparisons are shown in Table 2.

Genotypic Characterization

Five of the 8 specimens from the index patient and secondary

Table 2. Association between personal protective equipment usage and infection status: results of the Fisher exact test

PPE	Negative ($n = 19$)	Positive ($n = 8$)	OR (95% CI)	p[a)]
Gloves			2.14 (0.32–14.7)	0.6
Not worn	4 (21.1)	3 (37.5)		
Worn	15 (78.9)	5 (62.5)		
Gown			1.70 (0.30–9.65)	0.7
Not worn	7 (36.8)	4 (50.0)		
Worn	12 (63.2)	4 (50.0)		
Mask			4.80 (0.62–36.8)	0.3
Not worn	3 (15.8)	3 (37.5)		
Dental	7 (36.8)	4 (50.0)		
KF94	8 (42.1)	1 (12.5)		
N95	1 (5.3)	0 (0)		
Goggles/face shield			5.20 (0.57–47.2)	>0.9
Not worn	15 (78.9)	7 (87.5)		
Worn	4 (21.1)	1 (12.5)		

Data are presented as *n* (%) unless otherwise stated.
PPE, personal protective equipment; OR, odds ratio; CI, confidence interval; KF94, Korean Filter 94; N95, N95 respirator mask.
[a)]By Fisher exact test.

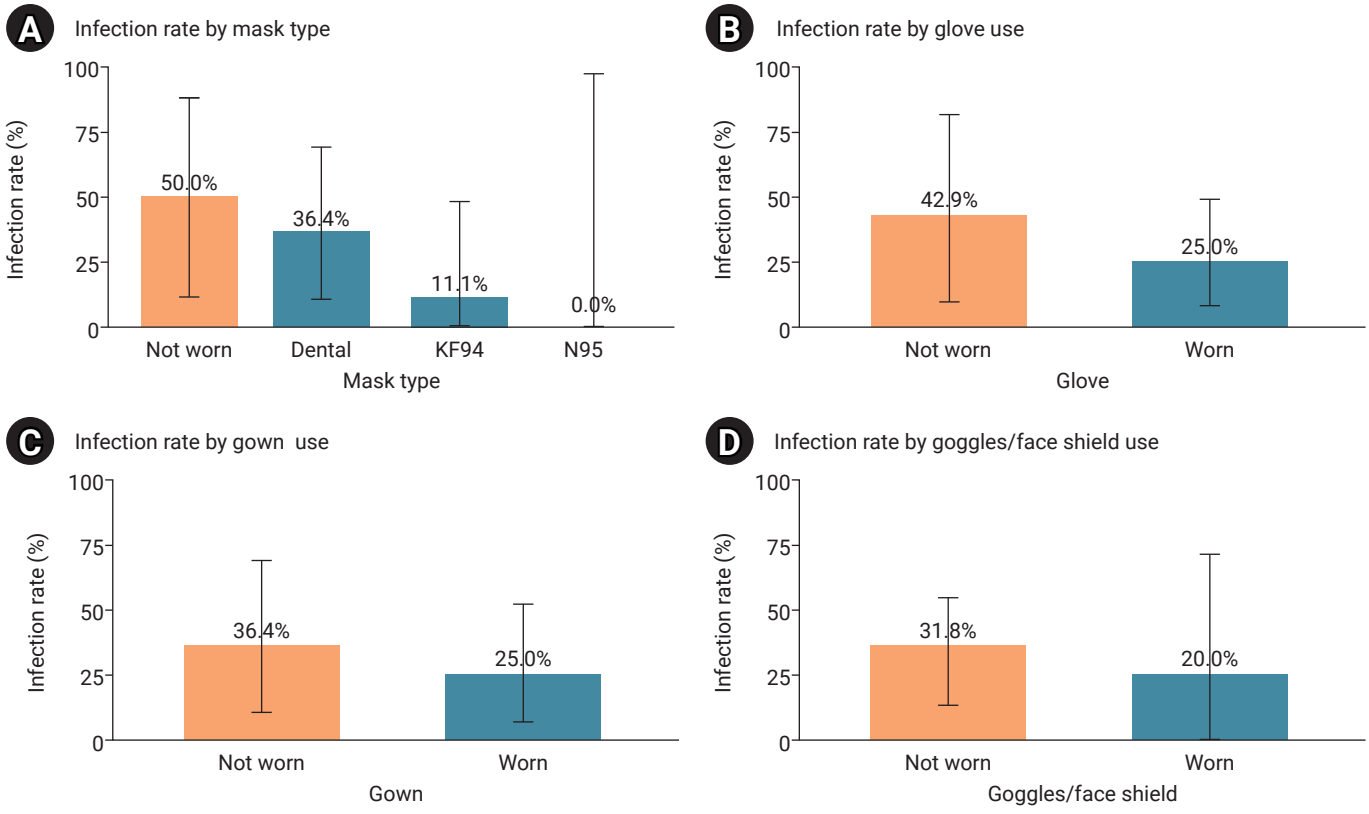


Figure 2. Infection rates according to personal protective equipment usage among close contacts of the severe fever with thrombocytopenia syndrome index case. Infection rate by (A) mask type, (B) glove use, (C) gown use, and (D) goggle/face shield use.

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cases were successfully genotyped, and all were classified as genotype B. Genotype B showed strong similarity to SFTSV strains previously reported in the Republic of Korea, indicating that these secondary infections were not imported but were instead caused by a locally circulating strain. Furthermore, the homology of the SFTSV S segment between the index case and 4 contacts was high, ranging from 99.6% to 100%, supporting a common source of infection. The remaining 3 cases had low viral loads and could not be analyzed (Table 3).

Discussion

In this study, 8 of 27 contacts who were directly or indirectly involved in medical procedures or postmortem handling of a patient with SFTS were confirmed to have secondary infection. None of the infected individuals reported a history of tick bites, and their shared involvement in high-risk clinical or postmortem procedures with the index patient strongly supports human-to-human transmission.

The 8 infected individuals included 2 physicians, 5 nurses, and 1 funeral director who participated in invasive procedures such as CPR, endotracheal intubation, central venous catheter insertion, sputum suctioning, and manual ventilation before and after the index patient's death. The presence of bloody sputum and likely aerosol generation during CPR created an environment with a high risk for virus transmission. The index patient exhibited a severe clinical course, characterized by markedly elevated liver enzymes (AST, 3,040 IU/L; alanine aminotransferase, 510 IU/L), elevated LDH (24,690 IU/L), and thrombocytopenia (PLT, 27×10^3/μL). These findings are consistent with previous research [19] indicating that severe SFTS is associated with liver dysfunction, thrombocytopenia, and elevated tissue injury markers such as LDH.

In contrast, most secondary SFTS cases presented with mild to moderate clinical manifestations. Laboratory findings showed relatively preserved PLT and lower levels of liver injury markers. Viral load also differed substantially from that of the index patient. The index patient had a markedly low Ct value (M segment, 14.07), whereas secondary cases had substantially higher Ct values (34.65–38.96), consistent with lower viral loads. These findings suggest that transmission likely occurred during high-risk procedures performed when the index patient had a high viral burden. However, the viral load detected in secondary cases was considerably lower.

To evaluate the effectiveness of PPE in preventing infection, the 27 contacts were surveyed regarding the use of 4 types of PPE: masks, gloves, gowns, and goggles/face shields. Regarding masks, infection rates were highest among individuals who did not wear masks (50%) or who wore dental masks (36.4%). In contrast, infection rates were lower among those wearing KF94 masks (11.1%) and absent among those wearing N95 respirators (0%)—both mask types known for higher filtration efficiency—indicating a clear protective effect. Similar patterns were observed for gloves, gowns, and eye protection, with higher infection rates among those who did not use PPE.

The Fisher exact test was performed to assess differences in infection rates across PPE types. No significant differences were observed, likely due to the limited sample size ($n=27$). Nonetheless, the 8 individuals who became infected either did not wear PPE or did not use it appropriately. Visual inspection of the results showed a consistent pattern of higher infection rates among those who did not wear PPE. Notably, the observed ORs were substantial, particularly for mask use (OR, 4.80) and eye protection (OR, 5.20). However, the CIs were wide and included 1, indicating considerable

Table 3. Genotypic analysis of SFTSV using conventional RT-PCR and sequence identity with the index case

	Conventional RT-PCR			Nucleotide sequence identity[a] (%)		
	L (483 bp)	M (560 bp)	S (567 bp)	L	M	S
Index case	Amplified	Amplified	Amplified			
#1	-	-	Amplified	-	-	100
#2	-			-		
#3	-	Amplified	-	-	100	-
#4	Amplified	-	Amplified	100	-	99.6
#5	-	Amplified	Amplified	-	100	100
#6	-	-	Amplified	-	-	100
#7	-			-		
#8	-			-		

SFTSV, severe fever with thrombocytopenia syndrome virus; RT-PCR, reverse transcription polymerase chain reaction; bp, base pairs; L, M, S, large, medium, and small genomic segments of SFTSV; -, genetic homology was assessed using the index case as the reference.
[a]Polymerase chain reaction, no amplification.

uncertainty around these estimates. Although based on a limited sample, these findings suggest that PPE may help prevent secondary human-to-human transmission and plays an important role in infection control. Furthermore, during prolonged emergency procedures such as CPR, large amounts of blood, droplets, and aerosols can be generated; in such situations, appropriate PPE use is especially critical to reduce infection risk.

Some individuals diagnosed with SFTS were found to have come into direct contact with the index patient without wearing gloves and gowns. Goggles and face shields, among other protective equipment, play a crucial role in preventing the spread of droplets and blood from the infected person to the facial mucosa. However, their use was inadequate in most cases.

Genotyping of 5 samples from the index patient and secondary cases identified genotype B, the predominant strain in the Republic of Korea. The S segment homology between the index and secondary cases was very high (99.6%–100%), suggesting the presence of identical viral strains and further supporting direct transmission from the index patient.

High-risk emergency procedures performed in medical facilities, such as CPR and endotracheal intubation, may increase the likelihood of person-to-person SFTSV transmission through exposure to blood, body fluids, and aerosols. In these settings, strict adherence to PPE protocols represents an effective measure for reducing infection risk. In addition to standard precautions for infection prevention, enhanced individual protection measures, including contact, droplet, and airborne precautions, are essential.

However, during urgent situations such as CPR, immediate patient care may limit adherence to recommended PPE protocols. In this cluster, many infected individuals were healthcare workers directly or indirectly involved in treating the index patient, as confirmed in this case, suggesting that PPE use may not have been feasible. Nevertheless, when managing patients with suspected or confirmed SFTS, infection risk should be considered at the outset. Appropriate PPE use and thorough decontamination before and after procedures are critical to reducing transmission risk. Given the elevated transmission risk during emergency interventions, systematic reinforcement of infection control protocols and PPE adherence within healthcare facilities is necessary.

The absence of funeral directors from Hospital A among the initially identified close contacts appears to reflect structural limitations in inter-institutional coordination rather than deficiencies in individual exposure assessment. At the time of this event, transfer of the deceased relied on informal communication rather than a standardized inter-hospital coordination system, which delayed identification, tracing, and exposure assessment of funeral personnel during the early investigation phase.

This case highlights a potential gap in infection control and epidemiological investigation systems, whereby postmortem transfer and funeral-related activities occurring outside healthcare facilities may not be fully captured. These findings underscore the need for clearer inter-institutional coordination mechanisms and defined responsibilities to ensure appropriate identification and protection of funeral personnel who may be occupationally exposed.

Funeral directors represent a high-risk occupational group due to the nature of their work. During body handling, mucosal contact with blood or body fluids, inhalation of aerosolized material, and direct pathogen exposure may facilitate transmission [20]. In SFTS cases, although excreta such as vomitus or stool from patients without bleeding are generally considered to pose a lower transmission risk than blood [21], the infection observed in a funeral director in this study demonstrates that transmission can occur during postmortem handling. Strict infection control measures are therefore essential during funeral and mortuary procedures involving patients with SFTS.

Limitations

This study analyzed secondary infections arising from a single medical institution and included 27 contacts. This limited sample size may have contributed to the lack of statistically significant findings.

PPE use and exposure information were collected retrospectively through surveys and record review, introducing the potential for recall bias and incomplete data. Furthermore, PPE adherence was determined primarily by self-report or indirect confirmation. Any resulting misclassification is likely to have been non-differential between infected and non-infected individuals, which would bias effect estimates toward the null and potentially underestimate the true effect of PPE use.

The precise timing and degree of exposure among secondary cases could not be determined, limiting the ability to quantify the protective effect of PPE.

Ct values were used as indirect indicators of viral concentration; however, comparisons are limited by potential variability in exposure timing and viral load. In addition, low viral concentrations in some secondary cases precluded genotyping and limited verification of genetic concordance among all confirmed cases.

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Conclusion

This study provides evidence supporting the protective effects of PPE in a case of human-to-human transmission of SFTS within a healthcare facility. Failure to wear appropriate PPE was associated with increased infection risk, with mask use appearing particularly important. Strict adherence to standardized PPE protocols is essential during high-risk emergency procedures, and systematic infection prevention measures should also be implemented during postmortem care for patients who have died from SFTS.

Supplementary Material

Table S1. Individual-level exposure characteristics and personal protective equipment use among the 27 personnel involved in patient care and mortuary services. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0481.

Notes

Ethics Approval

This study was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (KDCA) (IRB No. 2025-08-03-PE-01).

