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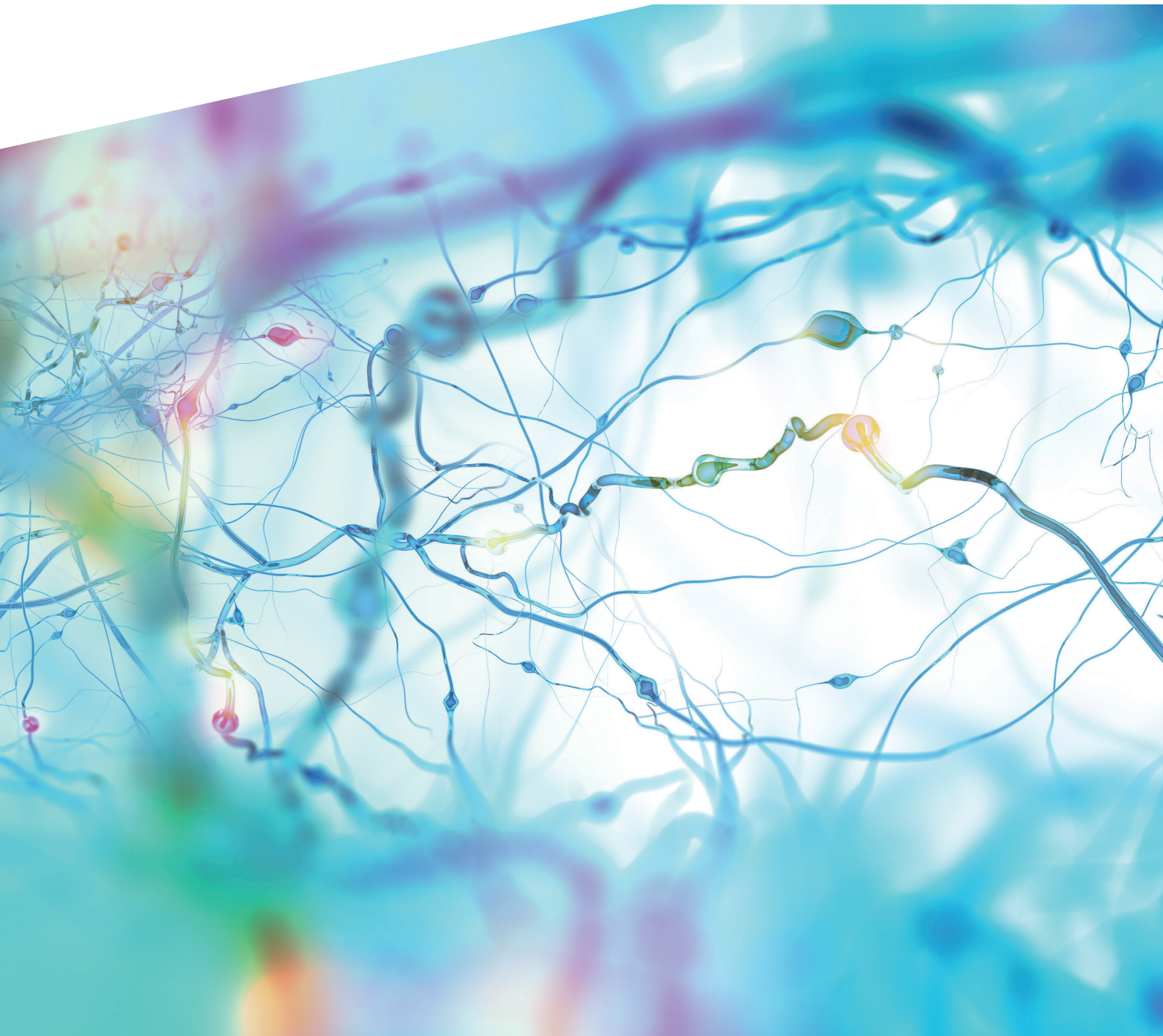

Ewha Medical Journal

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Aims & scope

Aims

Ewha Medical Journal aims to provide medical professionals with essential healthcare information and fundamental medical knowledge. The journal will contribute to improving and serving human society based on the Christian values of education, truth, goodness, and beauty. Additionally, the journal strives to nurture young editors, enabling them to demonstrate exceptional women's editorial leadership and provide innovative learning methods.

Scope

Its scope includes:

- Up-to-date medical knowledge and skills essential for patient care
- Preparing for the future of medicine
- Effective interprofessional communication
- Ensuring gender equity and diversity
- Medical education materials
- Sharing data and protocols

Regional scope

The journal primarily focuses on Korea but welcomes submissions from researchers worldwide.

Copyright & Open access policy

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Editorial board

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Editorial

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The Ewha Medical Journal

Leaving behind fond memories, I am stepping away from my role as editor of the *Ewha Medical Journal* after finalizing this issue's theme

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Joyful memories of editing

"I have revised the source code and redrawn the figures in the manuscript. Thank you for your help."

This brief message came from undergraduate student Yoonseo Jang when she submitted her revised manuscript. While preparing a machine learning paper using the publicly available diabetes dataset from Scikit-learn, she had been asked to revise the Python code and redraw the receiver operating characteristic curves for each model. She submitted the revised version with precisely corrected code and updated figures [1]. It was immensely gratifying to see her deep understanding of machine learning and data analysis, which far exceeded expectations for an undergraduate author. During my 2 years as the editor of the *Ewha Medical Journal*, beginning in September 2023 [2], the most rewarding experiences were receiving manuscripts from undergraduate authors, guiding them through peer review and revision, and ensuring that their papers adhered to reporting guidelines while preserving the integrity of data analysis. Beyond Ms. Jang, numerous undergraduates submitted diverse manuscripts, including original articles, reviews, correspondence, and interviews—that I was pleased to edit and publish. As noted in a 2012 Letter to the Editor [3], we have been fortunate to dedicate space for publishing research by undergraduate and graduate students. This is one of the defining features of the *Ewha Medical Journal* as a college-based publication.

I was also delighted to collaborate closely with members of the editorial board, maintaining constant communication throughout the editing process. The current Associate Editors and Assistant Editor have demonstrated exceptional expertise in both research and clinical practice, and they have rapidly acquired a wide range of editorial skills. Just as training is essential in research and clinical work, effective editing requires broad interdisciplinary knowledge, the ability to evaluate manuscripts from multiple perspectives, and discernment in selecting submissions that align with the journal's mission. As former Editor Dr. Ryung-Ah Lee observed, we were fortunate to have active participation from leading faculty members.

In taking on the editorial role, I also took great satisfaction in restructuring the journal's website to meet the standards of leading international academic journals and to provide comprehensive information on editorial policies. The core of any journal lies, of course, in the scientific rigor, originality, and relevance of its papers. While the technical refinement of the website was outsourced to a specialized company, the editor is ultimately responsible for supplying the necessary content. Editors of Korean academic journals and university presses often serve as both editor and publisher, handling numerous detailed tasks that editors at large commercial publishing houses typically do not manage [4]. For instance, they must implement various Crossref services, such as assigning Digital Object Identifiers (DOIs) [5]; generate JATS XML files that meet the standards required for PubMed Central (PMC) indexing [6]; understand the entire editorial workflow, including manuscript editing [7]; and communicate effectively with service providers. All of these tasks were successfully completed with the strong support of the executive board of Ewha Womans University College of Medicine.

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Goals achieved and not fulfilled

For the October 2023 issue, as a new editor, I prioritized 2 main goals: increasing the number of published papers and achieving inclusion in international indexing databases. From the January to July 2023 issues, a total of 8 papers were published. Thereafter, 25 additional papers were added, bringing the total to 33. In 2024, 74 papers were published, followed by 73 in 2025. In total, 202 papers were published over 2 years under my leadership—a clear achievement of one of our primary goals. However, inclusion in major international databases remains an unfulfilled ambition. Although we succeeded in being indexed in DOAJ and PMC, our application to Scopus was unsuccessful, which remains a disappointment. The main reasons cited included the low annual publication volume, the presence of multiple subject areas without a clear central focus, a relatively high proportion of international submissions, and a perceived lack of coherence in editorial direction [4].

While increasing the number of papers is feasible, achieving thematic cohesion across diverse topics is inherently difficult for a general medical journal. We have welcomed submissions from international authors, even when their primary regional focus was Korea, as long as their work contributed meaningfully to clinical practice. There was no reason to reject manuscripts based on nationality alone. The criticism of limited editorial focus remains a challenging issue. Nonetheless, the *Ewha Medical Journal*'s editorial policy is firmly centered on publishing manuscripts that strictly follow reporting guidelines to ensure scientific rigor. To support this goal, we developed an author template that integrates key elements from reporting guidelines. Few journals internationally have taken such systematic steps to encourage precise adherence to these standards. This policy of prioritizing scientific rigor is expected to demonstrate its full value through increased citation rates in the near future. Since the *Ewha Medical Journal* became searchable in PMC as of August 25, 2025 [8], its citation rate is projected to rise significantly beginning in 2026, as has been observed in other PMC-indexed journals [9].

Where should editorial standards be set in medical journal publishing?

We often assume that the editorial process is simply about carefully selecting and publishing the highest-quality manuscripts. However, according to the late Dr. Seung-Yull Cho (1943–2019) [10], a pioneer in Korean medical journal editing, the goal is to "select manuscripts meeting minimum standards and of a certain level" for publication. Some high-impact SCIE journals may indeed be able to select manuscripts of the highest caliber from both domestic and international authors. However, the reality for most journals is that they must publish manuscripts that meet a consistent standard to maintain a uniform level of quality across published articles.

Why is this necessary? Just as the most fundamental priorities in patient care are patient safety and protection of personal information, academic journals also require baseline standards that ensure ethical and scientific soundness, particularly for research involving patients or human subjects. Unlike other academic disciplines, medical research is directly linked to patient safety, making such standards indispensable. The acceptance threshold of a journal ultimately depends on the quality of the papers it receives. If a journal aims to publish a certain number of articles each year at a specific standard, manuscripts are selected relative to that benchmark. Over the past 2 years, I have consistently upheld these editorial standards, though it remains challenging to judge whether every accepted manuscript truly meets the threshold. Third-party evaluations, such as those by the Scopus Content Selection and Advisory Board, have sometimes differed from assessments by PMC reviewers, with Scopus concluding that we fell short of their criteria.

To help ensure compliance with minimum standards, the use of generative artificial intelligence (AI) [11] and vibe coding [12] will be increasingly valuable. Although only 3 years have passed since the release of the first publicly available generative AI, ChatGPT, the quality of AI-generated responses has improved remarkably. AI tools can sometimes identify issues that editors may overlook during manuscript review, particularly in areas such as adherence to reporting formats or consistency in reference styles. They are especially effective in checking the basic structure and formatting of manuscripts, thereby supporting editors in maintaining uniform quality and efficiency. The journal's policy on the use of generative AI in manuscript review does not prohibit its use, provided confidentiality is maintained [13].

Three special topics in this issue

The first of the 3 review topics in this issue addresses "lifestyle modification for disease management in primary care." The clinical message for primary care providers is clear: prioritize lifestyle prescriptions as first-line treatment and ensure continued support for adherence. The authors specifically focus on diabetes, hypertension, and obesity. Their recommendations are clear, evidence-based, and directly applicable to patient care, providing practical guidance for clinicians managing these common chronic diseases.

The second group of reviews focuses on "integrated, person-centered geriatric care aimed at preserving functional ability." These papers include detailed discussions on geriatric rehabilitation, post-polio syndrome among polio survivors, and hip fractures complicated by cognitive impairment. One policy-oriented paper highlights systemic reforms underway in Korea, emphasizing the shift from provider-centered to person-centered integrated care under the 2024 Integrated Community Care Support Act. This transformation requires redefining long-term care facilities, developing a professional care manager workforce, enabling data interoperability, aligning reimbursement systems with outcomes, and expanding community-based alternatives to institutional care.

The third topic centers on "tailoring perioperative anesthesia and analgesia to the patient, the surgical procedure, and the goal of functional recovery." The papers in this section explore personalized perioperative pain management, the optimal combination of regional and general anesthesia, and the distinctive considerations in pediatric anesthesia. Because children are not "small adults," clinicians must carefully optimize oxygen levels to prevent both hypoxia and hyperoxia, use quantitative neuromuscular monitoring, maintain normothermia with core temperature monitoring, and individualize airway management and extubation strategies.

I also hope readers will enjoy other engaging features in this issue, beyond the 3 major review topics, including interviews with graduates of Ewha Womans University College of Medicine who have pursued medical careers abroad.

Praying for the *Ewha Medical Journal* to shine even brighter

After serving as editor for 2 years, I now step down from this role. The new editor will continue to develop strategies to ensure the ongoing success of the *Ewha Medical Journal*. Fortunately, since the journal's inclusion in PMC, the number of submissions has increased, creating a more favorable environment than before. I am confident that Dr. Ji Yeon Byun, who will assume the editorial position, will lead the journal to new heights. As long as the full publication budget continues to be supported by the executive board of Ewha Womans University College of Medicine, there should be no difficulties in maintaining its operations.

It has been a great honor to serve as editor of the *Ewha Medical Journal* over the past 2 years. Although not all of my initial goals were fully realized, it was an immensely rewarding experience to edit a general medical journal and contribute to its development. I sincerely hope that by 2027, when Volume 50 is published, the *Ewha Medical Journal* will achieve inclusion in Scopus—allowing the journal, nurtured by the efforts of countless editors and authors over the past half century, to shine even brighter. I extend my heartfelt gratitude to the editorial board members, reviewers, authors, and editors of various collaborating journals who contributed to special issues during these past 2 years, as well as to the executive board of Ewha Womans University College of Medicine for their steadfast and generous support.

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Authors' contribution

All work was completed by Sun Huh.

Conflict of interest

Sun Huh has served as the editor of the *Ewha Medical Journal* since September 2023. However, he was not involved in the peer review process or decision-making for this article. No other potential conflicts of interest relevant to this article were reported.

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Opinion

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The Ewha Medical Journal

Probability of criminal punishment of physicians in Korea is remarkably higher than in Japan and France

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Is the criminal prosecution of physicians in Korea excessive?

Recently, a Korean government report—commissioned by the Ministry of Health and Welfare (MOHW) and conducted by the Korea Institute for Health and Social Affairs—examined the criminal prosecution of physicians in Korea [1]. On average, 38 criminal trials took place annually.

Korea's 38 cases: among the highest global rates of criminal trials

This figure is striking. Even acknowledging the research limitations and the report's scope, the finding that 38 physicians are criminally prosecuted each year for adverse medical outcomes is significant. A straightforward international comparison suggests that, in a country with about 100,000 practicing physicians, 38 prosecutions annually for medical-related incidents places Korea among the highest in the world. For example, although the data are older, one review indicated that the province of Ontario, Canada, recorded only one case in 108 years in which a physician was criminally convicted for a medical incident—an anesthesiologist who self-reported leaving their post, resulting in a medical accident [2]. Apart from this case, there are no verifiable instances of criminal prosecution for medical-related incidents in Ontario. Table 1 compares outcomes of first-instance criminal trials for occupational negligence resulting in death or injury among physicians in Korea—based on a complete enumeration by the Korean Medical Association Research Institute for Healthcare Policy (RIHP)—with those in Japan and the United Kingdom. Between 1999 and 2016 (18 years), Japan recorded 202 first-instance criminal judgments against physicians for occupational negligence resulting in death or injury, of which only 32 resulted in convictions—an average of 1.8 per year. Moreover, Japan's scope included the management and supervision of medical assistants as well as the operation of medical equipment, suggesting that the number of cases involving purely medical malpractice is likely smaller. In Commonwealth and Nordic countries—often highlighted as examples of robust public healthcare systems—criminal prosecutions of physicians are so rare that official statistics are almost nonexistent. A fairly recent UK judiciary report recorded only 4 physician convictions over a 6-year period [3,4]. Fig. 1 presents the relative average number of criminal trials for occupational negligence resulting in death or injury by physicians, normalized to the United Kingdom as 1.

Differences in legal systems are not a sufficient explanation

Explanations that attribute Korea's high incidence of criminal prosecutions in medical cases to differences in legal tradition—namely, the distinction between its continental legal system and the Anglo-American common law system—are inadequate when tested against empirical evidence from other civil-law jurisdictions. In Germany, criminal prosecutions of physicians for medical malpractice are exceptionally rare. France, despite its reputation for a comparatively stringent criminal liability framework, has an annual average of only 10–13 cases [5]. Notably, these figures en-

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Table 1. Criminal trial outcomes for occupational negligence resulting in death or injury

	Korea, 2010–2020, 11 yr (average)	Japan, 1999–2016, 18 yr (average)	United Kingdom,2013–2018, 6 yr (average)
Average no. of physicians	140,075	407,201	216,001
Causes	Occupational negligence resulting in death or injury	Medical practice (including occupational negligence resulting in death or injury)	Manslaughter by negligence
Total (average/yr)	354 (32.2)	202 (11.2)	7 (1.4)
Conv. (average/yr)	239 (21.7)	32 (1.8)	4 (0.8)
Acq. (average/yr)	115 (10.5)	6 (0.3)	3 (0.6)

From Kim HS, Lee JK, Kim KY. Current status and implications of the criminalization of medical practice [Internet]. Korean Medical Association, Research Institute for Healthcare Policy; 2022 [cited 2025 Aug 6]. Available from : https : //rihp.re.kr/bbs/board.php?bo_table=research_report&twr_id=338 [4].
Conv., convictions; Acq., acquittals.

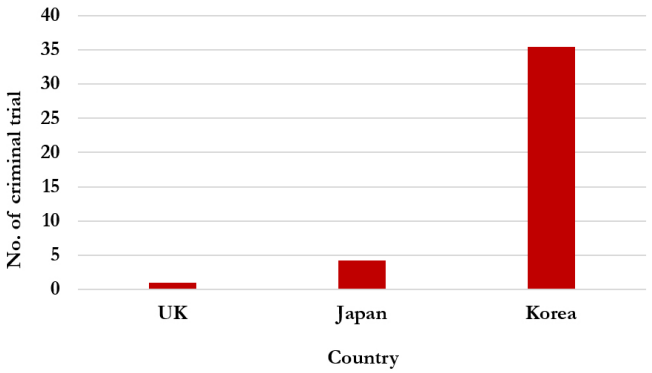

Fig. 1. Relative average number of criminal trials for occupational negligence resulting in death or injury by physicians, normalized to the United Kingdom as 1. From Kim HS, Lee JK, Kim KY. Current status and implications of the criminalization of medical practice [Internet]. Korean Medical Association, Research Institute for Healthcare Policy; 2022 [cited 2025 Aug 6]. Available from: https://rihp.re.kr/bbs/board.php?bo_table=research_report&twr_id=338 [4].

compass a broad range of criminal offenses, including violence, rape, and sexual assault, rather than being limited to medical negligence. A peer-reviewed and widely cited international study further reveals that prosecutions directly attributable to medical practice account for less than half of such totals. Corroborating this, a review of expert opinions submitted to prosecutors by the Bonn Institute of Forensic Medicine—which has jurisdiction over the state of Nordrhein–Westphalia—between 1989 and 2003 (a span of 15 years) found only one instance in which a physician was convicted of negligent manslaughter. Notably, even that case involved additional criminal conduct beyond the scope of medical negligence [6]. Overall, these findings indicate that differences in legal tradition cannot fully account for the markedly higher rates of criminal prosecution observed in Korea's medical sector.

Adjusted for population, Korea's criminal prosecution rate for medical practice is up to 60 times higher than those of France, the United Kingdom, and Germany

Even in France—with its relatively high rate of criminal prosecution for medical incidents compared to other developed nations—the number of cases directly involving medical practice is about 5–6 annually, with most resulting in suspended sentences or fines. On rare occasions, prison sentences of 7–10 years have been imposed for crimes such as rape and assault [5]. When Korea's 38 cases per 100,000 active physicians are compared to France's minimum of 200,000 physicians, the difference is stark: Korea's rate is over 10 times higher than that of France and at least 60 times higher than the rates in the United Kingdom and Germany. This is a striking contradiction; one would not expect a nation that prides itself on having a world-class healthcare system and highly skilled medical professionals to lead the world in criminal prosecutions of physicians. In the United Kingdom, France, and Germany, legal proceedings for medical incidents are handled under tort law, which prioritizes pre-trial mediation and resorts to criminal law only in exceptional cases. These countries maintain stable systems for compensating medical accidents and handling inevitable adverse outcomes. By contrast, Korea's inadequate compensation framework raises concerns that criminal prosecution may be used to pressure physicians, thus casting doubt on the fairness of the legal process. Whether this stems from differences in legal education, professional standards, or institutional culture, international comparisons suggest that Korea's judicial approach remains difficult for the medical community to accept.

Who will treat patients if misunderstandings about medical uncertainty turn physicians into criminals?

Even now, obtaining accurate data remains challenging and complex. Any research on this topic inevitably involves considerable estimation. If the likelihood of criminal prosecution in Korea is 10 to 60 times higher than in some other countries, a pressing question arises: Who would willingly become a physician, knowing they might face a criminal record simply for practicing medicine? Accordingly, this possibility of excessive criminal punishment may pose a serious threat to future physicians' career choices. Table 2 compares the outcomes of all first-instance criminal trials involving charges of occupational negligence resulting in death or injury, using 2014–2018 data from the RIHP and 2019–2023 data from the MOHW [4].

The period covered by the Ministry's investigation—marked by the coronavirus disease 2019 pandemic and heightened disputes between the medical profession and the government—was characterized by unprecedented instability in the healthcare sector. Compared with the preceding 5 years, the number of physicians tried for medical negligence at the first-instance level increased by 19 and convictions rose by 18, while acquittals remained largely unchanged. These findings provide empirical evidence that both the incidence of criminal trials and conviction rates have increased in parallel with the structural instability of the medical field.

With nearly 700 apprehensions annually, will "medical deserts" worsen?

Even now, accurate statistics for comprehensive cases remain elusive. In a statistical report from the Public Prosecutors' Office, "Crime analysis," the category of "professionals" includes physicians alongside 6 other professional occupations and "other professionals." These statistics are compiled under the heading "occupation of offenders"—a misnomer, as the data include suspects regardless of conviction—rather than "defendants."

Tables 3 and 4 present Prosecutors' Office data on cases involv-

Table 2. Comparison of criminal trial outcomes for occupational negligence resulting in death or injury between the Ministry of Health and Welfare and the KMA Research Institute for Healthcare Policy

Category	MOHW	RIHP	Difference
Investigated period	2019–2023 (5 yr)	2014–2018 (5 yr)	-
Total cases	192	173	19
Convictions	135	117	+18
Acquittals	57	56	+1

From Kim HS, Lee JK, Kim KY. Current status and implications of the criminalization of medical practice [Internet]. Korean Medical Association, Research Institute for Healthcare Policy; 2022 [cited 2025 Aug 6]. Available from : https://rihp.re.kr/bbs/board.php?bo_table=research_report&wr_id=338 [4].
KMA, Korean Medical Association; MOHW, Ministry of Health and Welfare; RIHP, KMA Research Institute for Healthcare Policy.

Table 3. Prosecutor's office handling of cases involving physicians: occupational negligence resulting in death or injury: RIHP (2014–2018)

RIHP (2014–2018)	Year					
	2014	2015	2016	2017	2018	Average
Professionals	895	1,024	1,016	1,051	1,248	1,047
Physicians	677 (75.6)	719 (70.2)	704 (69.3)	720 (68.5)	877 (70.3)	739 (70.6)

Values are presented as persons or persons (% relative to total professionals). From Prosecution Service. Annual crime analysis 06 crime statistics table-III : characteristics of offenders [Internet]. Prosecution Service; 2023 [cited 2025 Aug 6]. Available from : https://www.spo.go.kr/site/spo/crimeAnalysis.do [7].
RIHP, Korean Medical Association Research Institute for Healthcare Policy.

Table 4. Prosecutor's office handling of cases involving physicians: occupational negligence resulting in death or injury: MOHW (2019–2023)

MOHW (2019–2023)	Year					
	2019	2020	2021	2022	2023	Average
Professionals	1,118	1,248	1,032	1,077	1,199	1,135
Physicians	783 (70.0)	868 (69.6)	645 (62.5)	668 (62.0)	711 (59.3)	735 (64.8)

Values are presented as persons or persons (% relative to total professionals). From Prosecution Service. Annual crime analysis 06 crime statistics table-III : characteristics of offenders [Internet]. Prosecution Service; 2023 [cited 2025 Aug 6]. Available from : https://www.spo.go.kr/site/spo/crimeAnalysis.do [7].
MOHW, Ministry of Health and Welfare.

ing professionals and physicians charged with occupational negligence resulting in death or injury [7]. However, no statistical data are available regarding whether these individuals were formally indicted and brought to trial. Of note, the MOHW's analysis indicates that the number of cases handled by the prosecution during 2019–2023 declined slightly compared with the preceding 5 years. This suggests that although the total number of cases involving physicians charged with occupational negligence resulting in death or injury has remained stable or decreased marginally, the number of first-instance criminal trials and convictions has increased—potentially indicating a shift toward stricter criminal accountability.

Unintended consequences of criminal punishment of medical practice

The fact that physicians in Korea are subjected to police investigations for actions performed in their medical practice is, when compared with other countries, difficult to regard as reasonable. It is difficult to overstate the shock and trauma these investigations inflict on professionals who have dedicated years of their lives to rigorous education and training. For many physicians, this experience leaves a permanent psychological scar. The situation of the Ewha Mokdong Hospital medical staff—who were imprisoned for months before being acquitted [8]—illustrates the devastating personal and professional impact. Dismissing the possibility that excessive prosecution drives avoidance of essential specialties only obscures the unintended consequences of the criminal punishment of medical practice. The indiscriminate criminal prosecution of physicians reflects a dangerous indifference to the severe healthcare crisis currently unfolding in Korea.

Koreans, who have benefited from some of the highest levels of medical care in the world, must act to end these cruel punishments of physicians. Government officials and lawmakers should also work to resolve this tragic problem to safeguard the population's health over the long term.

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Authors' contribution

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Review article

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The Ewha Medical Journal

Technologies, opportunities, challenges, and future directions for integrating generative artificial intelligence into medical education: a narrative review

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Generative artificial intelligence (GenAI), including large language models such as GPT-4 and image-generation tools like DALL-E, is rapidly transforming the landscape of medical education. These technologies present promising opportunities for advancing personalized learning, clinical simulation, assessment, curriculum development, and academic writing. Medical schools have begun incorporating GenAI tools to support students' self-directed study, design virtual patient encounters, automate formative feedback, and streamline content creation. Preliminary evidence suggests improvements in engagement, efficiency, and scalability. However, GenAI integration also introduces substantial challenges. Key concerns include hallucinated or inaccurate content, bias and inequity in artificial intelligence (AI)-generated materials, ethical issues related to plagiarism and authorship, risks to academic integrity, and the potential erosion of empathy and humanistic values in training. Furthermore, most institutions currently lack formal policies, structured training, and clear guidelines for responsible GenAI use. To realize the full potential of GenAI in medical education, educators must adopt a balanced approach that prioritizes accuracy, equity, transparency, and human oversight. Faculty development, AI literacy among learners, ethical frameworks, and investment in infrastructure are essential for sustainable adoption. As the role of AI in medicine expands, medical education must evolve in parallel to prepare future physicians who are not only skilled users of advanced technologies but also compassionate, reflective practitioners.

Keywords: Artificial intelligence; Curriculum; Formative feedback; Medical education; Natural language processing

Introduction

Background

Generative artificial intelligence (GenAI) refers to a class of machine learning technologies capable of producing novel content—including text, images, code, audio, and video—by learning patterns from large datasets rather than simply retrieving existing information [1]. Unlike traditional artificial intelligence (AI) systems designed primarily for classification or prediction, GenAI can synthesize entirely new outputs. This has significant implications for fields that depend on knowledge generation and communication, such as medicine and medical education [2]. Generally, GenAI denotes AI systems capable of creating new outputs across modalities (text, image, audio, code, video). In contrast, large language models (LLMs) represent a specific subclass of GenAI focused exclusively on language, trained on vast text corpora to generate and interpret human language. While all LLMs are GenAI, not all GenAI systems are LLMs—a distinction that will be maintained consistently throughout this manuscript (Fig. 1).

The emergence of advanced LLMs such as OpenAI's GPT-4, Google's Med-PaLM 2, and open-source platforms like LLaMA has accelerated the integration of GenAI into academic environments [3]. These models can answer complex biomedical questions, simulate patient interactions, and generate coherent, high-fidelity text with accuracy that in some cases approaches human performance [4]. Notably, ChatGPT has demonstrated passing-level performance across all 3 United States Medical Licensing

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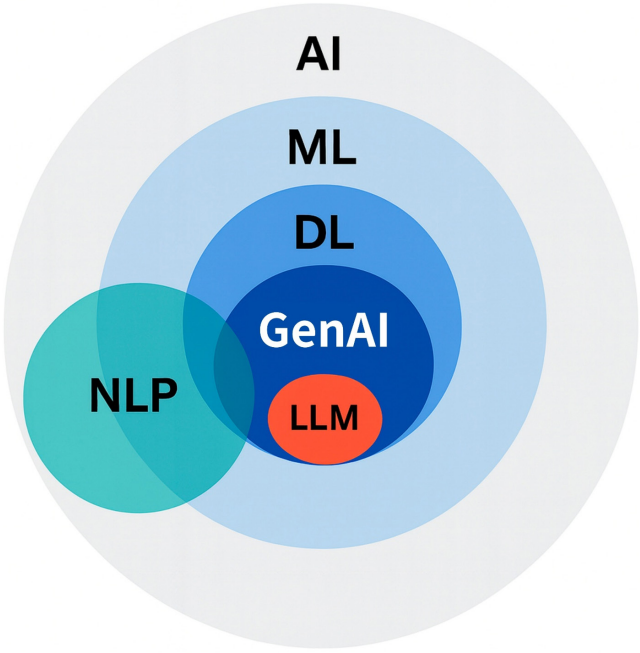

Fig. 1. Hierarchical relationship among artificial intelligence (AI), machine learning (ML), deep learning (DL), and generative artificial intelligence (GenAI). Large language models (LLMs) are depicted as a subset of GenAI, while natural language processing (NLP) overlaps multiple layers, reflecting its broad role in both traditional and GenAI applications. Figure generated by the authors using ChatGPT.

Examination (USMLE) Step exams without specialized medical training [5]. Comparable results have also been reported for licensing examinations in other countries, including Thailand [6]. In one study of the Thai National Licensing Examination, GPT-4 achieved 88.9% accuracy, substantially exceeding the national average and underscoring its potential as an equitable and multilingual preparatory tool [6]. This capability carries profound implications. If general-purpose LLMs can perform at or above the level of human trainees on standardized assessments, fundamental assumptions about how future physicians are taught, evaluated, and credentialed must be reconsidered [3]. The capacity of GenAI to serve as a real-time tutor, content generator, and even clinical reasoning assistant represents both a disruptive opportunity and a mandate for reform in medical pedagogy.

Since the public release of ChatGPT in late 2022, interest in GenAI tools among educators and learners has risen sharply [2]. Early adopters have applied these tools for exam preparation, note summarization, content development, and virtual patient scenario generation [1]. Institutions such as Harvard Medical School (HMS) have proactively incorporated GenAI into their curricula, introducing AI-focused courses and funding innovation projects that integrate GenAI into teaching and assessment [2]. Beginning in fall 2023, HMS required all incoming students on the Health Sciences and Technology track to complete a one-month introductory course on AI in healthcare, making it the first medical school to mandate comprehensive AI training at the outset of medical education [7]. This course explores contemporary applications of AI in medicine, critically examines limitations in clinical decision-making, and prepares students for a healthcare environment demanding "good data skills, AI skills, and machine-learning skills" [8]. Additionally, the Department of Biomedical Informatics has launched a PhD (Doctor of Philosophy) track in AI in medicine to cultivate future leaders in healthcare AI technologies [9].

Despite these advances, enthusiasm is tempered by caution. Educators and scholars have expressed concerns regarding the accuracy of AI-generated content, particularly the risk of "hallucinations"—plausible yet incorrect outputs—as well as the ethical consequences of excessive reliance on automated systems [10]. Broader issues such as academic dishonesty, data privacy, algorithmic bias, and unequal access to GenAI tools further underscore the need for a measured, policy-guided approach to adoption [11]. Recent systematic reviews have mapped both the opportunities and challenges of LLMs in medical education while highlighting unresolved research gaps [12]. Such reviews identify opportunities including personalized learning plans, clinical simulation, and writing support, but also emphasize risks related to academic integrity, misinformation, and ethics—areas that demand careful regulation [12].

Objectives

The aim of this narrative review is to synthesize current knowledge on the integration of GenAI into medical education, emphasizing both the opportunities and challenges associated with its use. We provide a structured analysis of GenAI technologies relevant to medical education, examine their pedagogical applications, discuss ethical and logistical barriers to implementation, and propose recommendations for future research and institutional policy development.

Through this review, we aim to provide a balanced resource that enables medical educators, learners, and administrators to navigate this transformative shift responsibly, effectively, and ethically.

Ethics statement

This is a literature-based study; therefore, neither approval by an institutional review board nor informed consent was required.

Overview of GenAI technologies relevant to medical education

GenAI encompasses a wide range of models and modalities that can generate new, human-like outputs. In medical education, the most relevant GenAI technologies include LLMs, image-generation systems, multimodal models, and simulation tools that integrate natural language with visual or audio data [2] (Fig. 2, Table 1).

LLMs, one of the most prominent subtypes of GenAI, include GPT-4 (OpenAI), Med-PaLM 2 (Google), and open-source variants such as LLaMA and BLOOM. These models can generate fluent, contextually appropriate text responses based on user prompts [1]. Trained on massive corpora of web texts, scientific publications, and human conversations, they are capable of engaging in Q&A, summarizing content, simulating dialogues, and generating exam questions or clinical cases.

Importantly, general-purpose LLMs—without domain-specific fine-tuning—have achieved near or above-passing scores on high-stakes medical licensing exams, including USMLE Step 1, Step 2

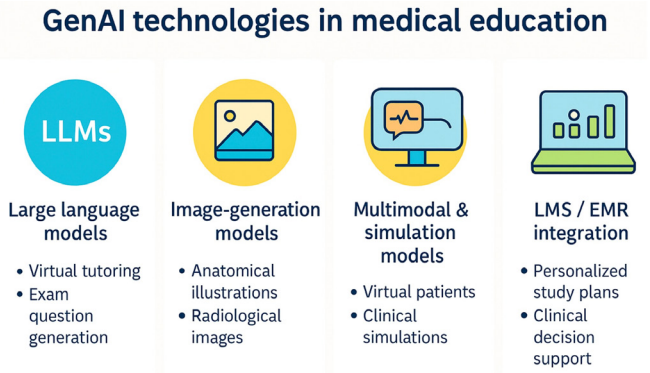

Fig. 2. Overview of generative artificial intelligence (GenAI) technologies in medical education. The infographic highlights 4 domains: large language models (LLMs) for tutoring and exam preparation; image-generation models for medical illustrations and dataset augmentation; multimodal and simulation models for immersive training; and integration with learning management systems (LMS) and electronic medical records (EMRs) for personalized support and clinical documentation. Figure generated by the authors using ChatGPT.

Table 1. Comparison of GenAI technologies in medical education

Technology type	Examples	Medical education applications	Key advantages	Limitations
LLMs	• GPT-4 (OpenAI) • Med-PaLM 2 (Google) • LLaMA • BLOOM	• Virtual tutoring and Q&A • Clinical reasoning support • Exam preparation • Content summarization • SOAP note generation	• 24/7 availability • Personalized responses • Passing scores on USMLE • Natural conversation • Scalable deployment	• Hallucinations • Knowledge cutoff dates • Lack of real-time data • Variable accuracy • No clinical judgment
Image-generation models	• DALL-E 3 (OpenAI) • Midjourney • Stable Diffusion • GANs	• Anatomical illustrations • Radiological findings • Dermatological cases • Histopathology slides • Clinical syndrome visualization	• Privacy protection • Unlimited variations • Rare case generation • No patient consent needed • Customizable features	• Potential inaccuracies • May generate unrealistic features • Limited medical specificity • Requires validation
Multimodal & simulation models	• GPT-4 with vision • AI-powered OSCEs • Virtual patient platforms • Integrated simulation environments	• Complete clinical encounters • Combined text/image/audio • Virtual standardized patients • Adaptive difficulty scenarios • Real-time feedback systems	• Immersive experiences • Multiple input types • Comprehensive training • Safe practice environment • Repeatable scenarios	• Technical complexity • High computational needs • Integration challenges • Limited emotional nuance
LMS/EMR integration	• AI-enhanced LMS platforms • EMR-integrated assistants • Performance analytics tools	• Personalized study plans • Documentation assistance • Performance tracking • Clinical decision support • Automated feedback	• Seamless workflow • Data-driven insights • Real-time assistance • Curriculum alignment • Progress monitoring	• Privacy concerns • System compatibility • Requires infrastructure • Policy barriers

GenAI, generative artificial intelligence; LLMs, large language models; SOAP, subjective, objective, assessment, and plan; USMLE, United States Medical Licensing Examination; GANs, generative adversarial networks; AI, artificial intelligence; OSCEs, objective structured clinical examinations; LMS, learning management systems; EMR, electronic medical records.

CK, and Step 3 [3,13], as well as specialty board examinations such as interventional radiology [14] and urology [15]. For example, GPT-4o correctly answered 67% of questions on the simulated European Board of Interventional Radiology exam, performing at a level comparable to trainees and even generating valid exam items for practice purposes [14]. By contrast, in a US urology knowledge assessment, GPT-4 outperformed GPT-3.5 (44% vs. 31%) but still fell below the 60% passing threshold, underscoring its role as a supplementary rather than standalone tool [15]. The ability of these models to approximate medical reasoning and generate coherent differential diagnoses positions them as valuable assistants for knowledge reinforcement and exam preparation. LLMs are also being adopted as conversational tutors in medical education. Students can interact with these systems to clarify complex concepts, explore reasoning pathways, or simulate patient interviews. In some studies, learners have reported using LLMs to create summaries, flashcards, and practice quizzes tailored to their weak areas [2].

Image-generation models

In addition to text, GenAI includes tools capable of producing high-quality images from textual prompts. Systems such as DALL-E 3 (OpenAI), Midjourney, and Stable Diffusion can generate visual materials—including realistic anatomical illustrations, radiological findings, and dermatological presentations—that may be integrated into medical teaching [16].

A notable advantage of image-generating models is their capacity to create synthetic yet realistic patient images without compromising privacy. For instance, DALL-E has been employed to produce diverse facial images displaying features of rare syndromes, thereby expanding access to visual cases while preserving patient confidentiality [12]. Similarly, histopathological images produced by generative adversarial networks have been shown to be virtually indistinguishable from real slides, enabling dataset augmentation in pathology education [17]. Furthermore, ChatGPT-4.0 has demonstrated competence in certain medical imaging evaluation tasks, suggesting potential applications in visually oriented medical fields [18]. However, its accuracy remains limited—for example, in radiographic positioning error detection, it achieved only partial recognition (mean score 2.9/5)—highlighting the need for continued radiography training despite its promise [18].

These technologies can enrich medical education by providing unlimited case variations, supporting visual diagnostic training, and mitigating the scarcity of publicly shareable clinical images.

Multimodal and simulation models

A particularly promising avenue is the development of multimodal AI systems that integrate textual, visual, and auditory inputs. Early examples include GPT-4 with image-input capabilities and models designed to interpret radiographs or simulate auscultatory findings. Such systems can replicate full clinical encounters, with text-based chatbots role-playing as patients [19].

In parallel, GenAI is increasingly being applied to create simulation environments and virtual patients. These include chatbot-based standardized patients (SPs), AI-driven objective structured clinical examination (OSCE) stations, and immersive scenarios that allow students to practice clinical reasoning, communication, and empathy in low-risk settings [20,21].

The scalability and flexibility of these AI-driven simulations offer particular advantages for institutions with limited access to human SPs or diverse clinical exposures. They also provide opportunities for repeated practice, real-time feedback, and adaptive difficulty adjustments based on learner performance [2].

Integration into learning management and clinical systems

Some institutions have begun piloting GenAI tools integrated directly into learning management systems (LMS) or electronic medical records. For example, GenAI can analyze student performance data in an LMS and generate personalized study recommendations [22]. Similarly, in clinical clerkships, AI-powered assistants can help students compose the Subjective, Objective, Assessment and Plan (SOAP) notes, formulate differential diagnoses, or draft patient instructions in real time—strengthening both documentation skills and clinical reasoning [3]. These applications blur the boundaries between education and clinical practice, underscoring the importance of ethical frameworks and institutional policies to ensure appropriate use [23].

The landscape of GenAI in medical education is expanding rapidly across multiple technological domains. LLMs provide a foundation for text-based tutoring and communication, image-generation models contribute to visual learning, and multimodal and simulation systems enable interactive, immersive experiences. As these technologies evolve, medical educators must remain aware of their capabilities and limitations in order to incorporate them effectively into curriculum design and instructional delivery.

Opportunities of GenAI in medical education

GenAI offers transformative opportunities across diverse aspects of medical education, from personalized learning to large-scale simulation and efficient content creation. By augmenting both teaching and learning processes, GenAI has the potential to

expand access, reduce faculty burden, and promote learner-centered education [2] (Fig. 3).

Personalized learning and tutoring

One of the most compelling applications of GenAI is its capacity to provide personalized, on-demand tutoring tailored to each learner's pace, knowledge level, and areas of weakness. LLMs such as ChatGPT can function as virtual tutors that answer questions, clarify difficult concepts, and create customized learning resources [1].

Unlike static textbooks or traditional lectures, GenAI tools interact conversationally with students, adapting in real time to individual needs. For example, a learner struggling with cardiology may request simplified explanations, analogies, or practice questions aligned with their specific knowledge gaps [2]. The ability to generate personalized quizzes, flashcards, and learning paths supports the principles of competency-based education [22].

Furthermore, these systems can deliver instant formative feedback, enabling learners to correct misconceptions before they become entrenched. Such feedback loops are particularly valuable for fostering self-directed learning and strengthening metacognitive skills [19].

Clinical simulation and virtual patients

GenAI is revolutionizing clinical skills training through the development of virtual patient simulations. LLMs can engage learners in natural language conversations that replicate history-taking, diagnostic reasoning, and management decisions [20]. Recent implementations have shown that ChatGPT-based virtual patients can be deployed at scale, at costs as low as US$0.006 per complete conversation, with more than 75% of students reporting enhanced learning effectiveness [20].

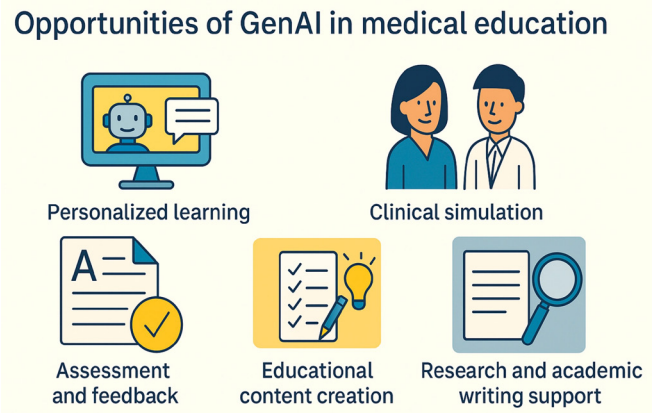

Fig. 3. Opportunities of generative artificial intelligence (GenAI) in medical education. Figure generated by the authors using ChatGPT.

Pilot studies have demonstrated that ChatGPT can serve as a chatbot-based standardized patient, providing learners with opportunities to practice interviewing skills in low-pressure environments. Students have reported improved confidence and communication skills, as well as reduced performance anxiety [20].

GenAI can also be applied to the design of OSCE cases, the generation of structured checklists for assessors, and the provision of real-time feedback on clinical reasoning and communication [21]. When combined with image-generation models, these simulations can incorporate synthetic photos, radiographs, or laboratory data, further enhancing realism [16,17].

Such simulations are particularly valuable in resource-limited settings where access to human SPs or diverse patient cases is constrained. They offer scalable, repeatable, and ethically safe training environments that strengthen experiential learning without compromising patient safety.

Assessment and feedback enhancement

GenAI creates new opportunities for efficient, scalable, and individualized assessment. LLMs can generate high-quality exam items, including multiple-choice questions, clinical vignettes, and open-ended prompts. These outputs can serve as foundations for exam construction or as self-assessment resources for students [24,25].

AI can also support automated grading. Natural language processing tools have been applied to assess OSCE performance and written responses, producing consistent and timely feedback. One study reported that AI-based graders achieved greater scoring consistency across OSCE domains, particularly in technical and checklist-based assessments [26].

In addition, AI-generated feedback can assist students in revising essays or reflective writing, identifying logical gaps in clinical reasoning, and visualizing learning progress over time. These features promote formative, learner-centered assessment by shifting the emphasis from punitive evaluation toward continuous improvement [2].

Educational content creation and curriculum design

GenAI also supports faculty by simplifying educational content development. Instructors can use LLMs to draft lecture slides, design case-based discussions, or create materials for problem-based learning. For example, by providing learning objectives, educators can prompt a GenAI tool to generate aligned case scenarios that include clinical data, differential diagnoses, and teaching questions [2].

Beyond content generation, GenAI can aid in curriculum mapping and optimization. AI tools can analyze curricular materials,

identify gaps or redundancies, and recommend improvements aligned with national licensing requirements or competency frameworks [27]. Additional benefits include language translation and accessibility. AI-generated materials can be adapted for learners with varying levels of proficiency or translated into multiple languages, thereby promoting inclusivity and broadening access to educational resources [2].

Research and academic writing support

Medical students and residents frequently struggle with the workload and complexity of academic writing. GenAI tools can assist with literature summarization, research idea generation, and manuscript drafting. They can rapidly synthesize large bodies of literature, suggest relevant citations, and enhance grammar and clarity—benefits that are especially valuable for non-native English speakers [28]. Nonetheless, such support must be applied carefully. While GenAI can improve productivity, risks remain regarding hallucinated references or inappropriate authorship practices [2].

When used transparently and ethically, however, GenAI can significantly reduce barriers to academic engagement, enabling learners to focus more on critical thinking and data interpretation rather than formatting or summarization.

Challenges and risks of GenAI in medical education

Despite its transformative potential, the integration of GenAI into medical education introduces major challenges. These risks span technical, ethical, educational, and legal domains. Without thoughtful implementation, GenAI could unintentionally undermine core educational values and exacerbate existing disparities [1,2] (Fig. 4).

Ethical concerns: bias, equity, and humanistic values

One of the most pressing concerns is the inherent bias in AI-generated content. Because GenAI systems are trained on large datasets that reflect existing disparities in medical literature, they may produce biased outputs that underrepresent certain ethnicities, genders, or cultural perspectives [3]. This increases the risk that AI-generated cases or explanations may perpetuate stereotypes or deliver unequal educational value across populations.

The digital divide poses an additional equity concern. Access to high-performance GenAI tools often depends on paid subscriptions, stable internet connections, and advanced computing infrastructure. Students in resource-limited settings may therefore be disadvantaged [2].