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

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

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Original Article

Association of quantity and quality of fat intake with sleep quality: a cross-sectional study in Iran

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ABSTRACT

Objectives: The association between dietary fat intake and sleep quality remains unclear. This study investigated the impact of both dietary fat quality and quantity on sleep quality.
Methods: In this cross-sectional study, participants completed a food frequency questionnaire and Pittsburgh Sleep Quality Index to assess quantity and quality of fat intake and sleep quality.
Results: A total of 1,904 participants (55% female) were included in the study. Participants in the highest tertile of polyunsaturated fatty acids (PUFA) intake, compared with those in the lowest tertile, had significantly higher total sleep quality scores (odds ratio [OR], 1.27; 95% confidence interval [CI], 1.01–1.62) and longer sleep onset latency (OR, 1.40; 95% CI, 1.08–1.83). Participants with higher animal fat intake exhibited higher total sleep quality scores (OR, 1.44; 95% CI, 1.09–1.89) and increased sleep disturbances (OR, 1.37; 95% CI, 1.02–1.83). Among women, those in the highest tertile compared with the lowest tertile showed increased odds of higher total sleep quality scores with total fat (OR, 1.37; 95% CI, 1.04–1.82), PUFA (OR, 1.41; 95% CI, 1.07–1.87), monounsaturated fatty acids (OR, 1.44; 95% CI, 1.09–1.90), saturated fatty acid (OR, 1.33; 95% CI, 1.01–1.77), and animal fat (OR, 1.58; 95% CI, 1.18–2.11).
Conclusion: These findings suggest that higher intakes of PUFA and animal fat are associated with higher total sleep quality scores. When stratified by sex, higher intake of total fat and unsaturated fats was associated with higher total sleep quality scores in women only.

Keywords: Cross-sectional studies; Dietary fats; Polyunsaturated fatty acids; Sleep quality

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Introduction

Background

Sleep is a fundamental physiological process that is critical for maintaining healthy brain function and overall well-being. Poor sleep quality disrupts normal circadian rhythms and adversely affects both psychological well-being and physical health [1]. It is associated with an increased risk of medical and psychiatric complications, reduced quality of life, and diminished work efficiency [2]. Sleep quality encompasses multiple dimensions, including sleep duration, sleep onset latency, sleep disturbances, daytime dysfunction, and sleep efficacy [3]. In Iran, the prevalence of insomnia reached 35% in 2022, representing a substantial public health concern [1]. Lifestyle modifications, particularly dietary interventions combined with regular physical activity, have been shown to improve sleep management and reduce associated health risks [3]. Regular consumption of macronutrients plays a crucial role in sleep physiology and related health outcomes [4].

Fats are essential macronutrients that serve multiple vital functions, including energy provision, formation of structural components of cell membranes, and facilitation of fat-soluble vitamin absorption [5]. The type of dietary fat consumed directly influences neuroendocrine systems involved in sleep regulation [6]. High intake of saturated or processed fats increases systemic inflammation, which can disrupt sleep architecture [7]. In contrast, polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA), particularly long-chain omega-3 fatty acids, help maintain neuronal membrane integrity and optimize signaling pathways for sleep-regulating neurotransmitters such as gamma-aminobutyric acid, thereby enhancing nocturnal melatonin production [8]. Appropriate dietary fat intake is therefore considered an important component of effective sleep hygiene [9]. Although the essential role of dietary fats in overall health is well recognized, the literature examining their association with sleep quality remains inconsistent. Previous studies assessing total fat intake and sleep outcomes have produced contradictory findings: some cross-sectional studies report that higher total fat intake is associated with poorer sleep quality [4], whereas cohort studies suggest that lower fat intake may paradoxically be associated with worse sleep quality [9]. Moreover, most existing research has emphasized fat quantity rather than fat quality [10].

Indices of fat quality, such as PUFA/saturated fatty acid (SFA) and (PUFA+MUFA)/SFA ratios, may more accurately predict sleep outcomes than total fat consumption alone. Furthermore, the dietary source of fat, whether vegetable- or animal-derived, may influence sleep outcomes through distinct biological mechanisms [11,12]. Despite these considerations, the independent and combined effects of dietary fat quantity and quality on sleep architecture remain insufficiently characterized in large population-based studies.

HIGHLIGHTS

- Poor sleep quality and longer time to fall asleep were associated with higher intake of polyunsaturated fatty acids (PUFA).
- Consuming more animal fat was associated with worse sleep quality and increased sleep disturbances.
- Saturated fatty acids also contributed to an increase in sleep disturbances.
- Higher overall fat intake, particularly consumption of PUFA and monounsaturated fatty acids, was associated with a significantly higher likelihood of using sleep medication.
- The study suggests that the type and amount of dietary fat contribute to regulating sleep.

Study Objectives

This study addresses the existing evidence gap by examining the associations between both the quantity and quality of dietary fat intake and sleep quality in a large sample of Iranian adults [1]. Specifically, we aimed to assess dietary fat intake patterns, including total fat and the relative contributions of PUFA, MUFA, and SFA; calculate indices of fat quality using established ratios; and examine the associations of fat quantity and quality with overall sleep quality scores as well as individual sleep components, including subjective sleep quality, sleep onset latency, sleep duration, sleep disturbances, sleep efficiency, sleep medication use, and daytime dysfunction [13].

Materials and Methods

Study Design and Setting

This cross-sectional study was conducted among healthy adults to examine the association between the quantity and quality of dietary fat intake and sleep quality.

Setting

The study was conducted from 2017 to 2019. Healthy adults visited primary health care centers in Kerdabad, located in Isfahan province. Kerdabad was selected for this study

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because of its diverse population, which encompasses a wide range of income levels and social statuses. This diversity enhances the generalizability of the study's findings to the broader population of Isfahan province [14,15]. Households were examined using a census-based sampling method. All households in districts 4 and 5 of Kerdabad approximately n=4,000 were enumerated. From each household, 1 adult member was randomly selected with equal probability for all household members. Non-eligible individuals were replaced through random selection of another household member from the same household.

Participants

In this study, "healthy adults" refers to individuals without known chronic diseases or acute medical conditions. In Iran, generally healthy individuals routinely visit primary health care centers for preventive services or routine health checks, which explains why healthy adults were recruited from these centers.

The inclusion criteria for participants were as follows: (1) adults who appeared to be healthy; (2) individuals aged between 18 and 65 years; and (3) those capable of visiting the local health center and completing the questionnaire for data collection. Exclusion criteria included: (1) non-Iranian nationals; (2) pregnant or breastfeeding women; (3) individuals experiencing menopause; (4) those who had followed a special diet within the previous 3 months; and (5) individuals with significant physical or mental disabilities that would prevent them from visiting a local health center or participating in the data collection process. The following expression was used to estimate the appropriate sample size for assessing the association between diet and sleep [16].

$$m' = \frac{\left[c_{a/2}\sqrt{(r+1)\overline{P}\,\overline{Q}} - c_{1-\beta}\sqrt{rP_1Q_1 + P_2Q_2}\right]^{\acute{2}}}{r(Pw_2 - P_1)^2}$$

$$m = \frac{m'}{4}\left[1 + \sqrt{1 + \frac{2(r+1)}{m'r|P_2 - P_1|}}\right]^2$$

$P=(p_1+p_2)/(1+r)$

$Q_1=1-P_1$, $Q_2=1-P_2$, $Q=1-P$

$n_1=m$

$n_2=mr$

$n=n_1+n_2$

The significance level, α (type I error), was set at 0.05, and the probability of a type II error, β, was set at 0.20, resulting in a study power of 80%. The initial estimated sample size was calculated to be 1,246 individuals. After accounting for an anticipated dropout rate of 30%, the final target sample size required for the cross-sectional analysis was set at 1,904 participants. All participants received a detailed explanation of the study's purpose and provided written informed consent prior to enrollment. All methods were conducted in accordance with relevant guidelines and regulations.

Variables

Participants completed a food frequency questionnaire (FFQ) to assess intake of total fat, PUFA, MUFA, SFA, animal fat, and vegetable oil. Sleep quality was evaluated using the Pittsburgh sleep quality index (PSQI).

Data Sources/Measurement

Data on dietary intake, and quantity and quality of fat intake

Dietary information was collected using a validated FFQ comprising 106 food items and designed in the Willett format. The validity and reliability of this FFQ have been established in previous studies [17]. This questionnaire assesses the frequency of food consumption over the previous year, thereby providing an estimate of long-term dietary intake. To convert FFQ data into nutrient values, the gram amount of food intake for each participant was calculated based on the reported consumption frequency and portion sizes. Each food item was then coded and entered into Nutritionist IV software, which facilitated the conversion of food items into specific nutrient data. Using this software, the amounts and percentages of energy, fat, and other nutrients consumed by each participant were calculated [18]. Although the FFQ is semi-quantitative, frequency categories were converted into numerical intake estimates by multiplying reported consumption frequencies by standard portion sizes and nutrient composition values.

Regarding the evaluation of fat quality, animal fat, vegetable oil, PUFA/SFA, and (PUFA+MUFA)/SFA ratios were calculated [19–22].

Structure of the PSQI

The validity [23] and reliability [23] of the PSQI have been previously established. This questionnaire consists of 19 questions organized into 7 components [24]: (1) subjective sleep quality, which assesses the individual's personal perception of overall sleep quality; (2) sleep onset latency, which measures the severity and frequency of difficulty falling asleep, particularly when sleep onset exceeds 30

minutes; (3) sleep duration, for which scores are determined based on whether total sleep time is less than 6 hours, indicating a disturbance; (4) sleep efficiency, calculated as the ratio of actual sleep time to total time spent in bed multiplied by 100, with values below 75% indicating impairment in this component; (5) sleep disturbances, evaluated through questions addressing factors that may disrupt sleep, including environmental discomfort (such as feeling too hot or too cold), breathing difficulties, frequent awakenings, early awakening, pain, coughing, and related issues; (6) sleep medication, for which use is considered problematic when sleep medications are taken more than once or twice per week; and (7) daytime dysfunction, assessed through questions evaluating daytime sleepiness and difficulties with concentration during daily activities, including working, driving, eating, and other routine tasks.

Each component is scored on a scale from 0 to 3, with higher scores indicating poorer sleep quality. Scores from the 7 components are summed to generate a total scale score. This cumulative score serves as an overall indicator of sleep quality, with higher values reflecting poorer sleep quality.

Anthropometric assessment

Body weight and height were measured by trained research staff using standardized protocols. Weight was measured to the nearest 0.1 kg using a calibrated scale (SECA 700; SECA), with participants wearing light clothing and no shoes. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (SECA 220; SECA), with participants standing upright without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Participants were categorized into 4 groups according to the World Health Organization classification: underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), and obese (BMI ≥ 30.0 kg/m^2).

Assessment of other variables

In this study, sociodemographic variables were assessed using a general questionnaire designed to capture key participant characteristics, including age, sex, education level, marital status, number of family members, and home ownership status. Physical activity was assessed using the General Physical Activity Questionnaire (GPAQ), developed by the World Health Organization. The GPAQ includes 16 items that capture physical activity across 3 domains: (1) activity at work, (2) travel to and from places, and (3) recreational activities. The questionnaire also assesses sedentary behavior. Based on the total weekly minutes of moderate and vigorous physical activity, participants were categorized into 4 activity levels: never, less than 1 hour, 1–3 hours, and more than 3 hours per week. The GPAQ has demonstrated acceptable reliability and validity in previous studies, particularly in test–retest reliability assessments.

Bias

The present study minimized bias through several approaches. First, the large sample size enhanced the reliability and generalizability of the findings. Second, validated and reliable questionnaires were used, including the PSQI, a well-established instrument with demonstrated accuracy in measuring sleep quality. Third, sleep quality was assessed comprehensively by examining multiple indices, allowing for a more nuanced evaluation of factors influencing sleep patterns.

Quantitative Variables

The Kolmogorov-Smirnov test was used to assess data normality. Quantitative variables were described using means and standard deviations (SDs), whereas qualitative variables were reported as numbers and percentages. Sleep quality scores derived from the PSQI were categorized into tertiles: 0–3 (good), 4–5 (moderate), and > 5 (poor).

Statistical Methods

Participant characteristics were compared across sleep quality tertiles using the independent t-test for quantitative variables and the chi-square test for qualitative variables. Analysis of covariance (ANCOVA) was used to evaluate differences in food intake, adjusted for age, sex, and energy intake, except for energy intake itself, which was adjusted for age and sex only. Dietary fat quantity and quality were compared with sleep quality using ANCOVA, with further adjustment for marital status, physical activity, education level, BMI, and socioeconomic status. Binary logistic regression analysis was performed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for sleep quality components across tertiles of fat quantity and quality indices. Although the FFQ initially generated continuous intake values, these were categorized into tertiles (low, medium, high) for analytical purposes. Because the dependent variables were categorical rather than continuous, logistic regression was considered the appropriate analytical approach.

Ordinal regression analysis was conducted to explore the association between fat intake, including both quantity and quality, and overall sleep quality.

Analyses were conducted using 3 sequential adjustment models. Model 1 was adjusted for age, sex, and energy intake. Age and sex were included as fundamental demographic confounders influencing both sleep physiology and dietary

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patterns, while energy intake was included to account for total caloric consumption that could confound associations between macronutrient compositions and sleep outcomes. Model 2 (socioeconomic and lifestyle adjustment) additionally included socioeconomic status, education level, marital status, and physical activity, as these factors influence dietary behaviors and health-related outcomes. Model 3 (full adjustment model) further included BMI, which may partially mediate the association between dietary fat intake and sleep quality, given the established links between obesity, dietary fat consumption, inflammation, and sleep disturbances. Confounders were selected based on prior literature and their potential influence on both exposure and outcome to minimize bias.

All statistical analyses were performed using IBM SPSS ver. 25.0 (IBM Corp.), and a p-value < 0.05 was considered statistically significant.

Ethics Statements

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences and registered with the Iranian Registry of Clinical Trials (IR.TUMS.MEDICINE.REC.1401.624).

Results

Participants

A total of 1,904 participants were included in this analysis.

Descriptive Data

Fifty-five percent of the participants were female. The mean ± SD age and BMI of the study population were 39.63 ± 10.24 years and 27.08 ± 4.91 kg/m^2, respectively.

Outcome Data

The study identified an association between dietary fat intake and sleep quality. Higher consumption of animal fat and PUFAs was associated with higher total sleep quality scores and increased odds of longer sleep onset latency. Conversely, higher intake of animal fat and SFAs was associated with a greater likelihood of sleep disturbances. In addition, increased intake of PUFAs, MUFAs, and total fat was associated with higher odds of using sleep medication. When stratified by sex, higher intake of total fat and unsaturated fats was also associated with higher total sleep quality scores among women.

Main Results

The general characteristics of participants according to tertiles of total sleep quality score are presented in Table 1. Compared with participants in the lowest tertile, those in the highest tertile had a higher mean age and higher BMI ($p < 0.001$). In addition, they were more likely to be overweight or obese and to have postgraduate education ($p < 0.001$). A higher percentage of men were classified in the lowest tertile compared with the highest tertile, whereas a higher percentage of women were classified in the highest tertile compared with the lowest tertile ($p < 0.001$). With respect to socioeconomic status, participants in the third tertile of total sleep quality score were more likely to be in the medium socioeconomic category ($p = 0.005$). No other significant differences were observed in other general characteristics across tertiles of total sleep quality score.

Table 2 presents comparisons of dietary intake among participants across tertiles of total sleep quality score at baseline. The results showed that participants in the third tertile consumed less fiber ($p = 0.004$) compared with those in the first tertile. No other significant differences were observed in other dietary intakes among participants ($p > 0.05$).

The association between dietary fat quantity and quality and total sleep quality score is shown in Table 3. Individuals in the third tertile of PUFA intake, compared with those in the first tertile, had 27% higher odds of having a higher total sleep quality score (OR, 1.27; 95% CI, 1.006–1.62), which was statistically significant. Although modest, this increase may have some clinical relevance for adults with poor baseline sleep quality. Similarly, for animal fat intake, individuals in the third tertile compared with the first tertile had 44% higher odds of having a higher total sleep quality score (OR, 1.44; 95% CI, 1.09–1.89), which was also statistically significant and suggests a potentially meaningful association with sleep quality.

The associations between dietary fat quantity and quality and total sleep quality score stratified by sex are presented in Table 4. The findings indicate that among women, higher intake of total fat and specific types of fatty acids was associated with a higher likelihood of being classified in higher categories of total sleep quality score. In contrast, no statistically significant associations were observed among men.

Specifically, women in the third tertile of total fat intake, compared with those in the first tertile, had a higher likelihood of having a higher total sleep quality score (OR, 1.37; 95% CI, 1.04–1.82). In addition, being in the third tertile compared with the first tertile of PUFA intake (OR, 1.41; 95% CI, 1.07–1.87), MUFA intake (OR, 1.44; 95% CI, 1.09–1.90), SFA intake (OR, 1.33; 95% CI, 1.01–1.77), and animal fat intake (OR, 1.58; 95% CI, 1.18–2.11) was also associated with a higher likelihood of being in higher categories of total sleep quality

Table 1. General characteristics of participants at the beginning of the study according to tertiles of total sleep quality scores

Characteristic	Tertiles of total sleep quality			*p*
	First tertile (≤3, *n* = 780)	Second tertile (4–5, *n* = 278)	Third tertile (>5, *n* = 767)	
Quantitative variable				
Age (y)	38.26 ± 9.78	39.23 ± 10.25	40.97 ± 10.47	≤0.001
Body mass index (kg/m^2)	26.41 ± 4.40	26.84 ± 4.69	27.77 ± 5.41	≤0.001
Qualitative variables				
Classification of body mass index				≤0.001
Low weight	15 (1.9)	9 (2.3)	13 (1.9)	
Normal weight	277 (37.8)	119 (30.3)	208 (29.8)	
Overweight	298 (40.7)	165 (42.0)	262 (37.5)	
Obese	143 (19.5)	100 (25.4)	215 (30.8)	
Sex				≤0.001
Male	426 (54.6)	138 (49.6)	266 (34.7)	
Female	354 (45.4)	140 (50.4)	501 (65.3)	
Marital status				0.13
Married	580 (83.1)	319 (81.4)	605 (82.5)	
Widow	17 (2.4)	7 (1.8)	7 (1)	
Divorced	14 (2)	3 (0.8)	12 (1.6)	
Single	87 (12.5)	63 (16.1)	109 (14.9)	
Education (y)				≤ 0.001
<12	203 (27.9)	121 (30.8)	279 (40.4)	
≥12	524 (72.6)	272 (69.2)	411 (59.6)	
Socioeconomic status				0.005
Low	76 (12)	46 (13.3)	104 (16.5)	
Moderate	339 (53.6)	200 (58)	367 (58.1)	
High	218 (34.4)	99 (28.7)	161 (25.5)	
Physical activity (per week)				0.50
None	182 (40.4)	90 (20)	179 (39.9)	
<1 h	163 (38.2)	97 (22.7)	167 (39.1)	
1–3 h	158 (36.9)	97 (22.7)	173 (40.4)	
>3 h	184 (43.3)	91 (21.4)	150 (35.3)	

Data are presented as mean ± standard deviation or *n* (%). Values were obtained from 1-way analysis of variance to compare quantitative variables among more than 2 groups. The independent t-test was used to compare quantitative variables between 2 groups. The chi-square test was used to compare qualitative variables.

Table 2. Comparison of dietary food intake of the participants at the beginning of the study among tertiles of total sleep quality score

Variable	Tertiles of total sleep quality			*p*
	First tertile (≤3, *n* = 780)	Second tertile (4–5, *n* = 278)	Third tertile (≤5, *n* = 768)	
Energy (kcal/d)	2,529.29 ± 46.55	2,529.86 ± 62.95	2,529.61 ± 47.94	1.00
CHO (g/d)	321.16 ± 2.64	316.22 ± 3.58	317.09 ± 2.72	0.43
Protein (g/d)	93.28 ± 0.62	93.84 ± 0.84	92.92 ± 0.64	0.69
Fat (g/d)	102.04 ± 0.99	103.92 ± 1.35	103.76 ± 1.02	0.388
PUFA (g/d)	36.68 ± 0.43	37.08 ± 0.58	37.33 ± 0.44	0.569
MUFA (g/d)	27.11 ± 0.30	27.68 ± 0.42	27.45 ± 0.31	0.51
SFA (g/d)	24.03 ± 0.27	24.37 ± 0.37	24.29 ± 0.28	0.72
Animal fat (g/d)	10.16 ± 0.33	11.04 ± 0.44	10.79 ± 0.34	0.21
Vegetable oil (g/d)	44.34 ± 0.63	44.21 ± 0.86	45.51 ± 0.65	0.35
Fiber intake (mg/d)	16.21 ± 0.16	16.13 ± 0.22	15.50 ± 0.16	0.008

Data are presented as mean ± standard deviation. All values are adjusted for age, sex, and energy intake, except for energy intake, which is only adjusted for age and sex. *p*-values are obtained from analysis of covariance.
CHO, carbohydrate; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

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Table 3. Association between quantity and quality of fat intake and total sleep quality score

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)
Tertiles of fat intake	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)
Crude model	1.00	1.80 (0.76–1.16)	1.46 (0.89–1.35)
Model 1	1.00	0.98 (0.95–1.46)	1.18 (0.95–1.46)
Model 2	1.00	1.003 (0.79–1.26)	1.20 (0.94–1.52)
Model 3	1.00	1.01 (0.79–1.27)	1.20 (0.94–1.52)
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)
Crude model	1.00	1.10 (0.89–1.36)	1.20 (0.97–1.48)
Model 1	1.00	1.08 (0.87–1.34)	1.18 (0.95–1.47)
Model 2	1.00	1.16 (0.92–1.47)	1.27 (1.008–1.62)
Model 3	1.00	1.16 (0.92–1.47)	1.27 (1.006–1.62)
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)
Crude model	1.00	1.009 (0.81–1.24)	1.33 (0.83–1.26)
Model 1	1.00	1.05 (0.85–1.30)	1.15 (0.92–1.43)
Model 2	1.00	1.14 (0.90–1.44)	1.21 (0.96–1.54)
Model 3	1.00	1.13 (0.89–1.43)	1.20 (0.94–1.52)
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)
Crude model	1.00	1.03 (0.84–1.27)	1.06 (0.86–1.31)
Model 1	1.00	1.02 (0.83–1.27)	1.15 (0.93–1.43)
Model 2	1.00	1.06 (0.84–1.34)	1.17 (0.92–1.49)
Model 3	1.00	1.05 (0.83–1.33)	1.16 (0.91–1.47)
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)
Crude model	1.00	1.20 (0.97–1.48)	1.09 (0.88–1.35)
Model 1	1.00	1.30 (1.05–1.61)	1.40 (1.10–1.78)
Model 2	1.00	1.37 (1.08–1.74)	1.50 (1.15–1.96)
Model 3	1.00	1.32 (1.04–1.69)	1.44 (1.09–1.89)
Tertiles of vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)
Crude model	1.00	0.80 (0.65–0.99)	0.79 (0.64–0.97)
Model 1	1.00	0.90 (0.72–1.12)	0.90 (0.69–1.19)
Model 2	1.00	0.92 (0.72–1.18)	0.99 (0.73–1.33)
Model 3	1.00	0.92 (0.72–1.17)	0.98 (0.72–1.33)
Tertiles of PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)
Crude model	1.00	1.02 (0.83–1.26)	1.15 (0.93,1.42)
Model 1	1.00	0.95 (0.77–1.18)	1.03 (0.83–1.28)
Model 2	1.00	0.98 (0.77–1.24)	1.07 (0.84–1.35)
Model 3	1.00	0.99 (0.78–1.25)	1.08 (0.85–1.38)
Tertiles of PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)
Crude model	1.00	0.80 (0.65–0.99)	0.75 (0.61–0.93)
Model 1	1.00	0.85 (0.67–1.06)	0.81 (0.60–1.09)
Model 2	1.00	0.86 (0.67–1.10)	0.88 (0.64–1.22)
Model 3	1.00	0.84 (0.66–1.08)	0.88 (0.64–1.22)

Obtained from the ordinal regression test.
Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to previous items, adjusted for physical activity, marital status, socioeconomic status and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

score among women.

An examination of dietary fat profiles in relation to individual sleep components revealed several notable associations, as presented in Tables 5–11. A higher percentage of PUFAs was associated with increased sleep onset latency, which may adversely affect sleep efficiency in susceptible individuals (Table 6). Furthermore, higher intake of SFAs and total animal fat was associated with an increased probability of sleep disturbances, indicating a potentially important effect on sleep quality (Table 9). Elevated total fat intake, along with higher proportions of PUFAs and MUFAs, was positively associated with sleep medication

Table 4. Association between quantity and quality of fat intake and total sleep quality score, stratified by sex