A further ethical issue is the potential erosion of humanistic and

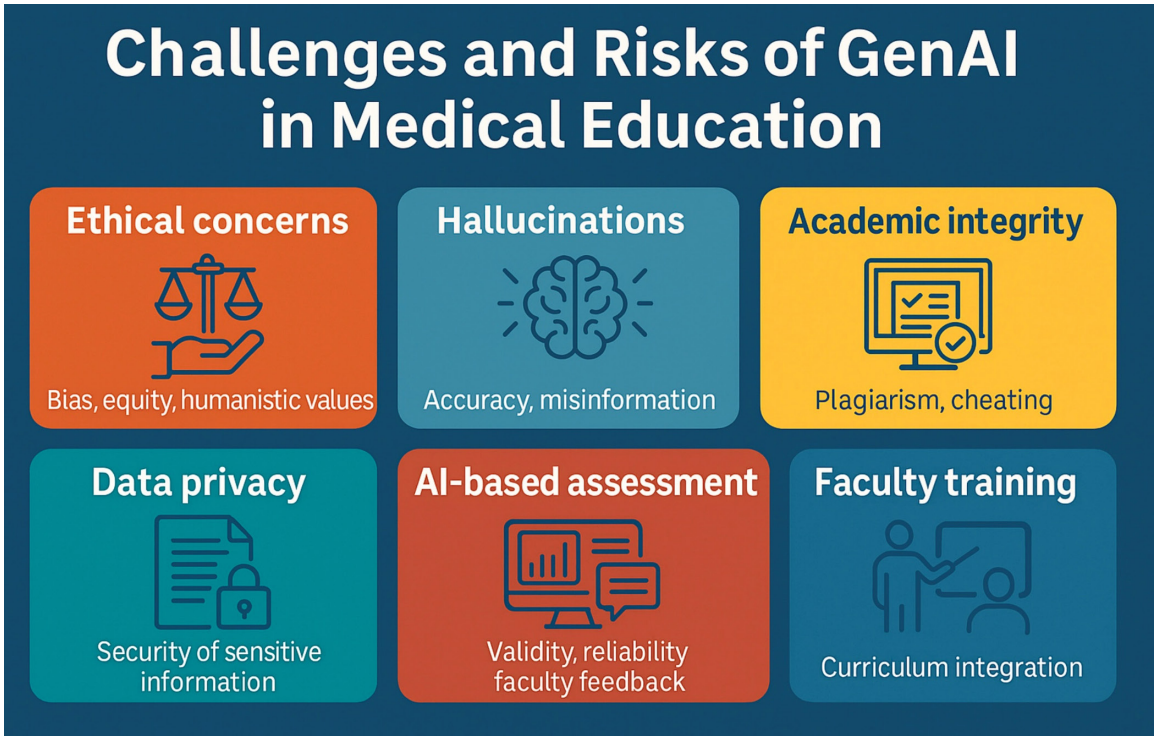

Fig. 4. Challenges and risks of generative artificial intelligence (GenAI) in medical education. Figure generated by the authors using ChatGPT.

professional values. Overreliance on AI tutors and simulations could reduce opportunities for real patient interaction and mentorship, both of which are critical for developing empathy, communication skills, and ethical judgment [20]. Thus, GenAI must be implemented in ways that augment, rather than replace, the human elements of medical education.

Hallucinations, accuracy, and misinformation

A well-recognized limitation of current LLMs is their tendency to hallucinate, producing fabricated or inaccurate information presented with unwarranted confidence. In medical education, this risk is especially concerning, as learners may accept such content uncritically [2]. For instance, ChatGPT has been shown to invent plausible-sounding references or provide incorrect clinical recommendations [10]. Moreover, models such as GPT-4 are trained on data with fixed cut-off dates, making them unaware of the most recent clinical guidelines or discoveries [1]. These limitations make human oversight essential. GenAI should be treated as a supplementary resource rather than an authoritative source, and students must be trained to critically appraise AI outputs, verify them against trusted references, and seek expert validation when necessary [2].

Academic integrity and plagiarism

Another pressing challenge involves academic integrity. GenAI tools can generate essays, solve problems, or compose reflective statements, raising concerns about "technological plagiarism" [2]. Students may misuse AI outputs in assignments or assessments, undermining the validity of evaluations.

Medical schools are beginning to adapt their academic integrity policies in response. Some now explicitly forbid the submission of AI-generated content without disclosure, while others are experimenting with AI-detection tools. However, such detectors remain imperfect and prone to false positives [2].

AI-assisted cheating during exams—particularly in remote or open-book formats—also poses a significant risk. Given that GenAI models perform well on licensing-style questions, assessment formats and proctoring strategies will need to be reevaluated [25].

Data privacy and security

The use of cloud-based GenAI platforms raises important privacy and security concerns, especially when students or faculty input clinical cases or patient information. Even de-identified data may inadvertently breach confidentiality if processed on third-party servers [3]. Educational institutions must therefore establish strict guidelines that prohibit entering protected health information into public GenAI tools. Some schools are developing encrypted or locally hosted AI systems to ensure that data remain within institutional firewalls, though such solutions require considerable technical investment [1].

Another unresolved issue involves the governance of student data. Many GenAI platforms store user interactions, yet policies regarding how this data is used, how long it is retained, and whether it contributes to future model training remain unclear. Transparent agreements between educational institutions and AI providers are essential to address these concerns.

Limitations in AI-based assessment and feedback

While GenAI can enhance efficiency in grading and feedback, concerns persist regarding validity and reliability. AI graders may overestimate performance in structured domains while failing to capture nuanced competencies such as empathy, ethical reasoning, or reflective writing [26].

Excessive reliance on AI-driven feedback also risks reducing faculty–student interaction, depriving learners of mentorship and contextual insight that only human educators can provide. In addition, students may receive inconsistent or oversimplified feedback if AI systems lack sufficient contextual awareness of local curricular objectives [2]. For these reasons, AI-based assessment should be employed as a supplement rather than a substitute, with continuous monitoring and quality assurance to ensure fairness and accuracy.

Faculty training and curriculum integration

Successful integration of GenAI requires targeted faculty development and deliberate curricular reform. Many educators lack familiarity with GenAI tools, leading to inconsistent implementation, skepticism, or undue reliance on unverified outputs [23]. To address these gaps, workshops, continuing education programs, and collaborative pilot projects are necessary to strengthen faculty AI literacy. Equally important is the thoughtful integration of AI-related content into medical curricula. Topics such as prompt engineering, ethical usage, and critical appraisal of AI outputs should be aligned with accreditation standards and professional competencies [20].

Without institutional support, AI tools risk being underused or misapplied, resulting in wasted resources or unintended consequences. Administrative leadership, resource allocation, and cross-disciplinary collaboration are therefore essential for effective adoption [1].

Current implementations and case studies

GenAI adoption in medical education has accelerated since

2022, largely due to the accessibility of tools such as ChatGPT and DALL-E. While most institutions remain in exploratory or pilot phases, several pioneering medical schools have already begun integrating GenAI into curricula, assessments, and clinical simulations [29].

Institutional adoption trends

A recent survey of US Osteopathic Medical Schools reported that 93% lacked formal GenAI policies and 73% had no plans to introduce mandatory AI-related education [29]. Nonetheless, adoption is evolving rapidly, with a clear divide emerging between early adopters and institutions still in preliminary planning. Whereas some schools experiment within individual courses, leading institutions have established comprehensive, structured programs.

Notable examples include:

Harvard Medical School

HMS launched a formal course, AI in healthcare, for incoming students and provided innovation grants to support faculty-led GenAI initiatives [2]. Designed collaboratively with faculty from HMS, MIT, and the Harvard T.H. Chan School of Public Health, the course covers technical foundations, ethical considerations, bias mitigation, and clinical integration strategies [8]. Students engage with case studies, hands-on programming, and discussions on health equity. HMS also established the AI in medicine program, serving as a hub for AI research, education, and innovation across the institution [30].

Mount Sinai's Icahn School of Medicine

Mount Sinai became the first medical school to integrate ChatGPT Edu across all levels of education—from preclinical coursework to clinical clerkships—under a formal agreement with OpenAI ensuring HIPAA compliance and data protection. Their approach emphasizes training students to use AI as an assistant rather than a replacement, with applications spanning clinical reasoning, case analysis, research, and curriculum development [31].

NYU Grossman School of Medicine

NYU introduced a precision education initiative that uses AI to personalize curricula and study aids according to students' learning styles and goals. Early pilot efforts involve first-year students, with AI operating within the student portal to deliver seamless, unobtrusive support. Applications extend to integration with electronic health record data, predictive analytics, and virtual learning tools [32].

These examples highlight early institutional willingness to explore GenAI's potential in enhancing both teaching and learning.

Applications in the classroom and beyond

In classroom settings, faculty have reported using LLMs to co-develop lecture slides, generate interactive quizzes, and facilitate real-time Socratic questioning via chatbots. In anatomy courses, AI-generated images and 3-dimensional visualizations have been used to supplement cadaver-based learning, particularly in remote or hybrid environments [16].

During clinical rotations, students have employed AI assistants to draft SOAP notes, review clinical guidelines, and simulate differential diagnoses in real time—transforming GenAI into a bedside learning companion [3].

In a notable simulation study, ChatGPT was deployed as a virtual standardized patient during mock OSCEs. The AI system simulated diverse emotional tones and symptom narratives during history-taking interviews. Learners reported reduced anxiety, improved confidence, and greater flexibility in practicing complex cases [20].

Faculty have also leveraged GenAI to create OSCE case checklists, rubrics, and feedback forms, thereby streamlining the development of standardized assessments and reducing examiner workload [21].

Policy gaps and institutional challenges

Despite the rapid adoption described earlier, policy development has not kept pace. Key concerns include: (1) Whether students must disclose AI assistance in assignments; (2) How to prevent and detect AI-generated plagiarism; (3) Who is accountable for AI-generated errors in student submissions; and (4) Whether AI output can be cited in academic writing.

In the absence of clear institutional guidance, usage patterns vary widely. Some faculty permit unrestricted use of GenAI as a writing or brainstorming tool, while others strictly prohibit it, citing concerns over fairness and academic integrity [2].

Student and faculty perspectives

Emerging qualitative studies indicate that students are eager adopters of GenAI, particularly Generation Z learners who value productivity, personalization, and efficiency [26]. Common student uses include (1) summarizing complex lectures, (2) practicing board-style questions, and (3) drafting structured reflections or research outlines.

At the same time, many students report uncertainty about how far they can ethically use these tools. Some have requested clearer institutional policies and formal training on appropriate AI usage

[2]. Faculty perspectives have been more diverse, ranging from enthusiastic experimentation to strong skepticism. While some educators regard GenAI as a productivity enhancer, others worry that it could erode fundamental clinical reasoning skills or be misused in high-stakes assessments [23].

Notably, educators who use GenAI most effectively often benefit from institutional support, training, or collaborative platforms, underscoring professional development as a key enabler of responsible adoption [33].

Future directions and recommendations

Responsible integration of GenAI into medical education requires a multi-layered approach, summarized in our framework (Fig. 5). This framework consists of 4 interconnected layers: core principles that guide all activities, a foundation of AI literacy and ethical guidelines, implementation through pilot programs and curricular integration, and outcomes such as enhanced learning and ethical AI use. Recommendations are organized according to these layers to provide a coherent roadmap for sustainable integration of GenAI. For example, "developing AI literacy and competency" aligns with the foundation, "reimagining assessment" with implementation, and "human–AI interaction" with outcomes.

Developing AI literacy and competency

Ensuring the safe and effective use of GenAI in medical education is essential. Both students and faculty must build AI literacy—the ability to understand how these systems function, recognize their limitations, and apply them ethically [20]. As a cornerstone of the foundation layer, AI literacy provides the knowledge base upon which all subsequent implementation strategies and desired outcomes depend. Without this foundation, neither educators nor learners can deploy, evaluate, or benefit from GenAI tools effectively.

Educational initiatives should establish structured programs that cover fundamental principles of AI and machine learning, ensuring that both students and faculty understand the concepts driving these technologies. Curricula should also include practical training in prompt engineering for LLMs, equipping learners with the skills to interact effectively with AI systems. Equally important are evaluation skills—learners must be able to assess AI-generated outputs against trusted sources to foster a culture of verification and scholarly rigor. Case-based discussions that highlight ethical use and misuse scenarios provide valuable opportunities for learn-

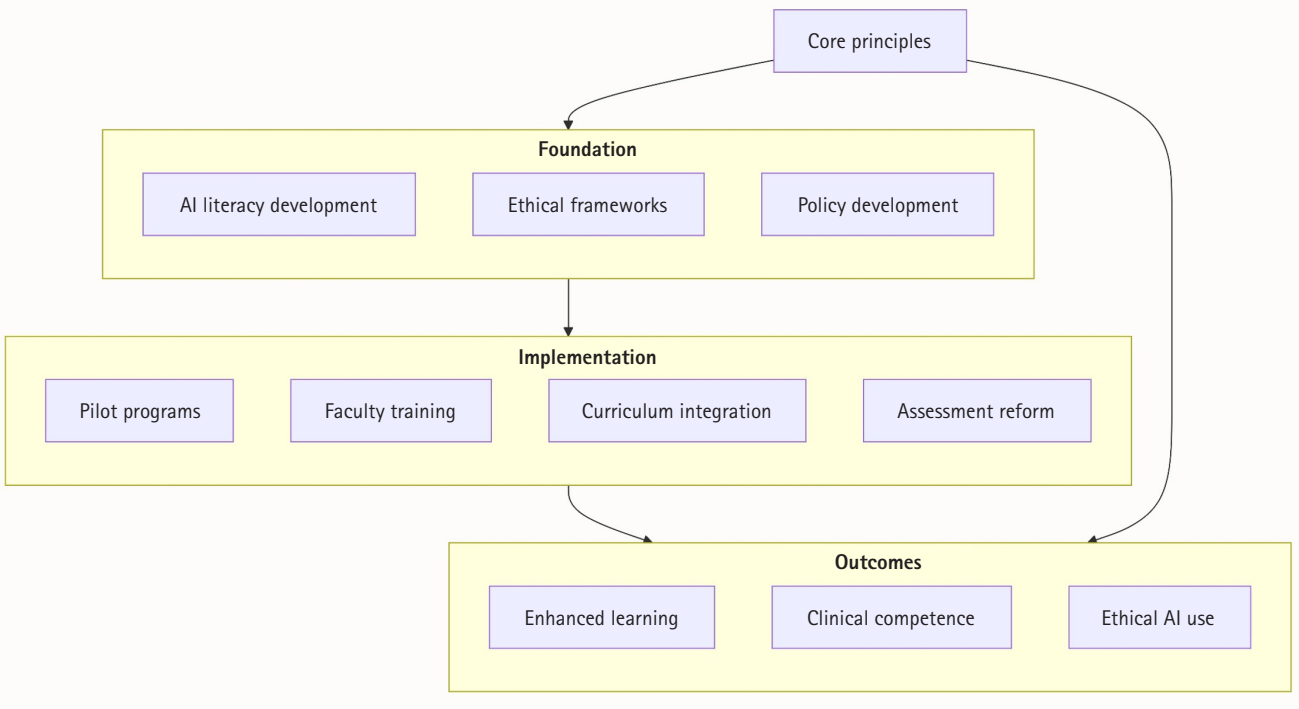

Fig. 5. Framework for responsible generative artificial intelligence (GenAI) integration in medical education. This framework illustrates the multi-layered approach required for responsible GenAI integration, emphasizing the interconnected nature of foundational elements, implementation strategies, and desired outcomes. All layers are guided by core principles and sustained through stakeholder engagement and continuous quality improvement.

ers and educators to practice navigating complex decisions about appropriate AI applications in medical contexts. Future research should explore the relative impact of stand-alone AI courses versus embedded instruction throughout the curriculum to determine the most effective teaching strategies [1].

Reimagining assessment in the AI era

As AI becomes increasingly capable of answering standard medical exam questions, educators must reconsider traditional assessment models. This transformation represents the Implementation layer of our framework, where foundational AI literacy must translate into concrete curricular reforms—particularly in assessment methods that safeguard academic integrity while leveraging AI's educational potential. Future assessments must emphasize higher-order cognitive skills, including complex clinical reasoning, ethical decision-making, and the demonstration of empathy in patient interactions. To this end, institutions should incorporate oral examinations and OSCEs that assess real-time thinking and adaptive problem-solving, providing authentic evaluations of clinical competence while reducing the risk of AI manipulation. The design of AI-resilient assessment formats is also crucial. These should focus on domains where GenAI tools cannot effectively substitute for personal reflection, experiential learning, and hands-on performance requiring human judgment and interpersonal skills [2]. At the same time, research is needed to validate whether AI-generated test items predict student performance and whether AI-assisted grading aligns with human judgment [26].

Human-AI interaction and educational outcomes

Understanding human–AI interaction in medical education requires rigorous empirical investigation. This research directly connects the implementation layer to the outcomes layer of our framework, measuring whether strategic changes in curriculum and assessment actually produce the enhanced learning, improved clinical competence, and ethical AI use that constitute our ultimate goals.

A central recommendation for guiding learner–AI interactions is the DEFT-AI framework (Diagnosis, Evidence, Feedback, Teaching, and recommendations for AI use). This framework provides supervisors with a structured method to promote critical thinking during learner–AI interactions [34]. By distinguishing among delegation, evaluation, and collaborative use, DEFT-AI encourages learners to verify AI outputs before relying on them, reinforcing the "verify before trust" paradigm. Incorporating this framework ensures that AI functions as a tool to strengthen, rather than weaken, clinical reasoning capabilities.

Mitigating algorithmic bias and ensuring equity

Addressing algorithmic bias and ensuring equitable access to GenAI technologies is a critical priority for medical education institutions. Equity, as a core principle of our framework, must permeate every layer—from ensuring diverse representation in AI literacy programs, to piloting initiatives in underserved contexts, to measuring disparities in educational outcomes across different student populations. Systematic efforts are needed to audit and mitigate biases embedded in GenAI training datasets. Collaboration between developers and educators will be essential to fine-tune models using diverse, representative data that encompass a broad range of medical conditions, populations, and cultural contexts. Integrating bias-detection mechanisms into AI systems can provide ongoing monitoring and quality assurance, while involving students in bias-identification exercises can cultivate the critical consciousness required for ethical medical practice [23]. These educational approaches provide learning opportunities, fostering awareness of inequities in GenAI processes and promoting culturally competent healthcare delivery. Equally important is equitable access. Pilot programs in underserved regions should explore lightweight or offline GenAI solutions and assess their effects on learning outcomes [2].

Establishing ethical and regulatory frameworks

Robust institutional policies and ethical guidelines must underpin all applications of GenAI. These frameworks embody the core principles of transparency and responsibility, while also forming part of the Foundation layer that enables subsequent implementation and ensures sustainable outcomes. Recent scholarship suggests that competency-based medical education frameworks may provide useful analogues for AI regulation, given similar challenges in governing adaptive systems with opaque processes [35]. Institutional policies must address critical aspects of disclosure and attribution of AI assistance, ensuring transparency in academic work while upholding scholarly honesty and intellectual property standards. Clear distinctions between acceptable and prohibited uses of GenAI in coursework and assessments are essential for maintaining educational validity and preventing misconduct. Equally important are comprehensive data privacy protections for AI-generated materials to ensure compliance with regulatory requirements. Furthermore, accountability structures must be established to address potential harms associated with AI use. These should include defined responsibility chains and remediation processes to protect both learners and institutions from negative consequences [1]. Professional organizations and accrediting bodies should also consider establishing competency standards for AI literacy in medical education and recommending shared

ethical usage norms across institutions.

Advancing domain-specific medical AI tools

To improve accuracy and safety, future GenAI applications should prioritize the development of medical-specific LLMs trained exclusively on curated, peer-reviewed clinical data [3]. These technological advances apply across all layers of the framework—strengthening the foundation with more reliable educational tools, enabling implementation through sophisticated clinical simulations, and contributing to outcomes of enhanced learning and clinical competence. Specialized models offer superior factual reliability and domain relevance compared with general-purpose systems that may lack medical precision. Integrating multimodal capabilities—such as combining voice, image, and text inputs—holds transformative potential for creating immersive simulations that closely replicate real clinical scenarios. Such innovations are particularly valuable in specialized fields like radiology, dermatology, and procedural training [19]. These advancements will require sustained collaboration among AI developers, clinicians, and educators to ensure that tools are pedagogically appropriate. Trials of instructor-facing AI systems that deliver cohort-level performance analytics or targeted teaching recommendations can further improve educational effectiveness and guide curriculum development [22].

Conclusion

GenAI presents vast opportunities for medical education, including personalized learning, advanced simulations, and efficient content development, thereby enhancing engagement and scalability. At the same time, it introduces significant challenges, such as hallucinations, inherent biases, threats to academic integrity, and data privacy concerns, all of which may undermine critical thinking and empathy. Successful integration depends on preserving the humanistic values of medical education. This requires clear institutional guidelines, comprehensive faculty development, essential AI literacy for learners, and robust ethical frameworks. AI should serve as a vital collaborator rather than a replacement for human expertise, helping cultivate physicians with strong clinical judgment, sound ethical reasoning, and profound empathy. Aligning technological innovation with foundational medical competencies will ensure that GenAI strengthens, rather than diminishes, the mission of medical education.

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Supplementary materials

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Lifestyle prescriptions for obesity treatment in primary care: a narrative review

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Purpose: This review aims to synthesize the most up-to-date evidence on effective lifestyle prescriptions for managing patients with obesity in the primary care setting.
Methods: A comprehensive literature search was conducted through June 2025 using major domestic and international databases, including PubMed, Google Scholar, and RISS, as well as the websites of relevant academic societies. The search strategy employed keywords such as "obesity," "primary care," "lifestyle intervention," "diet," "exercise," and "behavioral therapy" in both English and Korean.
Results: Effective obesity management should be grounded in the new paradigm of adiposity-based chronic disease, which focuses on preventing and treating the medical complications associated with excessive fat accumulation. The essential components of a successful lifestyle prescription comprise 3 pillars: diet, exercise, and behavioral therapy. An individualized dietary plan that achieves an energy deficit of 500–750 kcal is fundamental. Exercise prescriptions should recommend a combination of aerobic and resistance training, along with strategies to minimize sedentary time. In behavioral therapy, high-intensity behavioral counseling, the 6A model (ask, assess, advise, agree, assist, arrange), self-monitoring, and cognitive-behavioral therapy techniques have all demonstrated efficacy.
Conclusion: Primary care physicians are not only capable but also uniquely positioned to lead long-term, patient-centered obesity management. Their comprehensive and integrative perspective makes them one of the most efficient and scalable resources in addressing the obesity epidemic.

Keywords: Behavioral therapy; Dietary therapy; Exercise therapy; Obesity; Primary care

Introduction

Obesity has emerged as a global public health crisis that extends far beyond issues of individual willpower. Projections suggest that by 2030, over half of the world's adult population will be either overweight or obese [1]. South Korea mirrors this global trend, with the prevalence of adult obesity continuing to rise at an alarming rate [2]. Data from the 2019–2021 Korea National Health and Nutrition Examination Survey indicate a particularly high prevalence among young adults aged 19 to 39 (45.4% in men and 20.5% in women), serving as a critical warning for a likely future increase in the burden of cardiometabolic diseases [3].

Within this context, the medical understanding of obesity is undergoing a fundamental paradigm shift. Moving away from the outdated notion of obesity as merely excess body weight, it is now recognized as a complex, multifactorial adiposity-based chronic disease (ABCD)—a classification officially endorsed by leading medical organizations, including the American Medical Association [4]. This conceptual shift reframes the management goal from short-term weight loss to long-term disease control, paralleling chronic conditions such as hypertension and diabetes [5,6].

Primary care physicians are uniquely positioned to drive this transformation. Their holistic understanding of the patient, continuity of care, and familiarity with medical and psychosocial histories allow them to view obesity not in isolation but as part of a broader network of cardiometabolic, behavioral, environmental, and psychosocial determinants [7]. Unlike subspecialists, who typically address obesity-related complications within their own

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fields (e.g., endocrinology, cardiology, or orthopedics), primary care physicians can coordinate, assess, and tailor lifestyle interventions using a systems-based approach [8].

Furthermore, primary care offers the optimal environment for lifestyle counseling, sustained behavioral change, and early detection of weight-related comorbidities. The longitudinal therapeutic alliance between physician and patient enhances the feasibility of staged, patient-centered management strategies, including motivational interviewing, goal setting, progress monitoring, and, when indicated, pharmacologic escalation [9]. Thus, the integrative and comprehensive role of primary care in obesity management is not only complementary to specialist involvement but also forms the foundation for achieving sustainable long-term outcomes.

Objectives

The objective of this review is to systematically present an evidence-based framework for lifestyle interventions in managing patients with obesity in primary care settings. To achieve this, we analyze international guidelines and the most recent research on dietary therapy, physical activity, and behavioral modification. By integrating findings from studies conducted in Korean populations, this review aims to offer a practical, evidence-based framework tailored for clinical application in Korea.

Methods

Ethics statement

As this study is based entirely on a review of existing literature, neither institutional review board approval nor informed consent was required.

Study design

This work is a narrative review grounded in a comprehensive search of academic databases and relevant scholarly sources.