Sex	Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)
Percentage of fat intake Tertiles of fat intake		<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)
Male	Crude model	1.00	1.02 (0.70–1.49)	0.88 (0.67–1.16)
	Adjusted model	1.00	1.00 (0.67–1.63)	0.97 (0.70–1.32)
Female	Crude model	1.00	0.90 (0.63–1.25)	1.32 (1.03–1.69)
	Adjusted model	1.00	0.98 (0.67–1.40)	1.37 (1.04–1.82)
Tertiles of PUFA percentage from energy		<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)
Male	Crude model	1.00	0.97 (0.66–1.40)	0.97 (0.73–1.27)
	Adjusted model	1.00	0.92 (0.60–1.39)	1.03 (0.75–1.43)
Female	Crude model	1.00	0.99 (0.70–1.53)	1.32 (1.03–1.69)
	Adjusted model	1.00	0.97 (0.66–1.40)	1.41 (1.07–1.87)
Tertiles of MUFA percentage from energy		<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)
Male	Crude model	1.00	0.91 (0.62–1.32)	0.86 (0.65–1.13)
	Adjusted model	1.00	0.99 (0.64–1.49)	0.92 (0.66–1.25)
Female	Crude model	1.00	1.01 (0.71–1.41)	1.29 (1.01–1.68)
	Adjusted model	1.00	1.12 (0.78–1.64)	1.44 (1.09–1.91)
Tertiles of SFA percentage from energy		<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)
Male	Crude model	1.00	0.97 (0.66–1.40)	0.89 (0.67–1.17)
	Adjusted model	1.00	1 (0.67–1.56)	1 (0.73–1.37)
Female	Crude model	1.00	0.92 (0.65–1.28)	1.28 (1.003–1.64)
	Adjusted model	1.00	0.92 (0.63–1.32)	1.33 (1.01–1.77)
Tertiles of animal fat (g/d)		<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)
Male	Crude model	1.00	0.77 (0.52–1.11)	0.96 (0.72–1.27)
	Adjusted model	1.00	0.90 (0.57–1.41)	1.03 (0.74–1.46)
Female	Crude model	1.00	0.79 (0.56–1.11)	1.61 (1.24–2.07)
	Adjusted model	1.00	0.85 (0.57–1.24)	1.58 (1.18–2.11)
Tertiles of vegetable oil (g/d)		<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)
Male	Crude model	1.00	0.93 (0.63–1.34)	0.87 (0.65–1.15)
	Adjusted model	1.00	1.11 (0.69–1.82)	0.90 (0.63–1.29)
Female	Crude model	1.00	0.72 (0.51–1.02)	1 (0.77–1.28)
	Adjusted model	1.00	1 (0.64–1.56)	1.09 (0.79–1.52)
Tertiles of PUFA/SFA		<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)
Male	Crude model	1.00	1.04 (0.71–1.52)	1.04 (0.78–1.37)
	Adjusted model	1.00	0.97 (0.63–1.46)	0.99 (0.72–1.36)
Female	Crude model	1.00	0.94 (0.67–1.32)	1.02 (1.03–1.12)
	Adjusted model	1.00	0.92 (0.63–1.33)	1.10 (0.84–1.44)
Tertiles of PUFA+MUFA/SFA		<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)
Male	Crude model	1.00	0.81 (0.56–1.18)	0.75 (0.56,0.99)
	Adjusted model	1.00	0.89 (0.53–1.49)	0.74 (0.50–1.08)
Female	Crude model	1.00	1.08 (0.52,1.04)	1.10 (0.86,1.41)
	Adjusted model	1.00	0.98 (0.60–1.58)	1.46 (0.02–2.09)

Obtained from the ordinal regression test.
Ref., reference; OR, odds ratio; CI, confidence interval; adjusted model, adjusted for age, energy intake, physical activity, marital status, socioeconomic status, education and body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

use, highlighting a clinically relevant implication (Table 10). No other significant associations were observed for other dietary intakes. Detailed results are provided in Tables 4–10.

Discussion

Key Results

In this cross-sectional study, several associations between dietary fat intake and sleep quality were observed. Higher PUFA intake and higher animal fat intake were associated with higher total sleep quality scores. Among women in

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Table 5. Investigating the association between the quantity and quality of fat intake with the subjective sleep quality in the participants in the study

Models	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	0.80 (0.60–1.06)	1.05 (0.80–1.06)	0.68
Model 1	1.00	0.88 (0.66–1.17)	1.06 (0.80–1.40)	0.66
Model 2	1.00	0.95 (0.69–1.30)	1.19 (0.87–1.63)	0.27
Model 3	1.00	0.85 (0.62–1.17)	1.15 (0.84–1.57)	0.36
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	1.01(0.76–1.35)	1.20 (0.91–1.59)	0.18
Model 1	1.00	0.98 (0.73–1.31)	1.14 (0.86–1.51)	0.34
Model 2	1.00	1.13 (0.82–1.55)	1.24 (0.90–1.70)	0.18
Model 3	1.00	1.13 (0.82–1.55)	1.24 (0.90–1.71)	0.17
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	0.82 (0.62–1.09)	1.02 (0.78–1.35)	0.84
Model 1	1.00	0.82 (0.61–1.09)	1.05 (0.79–1.39)	0.72
Model 2	1.00	0.85 (0.61–1.16)	1.14 (0.84–1.55)	0.40
Model 3	1.00	0.84 (0.61–1.15)	1.13 (0.83–1.54)	0.43
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	0.89 (0.67–1.18)	1.04 (0.79–1.38)	0.73
Model 1	1.00	0.88 (0.66–1.17)	1.06 (0.80–1.40)	0.66
Model 2	1.00	0.95 (0.69–1.30)	1.19 (0.87–1.30)	0.27
Model 3	1.00	0.94 (0.68–1.28)	1.18 (0.86–1.62)	0.29
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	1.13 (0.86–1.49)	0.98 (0.73–1.30)	0.89
Model 1	1.00	1.20 (0.90–1.59)	1.15 (0.84–1.59)	0.34
Model 2	1.00	1.25 (0.91–1.70)	1.17 (0.82–1.67)	0.33
Model 3	1.00	1.17 (0.85–1.61)	0.98 (0.73–1.30)	0.61
Tertiles of vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	0.83 (0.63–1.10)	0.81 (0.61–1.06)	0.13
Model 1	1.00	0.87 (0.65–1.17)	0.85 (0.59–1.22)	0.36
Model 2	1.00	0.91 (0.66–1.26)	0.86 (0.57–1.29)	0.46
Model 3	1.00	0.91 (0.66–1.26)	0.87 (0.58–1.31)	0.51
Tertiles of PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	0.83 (0.62–1.01)	1.14 (0.87–1.50)	0.32
Model 1	1.00	0.79 (0.59–1.05)	1.05 (0.80–1.39)	0.65
Model 2	1.00	0.79 (0.57–1.09)	1 (0.73–1.36)	0.93
Model 3	1.00	0.80 (0.58–1.10)	1.01 (0.74–1.39)	0.86
Tertiles of PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	0.84 (0.64–1.11)	0.77 (0.58–1.02)	0.07
Model 1	1.00	0.86 (0.64–1.15)	0.77 (0.52–1.14)	0.18
Model 2	1.00	0.86 (0.62–1.18)	0.75 (0.49–1.16)	0.19
Model 3	1.00	0.85 (0.61–1.18)	0.75 (0.49–1.16)	0.19

Obtained from the binary regression test.

Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to previous items, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

particular, higher intakes of total fat, PUFA, MUFA, SFA, and animal fat were associated with a higher likelihood of being classified in higher categories of total sleep quality score.

Limitations

Several limitations should be acknowledged, including (1) the cross-sectional design, which does not allow causal relationships to be established and limits inference regarding directionality; (2) the potential for recall and

Table 6. Associations between the sleep onset latency component and indices of quantity and quality of dietary fat intake

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	1.03 (0.82–1.29)	1.18 (0.94–1.48)	0.15
Model 1	1.00	1.06 (0.83–1.34)	1.24 (0.98–1.57)	0.06
Model 2	1.00	1.08 (0.83–1.40)	1.25 (0.96–1.63)	0.08
Model 3	1.00	1.08 (0.83–1.40)	1.25 (0.96–1.63)	0.08
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	1.17 (0.92–1.47)	1.44 (1.15–1.82)	0.001
Model 1	1.00	1.12 (0.88–1.42)	1.39 (1.1–1.76)	0.006
Model 2	1.00	1.22 (0.94–1.58)	1.40 (1.08–1.83)	0.01
Model 3	1.00	1.22 (0.94–1.58)	1.40 (1.08–1.83)	0.01
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	1.04 (0.83–1.31)	1.11 (0.89–1.40)	0.33
Model 1	1.00	1.06 (0.83–1.34)	1.22 (0.96–1.54)	0.10
Model 2	1.00	1.16 (0.89–1.51)	1.29 (0.99–1.67)	0.05
Model 3	1.00	1.15 (0.89–1.50)	1.27 (0.98–1.65)	0.06
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	1.21 (0.96–1.52)	1.04 (0.83–1.31)	0.70
Model 1	1.00	1.24 (0.98–1.56)	1.12 (0.88–1.42)	0.33
Model 2	1.00	1.25 (0.96–1.61)	1.18 (0.90–1.53)	0.21
Model 3	1.00	1.24 (0.96–1.60)	1.16 (0.89–1.52)	0.24
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	0.99 (0.78–1.24)	0.91 (0.72–1.15)	0.47
Model 1	1.00	1.07 (0.85–1.36)	1.17 (0.90–1.52)	0.23
Model 2	1.00	1.14 (0.88–1.47)	1.27 (0.95–1.70)	0.09
Model 3	1.00	1.09 (0.83–1.42)	1.21 (0.90–1.64)	0.19
Tertiles of vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	0.85 (0.67–1.07)	0.93 (0.74–1.17)	0.54
Model 1	1.00	0.98 (0.77–1.26)	1.17 (0.86–1.58)	0.33
Model 2	1.00	0.97 (0.74–1.27)	1.22 (0.87–1.70)	0.27
Model 3	1.00	0.97 (0.74–1.27)	1.21 (0.87–1.70)	0.27
Tertiles of PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	1.26 (1.002–1.58)	1.34 (1.07–1.69)	0.01
Model 1	1.00	1.16 (0.92–1.48)	1.17 (0.93–1.49)	0.17
Model 2	1.00	1.14 (0.88–1.48)	1.15 (0.88–1.49)	0.30
Model 3	1.00	1.16 (0.89–1.51)	1.17 (0.90–1.53)	0.24
Tertiles PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	0.84 (0.67–1.06)	0.88 (0.70–1.10)	0.28
Model 1	1.00	0.94 (0.73–1.20)	1.07 (0.77–1.47)	0.74
Model 2	1.00	0.89 (0.68–1.17)	1.11 (0.78–1.58)	0.64
Model 3	1.00	0.88 (0.67–1.16)	1.11 (0.78–1.58)	0.64

Obtained from the binary regression test.

Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to the previous models, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

response bias, as the use of self-reported questionnaires, such as the FFQ for dietary intake and the PSQI for sleep quality, may affect measurement accuracy; (3) limited generalizability, as the findings may not be applicable to broader populations or different settings; (4) the possibility of residual confounding, which cannot be excluded and may have influenced the observed associations; (5) the absence of objective sleep assessment methods, such as actigraphy or polysomnography, which could provide more precise measures of sleep quality; and (6) recruitment from primary health care centers, which may further restrict generalizability to the wider population.

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Table 7. Associations between sleep duration and indices of quantity and quality of dietary fat intake

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	0.76 (0.57–1.00)	0.73 (0.55–0.96)	0.02
Model 1	1.00	0.82 (0.62–1.09)	0.81 (0.61–1.08)	0.14
Model 2	1.00	0.82 (0.60–1.11)	0.83 (0.61–1.13)	0.22
Model 3	1.00	0.82 (0.60–1.11)	0.82 (0.60–1.12)	0.20
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	0.84 (0.64–1.11)	0.93 (0.70–1.22)	0.61
Model 1	1.00	0.87 (0.66–1.16)	0.98 (0.74–1.30)	0.91
Model 2	1.00	0.94 (0.69–1.28)	1.08 (0.8–1.47)	0.59
Model 3	1.00	0.95 (0.69–1.29)	1.08 (0.79–1.47)	0.62
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	0.88 (0.67–1.16)	0.71 (0.54–0.95)	0.02
Model 1	1.00	0.95 (0.72–1.25)	0.80 (0.60–1.07)	0.15
Model 2	1.00	0.98 (0.73–1.32)	0.84 (0.61–1.15)	0.29
Model 3	1.00	0.97 (0.72–1.32)	0.82 (0.60–1.13)	0.20
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	0.73 (0.56–0.97)	0.73 (0.55–0.96)	0.02
Model 1	1.00	0.76 (0.58–1.01)	0.81 (0.61–1.08)	0.14
Model 2	1.00	0.74 (0.55–1)	0.84 (0.61–1.14)	0.23
Model 3	1.00	0.73 (0.54–0.99)	0.82 (0.60–1.12)	0.19
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	1.03 (0.78–1.36)	1.04 (0.78–1.38)	0.76
Model 1	1.00	1.05 (0.79–1.39)	1.11 (0.81–1.52)	0.49
Model 2	1.00	0.98 (0.72–1.34)	1.07 (0.76–1.51)	0.67
Model 3	1.00	0.94 (0.68–1.29)	1.02 (0.71–1.45)	0.91
Tertiles of vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	0.57 (0.43–0.76)	0.82 (0.63–1.07)	0.14
Model 1	1.00	0.60 (0.45–0.82)	0.81 (0.57–1.16)	0.16
Model 2	1.00	0.62 (0.45–0.86)	0.77 (0.52–1.13)	0.12
Model 3	1.00	0.62 (0.45–0.86)	0.76 (0.52–1.12)	0.10
Tertiles of PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	0.91 (0.69–1.20)	1.01 (0.77–1.33)	0.91
Model 1	1.00	0.87 (0.65–1.16)	0.96 (0.72–1.28)	0.81
Model 2	1.00	0.88 (0.64–1.20)	0.96 (0.70–1.31)	0.83
Model 3	1.00	0.89 (0.65–1.12)	0.98 (0.72–1.34)	0.94
Tertiles PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	0.67 (0.50–0.89)	0.84 (0.64–1.01)	0.20
Model 1	1.00	0.68 (0.51–0.93)	0.81 (0.55–1.18)	0.19
Model 2	1.00	0.70 (0.51–0.97)	0.74 (0.49–1.11)	0.10
Model 3	1.00	0.69 (0.50–0.95)	0.74 (0.49–1.12)	0.10

Obtained from the binary regression test.
Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to the previous models, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

Interpretation

The findings suggest that different types of dietary fats may be differentially associated with sleep-related outcomes. The observed association between higher PUFA intake and poorer sleep quality is consistent with some previous studies [25,26], although the overall literature remains inconsistent. For example, some evidence indicates beneficial effects of ω-3 fatty acids, whereas other studies suggest more complex or potentially adverse associations with ω-6 fatty acids [25]. Given that PUFA intake in Iran predominantly derives from ω-6–rich oils such as sunflower, corn, and soybean oils [26], these dietary patterns may partly explain