Information sources and search strategy

A literature search was performed through June 2025 across major domestic and international databases, including PubMed, Google Scholar, and RISS, as well as the official websites of relevant academic societies. The search strategy incorporated keywords such as "obesity," "primary care," "lifestyle intervention," "diet," "exercise," and "behavioral therapy."

Selection process

Inclusion criteria were restricted to KCI- or SCI(E)-indexed review articles, randomized controlled trials, and major clinical practice guidelines addressing lifestyle interventions (diet, exercise, and behavioral therapy) for patients with obesity in the primary care setting. Studies limited to pharmacological or surgical interventions, case reports, and non–peer-reviewed materials were excluded.

Two independent researchers conducted the selection process, beginning with screening of titles and abstracts, followed by full-text review of eligible articles. Data extraction focused on diagnostic criteria, intervention components, treatment efficacy, considerations for specific populations, and barriers to implementation in clinical settings. To minimize bias, the review prioritized high-level evidence—such as systematic reviews and clinical practice guidelines from recognized academic societies—to ensure methodological rigor and qualitative validity.

Diagnosis and evaluation of obesity in primary care

Effective obesity management begins with accurate diagnosis and thorough clinical evaluation. Primary care physicians must employ standardized metrics to screen for and diagnose obesity while simultaneously assessing a patient's overall health status and comorbid risk to establish the foundation for a personalized treatment plan.

The body mass index (BMI) remains the most fundamental screening tool and is recommended for all adults [10]. According to the World Health Organization, a BMI of 25.0–29.9 kg/m^2 is classified as overweight, and a BMI of 30.0 kg/m^2 or higher indicates obesity [5]. However, it is well recognized that East Asian populations, including Koreans, experience metabolic and cardiovascular complications at lower BMI thresholds than Western populations [6]. Accordingly, the Korean Society for the Study of Obesity (KSSO) adapted these standards for the domestic population, defining a BMI of 23.0–24.9 kg/m^2 as pre-obesity (overweight) and 25.0 kg/m^2 or higher as obesity, recommending earlier and more proactive management [6].

Waist circumference (WC) is another essential measure that should complement BMI assessment. For individuals with a BMI between 25 and 35 kg/m^2, WC measurement is particularly important for detecting abdominal obesity and cardiometabolic risk, which BMI alone may not adequately capture [5,6]. Abdominal obesity reflects visceral fat accumulation and is more closely associated with insulin resistance and related metabolic complications. The KSSO defines abdominal obesity as a WC ≥90 cm in men and ≥85 cm in women [6,11].

Recently, obesity care has shifted from a focus on BMI reduc-

tion toward evaluating the actual health impact of excessive adiposity. This shift is embodied in the ABCD model, which redefines treatment goals: rather than pursuing weight loss as an end in itself, the aim is to prevent and manage complications resulting from excess adiposity [4]. This reconceptualization has significant clinical implications. It reframes physician–patient communication from a superficial or judgmental directive ("You need to lose weight") to a medically grounded, collaborative discussion ("Your excess weight has contributed to prediabetes and hypertension. Let's work together to manage these conditions through lifestyle improvements"). Such reframing strengthens patient engagement and motivation [12].

Accordingly, primary care physicians should complement the diagnosis of obesity with a comprehensive evaluation for weight-related comorbidities, including prediabetes, type 2 diabetes, dyslipidemia, hypertension, nonalcoholic fatty liver disease, osteoarthritis, sleep apnea, and depression [5].

To formulate a personalized treatment plan, a comprehensive patient history is essential [5,12,13]: (1) Weight history: Age of obesity onset, maximum and minimum body weight, and patterns of weight change. History of weight loss attempts: Methods used, amount and duration of weight loss, and factors contributing to success or failure. (2) Dietary patterns: Current eating habits, frequency of problematic food intake, and alcohol consumption. (3) Physical activity patterns: Level of physical activity, duration of sedentary time, and methods and frequency of exercise. (4) Psychosocial factors: Stress levels, sleep duration and quality, quality of life, depressive symptoms, and social support systems. (5) Medication history: Use of medications that may affect body weight (e.g., certain antidepressants, steroids). (6) Patient's perceptions and motivation: Perception of their own weight, readiness for change, and level of motivation.

This multidimensional assessment enables physicians to identify the root causes of obesity, recognize both barriers and facilitators to lifestyle change, and design an individualized, evidence-based intervention strategy optimized for long-term adherence and effectiveness.

Core elements of a successful lifestyle prescription in primary care

Dietary prescription

Dietary therapy is a fundamental component of obesity management [14]. In the primary care setting, an effective dietary prescription should focus on helping patients establish realistic, sustainable, and healthy eating habits rather than enforcing complex or trend-based diets. The foundational principle of all weight-loss diets is to achieve a negative energy balance—where energy expenditure exceeds energy intake. Clinical guidelines generally recommend reducing energy intake by 500–750 kcal per day, leading to a gradual weight loss of approximately 0.5–0.7 kg per week [14-16]. This steady and moderate approach minimizes the risk of weight regain (the "yo-yo effect") and increases the likelihood of long-term maintenance [16].

Numerous dietary models, such as low-fat, low-carbohydrate (<45% of total energy per day), high-protein (25%–35% of total energy per day, 1.2–1.9 g/kg) and Mediterranean diets, have been claimed to show efficacy for weight loss [16]. However, long-term, large-scale studies reveal minimal evidence that any single macronutrient composition is superior to others for sustained weight loss when total caloric intake is equally restricted [16,17]. Therefore, the most effective diet is the one that the patient can consistently adhere to, customized to their lifestyle, preferences, and cultural background. Nevertheless, certain dietary patterns may provide distinct advantages. For instance, the Mediterranean diet not only promotes weight loss but also confers additional cardiovascular benefits, including improved blood pressure and lipid profiles [18]. A low-carbohydrate diet may lead to more rapid initial weight loss, which can boost early patient motivation, though this difference typically diminishes after 1 year [16]. In a meta-analysis comparing low-fat (<30% of total energy intake) and low-carbohydrate diets, weight loss was significantly greater with the low-carbohydrate diet at 6–12 months (by about 1.3 kg), but after 12 months, the results between the 2 diets were comparable [16]. Ultra-low-carbohydrate diets (<10% of total energy per day) should only be implemented for short durations under medical supervision. Since carbohydrate restriction increases protein and fat intake, careful attention must be paid to fatty acid composition and the sources of dietary fats [16]. Thus, the role of primary care physicians is not to uniformly prescribe a single diet but to present evidence-based options and collaborate with patients to determine the most suitable, sustainable approach.

Realistic dietary prescription strategies for primary care

Given the constraints of limited consultation time and varying nutritional expertise, the primary care physician's role more closely resembles that of a "health coach" than a "weight-loss specialist." Accordingly, it is more effective to guide patients toward specific, actionable, and sustainable dietary modifications. Practical strategies include:

Improving meal quality: Encourage patients to reduce consumption of processed and fried foods, sugar-sweetened beverages, and refined carbohydrates (e.g., white bread, pastries), while increasing intake of vegetables, fruits, whole grains, low-fat dairy

products, and lean proteins [14,15].

Ensuring adequate protein intake: To prevent muscle loss commonly associated with weight reduction, advise adequate intake of high-quality protein (e.g., 1.2–1.6 g per kg of ideal body weight per day or 20–30 g of protein per meal) [16]. This helps preserve the basal metabolic rate and improve body composition [14,15]. For practical guidance, a 70-kg adult requiring 1.2 g/kg/day would need approximately 84 g of protein, equivalent to 4 cups of milk, 1.5 chicken breasts (100 g each), or 10 eggs. Protein-containing food portions providing 20 g of protein include: 100 g lean meat, 100 g skinned poultry (e.g., chicken or duck), 130 g fish (about 2 medium pieces), 140 g eggs (2 eggs), 200 g tofu (2/3 block), or 50 g black or soy beans (about 5 tablespoons) [16].

Portion control: Teach patients to regulate intake through smaller plates or visual cues for portion size estimation [19]. This is particularly important in the Korean context, where cultural practices such as company dinners or large-portion food delivery can contribute to excessive caloric intake.

Meal replacements: Calorie-controlled products, such as shakes, bars, or pre-packaged meals, can be helpful—especially during the initial treatment phase—by simplifying calorie tracking and improving adherence [20].

Time-restricted eating: Although the long-term efficacy of intermittent fasting beyond 1 year remains uncertain [16], time-restricted eating—which aligns food intake with the body's circadian rhythm—has shown significant short-term benefits in reducing body weight and fat mass compared to traditional low-calorie diets, especially when combined with caloric restriction. The most effective regimen appears to be an 8-hour eating window beginning before 8 AM, emphasizing breakfast and minimizing late-night meals [16].

Recent studies have also highlighted the importance of hydration as a simple but potent adjunctive strategy. Kang et al. [21] in 2024, analyzing Korean adult data, found a significant inverse association between sufficient water intake and abdominal obesity, particularly among young adults aged 19–39 years. Therefore, practical recommendations such as "Drink a glass of water before each meal" can serve as cost-free, easily adoptable, and universally applicable behavioral reinforcements to any dietary plan [22].

Exercise and physical activity prescription

Exercise, together with diet, forms the twin pillars of obesity management. The goal of an exercise prescription should extend beyond calorie expenditure to include improving body composition, enhancing metabolic health, and actively counteracting the modern epidemic of sedentary behavior [23].

A key development in obesity research is the clear distinction between physical inactivity and sedentarism [24,25]. It is now well established that even individuals who meet recommended physical activity levels may remain at risk for adverse health outcomes if they spend most of their day sitting [26]. Park et al. [2] in 2020 reported that the average daily sitting time among Koreans is approximately 8.3 hours—an alarming statistic. Importantly, sedentary behavior has been identified as an independent risk factor for all-cause mortality, cardiovascular disease, type 2 diabetes, and certain cancers, regardless of overall physical activity. Even individuals engaging in 60–75 minutes of moderate-intensity exercise per day remain at elevated risk if they sit for more than 8 hours daily [27]. These findings necessitate a paradigm shift in exercise prescription, which must now be structured along 2 complementary axes: (1) promoting regular physical activity and (2) reducing total sedentary time. Advice such as, "At work, stand and move for at least 5 minutes every hour," has become as essential as "Go to the gym 3 times a week." This integrated 24-hour approach better reflects the realities of modern health behavior and enhances preventive care in primary care practice [28].

Realistic exercise prescription strategies in primary care

Synergy with diet: Exercise alone is often insufficient to achieve clinically significant weight loss; however, when combined with dietary modification, it produces strong synergistic effects [29].

Aerobic exercise: Aerobic activity forms the foundation of any exercise prescription. Current guidelines recommend at least 150–300 minutes per week of moderate-intensity aerobic exercise (e.g., brisk walking, cycling) or 75 minutes per week of vigorous-intensity activity (e.g., running, spinning) [5].

Resistance training: Resistance exercise is essential for preserving muscle mass, maintaining basal metabolic rate, and improving body composition during weight reduction. Training targeting all major muscle groups should be performed 2 to 3 times per week [5]. The combination of aerobic and resistance training represents the optimal strategy for reducing body fat while maintaining lean mass [29,30].

In addition to structured exercise, modifying everyday movement patterns is equally critical. Reducing sedentary behavior yields substantial independent health benefits.

Breaking up sitting time: Advise patients to stand up, stretch, or walk briefly every 30 to 60 minutes [27]. This is particularly relevant in the Korean context, where prolonged working hours and heavy reliance on food delivery can contribute to extended sedentary periods.

Increasing daily activity: Encourage patients to integrate movement into daily routines, such as taking stairs instead of elevators, walking short distances, or standing while on the phone [31].

Environmental changes: Suggest environmental modifications that reduce sitting time, such as using height-adjustable desks, performing light stretches while watching television, or placing printers farther from desks to encourage movement [32].

Studies show that replacing just 30 minutes of sitting time per day with light physical activity can lower mortality risk, demonstrating how powerful this intervention can be [2,27].

Behavioral modification therapy prescription

If diet and exercise answer the question of what to do, behavioral therapy provides the answer to how to maintain it. Behavioral modification is a critical pillar of comprehensive obesity management, functioning as the bridge between knowledge and sustained action [10]. Numerous studies have shown that the effectiveness of behavioral therapy is directly proportional to its intensity—that is, the frequency and continuity of patient contact [33]. This counseling can be delivered through various effective modalities, including in-person, telephone, or digital platforms [8]. This reinforces the understanding that behavior change is not achieved through a single intervention but through continuous skill development, motivation, feedback, and accountability [34].

Realistic behavioral modification strategies for primary care

While providing intensive behavioral counseling may be challenging in busy primary care environments, its key principles can be effectively applied using concise, structured approaches.

The 6A's model: This evidence-based framework helps structure obesity counseling [5,12]: (1) Ask: for permission to discuss weight and explore the patient's concerns. (2) Assess: health risks, readiness for change, and barriers. (3) Advise: on clear, personalized behavior changes. (4) Agree: on realistic, achievable goals collaboratively with the patient. (5) Assist: in achieving goals by addressing barriers and building skills and confidence. (6) Arrange: for follow-up to provide ongoing support and adjust the plan.

Core behavioral strategies [33]: (1) Self-monitoring: Daily recording of food intake and physical activity, along with weekly weighing, is a strong predictor of success. A food logging app or a digital tool with a smartphone/wearable step count function can make this easier. (2) Goal-setting: Collaboratively set SMART goals (small, measurable, achievable, relevant, time-bound). (3) Stimulus control: Remove cues for unhealthy behaviors from the environment (e.g., not keeping processed snacks at home). (4) Problem-solving: Proactively identify potential barriers and brainstorm specific solutions.

Cognitive behavioral therapy: This therapeutic modality focuses on reshaping distorted cognitions about food, body image, and self-worth, thereby facilitating healthier behaviors. Meta-analyses indicate that cognitive behavioral therapy is more effective than standard behavioral therapy for individuals with simple obesity, while behavioral therapy may be superior in cases of obesity accompanied by binge-eating disorder [35,36].

These strategies reaffirm that obesity management extends far beyond information delivery. It represents a process of behavioral skill acquisition—one that takes into account the patient's psychological state, environmental context, and habitual behaviors.

To enhance the clinical applicability of the preceding sections, Table 1 provides a concise summary of practical, evidence-based strategies for dietary, exercise, and behavioral prescriptions in the primary care setting.

The synergistic effect of a comprehensive approach

A strong consensus from clinical guidelines and systematic reviews indicates that a comprehensive, multi-component lifestyle program integrating diet, physical activity, and behavioral therapy is the most effective first-line treatment for obesity [5,6,12,14,15]. These components interact synergistically: dietary therapy induces weight loss through calorie deficit, physical activity sustains weight reduction while improving metabolic parameters, and behavioral therapy provides the psychological and environmental framework necessary for long-term adherence.

In obesity management, patient-centered care is not merely a slogan but a clinical imperative. Recent studies targeting specific Korean populations have provided clinical insights into why a 1-size-fits-all lifestyle prescription is prone to failure, underscoring the importance of a tailored approach [1,3,37]. Key related studies are summarized in Table 2.

Barriers in the primary care setting and future directions

Despite the robust evidence supporting lifestyle interventions, numerous practical barriers impede their implementation in real-world primary care settings. These challenges operate at multiple levels—physician, patient, and healthcare system—and collectively complicate the delivery of effective obesity management [5,7,36,37].

Physician-level barriers

Time constraints

Comprehensive obesity counseling is difficult to conduct

Table 1. Summary of key studies on lifestyle interventions in specific Korean populations

Component	Foundational principle	Specific guidelines	Evidence and clinical considerations
1. Diet	Creating an energy deficit and establishing long-term eating habits	• Calorie restriction: Recommend reducing energy intake by 500–750 kcal per day. • Improving meal quality: Encourage reducing processed foods, sugary drinks, refined carbohydrates, and increasing intake of vegetables, whole grains, and lean proteins. • Protein intake: Ensure sufficient intake of high-quality protein to prevent muscle loss. • Portion control: Use visual cues such as smaller plates (especially considering Korean cultural practices including company dinners and food delivery). • Adjunctive strategy: Recommend drinking a glass of water before each meal to increase satiety.	• Best diet: The one the patient can adhere to long-term. • Low-carbohydrate diet: May lead to faster initial weight loss, but the long-term effect is similar to that of a low-fat diet.
2. Exercise and physical activity	A 2-pronged approach: promoting physical activity and reducing sedentary time	• Aerobic exercise: At least 150–300 minutes of moderate-intensity activity or 75 minutes of vigorous-intensity activity per week. • Resistance training: Perform exercises targeting all major muscle groups 2–3 times per week. • Breaking up sitting time: Stand up and walk or stretch for at least 5 minutes every 30–60 minutes. • Increasing daily activity: Encourage using stairs, walking short distances, and increasing overall daily movement.	• Weight loss: Exercise alone is insufficient; it has a synergistic effect when combined with diet. • Sedentary time: Is an independent risk factor that must be managed separately from total exercise volume.
3. Behavioral therapy	Providing continuous skill training, motivation, feedback, and accountability for sustained change	• 6A's model: Utilize the framework: ask, assess, advise, agree, assist, arrange (for follow-up). • Self-monitoring: Daily recording of food logs and physical activity, along with weekly weighing. • Goal-setting: Collaboratively set SMART goals (specific, measurable, achievable, relevant, time-bound) with the patient. • Stimulus control: Remove cues for unhealthy behaviors from the environment.	• Intensity: Treatment effectiveness is proportional to the frequency of counseling. • Cognitive behavioral therapy: Helps in modifying distorted thoughts about food/weight and should be tailored based on the patient's psychological state.

during brief consultations that must also address other pressing medical issues.

Lack of training

Many physicians report insufficient education in nutrition, exercise prescription, and behavioral counseling, which undermines their confidence in managing obesity effectively.

Weight bias and stigma

Both implicit and explicit biases toward patients with obesity can negatively influence physician–patient communication and treatment engagement.

Patient-level barriers

Low motivation and unrealistic expectations

Patients frequently experience low motivation due to repeated past failures or frustration when rapid weight loss does not occur.

Cost and accessibility

Healthy foods, fitness facilities, and structured weight-management programs can impose significant financial burdens.

Table 2. Summary of key studies on lifestyle interventions in specific Korean populations

Study journal	Study population	Key findings	Clinical implications
Song [1] (2025), Korean J Fam Med	Older adults with sarcopenic obesity	Sarcopenic obesity was more strongly associated with reduced stair-climbing ability and increased pain than simple obesity or sarcopenia alone, severely impairing quality of life.	A dual-goal approach is essential: reducing fat while preserving or strengthening muscle. Simple calorie restriction should be avoided. The prescription must include resistance training alongside aerobic exercise and a diet ensuring sufficient intake of high-quality protein.
Lee et al. [3] (2024), Korean J Fam Pract	Young adults (aged 19–39)	Common risk factors for both sexes included lower education and high stress. For men, marital status, low income, alcohol, and smoking were additional factors. For women, manual labor jobs or unemployment were additional risks.	Counseling must address underlying socioeconomic and lifestyle factors. The prescription should include education on stress management, the caloric impact of alcohol, and empathetic support that acknowledges the unique challenges young adults face in the Korean context.
Nah et al. [37] (2024), PLoS One	Patients with metabolic dysfunction-associated steatotic liver disease	Compared to a control group receiving generic information, the group with a tailored intervention showed significant reductions in liver fat and improvements in metabolic markers.	This demonstrates that a "personalized solution" considering individual habits, capabilities, and preferences increases treatment adherence and success. It highlights the importance of a multidisciplinary team approach involving dietitians and nurses.

Psychosocial factors

Chronic stress, emotional distress, and unsupportive social environments can hinder the adoption and maintenance of healthy habits.

Healthcare system-level barriers

Inadequate reimbursement

The lack of reimbursement for time-intensive obesity counseling discourages physicians from providing comprehensive care.

Fragmented care

The absence of coordinated referral systems linking physicians with dietitians, exercise physiologists, and psychologists limits access to integrated, holistic management.

These obstacles collectively illustrate a substantial "implementation gap" between evidence-based guidelines—which emphasize high-intensity, longitudinal interventions—and the practical constraints of routine primary care characterized by limited time and resources. Bridging this gap represents the foremost challenge to effective obesity management in real-world settings.

Leveraging digital health

Smartphone apps, wearable devices, and telehealth platforms can overcome time and space limitations to deliver scalable and cost-effective high-intensity behavioral therapy [6,34]. For instance, digital health models can use self-monitoring tools (e.g., food logs, step counters) to collect data, provide automated personalized feedback, and support hybrid care systems where patients receive ongoing remote guidance from dietitians or health coaches between physician visits.

Enhancing education and training

Comprehensive obesity medicine education must be integrated into medical school curricula and residency training to ensure that future physicians are equipped with the necessary confidence and skills [38,39].

Policy and reimbursement reform

Establishing proper reimbursement systems for obesity counseling and team-based care is essential. In addition, public policies aimed at transforming obesogenic environments, such as urban designs that encourage physical activity, are vital for achieving sustained population-level impact [38,39].

In conclusion, the future of primary care–based obesity management should not involve asking physicians to "do more with less," but rather a fundamental redesign of the care model itself. Physicians should serve not merely as treatment providers but as coordinators or quarterbacks who orchestrate multidisciplinary human and technological resources. Realizing this vision requires systemic reform across clinical workflows, education, and reimbursement structures.

Conclusion

Obesity is a multifactorial chronic disease that extends far beyond individual responsibility, and its growing prevalence represents a global public health emergency. Nevertheless, it remains a manageable condition within primary care when approached through systematic, evidence-based strategies. The most effective

management model is a sustained, multi-component intervention integrating dietary modification with appropriate caloric restriction, exercise combining aerobic and resistance training, and intensive behavioral counseling to promote long-term adherence. Importantly, reducing sedentary time should be recognized as an independent therapeutic objective, distinct from total exercise duration.

Within this framework, primary care physicians play an indispensable role in the long-term management of obesity and related chronic diseases. Their continuous, enduring relationships with patients enable early detection of weight-related comorbidities, consistent counseling, and individualized interventions that address both medical and psychosocial determinants of health. Through an integrated, patient-centered approach, primary care facilitates coordinated management of obesity alongside conditions such as diabetes, hypertension, and dyslipidemia. This continuity and comprehensiveness make primary care not only the most accessible but also the most efficient and sustainable foundation for effective obesity treatment.

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Conceptualization: JHJ, YIH. Methodology: JHJ, YIH. Formal analysis/validation: JHJ, YIH. Project administration: JHJ, YIH. Writing–original draft: JHJ. Writing–review & editing: JHJ, YIH.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

This study did not generate any new data. All sources for the information presented are cited and listed in the references.

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Supplementary materials

None.

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Lifestyle prescriptions for diabetes management in primary care: a narrative review

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Diabetes mellitus is a complex chronic disease with a rapidly increasing global prevalence. For this condition, non-pharmacological lifestyle modification is as important as pharmacological treatment. This review aims to comprehensively examine lifestyle prescriptions for diabetes across multiple domains to integrate current insights and understanding. In medical nutrition therapy, which is central to diabetes treatment and management, excessive carbohydrate intake should be restricted, while individualized consumption of high-quality carbohydrates, protein, and unsaturated fatty acids is recommended. Intake of added sugars and sodium should also be limited. Physical activity should similarly be tailored to the individual, with a combination of aerobic exercise and resistance training recommended. Careful consideration of hypoglycemia risk and diabetes complications is essential. Additional strategies include limitations on uninterrupted sedentary time to less than 30 minutes, maintenance of a healthy body weight, smoking cessation, alcohol abstinence, sleep health improvements, and attention to psychosocial care. In primary care settings, patient-specific assessment, multidisciplinary lifestyle prescriptions, and education to support behavior modification are expected to play a pivotal role in the treatment and management of diabetes.

Keywords: Diabetes mellitus management; Healthy lifestyle; Nutrition therapy; Physical activity; Primary health care

Introduction

Background

Diabetes mellitus is among the chronic diseases with the most rapidly increasing global prevalence rates, with this trend driven by population aging, reduced physical activity, and rising rates of obesity [1]. According to the International Diabetes Federation, an estimated 537 million adults aged 20–70 years currently live with diabetes, and this number is projected to reach 783 million by 2045 [1]. In Korea, the Diabetes Fact Sheet 2024 reported that the prevalence of diabetes among adults aged ≥30 years increased from 11.8% in 2012 to 16.7% in 2020, corresponding to approximately 5.33 million people living with diabetes [2]. Beyond hyperglycemia, diabetes leads to a wide range of complications, including cardiovascular disease, neuropathy, and retinopathy, which substantially impair patients' quality of life [3] and impose a significant socioeconomic burden due to escalating healthcare costs. Therefore, systematic strategies for diabetes treatment and management are urgently needed.

Diabetes is a complex metabolic disorder that arises from an interaction between genetic predisposition and lifestyle-related factors [1]. Glycemic control is closely linked to behaviors such as diet and physical activity, making lifestyle modification indispensable in diabetes treatment and management. Lifestyle interventions encompass medical nutrition therapy (MNT), exercise therapy, and behavioral approaches, and evidence indicates that optimal diabetes control is achieved when pharmacological treatment is combined with dietary and exercise interventions [3]. The 2025 guidelines of both the American Diabetes Association (ADA) [4] and the Korean Diabetes Association (KDA) [5] emphasize the importance of comprehensive multidisciplinary care for patients with diabetes, involving primary and specialty care physicians, nurses, registered dietitian nutritionists, exercise specialists, pharmacists, dentists, podiatrists, behavioral health professionals, and diabetes care and education specialists.

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Objectives

This review aims to comprehensively examine lifestyle prescriptions for the treatment of diabetes in primary care, thus integrating current insights and understanding in this field.

Ethics statement

This is a literature-based study; therefore, neither institutional review board approval nor informed consent was required.

Medical nutrition therapy

MNT plays a central role in the treatment and management of diabetes [6]. Major clinical guidelines, including the 2005 ADA recommendations, have emphasized the importance of MNT (Table 1). The 2025 KDA guidelines further underscore the need for referral to registered dietitian nutritionists, particularly for patients with diabetes who also have comorbid conditions such as hypertension, dyslipidemia, heart failure, gastrointestinal disorders, chronic kidney disease (CKD), pregnancy-related nutritional issues, pediatric growth concerns, and obesity [5].

Numerous studies have consistently shown that individualized MNT provided by registered dietitian nutritionists effectively improves a variety of health outcomes in patients with diabetes, including glycated hemoglobin (HbA1c), body weight, waist circumference, low-density lipoprotein cholesterol, blood pressure, and dietary patterns [7]. Compared to pharmacologic treatment, MNT is associated with fewer adverse effects, is cost-effective, and is reportedly more effective in the long-term prevention of diabetes-related complications [4].

Dietary patterns and meal planning

No single standardized dietary pattern can be universally applied to patients with diabetes; therefore, meal planning should always be individualized [4]. Evidence supports several dietary patterns that improve glycemic control, facilitate weight reduction, and lower cardiovascular risk, including the Mediterranean, vegetarian, low-fat, low-carbohydrate, and Dietary Approaches to Stop Hypertension (DASH) diets [7]. Current diabetes care guidelines recommend incorporating these diverse dietary approaches into

Table 1. Recommendations for medical nutrition therapy in diabetes

Items	Recommendations
Provision of medical nutrition therapy	(1) Individualized medical nutrition therapy programs are essential for achieving therapeutic goals. (2) Such programs should be delivered by registered dietitian nutritionists. (3) Recommended target groups include patients with type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus.
Multicomponent intervention	(1) Medical nutrition therapy should be delivered in combination with physical activity and behavioral interventions.
Recommendation of evidence-based healthy dietary patterns	(1) Individualized meal planning is recommended for patients with diabetes. (2) Insufficient evidence is available to support a specific macronutrient distribution. (3) Guidance should emphasize non-starchy vegetables, fruits, legumes, lean protein, whole grains, nuts, and seeds, while minimizing red meat, sugar-sweetened beverages, and processed foods. (4) Reduction of carbohydrate intake may be beneficial for glycemic control in patients with diabetes and can be applied within personalized dietary patterns.
Restriction of sodium intake and high-salt diets	(1) Sodium intake should be limited to less than 2,300 mg per day, which should be achieved primarily through the reduction of processed food consumption.
Caution with micronutrient supplements, herbal medicine, and other complementary products	(1) Healthcare providers should assess supplement use and provide counseling when necessary. (2) Unless deficiencies are present, the benefits of micronutrient supplementation in patients with diabetes remain unclear; similarly, the benefits of herbal medicine and other dietary products are uncertain.
Avoidance of excessive alcohol consumption	(1) Patients with diabetes should preferably avoid alcohol consumption; if consumed, recommended limits should be followed. (2) Patients should be educated regarding the risk of hypoglycemia following alcohol intake, and blood glucose monitoring should be emphasized, particularly for those using insulin or insulin secretagogues.
Restriction of added sugars and non-nutritive sweeteners	(1) Sugar-sweetened beverages should be limited, and the consumption of water without non-nutritive sweeteners is recommended. (2) Non-nutritive sweeteners may be used in the short term to reduce calorie and carbohydrate intake; however, long-term use is not recommended.

The table summarizes and revises the medical nutrition therapy recommendations from the 2025 American Diabetes Association guidelines [4].

MNT as appropriate [4]. Despite their differences, these patterns share common features: an emphasis on non-starchy vegetables, fresh fruits, legumes, whole grains, nuts, seeds, and low-fat dairy products, alongside reduced consumption of red meat, beverages sweetened with sugar, sweets, refined grains, and processed or ultra-processed foods [4].

Meal patterns

Intermittent fasting, including time-restricted eating, has been reported to improve glycemic control and promote weight reduction in patients with type 2 diabetes [4]. Accordingly, since its 2023 guidelines, the ADA has included intermittent fasting among dietary patterns that may be used in diabetes management [4]. However, unlike the Mediterranean, vegetarian, low-fat, low-carbohydrate, and DASH diets, the long-term benefits of intermittent fasting—such as reductions in mortality—have not yet been established, and concerns persist regarding hypoglycemia from prolonged fasting and compensatory binge eating [4]. Continuous monitoring is particularly warranted for patients using glucose-lowering agents with a high risk of hypoglycemia. In addition, potential adverse effects such as eating disorders, gastrointestinal dysfunction, and alterations in sex hormone levels necessitate caution [8]. Intermittent fasting is contraindicated in children under 12 years of age, adults over 70 years, patients with a history of eating disorders, those with a body mass index <18.5 kg/m^2, and women who are pregnant or breastfeeding [8].

Macronutrients

There is no ideal ratio of calories from carbohydrates, protein, and fat for patients with diabetes. Rather, macronutrient distribution should be determined through an individualized assessment of the patient's current dietary habits, preferences, and metabolic goals [4].

Carbohydrates

For glycemic control and management, excessive carbohydrate intake should be restricted, while dietary strategies must be individualized to therapeutic goals and patient preferences. A 2022 meta-analysis showed that reducing carbohydrate intake improves glycemic outcomes in patients with diabetes, with low-carbohydrate diets (26%–45% of total energy from carbohydrates) benefiting both glycemic control and weight reduction [9]. However, very low-carbohydrate diets (<10% of total energy from carbohydrates) may increase the risk of essential nutrient deficiencies, hypoglycemia, and ketoacidosis [10]. Caution is required in patients receiving sodium–glucose cotransporter-2 (SGLT-2) inhibitors due to the elevated risk of ketoacidosis [11]. Moreover, restricting carbohydrates without reducing total energy intake often increases consumption of protein or fat. When these macronutrients are derived primarily from animal sources, a higher intake of saturated fatty acids may elevate cardiovascular risk [11]. Therefore, while reducing total carbohydrate intake can be beneficial for glycemic improvement, extreme restriction is not recommended for patients at risk of malnutrition, older adults, pregnant or lactating women, or those taking SGLT-2 inhibitors. Equally important is replacing reduced carbohydrates with appropriate sources of protein and fat.

In addition to the amount of carbohydrate intake, it is important to select carbohydrate sources that are high-quality, minimally processed, nutrient dense, and rich in dietary fiber [4]. Adequate qualitative intake of carbohydrates should be achieved through consumption of fiber-rich whole grains, legumes, vegetables, fresh fruits, and dairy products such as milk and yogurt. In its 2023 recommendations for carbohydrate intake, the World Health Organization (WHO) emphasized not only the proportion but also the quality of carbohydrates, recommending fiber-rich whole grains, legumes, vegetables, and fresh fruits instead of refined carbohydrates [12]. For patients with kidney disease, plant-based diets rich in such foods generally do not need to be restricted, as their phosphorus bioavailability is lower than that of animal-based foods; these diets also improve the sodium-to-potassium ratio while reducing cardiovascular risk. However, in cases of severely impaired renal function or when specific medications are used, caution is warranted due to a risk of electrolyte disturbances such as hyperkalemia [12].

The glycemic index (GI) classifies carbohydrates based on the glycemic response following food consumption, whereas the glycemic load accounts for both the GI and the amount of carbohydrate consumed. Studies in patients with diabetes have shown heterogeneous results due to variability in definitions; however, a recent large-scale meta-analysis of cohort studies reported that higher intake of high-GI foods was associated with increased incidence of type 2 diabetes (hazard ratio [HR], 1.27; 95% confidence interval [CI], 1.21–1.34), overall cardiovascular disease (HR, 1.15; 95% CI, 1.11–1.19), diabetes-related cancers (HR, 1.05; 95% CI, 1.02–1.08), and all-cause mortality (HR, 1.08; 95% CI, 1.05–1.12) [13]. For patients with type 1 or type 2 diabetes who administer insulin at mealtimes, ongoing and comprehensive education on nutritional composition and carbohydrate intake is essential. Regular education should emphasize the relationship between carbohydrate consumption and insulin requirements, particularly when meal timing or carbohydrate quantity is inconsistent. In addition, fat and protein intake can influence postprandial glycemic responses—both early and delayed—in a dose-de-

pendent manner [14]. Therefore, when adjusting insulin doses for high-fat, high-protein mixed meals, clinicians should exercise caution to mitigate the risk of delayed hyperglycemia [7].

Added sugars and free sugars are primarily consumed via sugar-sweetened beverages (SSBs), which have been consistently associated with increased diabetes risk. A recent meta-analysis reported that each additional daily serving of SSBs was associated with a 20% higher relative risk of type 2 diabetes and an 8% increase in all-cause mortality [15]. Accordingly, major diabetes care guidelines recommend limiting SSB intake as much as possible to minimize added sugar consumption [10]. As the detrimental effects of SSBs have become increasingly recognized, consumption of artificially sweetened beverages (ASBs) has risen. While some studies have shown significant benefits for weight reduction, no improvement in glycemic outcomes has been observed [16]. Current evidence regarding the metabolic effects and potential risks of ASBs is still insufficient. The American Heart Association permits temporary substitution of ASBs for individuals with high SSB consumption but ultimately recommends reducing intake of both SSBs and ASBs [17]. Excessive consumption of artificial sweeteners should therefore be approached with caution. Additionally, even natural sources such as fruit-derived concentrates are classified as added sugars. When consumed in liquid form, these products provide limited satiety, making portion control difficult and potentially leading to excessive intake with marked increases in postprandial glucose levels [18].

Protein

Protein restriction is generally not necessary in patients with diabetes, although both excessive intake and overly strict restriction should be avoided in those with kidney disease. Historically, protein restriction was suggested for patients with diabetes-related albuminuria or CKD to delay disease progression; however, many studies have reported insufficient evidence to support this recommendation. Current major diabetes care guidelines advise that patients with diabetic kidney disease (DKD) who are not on dialysis should consume protein at levels similar to the general population while avoiding excessive intake (>20% of total energy or >1.3 g/kg/day), as this may exacerbate albuminuria and accelerate renal function decline. Conversely, in patients with DKD receiving dialysis, protein restriction may worsen malnutrition due to energy loss; thus, a higher protein intake (1.0–1.2 g/kg/day) is recommended [4]. Although evidence remains limited, an increasing number of studies suggest that substituting plant-based for animal-based protein may improve HbA1c, fasting glucose, and serum cholesterol levels. A prospective observational study also demonstrated that individuals with higher consumption of plant-based foods and lower consumption of animal-based foods had a lower risk of developing diabetes [19].

A recent meta-analysis reported that 18% of patients with type 2 diabetes have concomitant sarcopenia, with higher HbA1c identified as a risk factor (odds ratio [OR], 1.16; 95% CI, 1.09–1.24) [20]. Concerns have been raised that weight reduction strategies such as glucagon-like peptide 1 (GLP-1) receptor agonists, dual agonists (glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonists), and bariatric surgery may increase the risk of malnutrition and sarcopenia in certain patients with diabetes. This risk is particularly elevated in patients with comorbid cardiovascular, renal, or hepatic disease and in those with obesity [21]. Therefore, in primary care, patients with diabetes who experience rapid or significant weight loss should be advised to engage in resistance training, ensure adequate protein intake, and undergo screening for sarcopenia [4].

Fat

Patients with diabetes are advised to follow general population guidelines regarding saturated fat, cholesterol, and trans fat intake [4]. Foods high in saturated and trans fatty acids should be replaced with those rich in unsaturated fatty acids. A systematic review showed that replacing saturated or trans fats with unsaturated fatty acids improves glycemic outcomes and reduces cardiovascular risk [22]. According to the 2022 Korean Society of Lipid and Atherosclerosis dyslipidemia guidelines [23], saturated fat intake should be limited to <7% of total energy and replaced with unsaturated fats whenever possible, while trans fat intake should be avoided. In patients with hypercholesterolemia, dietary cholesterol should be restricted to <300 mg/day.

Evidence is insufficient to support the benefit of unsaturated fatty acid supplementation for glycemic control or cardiovascular prevention, and the safety of excessive supplementation remains unclear [7].

Sodium restriction

The 2025 ADA guidelines and the 2020 Korean Dietary Reference Intakes recommend limiting sodium intake to ≤2,300 mg per day [4,24]. Numerous studies have reported that sodium intake affects glucose metabolism and glomerular filtration rate; therefore, sodium restriction is suggested as a useful strategy for patients with diabetes, regardless of the presence of kidney disease [25]. Given that hypertension and cardiovascular disease are major comorbidities of diabetes, reducing sodium intake may help lower blood pressure and decrease the risk of cardiovascular disease and diabetes-related complications. A meta-analysis of randomized controlled trials (RCTs) in patients with type 1 and type

2 diabetes demonstrated that sodium reduction effectively improved blood pressure [26]. Furthermore, an RCT in patients with type 2 diabetes showed that reducing sodium intake to an average of 2,310 mg/day in conjunction with the DASH diet improved blood pressure and other cardiovascular risk factors [27]. The most effective strategies for sodium restriction include reducing consumption of processed and ultra-processed foods—the main sources of dietary sodium—and avoiding the addition of salt during cooking or at the table [4].

Micronutrients

Vitamins and minerals are essential nutrients required for bodily structure and the regulation of various physiological processes; however, supplementation is generally not recommended for glycemic improvement in patients with diabetes [4]. A meta-analysis suggested that vitamin D supplementation, compared with other supplements, may provide some benefit in improving HbA1c, fasting glucose, and homeostatic model assessment for insulin resistance; however, this evidence remains insufficient [28]. Unless deficiencies are present, the benefits of micronutrient supplementation in diabetes are unclear [7]. Similarly, evidence supporting the use of herbal products and food-derived agents—such as aloe vera, cinnamon, turmeric, Jerusalem artichoke, and bitter melon—for glycemic control remains inadequate [7]. Nonetheless, supplementation may be considered when deficiencies are identified or highly likely, such as in pregnant or lactating women, older adults, vegetarians, or individuals on very-low-calorie or low-carbohydrate diets. Furthermore, long-term use of metformin has been associated with vitamin B12 deficiency; therefore, in patients receiving prolonged metformin therapy who present with unexplained anemia or peripheral neuropathy, measurement of vitamin B12 levels is recommended [29].

Non-nutritive sweeteners

The U.S. Food and Drug Administration has approved several non-nutritive sweeteners (NNS) for consumption by both the general population and patients with diabetes [7]. For patients with diabetes who regularly consume sugar-sweetened foods or beverages (e.g., regular soft drinks, juice drinks, or foods sweetened with cane sugar or high-fructose corn syrup), NNS can serve as appropriate substitutes for nutritive sweeteners such as sugar, honey, or agave syrup [30]. Non-nutritive sweeteners appear to have no significant impact on glycemic control and, when not offset by increased caloric intake from other sources, may help reduce total energy and carbohydrate intake [7].

Physical activity

Physical activity plays a pivotal role in glycemic management and the prevention of complications, particularly in patients with type 2 diabetes [4]. Mechanistically, exercise acutely increases glucose uptake by skeletal muscle; over the long term, it improves glucose metabolism and alters body composition to enhance whole-body insulin sensitivity. These improvements are not only attributable to weight reduction but also relate to reduced visceral adiposity, increased muscle mass, improved lipid metabolism, reduced systemic inflammation, and enhanced endothelial function [31]. Consequently, regular physical activity improves glycemic control, reduces cardiovascular risk, and contributes to weight loss [31].

According to the 2025 KDA guidelines, the type, frequency, duration, and intensity of exercise should be individualized based on age, physical capacity, and comorbidities (including microvascular complications), and referral to exercise specialists for exercise prescription is recommended [5]. Before initiating an exercise program, patients should be evaluated for the presence of cardiovascular disease and microvascular complications, and potential contraindications should be identified. More detailed assessments may be required for patients with established diabetes-related complications. In high-risk patients, it is advisable to begin with short sessions of low-intensity exercise and gradually increase the duration and intensity.

Additionally, clinicians should assess for conditions that may contraindicate certain types of exercise or increase the risk of injury. These include uncontrolled hypertension, untreated proliferative retinopathy, autonomic neuropathy, orthostatic hypotension, peripheral neuropathy, balance disorders, diabetic foot ulcers, and a history of Charcot foot [5].

Frequency and type of physical activity

According to the 2025 ADA guidelines, patients with diabetes are recommended to engage in at least 150 minutes per week of aerobic exercise at moderate or higher intensity, spread over a minimum of 3 days per week, with no more than 2 consecutive days without activity, given that the effects of aerobic exercise on insulin sensitivity persist for 24–72 hours [4]. The goal should be a gradual increase in exercise intensity, frequency, and duration over time.

High-intensity interval training (HIIT)—defined as performing aerobic exercise at 65%–90% of peak oxygen consumption (VO_2peak) or 75%–95% of maximal heart rate for intervals lasting 10 seconds to 4 minutes, interspersed with 12 seconds to 5 minutes of active or passive recovery—has been shown to induce sig-

nificant physiological and metabolic adaptations in both type 1 and type 2 diabetes [32]. However, HIIT may cause transient post-exercise hyperglycemia, necessitating bolus insulin correction in patients with type 1 diabetes, while blood glucose monitoring is recommended when initiating HIIT in patients with type 2 diabetes [32].

Resistance exercise is recommended at least twice per week. High-load resistance exercise (e.g., dumbbells, weight machines) may be particularly effective for improving glycemic control and muscle strength; however, resistance exercise of all intensities has been shown to benefit the maintenance of muscle strength, balance, and functional capacity [4]. Notably, resistance exercise is not associated with an increased risk of cardiac ischemia or stroke compared with aerobic exercise and is therefore recommended even in middle-aged and older adults with diabetes [4].

Combining aerobic and resistance exercise provides additional benefits for glycemic control and is therefore strongly recommended [33]. In older adults with diabetes, flexibility and balance exercises are also important for maintaining joint mobility, muscle strength, and postural stability. Activities such as yoga and tai chi can be valuable adjuncts in this regard [34].

Hypoglycemia and hyperglycemia

In patients treated with insulin and/or insulin secretagogues, exercise-induced hypoglycemia can occur if medication dosages or carbohydrate intake are not adjusted before, during, and after physical activity. For such patients, carbohydrate supplementation may be necessary when pre-exercise blood glucose is <90 mg/dL [35]. In contrast, hypoglycemia is uncommon in patients not using insulin or secretagogues, and routine preventive measures are generally unnecessary.

High-intensity exercise should be avoided in the presence of diabetic ketoacidosis. However, in the absence of ketoacidosis and when overall clinical status is stable, exercise does not need to be postponed or contraindicated even in the setting of hyperglycemia [36]. Therefore, patients with diabetes should be trained either in self-monitoring of blood glucose before and after exercise or in the use of continuous glucose monitoring. They also should understand the impact of exercise on glycemia, including both immediate and delayed effects according to exercise intensity and duration [36].

Exercise in the presence of microvascular complications

A meta-analysis reported that higher levels of physical activity were associated with reduced risks of cardiovascular disease, mortality, and microvascular complications compared with lower activity levels [37]. Furthermore, a dose–response meta-analysis showed that even relatively low levels of physical activity can help reduce the risk of diabetes-related complications [37].

Diabetic retinopathy

In patients with proliferative diabetic retinopathy or severe nonproliferative diabetic retinopathy, vigorous aerobic or resistance exercise is not recommended because of the risk of vitreous hemorrhage and retinal detachment [36]. Consultation with an ophthalmologist may be appropriate before initiating high-intensity exercise.

Diabetic peripheral neuropathy

Reduced pain sensation and elevated pain thresholds in peripheral neuropathy may increase the risk of skin injury, infection, and Charcot joint destruction during certain activities. Careful assessment of motor and proprioceptive function is therefore essential, particularly in patients with advanced neuropathy. When appropriate footwear is used, moderate-intensity walking does not appear to increase the risk of foot ulceration or recurrent ulcers in patients with diabetic peripheral neuropathy [38]. Moreover, 150 minutes per week of moderate-intensity exercise has been shown to improve clinical outcomes in patients with prediabetic neuropathy [39]. Accordingly, all patients with peripheral neuropathy should wear protective footwear and perform daily foot inspections for early detection of lesions. If foot injury or open wounds are present, weight-bearing exercise should be limited and replaced with non–weight-bearing activities.

Diabetic autonomic neuropathy

Autonomic neuropathy can increase the risk of exercise-related adverse events through mechanisms such as impaired cardiovascular responses, orthostatic hypotension, impaired thermoregulation, night vision deficits from pupillary dysfunction, and heightened susceptibility to hypoglycemia [40]. Cardiovascular autonomic neuropathy, in particular, is an independent risk factor for cardiovascular mortality and silent myocardial ischemia [40]. Therefore, a cardiac evaluation is recommended before patients with diabetic autonomic neuropathy initiate exercise beyond habitual intensity.

Chronic kidney disease

Physical activity can acutely increase urinary albumin excretion [4]; however, no evidence suggests that vigorous exercise accelerates CKD progression, and no specific exercise restrictions are generally required for patients with CKD [36].

Sedentary behavior

Prolonged sedentary behavior is associated with adverse health outcomes, including increased risk of diabetes, higher cardiovascular risk, and elevated mortality [41]. It is therefore recommended to interrupt sitting time at least every 30 minutes by standing, walking, or engaging in light activity. Participation in leisure-time physical activities and avoidance of prolonged sedentary behavior can help prevent type 2 diabetes and improve glycemic control in patients with diabetes [4]. Recent studies have shown that, in patients with type 2 diabetes and low habitual activity levels, interrupting sedentary time with 3 minutes of light walking or resistance exercise every 30 minutes improves glycemic and insulin-related markers [42]. Furthermore, a meta-analysis demonstrated that interventions targeting interruptions of sedentary behavior contribute to improvements in 24-hour glucose levels and postprandial glycemia [42].

Weight control

Weight management is a critical component of care for patients with diabetes who have overweight or obesity. In patients with type 2 diabetes and concomitant overweight or obesity, at least a 5% reduction in body weight is required to achieve benefits in glycemic, lipid, and blood pressure control [4]. The 2025 KDA guidelines recommend that patients with diabetes who have overweight or obesity reduce their weight by ≥5% and maintain this reduction through MNT (including caloric restriction) and appropriate physical activity [5]. Greater weight loss has been associated with further improvements in glycemia, blood pressure, and lipid profiles, as well as reductions in cardiovascular disease incidence and mortality [43]. In addition, for patients with type 2 diabetes and obesity, the guidelines recommend considering anti-obesity pharmacotherapy as an adjunct to lifestyle modification for weight reduction [5].