Table 8. Associations between the sleep efficiency component and indices of the quantity and quality of fat

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	0.82 (0.55–1.21)	1.01 (0.70–1.48)	0.91
Model 1	1.00	0.84 (0.56–1.25)	1.08 (0.74–1.59)	0.66
Model 2	1.00	0.87 (0.57–1.35)	1.06 (0.69–1.63)	0.77
Model 3	1.00	0.87 (0.57–1.35)	1.04 (0.68–1.60)	0.85
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	0.79 (0.53–1.17)	1.02 (0.70–1.48)	0.88
Model 1	1.00	0.75 (0.50–1.12)	0.96 (0.65–1.41)	0.88
Model 2	1.00	0.81 (0.52–1.26)	1.03 (0.67–1.58)	0.85
Model 3	1.00	0.81 (0.52–1.26)	1.02 (0.66–1.56)	0.92
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	1.17 (0.80–1.71)	0.89 (0.59–1.32)	0.57
Model 1	1.00	1.20 (0.82–1.77)	0.98 (0.65–1.48)	0.97
Model 2	1.00	1.22 (0.80–1.85)	0.98 (0.63–1.54)	0.99
Model 3	1.00	1.04 (0.66–1.63)	1.26(0.81–1.95)	0.89
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	0.92 (0.62–1.36)	1.01 (0.69–1.49)	0.91
Model 1	1.00	0.94 (0.63–1.39)	1.12 (0.75–1.65)	0.56
Model 2	1.00	0.97 (0.63–1.48)	1.04 (0.67–1.61)	0.84
Model 3	1.00	0.96 (0.63–1.47)	1.01 (0.65–1.57)	0.94
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	1.19 (0.82–1.74)	0.86 (0.57–1.30)	0.49
Model 1	1.00	1.29 (0.87–1.89)	1.06 (0.67–1.67)	0.70
Model 2	1.00	1.28 (0.84–1.95)	0.96 (0.58–1.58)	0.97
Model 3	1.00	1.24 (0.80–1.91)	0.92 (0.55–1.53)	0.79
Tertiles of vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	0.51 (0.34–0.76)	0.79 (0.55–1.14)	0.18
Model 1	1.00	0.58 (0.38–0.90)	0.92 (0.57–1.51)	0.55
Model 2	1.00	1.04 (0.63–1.72)	1.35 (0.85–2.12)	0.92
Model 3	1.00	0.69 (0.43–1.11)	1.12 (0.66–1.92)	0.81
Tertiles of PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	0.61 (0.41–0.90)	0.83 (0.57–1.20)	0.31
Model 1	1.00	0.54 (0.36–0.81)	0.70 (0.48–1.02)	0.06
Model 2	1.00	0.60 (0.39–0.94)	0.79 (0.52–1.21)	0.31
Model 3	1.00	0.62 (0.40–0.96)	0.82 (0.54–1.25)	0.39
Tertiles PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	0.60 (0.40–0.89)	0.78 (0.54–1.12)	0.16
Model 1	1.00	0.67 (0.44–1.02)	0.88 (0.51–1.50)	0.47
Model 2	1.00	0.69 (0.44–1.10)	0.94 (0.53–1.67)	0.68
Model 3	1.00	0.67 (0.42–1.07)	0.95 (0.53–1.68)	0.68

Obtained from the binary regression test.

Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to the previous models, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

the observed associations. The biological pathways linking dietary fat intake to sleep outcomes remain uncertain. Several speculative mechanisms proposed in the literature include the following: higher intake of ω-6 PUFAs or SFAs may promote inflammatory responses that affect neural processes involved in sleep regulation [27,28]; certain ω-6–rich plant oils may interfere with melatonin production, although supporting evidence is limited [29,30]; and saturated and animal fats may influence sleep indirectly through effects on digestion, metabolic regulation, or alterations in the gut microbiome [6,31].

In this study, higher intake of total fat and specific fatty

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Table 9. Associations between the component sleep disturbance and indices of the quantity and quality of fat intake

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	1.03 (0.82–1.28)	1.23 (0.98–1.53)	0.06
Model 1	1.00	1.06 (0.84–1.34)	1.33 (1.06–1.68)	0.01
Model 2	1.00	1.11 (0.86–1.43)	1.35 (1.04–1.74)	0.02
Model 3	1.00	1.26 (0.56–2.82)	1.39 (0.62–3.09)	0.02
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	1.09 (0.87–1.37)	1.29 (1.03–1.61)	0.02
Model 1	1.00	1.07 (0.85–1.35)	1.28 (1.01–1.61)	0.03
Model 2	1.00	1.11 (0.86–1.43)	1.27 (0.98–1.64)	0.06
Model 3	1.00	1.12 (0.86–1.44)	1.27 (0.98–1.64)	0.06
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	1.004 (0.80–1.25)	1.10 (0.88–1.37)	0.37
Model 1	1.00	1.02 (0.81–1.28)	1.23 (0.97–1.54)	0.07
Model 2	1.00	1.12 (0.87–1.45)	1.27 (0.99–1.65)	0.06
Model 3	1.00	1.11 (0.86–1.44)	1.26 (0.97–1.63)	0.07
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	1.14 (0.92–1.43)	1.12 (0.90–1.40)	0.29
Model 1	1.00	1.17 (0.93–1.47)	1.24 (0.98–1.56)	0.06
Model 2	1.00	1.24 (0.96–1.60)	1.31 (1.01–1.69)	0.03
Model 3	1.00	1.23 (0.95–1.58)	1.29 (1.001–1.67)	0.04
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	1.20 (0.96–1.50)	1.08 (0.86–1.35)	0.51
Model 1	1.00	0.31 (1.04–1.65)	1.38 (1.07–1.79)	0.01
Model 2	1.00	1.43 (1.11–1.84)	1.45 (1.09–1.93)	0.008
Model 3	1.00	1.35 (1.04–1.76)	1.37 (1.02–1.83)	0.03
Tertiles vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	0.94 (0.75–1.17)	0.85 (0.68–1.06)	0.15
Model 1	1.00	1.05 (0.82–1.33)	0.95 (0.71–1.28)	0.80
Model 2	1.00	1.05 (0.80–1.36)	0.97 (0.70–1.34)	0.90
Model 3	1.00	1.04 (0.80–1.36)	0.97 (0.70–1.34)	0.90
Tertiles PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	0.99 (0.79–1.24)	1.22 (0.98–1.52)	0.07
Model 1	1.00	0.92 (0.73–1.16)	0.83 (0.66–1.05)	0.49
Model 2	1.00	0.88 (0.68–1.13)	1.03 (0.79–1.33)	0.78
Model 3	1.00	0.89 (0.69–1.15)	1.05 (0.81–1.36)	0.66
Tertiles PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	0.86 (0.69–1.07)	0.81 (0.65–1.01)	0.06
Model 1	1.00	0.92 (0.72–1.17)	0.88 (0.64–1.20)	0.41
Model 2	1.00	0.86 (0.66–1.13)	0.89 (0.63–1.26)	0.49
Model 3	1.00	0.85 (0.65–1.11)	0.89 (0.63–1.26)	0.47

Obtained from the binary regression test.
Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to the previous models, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

acids (PUFA, MUFA, SFA, and animal fat) was associated with poorer sleep outcomes among women, whereas no statistically significant associations were observed among men, suggesting a sex-specific relationship between dietary fat intake and sleep quality. Previous research on dietary fat and sleep has yielded mixed findings, and the present results are consistent with evidence indicating that women may be more sensitive to the effects of dietary fat on sleep quality [32]. Women in this study tended to have poorer baseline sleep quality than men, which may increase susceptibility to the adverse effects of both dietary factors and sleep disturbances. In addition, women are

Table 10. Associations between sleep medication and indices of quantity and quality of fat intake

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	1.07 (0.63–1.80)	1.51 (0.93–2.46)	0.08
Model 1	1.00	1.26 (0.74–2.16)	1.86 (1.12–3.07)	0.01
Model 2	1.00	1.26 (0.68–2.33)	2.01 (1.14–3.56)	0.01
Model 3	1.00	1.26 (0.68–2.33)	2.01 (1.14–3.56)	0.01
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	0.96 (0.56–1.64)	1.63 (1.01–2.63)	0.03
Model 1	1.00	1.07 (0.62–1.85)	1.84 (1.12–3.03)	0.01
Model 2	1.00	1.28 (0.68–2.43)	2.40 (1.34–4.29)	0.002
Model 3	1.00	1.28 (0.68–2.43)	2.40 (1.34–4.30)	0.002
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	1.66 (0.98–2.80)	1.71 (1.02–2.88)	0.04
Model 1	1.00	1.52 (0.90–2.58)	1.97 (1.17–3.30)	0.01
Model 2	1.00	1.61 (0.88–2.95)	2.13 (1.17–3.87)	0.01
Model 3	1.00	1.62 (0.88–2.97)	2.14 (1.18–3.87)	0.01
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	1.66 (0.98–2.80)	1.71 (1.02–2.88)	0.04
Model 1	1.00	1.74 (1.02–2.95)	1.98 (1.16–3.36)	0.01
Model 2	1.00	1.52 (0.84–2.73)	1.73 (0.95–3.14)	0.06
Model 3	1.00	1.52 (0.85–2.74)	1.74 (0.96–3.15)	0.06
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	0.95 (0.57–1.55)	1.10 (0.67–1.79)	0.68
Model 1	1.00	1.04 (0.62–1.73)	1.34 (0.78–2.32)	0.28
Model 2	1.00	1.03 (0.58–1.84)	1.16 (0.62–2.19)	0.63
Model 3	1.00	1.06 (0.58–1.91)	1.19 (0.62–2.28)	0.58
Tertiles vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	1.08 (0.67–1.74)	0.84 (0.51–1.39)	0.52
Model 1	1.00	1.24 (0.74–2.07)	1.11 (0.58–2.13)	0.67
Model 2	1.00	1.46 (0.80–2.66)	1.62 (0.78–3.37)	0.18
Model 3	1.00	1.46 (0.80–2.66)	1.62 (0.78–3.37)	0.18
Tertiles PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	0.90 (0.55–1.47)	0.93 (0.57,1.51)	0.78
Model 1	1.00	0.86 (0.52–1.42)	0.90 (0.55–1.49)	0.70
Model 2	1.00	0.96 (0.54–1.72)	1.07 (0.60–1.89)	0.81
Model 3	1.00	0.96 (0.54–1.72)	1.06 (0.59–1.88)	0.82
Tertiles PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	1.18 (0.73–1.91)	0.93 (0.56–1.54)	0.78
Model 1	1.00	1.37 (0.81–2.32)	1.38 (0.68–2.77)	0.32
Model 2	1.00	1.76 (0.95–3.26)	1.98 (0.89–4.38)	0.07
Model 3	1.00	1.76 (0.95–3.26)	1.97 (0.89–4.36)	0.07

Obtained from the binary regression test.
Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to the previous models, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

particularly sensitive to hormonal fluctuations, including changes in estrogen and progesterone, which can influence sleep quality, circadian rhythms, and fat metabolism [33]. Differences in fat storage and metabolism, such as subcutaneous versus visceral fat distribution, may further modify the effects of dietary fat on sleep among women [34]. Biologically, women may be more responsive to fat quality, including SFA, MUFA, and PUFA [32]. Higher intake of certain fats may disrupt sleep architecture in women by affecting sleep stages, increasing nighttime awakenings, and reducing overall sleep quality. In contrast, men may be less affected, as their dietary fat intake tends to vary less and their sleep

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Table 11. Associations between daytime dysfunction and indices of the quantity and quality of dietary fat intake