Alcohol abstinence

In patients with diabetes, alcohol intake should be limited to the same daily amounts recommended for the general population; however, because alcohol reduces hepatic gluconeogenesis and glucose output, the risk of hypoglycemia is increased [44]. Accordingly, the 2025 KDA guidelines recommend abstinence whenever possible [5]. For patients without diabetes-related complications or liver disease and with well-controlled glycemia, complete abstinence may not be necessary, and the intake limits used for the general population may be applied. The WHO recommends restricting alcohol consumption to no more than 1 drink per day for women and 2 drinks per day for men (based on standard drink sizes for each beverage) and abstaining from alcohol on at least 2 days per week [44]. Systematic reviews have suggested that, compared with abstainers, moderate alcohol consumption (up to 2 drinks per day for men and 1–1.5 drinks per day for women) is associated with a reduced risk of coronary artery disease and type 2 diabetes [45]. In contrast, a meta-analysis reported that excessive alcohol intake—≥50 g/day in women and ≥60 g/day in men—increases the risk of type 2 diabetes [46]. For patients treated with insulin or insulin secretagogues, alcohol consumption without adequate food intake may precipitate hypoglycemia [4]. To prevent this, alcohol should always be consumed with meals, and patients should monitor blood glucose frequently before and after drinking to minimize the risk of hypoglycemia [4].

Smoking cessation

The causal relationship between smoking and diabetes is well established [4]. Smoking contributes to the development of type 2 diabetes, whereas smoking cessation significantly reduces this risk over the long term [47]. Among patients with diabetes, both active smoking and exposure to secondhand smoke are associated with increased risks of macrovascular complications (including cardiovascular and peripheral vascular disease), microvascular complications (such as nephropathy and retinopathy), poor glycemic control, and premature mortality compared with nonsmokers [47]. Accordingly, the 2025 ADA guidelines recommend that all patients with diabetes abstain from tobacco use, including cigarettes, other tobacco products, and electronic cigarettes [4]. Systematic assessment of smoking status at every clinical encounter is a key strategy for prevention and cessation. In adults with diabetes, counseling combined with pharmacotherapy constitutes the standard of care, and the 2020 American Thoracic Society guidelines recommend varenicline as first-line pharmacologic therapy [48].

Sleep health

The relationship between sleep disturbances and diabetes is complex. Sleep disorders are recognized risk factors for the development of type 2 diabetes, and many patients with diabetes experience poor sleep quality or sleep disruption [49]. Common sleep disorders include obstructive sleep apnea, insomnia, and restless legs syndrome, all of which have been linked to microvascular and macrovascular complications [49]. Therefore, screening for sleep health should be considered in patients with diabetes, encompass-

ing symptoms of sleep disorders, sleep disruption related to diabetes symptoms or management, and sleep-related concerns [4]. Patients with severe sleep disturbances should be referred to sleep medicine specialists and behavioral health professionals, with a collaborative approach involving the diabetes care team [4]. In addition, patient education on healthy sleep practices and routines is essential [4]. Recommended strategies for improving sleep hygiene include maintaining consistent bedtimes and wake times; ensuring a dark, quiet environment; optimizing bedroom temperature and humidity; establishing a bedtime routine; silencing or turning off electronic devices (excluding diabetes management devices); engaging in daytime physical activity; limiting daytime naps; restricting caffeine and nicotine in the evening; and avoiding stimulating foods (e.g., spicy meals) and alcohol at night [4].

Psychosocial care

Studies indicate that clinically significant behavioral health disorders, such as depression and anxiety, are substantially more prevalent among patients with diabetes than among those without the disease. These conditions negatively affect self-management, contribute to glycemic instability, and are associated with increased complications and mortality [50]. Accordingly, the 2025 ADA guidelines recommend that all patients with diabetes receive psychosocial care, which should be integrated into routine medical care and delivered by trained health professionals using collaborative, patient-centered, and culturally appropriate approaches [4]. Screening protocols for psychosocial issues—including diabetes distress, depression, anxiety, fear of hypoglycemia, and disordered eating behaviors—should be implemented at least annually as well as when changes occur in disease status, treatment, or life circumstances. These include times such as diagnosis, routine follow-up visits, hospitalization, the onset of new complications, the transition from pediatric to adult care, treatment changes, poor glycemic control, reduced quality of life, or difficulties with self-management [4].

Referral to behavioral health specialists experienced in diabetes care, or to other trained healthcare professionals, should be made when necessary for further assessment and treatment of diabetes distress, depression, suicidal ideation, anxiety, fear of hypoglycemia, disordered eating, and cognitive dysfunction [4]. Evidence-based interventions include cognitive behavioral therapy and mindfulness-based therapies, and ongoing monitoring with individualized management is essential even after intervention [4]. Behavioral interventions may be delivered through multiple modalities, including face-to-face visits, digital health platforms, and group-based diabetes education or care programs [4].

Conclusion

Diabetes is a heterogeneous condition that requires individualized management strategies. Given its variability in pathophysiology and clinical presentation, lifestyle interventions should be tailored through multidisciplinary care, with clear goals and structured follow-up to support long-term adherence. Accordingly, lifestyle prescription in primary care represents a cornerstone of effective diabetes management.

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Authors' contribution

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Supplementary materials

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Lifestyle interventions for hypertension management in primary care: a narrative review

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Hypertension is one of the leading chronic diseases globally and a major contributor to cardiovascular morbidity and mortality. Despite advances in pharmacological therapy, medication alone remains limited in achieving optimal control. This review synthesizes recent hypertension management guidelines, including those from the European Society of Cardiology (ESC, 2024), American Heart Association/American College of Cardiology (AHA/ACC, 2025), Taiwan Society of Cardiology/Hypertension Society (2022), and Korean Society of Hypertension (KSH, 2018). All guidelines consistently emphasize sodium restriction, weight reduction, regular exercise, moderation of alcohol intake, smoking cessation, and adoption of healthy dietary patterns such as the Dietary Approaches to Stop Hypertension, Mediterranean, or culturally adapted diets. The ESC 2024 guideline elevates lifestyle modification to Class I, Level A, specifying targets for sodium (<2 g/day) and potassium (≥3.5 g/day). The AHA/ACC 2025 guideline provides quantitative estimates, reporting approximately 1/1 mm Hg blood pressure reduction per kilogram of weight loss, and incorporates newer strategies such as glucagon-like peptide-1 receptor agonists and bariatric surgery when lifestyle measures alone are insufficient. Taiwan's 2022 guideline frames recommendations under the S-ABCDE (sodium restriction, alcohol limitation, body weight reduction, cigarette cessation, diet adaptation, exercise adoption) mnemonic and uniquely includes genetic factors such as *ALDH2* polymorphisms. The KSH 2018 guideline emphasizes salt restriction (<6 g/day), maintaining a body mass index <25 kg/m^2, and adherence to traditional Korean diets. Lifestyle modification remains the cornerstone of hypertension prevention and management, particularly in primary care. Future directions should focus on integrating these approaches with pharmacotherapy, digital health strategies, and personalized prescriptions.

Keywords: Hypertension; Life style; Diet; DASH; Sodium; Guideline

Introduction

Hypertension is among the most prevalent chronic diseases worldwide and a leading cause of cardiovascular morbidity and mortality [1]. The current definition of hypertension is based on the blood pressure (BP) threshold at which pharmacological treatment has been shown to be effective in randomized clinical trials. Accordingly, the Korean Society of Hypertension (KSH) defines hypertension as a systolic blood pressure (SBP) ≥140 mm Hg or a diastolic blood pressure (DBP) ≥90 mm Hg, further classified into grade 1 and grade 2 hypertension based on severity and office BP measurements [2]. Normal BP is defined as SBP <120 mm Hg and DBP <80 mm Hg, which is associated with the lowest cardiovascular risk and serves as the reference category when evaluating the risks of elevated BP values [3,4].

In Korea, the burden of hypertension continues to rise. According to the KSH fact sheet 2023, the prevalence of hypertension among adults aged ≥20 years is approximately 28%, representing nearly 12.3 million individuals. Among those with hypertension, awareness was 74.1%, treatment 70.3%, and control 56.0% [5].

Despite advances in pharmacological therapy, antihypertensive medication alone is insufficient for optimal BP control and long-term complication prevention. Consequently, lifestyle modification has been consistently emphasized as the cornerstone of both prevention and management of hypertension [2,5-10]. The KSH guidelines explicitly recommend lifestyle modification alongside pharmacotherapy, with the 2018 update highlighting that interventions such as salt restriction and weight loss can lower BP by amounts comparable to a single antihypertensive drug [2]. International guidelines similarly emphasize that lifestyle modification

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should continue even when medications are prescribed. Among various interventions, the Dietary Approaches to Stop Hypertension (DASH) diet has demonstrated robust effects, reducing SBP by about 11 mm Hg and DBP by 6 mm Hg in controlled studies—comparable to first-line antihypertensive agents [11]. Korean observational evidence supports these findings. In a primary care cohort study, reduced salt intake and increased physical activity were significantly associated with improved BP control, whereas failure to implement these behaviors nearly doubled the likelihood of uncontrolled hypertension [12]. Consistent with global evidence, additional studies in Korean populations confirm that reducing sedentary behavior and engaging in regular physical activity are crucial for lowering BP [13,14]. These findings underscore the clinical importance of incorporating lifestyle interventions into routine hypertension management, particularly in primary care settings where continuous patient education and monitoring are feasible [15].

Recently updated guidelines from the KSH [3], the American Heart Association/American College of Cardiology (AHA/ACC) [9], and the European Society of Cardiology (ESC) [8] have further refined lifestyle management recommendations. This review summarizes these updated recommendations, focusing on their applicability in primary care practice.

Methods

Ethics statement

As this study is based entirely on published literature, neither approval from an institutional review board nor the obtainment of informed consent was required.

Study design

This narrative review examined 4 major hypertension guidelines—those from the United States (ACC/AHA 2025), Europe (ESC 2024), Korea (KSH 2018), and Taiwan (TSOC/THS 2022). These were selected based on 4 key criteria: recency, accessibility, applicability to Korean primary care, and inclusion of Asian-specific factors. The Taiwanese guideline was specifically chosen because it represents the most recent and English-accessible Asian guideline that explicitly incorporates genetic and cultural factors—most notably the *ALDH2* polymorphism ("Asian flush")—into its recommendations on alcohol consumption. This population-specific element is particularly relevant to Koreans, who share similar genetic and lifestyle backgrounds. By contrast, the Japanese (JSH 2019) and Chinese (2024 revision) guidelines were excluded from the main comparative synthesis for practical and methodological reasons.

Results

The 2024 European Society of Cardiology guideline

The 2024 ESC guideline positions lifestyle modification as a central strategy in hypertension management and provides the following specific recommendations [8].

Dietary sodium and potassium

For adults with elevated BP or hypertension, sodium intake should be restricted to approximately 2 g/day (equivalent to 5 g of salt or roughly 1 small teaspoon) (Class I, Level A) [16]. In patients without moderate-to-advanced chronic kidney disease (CKD) and with high sodium consumption, increasing potassium by 0.5–1.0 g/day through potassium-enriched salt (75% NaCl/25% KCl) or diets rich in fruits and vegetables is advised (Class IIa, Level A) [17,18]. For those with CKD or those receiving potassium-sparing medications (e.g., certain diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, or spironolactone), serum potassium should be monitored when increasing dietary potassium (Class IIa, Level C) [8]. The World Health Organization recommends a daily potassium intake of at least 3.5 g; excessive supplementation should be avoided, and potassium limited to <2.4 g/day in advanced CKD [19].

Weight reduction and diet

A stable, healthy body mass index (BMI; 20–25 kg/m^2) and waist circumference below 94 cm for men and 80 cm for women are recommended (Class I, Level A). On average, a 5 kg weight loss reduces SBP/DBP by approximately 4.4/3.6 mm Hg, and a 13% reduction in BMI from 40 kg/m^2 is associated with a 22% lower risk of incident hypertension. Sustained 5%–10% weight loss improves BP, glucose regulation, and lipid metabolism, and may reduce premature mortality [20,21]. Glucagon-like peptide-1 (GLP-1) receptor agonists, such as semaglutide, can reduce both body weight and BP [22]. Adoption of a Mediterranean or DASH diet is strongly recommended (Class I, Level A), with additive BP-lowering effects when combined with weight loss and sodium restriction [23].

Physical activity and exercise

Regular aerobic exercise can reduce SBP by up to 7–8 mm Hg and DBP by up to 4–5 mm Hg. In non-White individuals with hypertension, dynamic resistance training may produce BP reductions comparable to those achieved with aerobic activity. Recommended targets include at least 150 minutes per week of moderate-intensity aerobic exercise (≥30 minutes on 5–7 days per week) or 75 minutes per week of vigorous-intensity exercise spread over

at least 3 days. These should be complemented by low- to moderate-intensity dynamic or isometric resistance training 2 to 3 times per week (Class I, Level A) [24]. High-intensity interval training produces BP reductions comparable to moderate continuous exercise and may yield superior fitness gains [25]. However, high-intensity exercise should be avoided in individuals with uncontrolled resting hypertension.

Alcohol, coffee, and sugar-sweetened beverages

Alcohol intake should be limited to ≤100 g of pure alcohol per week, with complete abstinence encouraged for optimal cardiovascular outcomes (Class I, Level B) [26]. Coffee consumption is not associated with increased hypertension risk and may even confer protective effects; evidence for tea is mixed but suggests potential BP-lowering benefits [27]. In contrast, energy drinks can elevate BP and increase cardiovascular complications. Free sugar intake should be restricted to ≤10% of total daily energy [28], and the consumption of sugar-sweetened beverages should be discouraged from early life (Class I, Level B).

Smoking

Complete abstinence from tobacco is strongly recommended (Class I, Level A), with proactive counseling and referral to cessation services [29]. The effects of e-cigarettes on BP remain uncertain, though emerging evidence indicates a potential for BP elevation [30].

The 2025 AHA/ACC guideline

The 2025 AHA/ACC guideline identifies lifestyle modification as a core strategy for all adults with hypertension and those at elevated risk [9].

Sodium restriction

Lower sodium intake reduces BP across the life span and helps prevent incident hypertension. Compared with an intake of approximately 4,500 mg/day, a low-sodium diet (≤1,500–2,300 mg/day) reduces BP by about 3/2 mm Hg in normotensive individuals and by 7/3 mm Hg in those with hypertension [31,32]. Because most dietary sodium derives from processed and restaurant foods, population-level interventions are needed to achieve sustained reduction [33].

Salt substitutes and potassium

Potassium-enriched salt formulations (e.g., 75% NaCl/25% KCl) reduce BP by approximately 3.3–5/1.5 mm Hg and, in large clinical trials, decrease the incidence of stroke, major adverse cardiovascular events, and all-cause mortality by about 12%–14%, without increasing hyperkalemia risk [17]. Increased dietary potassium from fruits, vegetables, and legumes—or moderate supplementation—lowers BP by about 6/4 mm Hg, particularly in individuals with hypertension and high sodium intake. However, supplementation exceeding 80 mmol/day should be avoided, and caution is advised for patients with CKD or those taking potassium-retaining drugs [34].

Weight reduction

For non-Asian adults with BMI 25.0–29.9 kg/m^2 or ≥30 kg/m^2 and Asian adults with BMI 23.0–27.4 kg/m^2 or ≥27.5 kg/m^2, weight loss is a key intervention for improving overall health and controlling BP [35]. On average, each kilogram of weight loss reduces BP by approximately 1/1 mm Hg (SBP/DBP) [20]. A reduction of ≥5% of body weight or ≥3 kg/m^2 in BMI yields larger BP decreases, regardless of hypertension status, and shows synergistic effects when combined with the DASH diet and sodium restriction [36]. When lifestyle interventions alone are insufficient, pharmacologic options (e.g., GLP-1 receptor agonists) or bariatric surgery may be considered [37].

Dietary pattern—DASH

The DASH dietary pattern remains the most evidence-based approach for BP control. It emphasizes fruits, vegetables, low-fat dairy products, and whole grains, supplying potassium, magnesium, calcium, and fiber [36]. Clinical trials demonstrate SBP reductions of 1–13 mm Hg and DBP reductions of 1–10 mm Hg, with greater effects observed among Black adults, individuals with higher baseline BP, and those with high sodium consumption [38]. BP-lowering effects are amplified when DASH is combined with weight reduction or sodium restriction.

Alcohol

Any baseline alcohol consumption is associated with increased long-term BP. The risk of incident hypertension rises progressively with greater alcohol intake, with abstainers showing the lowest risk. Reducing alcohol intake by ≥50%, particularly in individuals consuming ≥4–6 drinks per day, leads to meaningful BP reductions, whereas no significant BP improvement is seen when reducing intake from ≤2 drinks per day [39]. Given the balance of risks, abstinence appears optimal [40].

Physical activity

Leisure-time physical activity lowers BP in adults with hypertension [41]. Aerobic exercise reduces BP by approximately 4–7/3–4 mm Hg, dynamic resistance training by 3/2 mm Hg,

and isometric training by 8/4 mm Hg. A dose–response relationship exists, with an additional 2/1 mm Hg BP reduction per extra 30 minutes per week of aerobic activity, reaching maximal benefit at about 150 minutes per week [42]. Both continuous and interval training formats are effective.

Stress reduction

Short-term studies show that transcendental meditation can reduce BP by approximately 5/2 mm Hg, paced breathing by 5/3 mm Hg, and yoga by smaller but consistent amounts [43]. These interventions serve as supportive measures, although their effects are generally less pronounced than those achieved through diet, sodium restriction, or structured exercise [44].

In summary, the AHA/ACC 2025 guideline underscores weight reduction, the DASH diet, sodium restriction, potassium optimization, alcohol limitation (preferably abstinence), regular exercise, and stress management as central lifestyle strategies capable of achieving BP reductions comparable to those of pharmacologic therapy.

2022 Guidelines of the Taiwan Society of Cardiology and the Taiwan Hypertension Society for the Management of Hypertension

The Taiwan guideline summarizes lifestyle therapy using the S-ABCDE framework: sodium restriction, alcohol limitation, body weight reduction, cigarette cessation, diet adaptation, and exercise adoption. Lifestyle modification is central to both prevention and management of hypertension; however, sustaining long-term adherence remains a key challenge. Therefore, the guideline emphasizes cognitive-behavioral and multimodal strategies to enhance persistence with these interventions [10].

Sodium restriction

A daily sodium intake of 2–4 g (equivalent to 5–10 g of salt) is recommended. Taiwanese and international evidence links high sodium intake with increased stroke incidence and cardiovascular mortality. The Salt Substitute and Stroke Study demonstrated that potassium-enriched salt reduced SBP and stroke incidence by 14% [17]. Because a J-curve relationship has been observed at intakes below 2 g/day, the guideline advocates realistic and sustainable sodium restriction rather than overly aggressive targets [45].

Alcohol limitation

Abstainers should not be encouraged to start drinking. For those who consume alcohol, intake should be limited to <100 g/wk for men and <50 g/wk for women. Given the high prevalence (approximately 40%–50%) of the *ALDH2**2 polymorphism in Taiwan, which predisposes to alcohol flushing, stricter limits are recommended: <64 g/wk for men and <28 g/wk for women [46].

Weight reduction

A BMI target of 20–24.9 kg/m^2 is recommended, with a 5 kg weight loss associated with an approximate 4.4 mm Hg reduction in SBP [20]. For individuals with severe obesity, anti-obesity pharmacotherapy or bariatric surgery may be considered.

Smoking cessation

Complete cessation of both conventional and electronic cigarettes is advised. The principal benefit of smoking cessation lies in reducing overall cardiovascular risk rather than producing a direct, sustained BP-lowering effect.

Diet adaptation

The DASH diet is prioritized, with an average BP reduction of about 11/6 mm Hg. While the Mediterranean diet is acceptable, the guideline generally favors DASH, reflecting Taiwan's high stroke burden and genetic context. Both green and black tea may offer modest BP-lowering effects of approximately 1–2 mm Hg [47,48].

Exercise adoption

At least 30 minutes of moderate aerobic activity is recommended on 5–7 days per week, supplemented by resistance or neuromotor exercises such as tai chi, yoga, or meditation [49]. Randomized controlled trials show reductions of approximately 3.5/2.5 mm Hg with aerobic exercise and 10.9/6.2 mm Hg with isometric exercise. Even under levels of PM2.5 (particulate matter with a diameter of 2.5 μm or less) exposure typical in many urban areas, the benefits of regular physical activity outweigh potential risks, and exercise remains strongly encouraged [50].

Overall, the Taiwan guideline positions lifestyle therapy as a foundational pillar of hypertension care—one tailored to Asian genetic, dietary, and environmental contexts—and highlights multimodal, adherence-enhancing strategies as essential for long-term success.

The KSH 2018 guideline

The KSH emphasized the central role of lifestyle modification in both its 2013 and 2018 guidelines [2,6]. Both editions identify

non-pharmacologic measures—healthy diet, regular exercise, smoking cessation, and moderation of alcohol intake—as the foundation of hypertension management, noting that their BP-lowering effects are comparable to those of a single antihypertensive medication (Class I, Level A). The 2018 update advances the 2013 framework by specifying recommendation classes and evidence levels, integrating contemporary domestic data, and improving clinical applicability. Notably, while the 2013 guideline used general descriptors such as "strongly recommended," the 2018 version formally assigns classes and levels of Evidence (e.g., Class I, Level A). It also broadens the target population to include individuals with elevated BP (prehypertension), thereby strengthening the emphasis on prevention.

Sodium restriction

The 2013 guideline reported an average daily salt intake of approximately 12.2 g among Koreans and recommended reducing it to <6 g/day, while acknowledging uncertainty—such as a possible J-curve—regarding the relationship between salt restriction and cardiovascular outcomes. The 2018 guideline incorporates updated Korea National Health and Nutrition Examination Survey data, citing a mean intake of 10 g/day [51], and again recommends <6 g/day (Class I, Level A). Beyond BP reduction, it highlights central hemodynamic considerations for cardiovascular event prevention. The guideline further specifies that salt restriction yields greater benefits in salt-sensitive groups (older adults, individuals with obesity, diabetes, or a family history of hypertension). It adds practical strategies such as increasing low-salt food options, avoiding processed foods high in sodium, and favoring natural ingredients during cooking. Importantly, it newly underscores potassium-rich foods as a means of offsetting sodium-related BP increases, with appropriate caution for patients with CKD or risk of hyperkalemia [3].

Weight management

The 2013 guideline noted that even a 5 kg weight loss can reduce BP and described associations among abdominal obesity, hypertension, metabolic disorders, and cardiovascular mortality. The 2018 update retains these points and incorporates Korean cohort data showing the lowest all-cause mortality at BMI 23.0–24.9 kg/m^2. It recommends maintaining BMI <25 kg/m^2 and specifies Korean-specific waist circumference thresholds (<90 cm in men and <85 cm in women) [52], offering a broader and more practical approach than the previous 80 cm threshold for women in the 2013 guideline (Class I, Level A).

Alcohol

The 2013 guideline advised 20–30 g/day for men and 10–20 g/day for women, cautioning against the elevated stroke risk in heavy drinkers. The 2018 guideline simplifies this to fewer than 2 drinks per day (Class I, Level A) [53].

Exercise

Whereas the 2013 guideline primarily emphasized aerobic exercise with isometric activity as a supplement, the 2018 update provides detailed prescriptions: 5–7 sessions per week, 30–60 minutes per session (≥90–150 minutes per week total), including 5-minute warm-up and cool-down periods. It also specifies resistance protocols—dynamic resistance (2–3 sets) and isometric handgrip training at 30%–40% of maximal strength, held for 2 minutes with 1-minute rests, repeated 4 times, 3 sessions per week—allowing "recipe-level" guidance for clinical counseling [3] (Class I, Level A).

Smoking cessation

As in 2013, the 2018 guideline mandates complete cessation and supports combined nicotine replacement and behavioral therapy. The update elevates this recommendation to Class I, Level A, underscoring active physician counseling and referral to cessation programs [54] (Class I, Level A).

Dietary management

The 2018 guideline continues to endorse healthy dietary patterns such as the DASH and Mediterranean diets, while emphasizing that a Korean-style diet—rich in tofu, legumes, vegetables, fruits, and fish—is associated with a lower prevalence of hypertension [55,56]. It further reiterates that higher intake of calcium, magnesium, and potassium can yield an additional 11/6 mm Hg BP reduction in hypertensive patients [11,57]. Among older adults, increasing fruit and vegetable intake alone lowers BP by 3/1 mm Hg, with an additional 6/3 mm Hg reduction when combined with reduced fat consumption [11,57].

In summary, the 2018 KSH guideline retains the core principles of 2013 while introducing formalized grading, expanded domestic evidence, increased emphasis on potassium intake, detailed exercise prescriptions, and updated waist circumference thresholds. These refinements enhance practical applicability in real-world care. Lifestyle modification remains a first-line strategy with BP-lowering effects comparable to pharmacotherapy, while offering broad cardiometabolic protection.

Table 1 provides a comparative summary of lifestyle intervention recommendations across recent hypertension guidelines.

Table 1. Comparison of lifestyle modification recommendations for hypertension management across guidelines

Lifestyle factor	Europe (ESC 2024)	USA (AHA/ACC 2025)	Korea (KSH 2018)
Sodium restriction	~2 g sodium/day (≈5 g salt); supported by long-term outcome trials (SSaSS, DECIDE-Salt)	1,500–2,300 mg/day (optimal <1,500); salt substitutes reduce SBP by ~3.3 mm Hg	<6 g salt/day (≈2.4 g sodium)
Potassium intake	≥3.5 g/day (WHO target); increased intake recommended unless advanced CKD	Diet rich in fruits/vegetables; moderate supplementation lowers BP by ~6/4 mm Hg; avoid >80 mmol/day	Potassium-rich foods encouraged (esp. with salt restriction); caution in CKD
Weight reduction	Stable BMI 20–25 kg/m^2; WC <94 cm (men), <80 cm (women); 5 kg loss → SBP ↓ 4.4 mm Hg	≥5% body weight or ≥3 kg/m^2 BMI loss; ~1/1 mm Hg per kg loss; GLP-1 RAs or bariatric surgery if needed	Target BMI <25 kg/m^2; lowest mortality at 23–24.9 kg/m^2; WC <90 cm (men), <85 cm (women)
Dietary pattern	Mediterranean or DASH diet strongly recommended	DASH diet most effective (SBP ↓ 1–13, DBP ↓ 1–10 mm Hg); Mediterranean, vegetarian also beneficial	DASH or Korean-style diet (vegetables, tofu, fish, fruits) associated with lower HTN prevalence
Alcohol consumption	<100 g/wk pure alcohol; ideally abstain	Abstinence optimal; <2 drinks/day men, <1 drink/day women; dose-response ↑ risk	<20–30 g/day men, <10–20 g/day women
Exercise	≥150 min/wk moderate or 75 min vigorous aerobic; + resistance 2–3×/wk; avoid high intensity if uncontrolled HTN	Aerobic: 150 min/wk (SBP ↓ 4–7 mm Hg); dynamic resistance: ↓ 3/2; isometric: ↓ 8/4	≥30–50 min/day, ≥5 days/wk aerobic; isometric exercise 2–3×/wk; caution with isotonic heavy lifting
Smoking cessation	Strongly recommended; link to CV mortality; e-cigarettes not recommended	Strongly recommended; part of CV risk reduction	Strongly recommended at every visit; nicotine replacement + behavioral therapy
Sugar intake	Restrict free sugar <10% of daily energy; discourage soft drinks/fruit juices early in life	Restrict free sugar <10% of daily energy; avoid sugar-sweetened beverages	Not specifically emphasized in 2018 KSH
Stress management	Stress reduction (mindfulness, relaxation) considered beneficial, though evidence limited	Meditation ↓ ~5/2 mm Hg; breathing ↓ 5/3 mm Hg; yoga modest effect	Stress reduction acknowledged but evidence insufficient

ESC, European Society of Cardiology; AHA, American Heart Association; ACC, American College of Cardiology; KSH, Korean Society of Hypertension; SSaSS, Salt Substitute and Stroke Study; DECIDE-Salt, Diet, Exercise and Cardiovascular Health–Salt Trial; SBP, systolic blood pressure; WHO, World Health Organization; CKD, chronic kidney disease; BP, blood pressure; BMI, body mass index; WC, waist circumference; GLP-1 RA, glucagon-like peptide-1 receptor agonist; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; HTN, hypertension; CV, cardiovascular.

Discussion

This review compared and analyzed lifestyle modification strategies across the most recent hypertension guidelines from Europe, the United States, Taiwan, and Korea. All 4 guidelines consistently emphasize sodium restriction, weight reduction, regular exercise, smoking cessation, moderation of alcohol intake, and adherence to healthy dietary patterns such as the DASH or Mediterranean diets as the foundation of hypertension management. Collectively, these interventions provide BP-lowering effects comparable to those achieved with a single antihypertensive medication.

The ESC 2024 guideline elevates lifestyle modification to a Class I recommendation, equivalent in importance to pharmacologic therapy, and establishes specific intake targets for sodium (<2 g/day) and potassium (≥3.5 g/day). It underscores the broader health benefits of lifestyle interventions beyond BP control, highlighting their roles in improving metabolic health and reducing overall cardiovascular risk. Furthermore, the guideline calls for coordinated societal and policy-level measures to strengthen adherence and expand population-level impact.

The AHA/ACC 2025 guideline provides detailed quantitative evidence, reporting an approximate 1/1 mm Hg BP reduction per kilogram of weight loss and up to 13/10 mm Hg reduction with adherence to the DASH diet, and places particular emphasis on integrating adjunctive strategies. These include the use of anti-obesity pharmacotherapy, such as GLP-1 receptor agonists, and bariatric surgery when lifestyle measures alone fail to achieve adequate BP control.

The Taiwan Society of Cardiology/Hypertension Society (2022) guideline organizes its recommendations using the mnemonic S-ABCDE (sodium restriction, alcohol limitation, body weight reduction, cigarette cessation, diet adaptation, exercise adoption). It uniquely incorporates genetic considerations, particularly *ALDH2* polymorphisms associated with "Asian flush," into its alcohol recommendations, and integrates culturally relevant components such as tea consumption, meditation, and tai chi into its lifestyle framework.

The KSH (2018) guideline reflects the local context of high-

salt dietary patterns and the substantial burden of cerebrovascular disease in Korea. It strongly recommends reducing salt intake to <6 g/day and promotes Korean-style dietary patterns rich in tofu, legumes, fish, vegetables, and fruits. Specific anthropometric targets include maintaining BMI <25 kg/m^2 and waist circumference <90 cm for men and <85 cm for women. The 2022 Focused Update of the KSH guidelines primarily addressed pharmacologic treatment strategies, diagnostic thresholds, and management of special populations. Notably, it did not revise lifestyle modification recommendations. Therefore, the principles of non-pharmacologic management, including sodium restriction, weight control, regular physical activity, moderation of alcohol intake, smoking cessation, and adherence to dietary patterns such as the DASH diet, remain those established in the 2018 guideline. In current clinical practice, these 2018 recommendations continue to serve as the standard reference for lifestyle-based hypertension management in Korea.

Mechanisms of blood pressure reduction by lifestyle modification

Lifestyle modification lowers BP through multiple interrelated physiological pathways. Sodium restriction decreases extracellular fluid volume and cardiac output, thereby reducing systemic BP [58]. Weight reduction improves insulin sensitivity, attenuates sympathetic nervous system activity, and diminishes renal sodium reabsorption [20]. Regular physical activity enhances endothelial function and arterial compliance, leading to decreased peripheral vascular resistance [59]. Limiting alcohol intake reduces sympathetic stimulation and suppresses activation of the renin–angiotensin–aldosterone system [53]. Increased potassium consumption promotes natriuresis and induces relaxation of vascular smooth muscle, contributing to vasodilation [60]. Lastly, stress management mitigates hyperactivation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal axis, further supporting BP regulation [44].

Strengths and limitations of this review

The strength of this review lies in its comprehensive synthesis of the most recent national and international hypertension guidelines, supported by evidence from large-scale meta-analyses. By comparing recommendations from Korea, the United States, Europe, and Taiwan, this review provides practical, contextually relevant strategies for implementing lifestyle modification in primary care settings. Additionally, the quantitative estimation of BP-lowering effects across individual interventions offers clinicians clinically meaningful guidance for patient management.

Nevertheless, several limitations should be acknowledged. First, the magnitude of BP reduction achieved through lifestyle modification varies across studies, depending on the intensity, duration, and adherence to interventions. Second, much of the available evidence is derived from Western populations, whereas long-term, prospective data from Korean and other Asian cohorts remain limited. Third, although short- and medium-term BP reductions are well documented, the long-term effects of lifestyle interventions on cardiovascular morbidity and mortality are still insufficiently established.

Conclusion

In conclusion, all major hypertension guidelines reaffirm lifestyle modification as the cornerstone of hypertension prevention and management. Core components—including sodium restriction, weight reduction, regular physical activity, a balanced diet, smoking cessation, and moderation of alcohol intake—are universally endorsed. However, regional distinctions exist. The United States emphasizes quantitative evidence and integration of obesity therapeutics; Europe underscores policy-level and population-based strategies; Korea focuses on culturally adapted low-salt diets; and Taiwan incorporates genetic and cultural specificity, particularly in its alcohol-related recommendations. Building on these perspectives, the Korean guideline could be further enhanced by defining explicit quantitative targets for sodium and potassium intake (e.g., Na <2 g/day, K ≥3.5 g/day) and by integrating Asian-specific genetic considerations such as the *ALDH2* polymorphism influencing alcohol metabolism. Moreover, greater attention to sleep hygiene, stress regulation, and mental health would support a more holistic approach to hypertension care within primary practice. Looking forward, the incorporation of digital health technologies, artificial intelligence-driven precision approaches, and genetic or microbiome-informed personalization will be pivotal to optimizing lifestyle-based hypertension management, particularly among Asian populations, including Koreans.

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Conflict of interest

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Supplementary materials

None.

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Core principles and structures of geriatric rehabilitation: a narrative review

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Globally, rapid population aging—particularly in Korea—has extended life expectancy but not proportionally extended healthy life expectancy, resulting in longer periods of illness or disability and a higher demand for complex medical and social care. Therefore, prolonging healthy life and improving health-related quality of life have become primary objectives in geriatric medicine and rehabilitation. Geriatric rehabilitation is a critical intervention aimed at optimizing the functioning of older adults and pre-morbidly frail individuals who have lost independence due to acute illness or injury. For many older patients, the goal shifts from complete recovery to achieving a new equilibrium, maximizing autonomy despite greater dependency. Geriatric rehabilitation also targets key geriatric syndromes such as frailty, recognizing it as a dynamic and potentially reversible state that provides a crucial "time window" for intervention. This review summarizes the core principles and structural elements essential for geriatric rehabilitation, emphasizing the implementation challenges within the Korean healthcare system. Unlike the European consensus, which supports structured inpatient and outpatient services with seamless transitions of care guided by Comprehensive Geriatric Assessment, the Korean healthcare system remains fragmented and heavily centered on acute hospitals. This highlights the urgent need for a systematic model to integrate care facilities and strengthen interprofessional collaboration to support community-based "aging in place." Effective geriatric rehabilitation requires multidisciplinary teams and multifaceted approaches to optimize quality of life, social participation, and independent living. Despite its importance, substantial awareness gaps and policy barriers persist, underscoring an urgent call to action.

Keywords: Aging; Frailty; Geriatric; Rehabilitation; Delivery of health care

Introduction

Globally, aging-related health challenges are reshaping the foundation of medical care. Korea entered a super-aged society in 2024, with individuals aged 65 years and older exceeding 20% of the population, drawing global attention as the country with the fastest aging rate in the world [1]. Korea is not only aging most rapidly but is also projected to have the world's highest life expectancy by 2030—91 years for women and 84 years for men [2]. Although increased life expectancy is often celebrated as a major public health achievement, it does not necessarily correspond to a proportional extension of healthy life expectancy. Without such parallel progress, societies face the inevitability of longer life spans accompanied by illness or disability and a rapid expansion in populations requiring complex medical and social care [3]. While healthy and independent aging remains a universal goal, the reality is that many individuals will experience prolonged periods of impaired health or functional dependency in later life.

Older adults often experience diminished independence due to functional decline associated with aging and multiple chronic diseases. Most geriatric diseases are chronic degenerative conditions closely linked to frailty and disabilities that limit independent daily activities, thereby reducing quality of life and creating a significant socioeconomic burden [4,5]. Thus, prolonging healthy life and improving health-related quality of life are central objectives of geriatric medicine and rehabilitation. Geriatric rehabilitation has evolved to help older adults with disabilities recover lost physical, psychological, or social functions so that they can regain greater independence, live in personally fulfilling environments, and sustain meaningful social engagement [4,6]. It involves com-

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prehensive programs designed to optimize the functioning of older adults, particularly those who were pre-morbidly frail and have lost independence following acute illness or injury.

In this review, we summarize the core principles of geriatric rehabilitation and outline the structural components necessary for its integration into clinical practice. Particular attention is given to the challenges of implementing geriatric rehabilitation in both hospital-based outpatient and inpatient settings, drawing on the Korean healthcare system's experience, where aging-related health concerns are rapidly intensifying. The discussion highlights the organizational, cultural, and policy factors that affect the accessibility and delivery of rehabilitation programs in real-world practice.

Ethics statement

This was a literature-based study; therefore, neither approval by the Institutional Review Board nor the obtainment of informed consent was required.

Definition and core concepts of geriatric rehabilitation

As population aging accelerates, geriatric diseases are becoming increasingly prevalent in clinical practice. Even without specialized geriatric care, the majority of outpatient and inpatient populations consist of older adults, and the number of the oldest old (i.e., those in their 80s and 90s) is rising particularly rapidly [7]. Most individuals in this age group experience degenerative changes and are predisposed to frailty and fragility [8,9]. The demand for comprehensive rehabilitation addressing conditions such as frailty, sarcopenia, osteoporosis, fragility fractures, and disuse syndrome—each contributing to significant functional decline and increased dependence in activities of daily living—has grown markedly in recent decades. This growing need has sparked interest in applying rehabilitation principles specifically to older adults who are physically frail and dependent, a movement that began to take shape in the early 1990s [10,11]. Grounded in the framework of the World Health Organization's International Classification of Functioning, Disability and Health (WHO-ICF) and the WHO rehabilitation cycle, geriatric rehabilitation has been conceptualized as a multidimensional process encompassing diagnostic, therapeutic, and rehabilitative interventions [12]. Its overarching goal is to optimize functional capacity, enhance activity levels, and maintain social participation in older adults living with impairments and disabilities [6]. However, for many older patients, especially those with multiple comorbidities and multifactorial deficits, full restoration of function may not be a realistic objective. Instead, the focus shifts toward achieving attainable, patient-centered goals. Thus, the appropriate aim is often to reach a new balance that may entail greater dependency while preserving autonomy and self-management to the greatest extent possible [13].

Geriatric rehabilitation programs emphasize patient-centered goals that reflect individual preferences established through co-creation with patients and their caregivers. These programs can be delivered in a variety of settings, depending on national policies, reimbursement structures, and local resources [13]. Geriatric rehabilitation may be implemented as outpatient, hospital-based, nursing home-based, or community-based services [6]. Patients suitable for rehabilitation are typically older adults whose intrinsic capacity and functional ability are compromised by multimorbidity and geriatric syndromes but who retain the potential to improve clinically and functionally through targeted interventions [14,15]. Such patients should be active participants in the rehabilitation process. Geriatric syndromes and diseases—most notably frailty (both physical and cognitive) and sarcopenia (including age-related and secondary forms)—represent quintessential conditions embodying the core principles of geriatric medicine [16-18]. Within the framework of geriatric rehabilitation, it is essential to recognize that geriatric syndromes do not correspond to discrete disease entities. Rather, they are interrelated conditions that profoundly affect functional ability, independence, and overall quality of life in older adults [19].

Frailty is a clinical state characterized by increased vulnerability to dependency and/or mortality when exposed to stressors [20]. It represents a biological syndrome of diminished physiological reserve and resistance to stress, arising from cumulative declines across multiple systems and resulting in susceptibility to adverse outcomes [21,22]. Frailty is a well-established predictor of disability and mortality and is also associated with poorer outcomes following rehabilitation interventions in geriatric settings [23]. Although various definitions of frailty exist, 2 major conceptual frameworks are widely recognized: the phenotype-based model [24] and the deficit accumulation model (frailty index) [25]. The frailty index is based on the accumulation of health deficits across physical, psychological, cognitive, and social domains. The phenotype-based model (Fried model) is the most widely used in clinical practice and comprises 5 interrelated features—slow gait speed, low grip strength, poor endurance, low physical activity, and unintentional weight loss. The presence of 3 or more criteria indicates frailty, while 1 or 2 denote pre-frailty. Frailty is not a standalone disease, nor is it a static or irreversible condition. It is a dynamic and potentially reversible state—especially if addressed during the "frailty time-window," a critical transitional period in the aging process during which individuals shift from relative in-

dependence ("full performance") toward frailty and are at risk of progressing to disability [26]. This concept holds particular importance in geriatric rehabilitation, as it represents a pivotal window of opportunity for timely and effective intervention [23].

Structures and settings of geriatric rehabilitation

The WHO Rehabilitation 2030 initiative was launched to make rehabilitation accessible to everyone who needs it [27,28]. This initiative is closely aligned with the United Nations Decade of Healthy Ageing and underscores rehabilitation as an essential component of integrated care, emphasizing its clinical value and social importance. Both initiatives affirm that aging well is not merely about living longer—it is about living better. Rehabilitation serves as the driving force behind healthy aging by enabling older adults to recover, adapt, and thrive despite chronic conditions or functional decline. The WHO Rehabilitation 2030 framework is not only compatible with geriatric rehabilitation but also provides a powerful global structure that can elevate and integrate it into healthcare systems worldwide [27,28]. However, the organization and delivery of rehabilitation vary widely across countries, leading to inconsistent outcomes and unequal access [13-15,29]. Grund et al. [6] reported substantial international differences in how geriatric rehabilitation is structured and delivered. They emphasized the need to achieve consensus on what geriatric rehabilitation should entail and to develop internationally harmonized approaches that could be applied consistently across rehabilitation settings.

According to the European consensus statement, the structure of geriatric rehabilitation encompasses both inpatient and outpatient settings. Inpatient rehabilitation can take place in nursing homes, geriatric rehabilitation centers, specialized geriatric hospitals, or acute care hospital units [14]. Admission to each setting should be determined by clearly defined clinical criteria that are objectively assessed and measured. Seamless care transitions should allow patients to move between different rehabilitation environments based on clinical progress and individual needs. Comprehensive Geriatric Assessment (CGA), incorporating the perspectives of patients and informal caregivers, should be applied within a co-creation framework to design tailored rehabilitation plans [22]. This structured model underscores the importance of defining roles across levels of care to ensure continuity, specialization, and efficiency in service delivery [30].

By contrast, the Korean healthcare system—although highly developed for advanced, disease-centered care—lacks an appropriate framework for comprehensive and integrated services such as geriatric care [1,31]. Geriatric rehabilitation in Korea remains largely concentrated in acute hospitals, with few dedicated rehabilitation centers or structured outpatient programs [27]. Consequently, older adults frequently experience fragmented transitions between hospitals, community-based facilities, and long-term care institutions, resulting in discontinuity of care. Establishing a systematic model that clearly delineates the functions of each facility and integrates them into the overall healthcare system is therefore a critical priority [27]. Such a model must be adapted to the specific supply–demand conditions of the Korean context, where rapid population aging has intensified the need for rehabilitation. Furthermore, successful implementation requires reorganizing healthcare delivery to enhance interprofessional collaboration and to promote seamless coordination across acute, post-acute, and community-based care settings [32].

Recently, Korea's national healthcare strategy for addressing the challenges of a super-aged society has increasingly emphasized community-based care [33,34]. This approach seeks to enable older adults to receive necessary health services while remaining in their homes and active within their communities—a concept widely recognized as "aging in place" [33]. This paradigm shift reflects growing recognition that institutional care alone cannot adequately meet the multifaceted and long-term needs of the aging population. According to a survey by the European Geriatric Medicine Society Special Interest Group on geriatric rehabilitation, the primary conditions leading to admission to geriatric rehabilitation units were neurological disorders—predominantly stroke—and fractures, particularly hip fractures [14]. These findings underscore the necessity of developing geriatric rehabilitation systems that address both acute disabling events and the long-term functional challenges they pose.

Specific considerations for rehabilitation programs

In geriatric care settings, rehabilitation should aim to minimize functional impairment and activity limitations while maximizing social participation, even when restoration of pre-morbid body structure and function is not feasible. This often requires the use of assistive technologies as well as cultural and environmental adaptations. Rehabilitation programs should integrate psychosocial components of health and well-being and employ evidence-based behavioral change approaches to enhance adherence and long-term outcomes [6,13,15,35].

Treatment intensity should be individualized according to each patient's needs. For older adults, adjustments are frequently required to accommodate reduced physical function and exercise

capacity. An exploratory study that examined the content and outcomes of physical fitness training in orthopedic geriatric rehabilitation found that most training programs were generally low in intensity compared with established guidelines [36]. Given these limitations, it is important to emphasize that effective geriatric rehabilitation typically requires longer training durations to achieve meaningful improvements.

Within the broad domain of geriatric rehabilitation, patients present with a wide array of specific conditions, including stroke, Parkinson's disease, hip fracture, amputation, chronic obstructive pulmonary disease, chronic heart failure, cognitive impairment, and COVID-19 (coronavirus disease 2019). Because each case involves distinct factors and varying degrees of multimorbidity, condition-specific protocols alone are insufficient. Environmental and contextual factors—such as family support, resilience, and patient motivation—must be carefully considered, as they strongly influence rehabilitation outcomes. Evidence from systematic reviews and clinical experience in both geriatric rehabilitation clinics and inpatient units supports the use of individualized, evidence-informed rehabilitation strategies tailored to older adults [13,23,37]. Inpatient geriatric rehabilitation encompasses a continuum of care designed to meet the needs of older adults experiencing functional decline. Patients may require rehabilitation following acute illness in an acute geriatric unit or due to chronic disease–related deterioration in a subacute unit. The indications for inpatient rehabilitation can extend to chronic functional decline, especially among those meeting criteria for frailty or sarcopenia. Older adults with progressive loss of independence in activities of daily living (ADLs), often resulting from declining mobility and cognitive function over 6 months to 1 year, are suitable candidates for short-term, comprehensive, and integrated rehabilitation programs. Additional indicators include recurrent falls, poor mobility following falls, and fragility fractures, all of which contribute to a downward trajectory in functional status. This progression reflects the lifelong vulnerability of frail individuals to fall-related injuries and subsequent disability. Without timely and appropriate intervention, these patients face a markedly increased risk of severe functional decline or death. However, accumulating evidence shows that when rehabilitation services are delivered promptly and effectively, many older adults can regain their pre-morbid functional levels, highlighting the crucial importance of early rehabilitation in preventing long-term disability [19,30,38,39] (Fig. 1).

A multifaceted rehabilitation approach is essential to effectively support frail older adults within geriatric rehabilitation programs [40]. The RESORT (Rituximab Extended Schedule or Retreatment Trial) study demonstrated that frailer geriatric inpatients tend to have more complex comorbidities and impaired nutritional, physical, and psychological parameters. Cognitive impairment, delirium, comorbid conditions, and anxiety at admission were predictive of worsening frailty during rehabilitation. The study recommended that these factors be assessed and addressed early through interdisciplinary care [23]. The key components of multifaceted rehabilitation include physical rehabilitation, nutritional support, cognitive and psychological care, social and environmental adjustment, and medical optimization.

Geriatric rehabilitation team

A geriatric rehabilitation team is fundamentally multidisciplinary, designed to address the complex, interrelated medical, psychological, and social needs of older adults. Since most geriatric patients present with multimorbidity, frailty, or disability, their care requires the coordinated expertise of multiple professionals

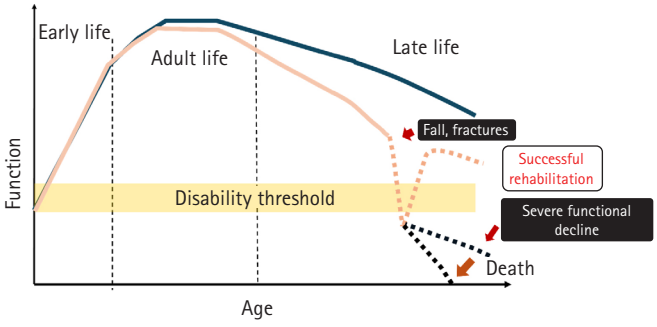

Fig. 1. Critical role of early rehabilitation in mitigating long-term disability.