Model	First tertile (ref.)	Second tertile (OR, 95% CI)	Third tertile (OR, 95% CI)	*p*-trend
Tertiles of fat percentage from energy	<33.7 (*n* = 631)	33.7–40.14 (*n* = 631)	>40.14 (*n* = 630)	
Crude model	1.00	0.81(0.60–1.09)	0.92 (0.69–1.24)	0.61
Model 1	1.00	0.85 (0.62–1.15)	1.03 (0.76–1.39)	0.85
Model 2	1.00	0.90 (0.64–1.25)	1.09 (0.78–1.52)	0.60
Model 3	1.00	0.90 (0.65–1.26)	1.10 (0.78–1.53)	0.59
Tertiles of PUFA percentage from energy	<11.96 (*n* = 631)	11–14.74 (*n* = 630)	>14.74 (*n* = 630)	
Crude model	1.00	0.92 (0.68–1.25)	1.15 (0.86–1.55)	0.31
Model 1	1.00	0.90 (0.66–1.23)	1.14 (0.84–1.54)	0.37
Model 2	1.00	1.03 (0.73,1.44)	1.25 (0.89–1.75)	0.17
Model 3	1.00	1.04 (0.74–1.46)	1.26 (0.90–1.77)	0.17
Tertiles of MUFA percentage from energy	<8.65 (*n* = 631)	8.65–10.70 (*n* = 630)	>10.7 (*n* = 630)	
Crude model	1.00	1.15 (0.85–1.55)	1.11 (0.82–1.49)	0.35
Model 1	1.00	1.01 (0.74–1.36)	1.004 (0.73–1.36)	0.97
Model 2	1.00	1.08 (0.77–1.50)	1.10 (0.79–1.55)	0.54
Model 3	1.00	1.05 (0.76–1.47)	1.09 (0.77–1.53)	0.60
Tertiles of SFA percentage from energy	<7.61 (*n* = 631)	7.61–9.46 (*n* = 631)	>9.46 (*n* = 630)	
Crude model	1.00	0.83 (0.62–1.12)	0.88 (0.65–1.18)	0.38
Model 1	1.00	0.85 (0.62–1.15)	0.98 (0.72–1.33)	0.91
Model 2	1.00	0.83 (0.60–1.16)	1.04 (0.74–1.45)	0.83
Model 3	1.00	0.83 (0.59–1.16)	1.01 (0.72–1.42)	0. 1
Tertiles of animal fat (g/d)	<6.33 (*n* = 631)	6.33–9.57 (*n* = 631)	>9.57 (*n* = 630)	
Crude model	1.00	1.07 (0.79–1.43)	0.91 (0.67–1.23)	0.55
Model 1	1.00	1.16 (0.86–1.58)	1.19 (0.84–1.67)	0.30
Model 2	1.00	1.17 (0.84–1.63)	1.24 (0.85–1.81)	0.24
Model 3	1.00	1.08 (0.77–1.51)	1.15 (0.79–1.69)	0.45
Tertiles vegetable oil (g/d)	<31.43 (*n* = 628)	31.43–47.63 (*n* = 665)	>47.63 (*n* = 628)	
Crude model	1.00	0.57 (0.42–0.78)	0.77 (0.58–1.02)	0.06
Model 1	1.00	0.69 (0.50–0.96)	1.01 (0.69–1.49)	0.83
Model 2	1.00	0.78 (0.55–1.11)	1.14 (0.75–1.75)	0.67
Model 3	1.00	0.79 (0.56–1.13)	1.16 (0.75–1.78)	0.64
Tertiles PUFA/SFA	<1.40 (*n* = 631)	1.40–1.73 (*n* = 631)	>1.73 (*n* = 630)	
Crude model	1.00	0.86 (0.64–1.16)	1.07 (0.79–1.43)	0.64
Model 1	1.00	0.78 (0.57–1.07)	0.92 (0.68–1.24)	0.62
Model 2	1.00	0.80 (0.57–1.12)	0.90 (0.64–1.25)	0.56
Model 3	1.00	0.82 (0.58–1.15)	0.93 (0.66–1.30)	0.71
Tertiles PUFA+MUFA/SFA	<27.67 (*n* = 631)	27.67–40.93 (*n* = 631)	>40.93 (*n* = 630)	
Crude model	1.00	0.61 (0.45–0.83)	0.78 (0.59–1.04)	0.08
Model 1	1.00	0.73 (0.52–1.01)	1.07 (0.70–1.63)	0.97
Model 2	1.00	0.72 (0.51–1.03)	1.10 (0.69–1.73)	0.93
Model 3	1.00	0.71 (0.49–1.01)	1.12 (0.71–1.78)	0.87

Obtained from the binary regression test.
Ref., reference; OR, odds ratio; CI, confidence interval; model 1, adjusted for age, sex, and energy intake; model 2, in addition to the previous models, adjusted for physical activity, marital status, socioeconomic status, and education; model 3, in addition to the previous models, adjusted for body mass index; PUFA, polyunsaturated fatty acid; MUFA, monounsaturated fatty acid; SFA, saturated fatty acid.

regulatory mechanisms may be more resilient, rendering sleep less sensitive to dietary fat exposure [35,36].

Similarly, higher MUFA and total fat intakes were associated with greater use of sleep medication. While some studies support this association [37,38] and others report opposing findings [39,40], several speculative mechanisms may account for these inconsistencies. MUFAs may influence lipid-related signaling pathways involved in sleep regulation, and individual differences in fat sensitivity, as well as variation in dietary MUFA sources, may further contribute to heterogeneous findings [41,42]. These explanations remain hypothetical and warrant further investigation.

Generalizability

The use of the validated PSQI instrument and multiple sleep-quality indices supports the reliability of sleep assessment in this study. However, the findings primarily reflect characteristics of participants from a single province in Iran and therefore may not be generalizable to other populations or cultural contexts.

Conclusion

This study demonstrates that both the quantity and quality of dietary fat intake are significantly associated with sleep quality.

Higher intakes of PUFA and animal fat were associated with higher total sleep quality scores. When stratified by sex, higher intake of total fat and unsaturated fats was associated with higher total sleep quality scores among women.

These findings underscore the need for future studies employing more robust methodological designs, including longitudinal or interventional approaches, and incorporating objective measures such as dietary records, actigraphy, or polysomnography. Such approaches are expected to improve the precision and validity of assessments.

Notes

Correction

This article was corrected on July 27, 2026, for an author affiliation.

Ethics Approval

This study was approved by the Institutional Review Board of Tehran University of Medical Science 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: MF, AE, PA, HR, AA; Data curation: AA, AF; Formal analysis: MF; Investigation: MF, AA; Methodology: HR, PA, AA; Project administration: PA, HR; Resources: AE; Supervision: LA, AE; Validation: MF, AA; Visualization: MF, LA; Writing–original draft: MF; Writing–review & editing: all authors. All authors read and approved the final manuscript.

Additional Contributions

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Brief Report

Hepatitis virus seroconversion among patients on maintenance hemodialysis in North India: a prospective cohort study

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ABSTRACT

Objectives: Patients receiving hemodialysis (HD) are at increased risk of acquiring hepatitis B virus (HBV) and hepatitis C virus (HCV) due to repeated blood exposure, vascular access procedures, and blood transfusions. The study aimed to determine the seroconversion rates of HBV and HCV among patients undergoing dialysis and to identify associated risk factors.
Methods: A total of 220 adult patients receiving dialysis who were seronegative for hepatitis B surface antigen (HBsAg) and anti-HCV antibodies at baseline were enrolled. Serologic testing was repeated at 6 months.
Results: Sixteen patients (7.3%) seroconverted to HBsAg positivity, and 23 (10.5%) seroconverted to anti-HCV positivity. HBV seroconversion was significantly associated with multiple dialysis center visits. HCV seroconversion was significantly associated with dialyzer reuse, multiple dialysis center visits, and dialysis duration ≥2 years. Elevated liver enzyme levels were strongly correlated with seroconversion for both viruses.
Conclusion: HBV and HCV seroconversion remain concerns in HD units. Standardized infection control practices, minimization of patient transfers, and strict adherence to national guidelines are essential to reducing risk.

Keywords: Hepatitis B virus; Hepatitis C virus; Renal dialysis; Seroconversion

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are major causes of global morbidity and mortality, particularly in low- and middle-income countries where access to preventive and therapeutic services remains limited [1,2]. In India, an estimated 29 million individuals are living with HBV infection and 5.5 million with HCV infection [2]. Among patients with chronic kidney disease (CKD) receiving dialysis, the risk of infection is increased because of frequent

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vascular access procedures, blood transfusions, and underlying immune dysregulation [3,4].

Hemodialysis (HD) centers face additional challenges, including lapses in infection control, equipment contamination, and patient transfers between facilities, all of which may increase the risk of hospital-acquired transmission [5,6]. Reported HCV prevalence in Indian dialysis units ranges from 15% to 80%, whereas HBV prevalence ranges from 3.4% to 43%, with variation by region and infection control standards [5]. The lower prevalence of HBV likely reflects vaccination efforts and higher rates of spontaneous viral clearance [6].

Despite advances in infection control strategies and antiviral therapies, new HBV and HCV infections continue to occur among patients receiving HD, underscoring the need for ongoing surveillance and preventive measures. This study aimed to determine the seroconversion rates of HBV and HCV among patients with CKD receiving maintenance HD and to identify demographic, dialysis-related, and biochemical factors associated with seroconversion.

HIGHLIGHTS

- In this prospective cohort of 220 patients receiving maintenance hemodialysis, the 6-month seroconversion rates were 7.3% for hepatitis B virus (HBV) and 10.5% for hepatitis C virus (HCV).
- Multiple dialysis center visits represented the strongest predictor of HBV seroconversion, whereas longer dialysis duration, dialyzer reuse, and multiple dialysis center visits were significantly associated with HCV seroconversion.
- Elevated liver enzyme levels were strongly correlated with seroconversion for both viruses.
- Strengthening infection control measures and limiting patient transfers are essential to reducing preventable viral transmission in dialysis units.

Materials and Methods

This prospective cohort study was conducted between January 2023 and July 2024 at a government-funded tertiary care hospital in New Delhi, India. Adult patients aged ≥18 years with CKD stage 5 on dialysis (CKD-5D) who were receiving maintenance HD and were seronegative for both hepatitis B surface antigen (HBsAg) and anti-HCV antibodies at baseline were eligible for inclusion. Patients with previous HBV or HCV infection or those receiving antiviral or immunosuppressive therapy were excluded. To minimize potential confounding from non–dialysis-related transmission routes, patients with the following risk factors were also excluded: (1) history of injection drug use; (2) high-risk sexual behavior; (3) household contact with individuals known to have HBV or HCV infection; (4) history of tattooing, body piercing, or acupuncture within 6 months before enrollment; and (5) history of blood transfusion, surgical procedures, or invasive interventions within 6 months before enrollment.

The required sample size was calculated assuming an expected seroconversion rate of 15%, a 95% confidence level, and 20% relative precision, yielding an initial estimate of 544 participants. After applying a finite population correction based on an estimated total eligible dialysis population of approximately 300 patients and accounting for a 10% anticipated loss to follow-up, the final target sample size was set at 220 participants.

Baseline demographic, clinical, and dialysis-related data were collected for all enrolled patients. Blood samples were obtained at baseline and again at the 6-month follow-up. Anti-HCV antibody testing was performed using a fourth-generation enzyme-linked immunosorbent assay (ELISA) kit (Merilisa Gen 4; Meril Diagnostics). HBsAg detection was performed using a third-generation ELISA kit (Trustwell HBsAg ELISA; Trustwell Diagnostics).

All patients who demonstrated seroconversion to HBsAg positivity or anti-HCV antibody positivity during the 6-month follow-up period underwent qualitative nucleic acid amplification testing (NAAT) for HBV DNA or HCV RNA to confirm active infection. All seroconverted patients tested positive for the corresponding viral nucleic acid.

The primary outcome was seroconversion to HBsAg positivity or anti-HCV antibody positivity during the 6-month follow-up period. Potential risk factors were assessed using a structured questionnaire. Measures implemented to minimize bias included standardized laboratory protocols, blinding of laboratory personnel to patient risk profiles, and uniform follow-up intervals for all participants.

Statistical analyses were performed using IBM SPSS ver. 22.0 (IBM Corp.). Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. Continuous variables were compared using the Student *t*-test. Logistic regression analysis was performed to calculate odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of <0.05 was considered to indicate statistical significance.

Ethical approval was obtained from the Institutional Ethics Committee of Vardhman Mahavir Medical College and Safdarjung Hospital (S. No: IEC/VMMC/SJH/Thesis/2023/CC-154). Informed consent was obtained from all participants.

Results

A total of 220 patients met the inclusion criteria, completed baseline testing, and were included in the analysis. All patients completed 6 months of follow-up. The mean age of the cohort was 42.8 ± 15.2 years (range, 18–84 years), and men comprised 61.4% (135/220) of the study population. Most patients (97.7%, 215/220) received HD 2 to 3 times per week. Demographic, clinical, and dialysis-related characteristics—including dialysis duration, number of dialysis centers visited, dialyzer reuse, and blood transfusion history—are presented in Table 1.

HBV seroconversion occurred in 7.3% (16/220) of patients during follow-up. HBV seroconversion was significantly associated with multiple dialysis center visits ($p = 0.008$). Elevated serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) levels were also significantly associated with HBV seroconversion ($p < 0.001$). No significant associations were observed with dialysis duration, dialysis frequency, or dialyzer reuse (Tables 1, 2).

Over 6 months, 10.5% (23/220) of patients developed anti-HCV antibody positivity. HCV seroconversion was significantly associated with multiple dialysis center visits (≥ 5 centers: 23.3% vs. 0% for 1 center; $p = 0.002$), dialysis duration ≥ 2 years (20% vs. 4.8% for ≤ 1 year; $p = 0.01$), and dialyzer reuse (13.8% vs. 0%, $p = 0.01$). Elevated SGOT and SGPT levels were strongly associated with HCV seroconversion (both $p < 0.001$) (Tables 1, 2).

Discussion

This study found 6-month seroconversion rates of 7.3% for HBV and 10.5% for HCV among patients receiving HD, which are higher than national prevalence estimates for the general population. According to the National Viral Hepatitis Control Program (NVHCP) operational guidelines, the estimated HBV prevalence is 1% to 2% in the general population of India and 3% to 4% among patients receiving dialysis. Similarly, estimated HCV prevalence is approximately 1% in the general population but increases to 4% to 5% in dialysis units [7,8]. Multiple center attendance emerged as the strongest predictor for both infections, consistent with prior studies [9,10]. This likely reflects inconsistent infection control and variable adherence to guidelines between facilities.

Patients treated at multiple dialysis centers had nearly twice the risk of acquiring HBV or HCV compared with those treated at a single center (Table 1), as also reported by Jasuja et al. [9]. This finding aligns with the NVHCP emphasis on continuity of care and standardized infection control practices [8]. Longer dialysis duration was associated with increased HCV seroconversion, whereas no such association was observed for HBV, consistent with the findings of Mittal et al. [6]. This difference may reflect greater awareness, higher vaccination coverage, and higher rates of spontaneous clearance for HBV.

In this cohort, a longer duration of dialysis was significantly associated with HCV seroconversion, with a higher incidence among patients undergoing dialysis for 3 years or longer compared with those with shorter dialysis duration. This pattern may reflect cumulative exposure from repeated vascular access, invasive procedures, and ongoing contact with the dialysis environment. In contrast, no clear association was observed between dialysis duration and HBV seroconversion. These observations are consistent with findings reported by Masoodi et al. [10].

Notably, dialyzer reuse appeared to be associated with a lower HCV seroconversion rate; however, this observation is difficult to interpret due to the small sample size and potential confounding, including the possibility of stringent reprocessing practices (Table 1). No significant association between dialyzer reuse and HBV seroconversion was observed (Table 1). NVHCP guidelines indicate that dialyzer reuse must follow strict reprocessing protocols and should not be considered safer without validated evidence [8].

Patients who seroconverted had elevated liver enzyme levels, consistent with active infection, whereas age, sex, dialysis frequency, and blood transfusion history were not significantly associated with new infections. Consistent with other studies [11,12], these findings suggest that institutional infection control practices, rather than patient demographic characteristics, represent key determinants of seroconversion risk in dialysis units.

Biochemical findings were consistent with the seroconversion patterns observed. Patients who seroconverted for HBV or HCV had significantly higher SGOT and SGPT levels, suggesting active hepatic inflammation (Table 2). In contrast, hemoglobin, creatinine, urea, sodium, and potassium levels did not differ significantly between seroconverted and non-seroconverted groups, consistent with findings reported by Patel et al. [13]. Although these parameters are important for monitoring kidney disease, they are not reliable indicators of viral seroconversion because their variability may be masked by underlying renal dysfunction and the effects of dialysis.

Strengths of this study include its prospective design, standardized testing, and complete follow-up. Limitations include the single-center design, relatively short follow-up, and the inability to assess all potential confounders, including comorbidities, adherence to infection control practices, socioeconomic factors, staff-to-patient ratios,

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Table 1. Demography and risk factors associated with HCV and HBV seroconversion among patients on maintenance HD

Risk factor	Patients screened for HCV	HCV positive	HCV seroconversion rate (%)	OR (95% CI)	*p*	Total patients screened for HBV	HBV positive	HBV seroconversion rate (%)	OR (95% CI)	*p*
Sex				0.79 (0.33–1.91)	0.24				1.97 (0.61–6.33)	0.24
Male	135	13	9.60			135	12	8.88		
Female	85	10	11			85	4	4.93		
Age (y)				0.98 (0.95–1.03)	0.44				0.99 (0.95–1.03)	0.75
< 20	7	0	0			7	0	0		
21–30	57	10	17.5			57	4	7		
31–40	47	5	10.6			47	6	12.7		
41–50	42	4	9.50			42	3	7.14		
51–60	30	1	3.30			30	1	3.33		
≥ 60	37	3	8.10			37	2	5.40		
No. of dialysis centers visited				1.81 (1.25–2.60)	0.01*				2.03 (1.31–3.15)	0.01*
1	24	0	0			24	0	0		
2	52	2	3.8			52	1	1.9		
3	69	6	8.6			69	2	2.89		
4	45	8	17			45	5	11.1		
≥ 5	30	7	23.3			30	7	23.3		
Frequency of dialysis per week				1.68 (0.72–3.92)	0.64				2.54 (0.81–6.77)	0.33
Once	5	0	0			5	0	0		
Twice	105	9	8.60			105	5	4.76		
Thrice	110	14	12.7			110	11	10		
Duration of dialysis (y)				1.04 (1.01–1.08)	0.01*				1.004 (0.95–1.05)	0.19
≤ 1	62	3	4.80			62	2	3.22		
1–2	93	7	7.50			93	8	8.60		
≥ 2	65	13	20			65	6	9.2		
Dialyzer reuse				0.08 (0.01–1.34)	0.01*				0.19 (0.01–3.13)	0.11
Yes	167	23	13.7			192	16	8.33		
No	30	0	0			28	0	0		
Blood transfusion				0.70 (2.91–1.70)	0.05*				1.14 (0.41–3.17)	0.11
Yes	103	11	10.6			103	8	7.76		
No	117	12	10.2			117	8	6.80		

HCV, hepatitis C virus; HBV, hepatitis B virus; HD, hemodialysis; OR, odds ratio; CI, confidence interval.
*$p < 0.05$.

Table 2. Biochemical parameters and their association with HCV and HBV seroconversion among patients on HD

Parameter (biological reference range)	HCV-negative patients (mean ± SD)	HCV-positive patients (mean ± SD)	OR (95% CI)	*p*	HBV-negative patients	HBV-positive patients	OR (95% CI)	*p*
					Mean ± SD	Mean ± SD		
Hb (≥12 g/dL)	9.5 ± 1.2	8.9 ± 1.8	0.97 (0.85–1.12)	0.84	9.57 ± 8.09	8.15 ± 1.71	0.78 (0.58–1.04)	0.05
SGOT (8–45 μ/L)	43.0 ± 87.4	274 ± 336.2	1.11 (0.95–1.29)	0.00*	46.6 ± 109.5	328.63 ± 312.37	1.03 (0.85–1.23)	0.00*
SGPT (7–56 μ/L)	42.4 ± 73.6	244 ± 322.5	1.01 (0.98–1.01)	0.00*	45.7 ± 99.69	291.56 ± 291.44	0.99 (0.99–1.007)	0.00*
S. creatinine (0.7–1.3 mg/dL)	10.47 ± 2.7	11.3 ± 2.8	1.016 (1.003–1.01)	0.1	10.55 ± 2.77	10.77 ± 2.69	1.006 (1.003–1.01)	0.75
S. urea (5–20 mg/dL)	192.9 ± 65.3	216.7 ± 66.9	1.007 (1.003–1.011)	0.1	195.54 ± 65.49	193 ± 21.28	1.006 (1.003–1.01)	0.88
S. sodium (135–145 mEq/L)	138.3 ± 6.3	139.9 ± 7.1	1.042 (0.974–1.105)	0.23	138.45 ± 6.43	138.31 ± 6.55	0.99 (0.921–1.07)	0.94
S. potassium (3.5–5.5 mEq/L)	3.9 ± 0.9	4.1 ± 1.0	1.239 (0.788–1.946)	0.36	3.92 ± 0.98	3.82 ± 1.13	0.904 (0.54–1.507)	0.7

HCV, hepatitis C virus; HBV, hepatitis B virus; HD, hemodialysis; SD, standard deviation; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; S., serum.
*$p < 0.05$.

and dialysis equipment characteristics. Although qualitative molecular confirmation was performed for all seroconverted patients, quantitative viral load testing and viral genotyping were not performed. Future studies incorporating quantitative polymerase chain reaction testing and viral characterization could provide additional insight into HBV and HCV transmission and disease course among patients receiving HD. A potential further limitation is that baseline screening relied on serologic testing without NAAT. Patients in the window period of acute HBV or HCV infection may test negative for HBsAg and anti-HCV antibodies despite detectable viral nucleic acid. If such patients were inadvertently enrolled, subsequent positive testing during follow-up could be misclassified as incident seroconversion, which could overestimate the true nosocomial transmission rate. Nevertheless, serologic screening remains the standard and most cost-effective approach for large-scale surveillance in resource-limited settings. Future studies incorporating baseline NAAT in addition to serology could more accurately differentiate pre-existing window-period infections from true incident seroconversions occurring during follow-up.

The clinical course and outcomes of acute HBV and HCV infections differ substantially, particularly with respect to spontaneous clearance, chronicity, and response to antiviral therapy [8]. In the present study, treatment outcomes following seroconversion could not be systematically assessed because therapeutic decisions and follow-up were determined by treating clinicians and were outside the predefined study objectives. Future prospective studies with longer follow-up are needed to assess antiviral treatment initiation, viral clearance, and long-term outcomes among seroconverted patients on HD.

The implications of this study include the need to standardize protocols across dialysis centers, strengthen HBV vaccination coverage, and consider eliminating dialyzer reuse to reduce infection risk. Routine biannual screening remains essential.

Conclusion

HBV and HCV seroconversion remain significant risks among patients receiving maintenance HD despite existing control measures. Inter-facility patient transfer and prolonged dialysis exposure are key modifiable factors. Strengthening infection control practices, ensuring HBV vaccination adherence, and maintaining regular monitoring are essential for prevention.

Notes

Ethics Approval

This study was approved by the Institutional Ethics Committee of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi–110029 (S. No. IEC/VMMC/SJH/Thesis/2023/CC-154), and was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from participants for publication of this study and accompanying images.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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None.

Availability of Data

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

Authors' Contributions

Conceptualization: SK, RK, DN; Data curation: PY, AP; Formal analysis:

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PY, AP; Methodology: SK, RK, DN; Supervision: SK, RK, DN; Validation: SK, RK; Visualization: SK, DN; Writing–original draft: PY, AP; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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Brief Report

Current status of hepatitis C treatment and its barriers in Jeonbuk, Republic of Korea

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ABSTRACT

Objectives: In alignment with the World Health Organization's goal of eliminating hepatitis C, this study assessed the current treatment status and reasons for non-treatment among patients with hepatitis C in Jeonbuk State, Republic of Korea, to inform strategies for improving care engagement.

Methods: Among 311 individuals diagnosed with hepatitis C and reported through the National Notifiable Infectious Disease Surveillance system between January 2023 and June 2024, 208 patients were surveyed after excluding those who had died or could not be contacted. Statistical analyses included the chi-square test, the Cochran-Armitage test for trend, and logistic regression.

Results: Overall, 116 participants (55.8%) reported having received antiviral therapy. Among the 92 untreated individuals, the most common reason for non-treatment was the absence of symptoms (n=23; 25.0%), followed by the burden of drug costs (n=21; 22.8%).

Conclusion: These findings highlight suboptimal treatment uptake and key barriers that may hinder progress toward hepatitis C elimination. Expanding screening and strengthening linkage-to-care strategies, while addressing financial barriers, will be essential to achieving national elimination targets.

Keywords: Cross-sectional studies; Health policy; Hepatitis C; Patient acceptance of health care; Republic of Korea; Therapeutic uses

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Introduction

According to the World Health Organization (WHO), an estimated 50 million people were living with hepatitis C worldwide in 2022, with approximately 1 million new infections occurring that

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year [1]. In the Republic of Korea, data from the Korea Disease Control and Prevention Agency (KDCA) estimated that 327,432 individuals were seropositive for hepatitis C virus (HCV) antibodies, and 102,970 were positive for HCV RNA as of 2020 [2]. The national incidence rate reported through the KDCA surveillance system in 2020 was 22.86 per 100,000 population [3].

Hepatitis C is the second most common cause of chronic viral hepatitis in the Republic of Korea after hepatitis B virus infection and accounts for approximately 10% of hepatocellular carcinoma cases [4]. According to data published by the Korean Association for the Study of the Liver (KASL), the nationwide hepatitis C management rate in 2019 was 78.2%, and the treatment rate was 58.1% [5]. The management rate refers to the proportion of patients who either visited medical institutions at least twice for hepatitis C–related care or received antiviral therapy within 18 months after diagnosis, whereas the treatment rate refers to the proportion of patients who received at least 1 antiviral prescription within 18 months. In Jeonbuk, the management rate was 75.8% and the treatment rate was 54.9%, ranking as the 4th lowest in the country [5].

In the Republic of Korea, hepatitis C transmission is not primarily driven by key populations such as people who inject drugs but is largely concentrated among older age cohorts in the general population [6]. This epidemiological pattern suggests that broad linkage-to-care strategies, rather than narrowly targeted interventions, may be required to achieve hepatitis C elimination targets.

To support the WHO elimination goal, Jeonbuk State, in collaboration with KASL, implemented a regional campaign to enhance awareness and evaluate the hepatitis C treatment cascade. This study analyzed provincial surveillance and survey data to assess the current treatment status of patients with hepatitis C and to identify reasons for non-treatment, thereby providing evidence to guide strategies for improving care engagement and treatment uptake.

Materials and Methods

All individuals newly diagnosed with hepatitis C and reported to the National Notifiable Infectious Disease Surveillance (NNIDS) system in Jeonbuk between January 2023 and June 2024 were included in the study. Age, sex, and date of notification were extracted from the surveillance data. As part of a regional awareness improvement campaign, a survey was conducted from July to September 2024 to investigate treatment status, treatment type, and reasons for non-treatment among untreated individuals. Individuals confirmed to have died before contact or those who could not be reached were excluded from the final analysis.

HIGHLIGHTS

- The hepatitis C treatment rate in Jeonbuk, Korea was 55.8%, which falls below the WHO 2030 target of 80%.
- Treatment uptake declined significantly with age, from 85.0% in patients aged ≤49 to 42.6% in those aged ≥80.
- Being asymptomatic (25.0%) and the financial burden of treatment (22.8%) were the leading barriers to treatment initiation.
- Among patients who received antiviral therapy, 83.6% reported being cured.
- Expanded awareness campaigns, improved linkage-to-care, and financial support are essential to achieve hepatitis C elimination goals.

For statistical analysis, the chi-square test and the Cochran-Armitage test for trend were used. Logistic regression analysis was also performed, and statistical significance was assessed at the 0.05 level using 2-tailed tests. All analyses were conducted using IBM SPSS Statistics for Windows, ver. 28.0 (IBM Corp.).

Ethics Statement

This study was approved by the Institutional Review Board (IRB) of Jeonbuk National University Hospital (IRB No: 2025-07-019). The informed consent was waived because of the retrospective nature of this study.

Results

A total of 311 patients were identified during the study period. Of these, 208 (66.9%) completed the survey (Table S1). Among respondents, 139 (66.8%) were female (Table 1). The mean age was 71.4 years, and the largest proportion of respondents was aged ≥80 years (32.7%).

Overall, 116 of 208 respondents (55.8%) reported having received antiviral therapy. Treatment uptake did not differ significantly by sex (50.7% in males vs. 58.3% in females; χ^2 test, $p=0.302$). In contrast, treatment uptake decreased significantly with increasing age (Cochran-Armitage test for trend, $p=0.014$). The proportion receiving treatment ranged from 85.0% among those aged ≤49 years to 42.6% among those aged ≥80 years (Table 1).

Among the 116 patients who received antiviral treatment, treatment outcomes were as follows: 97 (83.6%) reported being cured, 4 (3.4%) were still undergoing treatment, 3 (2.6%)

reported treatment failure or relapse, and 12 (10.4%) had an unknown treatment response.

Among the 92 individuals who had not undergone antiviral therapy, the most commonly reported reasons for non-treatment were being asymptomatic and concerns about medication costs (Table 2). Lack of awareness regarding the need for treatment and the presence of comorbidities were also frequently cited.

Reported barriers showed some variation by sex and age. Men more frequently reported a lack of awareness regarding the need for treatment, whereas women more commonly cited asymptomatic status and financial concerns (Table 2). By age group, lack of awareness was more common among those aged 60–79 years, whereas asymptomatic status was frequently reported in both the youngest and oldest groups (data not shown).

Discussion

Understanding the Republic of Korea's unique HCV epidemic is essential for interpreting these findings and formulating effective elimination strategies. Unlike in countries where HCV prevalence is 1%–2% or higher, the Republic of Korea has a relatively low anti-HCV seroprevalence of 0.6%–0.7% in the general population and approximately 100,000 HCV RNA-positive individuals requiring treatment [2]. However, the epidemiological profile is distinct: rather than being driven by young people who inject drugs, HCV infection in the Republic of Korea predominantly affects older age cohorts who were exposed through iatrogenic routes, including blood transfusions before 1992, when routine HCV screening of donated blood was introduced, and invasive procedures or interventions [6]. Prevalence rises sharply with age, from 0.32% in those aged 10–19 years to 1.93% in those aged ≥70 years [7]. Genotypes 1b and 2a/2c account for more than 90% of infections in the Republic of Korea

Table 1. Antiviral treatment status of hepatitis C patients in Jeonbuk State, Republic of Korea, 2023–2024

Variable	Category	Total	Had received antiviral treatment	Had not received antiviral treatment	OR (95% CI)
Total		208 (100.0)	116 (55.8)	92 (44.2)	
Sex[a]	Male	69 (33.2)	35 (50.7)	34 (49.3)	Ref.
	Female	139 (66.8)	81 (58.3)	58 (41.7)	0.737 (0.413–1.317)
Age (y)[b]	≤49	20 (9.6)	17 (85.0)	3 (15.0)	Ref.
	50–59	36 (17.3)	22 (61.1)	14 (38.9)	3.606 (0.891–14.600)
	60–69	42 (20.2)	25 (59.5)	17 (40.5)	3.853 (0.976–15.215)
	70–79	42 (20.2)	23 (54.8)	19 (45.2)	4.681 (1.190–18.414)
	≥80	68 (32.7)	29 (42.6)	39 (57.4)	7.621 (2.040–28.474)

Data are presented as *n* (%). ORs are presented for the risk of not having received antiviral treatment.
OR, odds ratio; CI, confidence interval; ref., reference.
[a]By chi-square test, $p = 0.302$. [b]By Cochran-Armitage test for trend, $p = 0.014$.

Table 2. Reasons for not receiving antiviral treatment in Jeonbuk State, Republic of Korea, 2023–2024

Category	Total (*n* = 92)	Male (*n* = 34)	Female (*n* = 58)
Lack of disease information	54 (58.7)	23 (67.6)	31 (53.4)
Asymptomatic	23 (25.0)	7 (20.6)	16 (27.6)
Unaware whether treatment is necessary	19 (20.7)	11 (32.4)	8 (13.8)
Belief that a cure is impossible	12 (13.0)	5 (14.7)	7 (12.1)
Limited access to healthcare services	28 (30.4)	9 (26.5)	19 (32.8)
Burden of medication costs	21 (22.8)	5 (14.7)	16 (27.6)
Difficulty visiting the hospital for care	4 (4.3)	1 (2.9)	3 (5.2)
Lack of hospital guidance	3 (3.3)	3 (8.8)	0 (0.0)
Personal reasons	28 (30.4)	9 (26.5)	19 (32.8)
Comorbidities	18 (19.6)	8 (23.5)	10 (17.2)
Old age	10 (10.9)	1 (2.9)	9 (15.5)
Other reasons	11 (12.0)	3 (8.8)	8 (13.8)
No response	12 (13.0)	5 (14.7)	7 (12.1)

Multiple responses were allowed; data are presented as *n* (%).

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[8], making pan-genotypic direct-acting antiviral (DAA) regimens highly suitable. Despite the availability of highly effective DAAs, awareness of HCV infection remains low: only 30.5% of HCV RNA-positive individuals are aware of their infection status [7]. This low awareness, combined with the Republic of Korea's aging HCV-infected population and historical iatrogenic transmission patterns, suggests that targeted patient education, management, and linkage-to-care strategies for diagnosed cases—rather than broad mass-media public awareness campaigns—may be the most efficient approach to achieving elimination targets in the Republic of Korea.

The WHO has set a goal of eliminating viral hepatitis, including hepatitis C, as a public health threat by 2030. To achieve this goal, the WHO aims to reduce the incidence of new hepatitis infections to fewer than 5 cases per 100,000 population and hepatitis-related mortality to fewer than 2 deaths per 100,000 population. Other key targets include diagnosing 90% of people with hepatitis C and treating 80% of those eligible for therapy.

Among strategies used for hepatitis C elimination in other countries, Canada pursued price negotiations in 2017 to reduce the cost of DAA agents, increasing the number of treatment initiators by approximately 2.3-fold, from 5,127 in 2014 to about 12,000 in 2017. In addition, rapid linkage-to-treatment policies were implemented after diagnosis, and in 2017, 83% of HCV antibody-seropositive individuals in the province of British Columbia completed HCV RNA testing, with 38% initiating treatment [9]. In Georgia, approximately 150,000 people—about 5.4% of the adult population—were infected with hepatitis C. In response, the country launched a national hepatitis C elimination program in 2015 and, with support from Gilead Sciences, established an integrated system connecting screening, laboratory diagnosis, and treatment services. Subsequently, between 2015 and 2019, around 60,000 individuals initiated treatment nationwide, achieving a high success rate of 96.1% [10]. In Egypt, a DAA-based program was implemented on a large scale in 2014, and more patients were able to receive treatment after support for treatment costs was introduced [11]. In 2018, the national screening program showed a cure rate of more than 98% among adults and 100% among adolescents [12]. In Taiwan, DAA treatment has been covered by health insurance since 2017, along with targeted screening programs and improved diagnostic-to-treatment linkage through government intervention. Through these comprehensive policies, the number of treated patients increased dramatically from 9,500 in 2017 to 46,000 in 2019 [13].

As illustrated by these international examples, strengthening patient management through government-led programs that link diagnosis and treatment, while improving treatment accessibility, appears necessary. In addition, strategies are needed to ensure a seamless process from identifying candidates for screening to confirmatory testing and subsequent treatment.

In line with the WHO goal of eliminating hepatitis C, KASL and the Korean Liver Foundation are conducting various awareness campaigns to increase the hepatitis C awareness rate to 90% by 2030 in the Republic of Korea. In addition, a portion of treatment costs has been covered by the National Health Insurance Service since November 2022, and hepatitis C antibody screening for 56-year-old adults has been a component of the national health checkup program since 2025. The KDCA is also implementing a program to support the costs of confirmatory RNA testing.

In this survey, the treatment rate among reported patients with hepatitis C in Jeonbuk State was 55.8%, which remains below the WHO target of 80% for hepatitis C elimination. When reasons for non-treatment were examined, many untreated patients reported being asymptomatic, not knowing whether treatment was necessary, or believing that cure was not possible. These findings suggest a need for improved patient information and awareness regarding hepatitis C and its treatment. In addition, 21 respondents (22.8%) reported that they did not receive treatment because of the burden of medication costs, making this the second most common reason for non-treatment and an important consideration for future policy development. Although DAA agents are reimbursed under the National Health Insurance system in the Republic of Korea, the estimated out-of-pocket cost for a full course of treatment is approximately 3 million Korean won (approximately 2,000 United States dollars). This level of copayment may still pose a meaningful financial barrier for some patients. Individuals who had not received treatment because of insufficient disease-related information accounted for 58.7% of untreated respondents, suggesting that awareness campaigns about hepatitis C treatment may have substantial potential to improve outcomes with relatively limited effort and thereby increase treatment uptake. In addition, strengthening provider-level education and clinical guidance may help ensure appropriate counseling and timely linkage to antiviral therapy after diagnosis.

This study is meaningful in that it identified reasons for non-treatment by using community public health personnel and the existing infectious disease epidemiological investigation system, encouraged and promoted treatment, and contributed to efforts to improve treatment rates. However, because the investigation relied on participants' recollections and statements, misclassification may have occurred due to the inability to review the medical records of the included patients. In addition, because no information

was available on income level or probable route of infection, treatment rates and reasons for non-treatment could not be evaluated according to socioeconomic status or risk category. Geographic variation in treatment uptake may exist even within the same province; however, this study did not examine such differences in detail, and further research is needed to better understand potential regional disparities. Finally, it should be noted that the treatment rate was assessed only among individuals reported through the NNIDS and therefore may not reflect undiagnosed prevalent cases.

This study investigated hepatitis C treatment rates and reasons for non-treatment in a province of the Republic of Korea, with the aim of providing a basis for policy development to improve treatment uptake. To our knowledge, it is the first study conducted in the Republic of Korea to examine reasons for untreated hepatitis C and includes survey data that reflect characteristics of local community population composition and medical resource utilization. Existing programs, such as those promoting hepatitis C prevention guidelines and conducting epidemiological investigations, should be continued. However, new initiatives—such as expanding hepatitis C screening within the national health checkup program and providing financial support for confirmatory testing—are also needed to identify undiagnosed hepatitis C cases and link diagnosis to treatment under the leadership of national and local governments.

Supplementary Material

Table S1. Study population and response rates by sex among reported hepatitis C patients in Jeonbuk State, Republic of Korea, 2023–2024. Supplementary data are available at https://doi.org/10.24171/j.phrp.2025.0516.

Notes

Ethics Approval

This study was approved by the IRB of Jeonbuk National University Hospital (IRB No: 2025-07-019).

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

None.

Availability of Data

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

Authors' Contributions

Conceptualization: CHL, IHK, JHL, JG; Data curation: JHK, YJM, UGK, JIP; Formal analysis: JHK; Funding acquisition: None; Investigation: JHK; Methodology: JHL, JG; Project administration: JHL, JG; Supervision: CHL, IHK, JHL, JG; Validation: JHL, JG; Visualization: JHK, JG; Writing–original draft: JHK; Writing–review & editing: all authors. All authors read and approved the final manuscript.

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

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

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

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

Table 1. Key features and limits of articles

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

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

Title Page

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

Abstract and Keywords

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

Highlights

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

Main Body

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

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

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

References

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

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

Please refer to the following examples.

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

Tables and Figures

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

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

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- ▫ The corresponding author (or the representative author of the co-corresponding authors) is the submitter of this manuscript.
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- ▫ Manuscripts should be double-spaced in A4-size pages.
- ▫ Manuscripts should include line numbers.
- ▫ All pages should be numbered consecutively, starting with the abstract.

Title Page

- ▫ The title page and the rest of the manuscript text are prepared separately in two files (not combined together).
- ▫ The title page is arranged in the following order: article title, authors' full name(s), affiliation(s), and corresponding author's information, running title (less than 50 characters), notes.
- ▫ The notes section including (1) ethics approval and consent to participate, (2) conflicts of interest, (3) funding, (4) availability of data, (5) author contributions, (6) additional contributions, and ORCID is in title page, not in the manuscript.

Abstract

- ▫ The abstract does not exceed 250 words (Objectives, Methods, Results, Conclusion) for original articles and 200 words for reviews. Up to 3–6 keywords are listed at the bottom of the abstract.

Main Text

- ▫ The manuscript is organized according to following sequence: Title page, Abstract and keywords, Main text, References, Tables, and Figure legends.

Tables and Figures

- ▫ All tables and figures are numbered in the order of their appearance in a main text.
- ▫ Tables are included at the end of the manuscript as editable text and not as images.
- ▫ Figures are as separate files, in jpg, ppt, tiff, or pdf format.

References

- ▫ References are listed in proper format.
- ▫ All references listed in the reference section are cited in the text and vice versa.

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