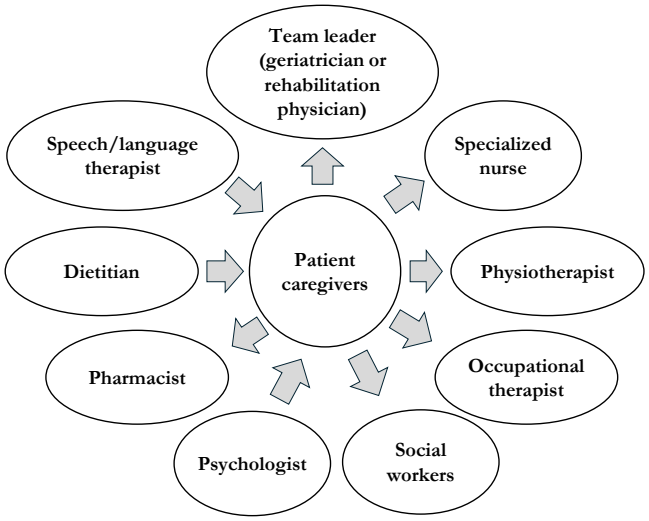

Fig. 2. Multidisciplinary teams in geriatric rehabilitation.

rather than a single discipline. Geriatric rehabilitation team consists of the team leader, core team members, extended team members and collaborators [6,13,35] (Fig. 2).

In Europe, most geriatric rehabilitation teams are led by geriatricians (95%, according to consensus surveys), reflecting the specialty's comprehensive focus on multimorbidity, polypharmacy, and geriatric syndromes [14]. In Korea and several other Asian countries, however, teams are often led by rehabilitation specialists, whose expertise lies in functional restoration, physical medicine, and disability management [41]. The team leader is responsible for coordinating assessments, setting rehabilitation goals, and ensuring alignment between medical management and rehabilitation priorities [15]. Core team members generally include specialized nurses, physical therapists, occupational therapists, and social workers. Extended team members typically comprise psychologists or neuropsychologists, dietitians, pharmacists, and speech and language therapists. The specialized nurse plays a pivotal role by providing ongoing patient monitoring, wound and medication management, and acting as a central communication link among patients, families, and the interdisciplinary team. The physical therapist focuses on mobility enhancement, balance training, gait correction, fall prevention, and individualized exercise regimens to restore functional movement. Occupational therapists facilitate independence in ADLs—such as dressing, feeding, toileting, and home adaptation—while supporting strategies to enhance safety and autonomy. The social worker evaluates social support networks, caregiver burden, and financial constraints, and coordinates access to community-based resources that promote long-term care and "aging in place."

Among the extended team members, the psychologist or neuropsychologist conducts cognitive and behavioral assessments, manages emotional well-being, and provides coping support for both patients and caregivers. The dietitian or nutritionist develops individualized nutrition plans targeting conditions such as sarcopenia, frailty, and post-fracture recovery, emphasizing adequate protein intake and supplementation. The pharmacist ensures safe and effective medication use, minimizes risks associated with polypharmacy, and provides education on medication adherence. The speech and language therapist assesses and rehabilitates swallowing disorders (dysphagia) and communication impairments, particularly following stroke or in neurodegenerative conditions.

The team operates under the framework of the CGA, which integrates multidisciplinary inputs into a unified and adaptive rehabilitation plan [42,43]. Families and caregivers are regarded as essential partners in this process, actively participating in goal setting, education, and ongoing follow-up. Regular multidisciplinary meetings facilitate the continuous review and adjustment of rehabilitation goals, early detection of complications, and effective communication among team members. Ultimately, the mission of the geriatric rehabilitation team extends beyond physical recovery to encompass the enhancement of quality of life, social participation, and independent living for older adults. Its effectiveness depends on the ability to balance medical stabilization, functional restoration, and psychosocial reintegration while respecting each patient's individual values and preferences.

Conclusion

Key strategies for effective geriatric rehabilitation include accurate diagnosis of underlying problems and the comprehensive use of assessment tools—particularly the active application of CGA. Continuous, longitudinal monitoring of aging-related changes and physical and cognitive function in older adults enables the development of tailored prevention, recovery, and adaptation strategies. Appropriate and timely medical and rehabilitative interventions should be implemented across various clinical settings, including acute hospitals, post-acute care facilities, long-term care institutions, and home or community environments. These strategies encompass multimodal exercise programs, nutritional optimization, management of geriatric syndromes, and individualized case management approaches. Despite the growing need, awareness of geriatric rehabilitation remains limited, and substantial policy barriers persist. Therefore, a concerted call to action is necessary to highlight the essential role of comprehensive and integrated rehabilitation in addressing geriatric health challenges and promoting healthy aging.

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Authors' contribution

All work was done by Jae-Young Lim.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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Aging with disability in polio survivors: a narrative review

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This study aimed to provide a comprehensive understanding of aging with disability among polio survivors who continue to live with long-term sequelae. Although poliomyelitis has been eradicated in most regions, survivors entering older age face a dual challenge, as age-related decline overlaps with pre-existing impairments, creating a need for integrated management strategies. This narrative review examined the epidemiology, clinical manifestations, and late effects of polio, with particular attention to post-polio syndrome, secondary musculoskeletal disorders, and other systemic conditions. International and Korean studies were compared to highlight similarities and contextual differences. Polio survivors frequently experience accelerated functional decline due to post-polio syndrome, fatigue, pain, musculoskeletal disorders (e.g., arthritis, osteoporosis, fractures), and cardiopulmonary dysfunction. Approximately 64% report major falls, with 35% sustaining fractures, often at vulnerable sites such as the hip or distal femur. Psychological distress, sleep disturbances, metabolic syndrome, and cardiovascular disease are also prevalent, further compounding frailty. In Korea, where most survivors are now over 60 years of age, epidemiological patterns differ from those of Western cohorts; however, systematic investigations remain limited. Polio survivors exemplify the dual burden of aging and long-term disability, underscoring the need to move beyond fragmented, symptom-focused care toward integrated, life course–oriented approaches. Anticipating and managing late effects, strengthening preventive strategies, and ensuring equitable healthcare access are essential for maintaining function, independence, and quality of life. Lessons drawn from polio survivors offer valuable insights for understanding aging with disability more broadly.

Keywords: Aging; Disability; Late effects; Poliomyelitis; Postpolio syndrome

Introduction

The global eradication of poliomyelitis through widespread vaccination represents one of the most remarkable public health achievements of the 20th century. However, tens of millions of polio survivors worldwide continue to live with the long-term sequelae of the disease [1]. As polio survivors enter older age, the typical functional decline associated with natural aging is superimposed on pre-existing dysfunction, creating various late effects that compound their vulnerabilities [2].

The concept of "late effects" refers to new or worsening health problems that arise over time as a consequence of long-standing impairments [3]. These effects exacerbate pre-existing disabilities and accelerate further functional decline in middle and older age [4]. Late effects of polio typically include post-polio syndrome (PPS), characterized by newly developed muscle weakness, fatigue, and pain decades after the acute infection, as well as secondary musculoskeletal complications such as joint stiffness, deformities, and premature degenerative changes, along with other secondary conditions (Fig. 1). These conditions are often accompanied by age-related changes in muscle mass, strength, and cardiopulmonary function, thereby accelerating frailty—a strong predictor of adverse outcomes [5]—and disability. Consequently, polio survivors experience premature aging, in which their biological age exceeds their chronological age. This aging process is accompanied by chronic comorbidities and declines in physical and functional capacity [6], ultimately leading to a deterioration in quality of life at a relatively younger age.

The global aging population represents one of the most prominent demographic trends of the 21st century [7], and worldwide attention to healthy and successful aging has been steadily increasing [8]. However, the needs of people aging with long-term dis-

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abilities have been relatively overlooked in both clinical practice and policy [4]. Polio survivors represent a paradigmatic group for examining these issues, given their clearly defined historical cohort, well-documented impairments, and increasing age. In Korea, the median age of polio survivors now exceeds 60 years, highlighting the urgency of addressing the health threats posed by late effects and their interaction with aging. Nonetheless, many healthcare providers continue to rely on fragmented approaches that focus primarily on patients' chief complaints or symptoms, leaving individuals without adequate care tailored to their specific needs and conditions [4]. As a result, the complex and multisystem challenges faced by this population remain insufficiently addressed.

From a life-course perspective, successful aging with disability should be understood as a multidimensional construct encompassing not only multidisciplinary medical care but also psychological resilience, social connectedness, and equitable access to healthcare services. For polio survivors, developing integrated strategies to prevent and mitigate late effects is essential for maintaining function and quality of life. This narrative review aims to synthesize current knowledge on aging with disability in polio survivors.

Ethics statement

This was a literature-based study; therefore, neither approval by an institutional review board nor the obtainment of informed consent was required.

Epidemiology of polio survivors and aging

Poliomyelitis is a disease caused by acute viral inflammation of motor neurons in the spinal cord that spread worldwide during the mid-20th century. While most infections were subclinical, a subset progressed to paralytic disease with lifelong sequelae. Mortality among paralytic cases ranged from 2% to 10%, with greater severity observed at older ages. With the introduction of effective vaccination programs, new cases dramatically declined worldwide. By the early 1980s, countries such as Korea had eliminated indigenous transmission, and in 2000, the World Health Organization declared the Western Pacific Region—including Korea—polio-free.

However, tens of millions of survivors remain worldwide [1]. The United States has approximately 1.6 million polio survivors [9], and European countries also report substantial numbers. In Scandinavia, where no new indigenous cases occur, immigration from polio-endemic regions has led to a dual demographic pattern of aging native-born survivors and younger immigrant survivors [10]. In contrast, in Asia—including Japan, Taiwan, and Korea—survivors constitute one of the largest global cohorts, although systematic studies and coordinated healthcare responses remain limited.

Korea's epidemiological trajectory lagged roughly a decade behind that of Western countries, with a peak incidence during the late 1950s and early 1960s, particularly in the aftermath of the Korean War. Consequently, the survivor population remains relatively large, with the majority now in their 60s or older [11]. Although official statistics on polio survivors in Korea are unavailable, an estimated 60,000 individuals are survivors based on data from the National Survey on Persons with Disabilities, which found that 5.2% of individuals with limb disabilities reported poliomyelitis as the cause [12]. This estimate is more than twice the number of survivors in Japan [13], likely reflecting delayed vaccine introduction and post-war sanitary conditions in Korea. Therefore, the demographic and clinical characteristics of Korean survivors may differ from those observed in developed countries where the disease has been more extensively studied [14,15].

International cohort studies consistently demonstrate that a large proportion of survivors experience new or worsening symptoms—such as fatigue, pain, and weakness—decades after the acute infection. Surveys in the United States suggest that up to 64% of survivors report new symptoms, and nearly half develop new weakness [16]. Italian and Israeli studies also highlight the high prevalence of PPS and increased comorbidity risks, including cardiovascular disease, diabetes, and chronic pain [17,18]. Similarly, data from Taiwan indicate significantly elevated risks of stroke, hypertension, and other chronic systemic diseases among survivors [19,20].

In Korea, the health challenges of polio survivors must be understood within the context of rapid socioeconomic development and substantial improvements in healthcare infrastructure over the past 6 decades. Such environmental and systemic transitions suggest that the clinical profiles and healthcare needs of Korean polio survivors may differ significantly from those reported in Western cohorts. To accurately capture these dynamics, a systematic nationwide study of Korean polio survivors is urgently needed. Such research would enable robust evaluation of long-term outcomes, inform tailored rehabilitation strategies, and guide policy development. More broadly, these efforts would contribute to understanding the broader phenomenon of aging with disability.

Late effects of polio

Depending on the stage of life, polio survivors experience a va-

riety of problems following the onset of the initial disease. As individuals age, the natural functional decline associated with aging is superimposed on pre-existing disabilities, resulting in multiple late effects [2,11]. The key issues include persistent or newly emerging problems such as pain, fatigue, muscle weakness, functional impairment, and disability, including PPS. Because of these challenges, polio survivors often face limitations in independent activity and daily living. They frequently report depression, psychological and emotional distress, anxiety, and pain. Quality of life is reduced due to changes in social relationships, difficulty maintaining employment, and economic hardship [21,22]. As survivors grow older, ordinary age-related decline is compounded by pre-existing dysfunction, leading to an accumulation of late effects. New medical problems unrelated to polio also emerge in approximately 35% of survivors [23]. These conditions may cause newly developed weakness due to denervation or impaired coordination of reinnervated muscles. Progressive deterioration of neuromuscular function results in muscle atrophy, reduced physical fitness, and cardiopulmonary dysfunction. In addition, polio survivors commonly experience psychological distress along with physical dysfunction and functional decline.

PPS, characterized by new weakness and fatigue decades after the initial infection, is widely regarded as the representative late effect of poliomyelitis. However, the range of late effects extends far beyond PPS, encompassing diverse neuromusculoskeletal complications such as osteoporosis, progressive muscle weakness, degenerative arthritis, trauma- and overuse-related syndromes (e.g., tendinitis, carpal tunnel syndrome), as well as fall-related injuries, balance disturbances, skeletal deformities, respiratory difficulties, cold intolerance, and systemic conditions including cardiovascular and metabolic disorders (Fig. 1) [24-26].

Post-polio syndrome

PPS encompasses a wide range of physical and psychological symptoms, including newly developed weakness and fatigue arising after a 25–30-year period of stability following acute poliomyelitis [4]. There has been ongoing controversy regarding its diagnostic criteria due to the absence of definitive objective evidence. Previously, newly observed muscle atrophy was proposed as an essential diagnostic feature of PPS, but this criterion was criticized for resulting in delayed diagnosis, as it typically reflects an end-stage manifestation. Currently, the European Federation of Neurological Societies diagnostic criteria, published in 2000, are most commonly used. These criteria include: (1) a confirmed history of poliomyelitis; (2) partial or near-complete functional recovery after the acute episode; (3) at least 15 years of stable neurological function; (4) gradual or abrupt onset of progressive and persistent muscle weakness or abnormal muscle fatigability (manifesting as decreased endurance, with or without generalized fatigue, muscle atrophy, or musculoskeletal pain); and (5) exclusion of other potential causes of the symptoms [27].

Common symptoms associated with PPS include muscle and joint pain on the affected or unaffected side (89%), fatigue (86%), and new-onset weakness (83%) on the affected (69%) or unaffected (50%) side. New muscle atrophy (28%) and difficulties in activities of daily living (78%)—such as impaired walking (64%), difficulty climbing stairs (61%), and problems with dressing (17%)—are also characteristic of PPS [28].

The presence and severity of PPS symptoms appear to correlate with the severity of the original poliomyelitis, and it has been suggested that factors such as residual muscle weakness, viral persistence, arthritis, and spinal stenosis act synergistically in its development [29].

Secondary musculoskeletal disorders

Secondary musculoskeletal disorders are a major issue and can often be misdiagnosed as PPS. Degenerative arthritis frequently develops due to the long-term use of joints under biomechanically suboptimal conditions. Although arthritis commonly occurs on the paralyzed side, it may also arise from overuse of the unaffected side. Sensory disturbances, wrist or hand arthritis, reduced agility, and weakness in the hands frequently result from chronic overuse. Other manifestations of overuse syndrome include upper-limb pain due to prolonged use of walking aids, joint pain in both upper and lower extremities, and spinal pain associated with asym-

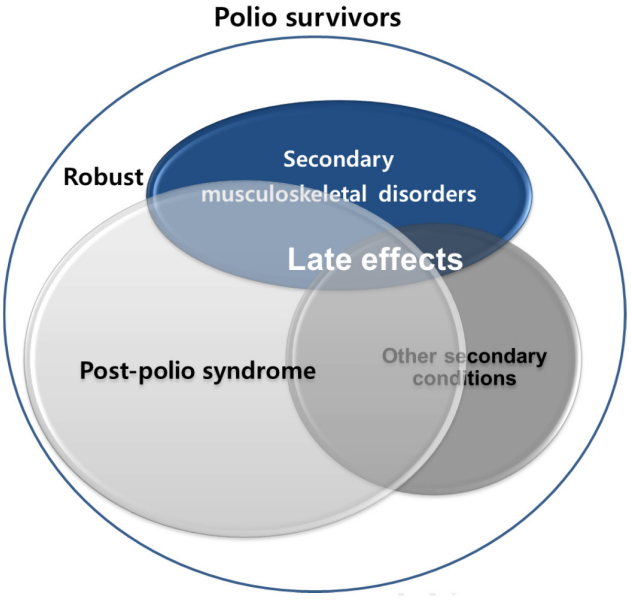

Fig. 1. Late effects of polio.

metry and abnormal gait patterns [30,31] (Table 1).

Inactivity and disuse stemming from muscle weakness and paralysis are major contributors to osteoporosis in polio survivors. Osteoporosis and fall-related fractures are frequently observed during middle age. Muscle strength directly affects bone mineral density through interconnected biomechanical and metabolic mechanisms [24], highlighting its crucial role in bone health. Most polio survivors are at high risk for fall-related injuries, as falls accelerate physical frailty and further deplete functional reserves [32]. Indeed, 64% of survivors report at least 1 major fall, and 35% sustain fractures as a result [33]. In a study of 317 Korean polio survivors, 68.5% reported at least 1 fall in the past year, and among those who fell, 42.5% experienced 2 or more falls within a single month [34].

These rates are more than twice as high as those observed for falls and fall-related fractures in the general population of older adults. Among survivors, 80% of fractures were caused by falls, typically occurring in limbs affected by atrophy. Of particular concern, most fractures involved sites such as the hip and distal femur, where mobility and physical function may deteriorate even after adequate healing [35]. Moreover, fear of falling itself is a major factor limiting physical activity. Comprehensive assessment and multidisciplinary management of fall-related problems are therefore essential for polio survivors.

Other secondary conditions

In addition to secondary musculoskeletal disorders, other conditions not encompassed by PPS are frequently observed [36] (Table 1). For instance, a rare neuromuscular disorder such as myotonic dystrophy has been reported to mimic PPS in a polio survivor [37], underscoring the need for careful differential diagnosis. The risks of pneumonia and respiratory distress increase due to respiratory muscle weakness, and sleep disorders, including central and obstructive complex sleep apnea, are common and contribute to poor sleep quality [38]. In cases of bulbar-type poliomyelitis, dysphagia and speech disorders may coexist [38,39]. Cold intolerance—strongly linked to neurogenic vascular insufficiency, venous stasis, and excessive heat loss—occurs in approximately 29% of survivors when their extremities are exposed to cold environments [39,40]. The prevalence of other chronic conditions, such as metabolic syndrome and cardiovascular disease, is also higher in polio survivors than in the general population. Reduced cardiovascular fitness, obesity, and hypercholesterolemia significantly increase cardiovascular risk [26,38]. Furthermore, pulmonary function in survivors shows a negative correlation with obesity, suggesting that body fat adversely affects lung capacity and may contribute to restrictive lung disease after controlling for muscle strength and activity level [41]. Older adults with a history of poliomyelitis share many of the multidimensional health challenges commonly seen in the general population of older adults, arising from physiological, psychosocial, and environmental factors [42].

Polio survivors also experience chronic emotional stress, anger (49%), and fear of falling (58%), along with a higher prevalence of peptic ulcers (80%) compared with the general population [3,43]. According to 3 North American studies, over 23% of polio survivors display a type A personality—characterized by competitiveness, time urgency, and a high-achieving temperament. Fa-

Table 1. Secondary musculoskeletal disorders and other secondary conditions as late effects

Late effects	Disorders
Secondary musculoskeletal disorders	Sensory disturbances (carpal tunnel syndrome or others)
	Joint pain in the upper and lower extremities
	Arthritis of the wrist or hand, knee
	Rotation cuff tear related to excessive use of the unaffected side
	Osteoporotic fractures
	Spinal pain related to asymmetry and abnormal gait patterns
	Decreased hand dexterity
Other secondary conditions	Pneumonia and respiratory diseases
	Sleep apnea
	Dysphagia and speech disorders
	Cold intolerance
	Metabolic syndrome
	Decreased fitness of the cardiovascular system
	Obesity
	Chronic emotional stress

tigue and muscle pain, accompanied by anxiety, frequent headaches, neck pain, and lower back pain, are more common among type A survivors than in non–type A individuals [44,45]. Moreover, polio survivors exhibit significantly lower health-related quality of life, particularly in the domains of mobility, activities of daily living, pain/discomfort, and anxiety/depression [46].

Causes of late effects

Why do late effects occur in polio survivors? Several hypotheses have been proposed. First, they may arise from the failure of reinnervation. Theoretically, maintaining axonal function becomes increasingly difficult after more than a decade, as neuronal metabolism becomes depleted due to abnormal axonal loss in surviving motor neurons. Consequently, gradual muscle weakness (approximately a 1% decrease per year on average), loss of muscle fibers, and progressive muscle atrophy develop. Second, late effects may result from chronic overuse of muscles previously affected by polio. With sustained overuse, these muscles remain in a state of continuous contraction, exacerbating weakness and functional loss [19,26,30,31]. A third hypothesis involves stress and hormonal alterations. Studies have reported that among polio survivors who developed new functional problems, significant decreases in growth hormone levels were observed in 9 out of 10 cases [29]. Furthermore, a diminished reactive response to external stimuli has been associated with dysfunction of the reticular activating system [30]. The impaired ability to maintain attention and process complex information rapidly appears to contribute to severe fatigue and exhaustion. In addition, the aging process itself may exacerbate functional decline in polio survivors through physiological changes across multiple organ systems—such as reduced respiratory capacity, elevated blood pressure, increased cholesterol and glucose levels, and joint stiffness. The number of spinal cord motor neurons remains relatively stable until approximately 60 years of age, after which it declines by about 1% annually, resulting in roughly a 30% loss by age 90. Similarly, both the number of muscle fibers and muscle strength are reduced by nearly half compared with young adults. Therefore, the combined effects of neuronal and muscular loss, together with declining cellular function associated with aging, likely contribute substantially to the development of late effects [24,31].

Conclusion

Polio survivors exemplify the unique challenges of aging with disability. Although the global eradication of poliomyelitis has eliminated new infections, the generation of survivors now entering older age faces a dual burden: the natural decline associated with aging compounded by the late effects of long-standing disability. These late effects accelerate functional deterioration and heighten vulnerability, underscoring the need for a paradigm shift from fragmented, symptom-focused care toward integrated, life course–oriented strategies for prevention and management [3,4]. Such an approach could more effectively address the needs of older adults with disabilities, reduce hospital utilization, and mitigate morbidity and mortality risks [47].

The medical paradigm for polio survivors has evolved considerably over time. In the mid-20th century, the primary focus was on eradicating poliovirus and managing acute paralysis. During the 1960s and 1970s, orthopedic surgery became the central issue in survivor care [26]. As these individuals transitioned into adulthood, the need for orthopedic interventions declined, and medical interest in polio correspondingly waned. Since the 1980s, however, as survivors have reached middle and older age, late effects have reemerged as major health concerns, reframing poliomyelitis not as a historical epidemic but as a lifelong condition [48].

The experiences of polio survivors provide broader insights into the phenomenon of aging with disability. Individuals aging with long-term disabilities consistently report that healthy aging involves more than medical treatment—it requires self-management, social participation, psychological resilience, and independence in daily life [5]. These perspectives reinforce the importance of anticipating late effects, designing preventive interventions, and ensuring equitable access to comprehensive, multidisciplinary care for those aging with long-standing disabilities. In caring for polio survivors, healthcare providers should adopt a life course approach grounded in a detailed assessment of functional abilities, activity patterns, residual sequelae, and the degree of functional limitation [3].

By focusing on polio survivors as a paradigmatic group, we gain valuable insight into the historical evolution of disability medicine, the ongoing transition toward life course–based approaches, and the strategies needed to promote health, functional capacity, and dignity across the lifespan.

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Conceptualization: GYS. Data curation: GYS. Methodology/formal analysis/validation: JHH. Project administration: GYS. Funding acquisition: GYS. Writing–original draft: GYS, JHH. Writing–review & editing: GYS, JHH.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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Hip fracture and cognitive impairment in older adults–integrated approaches to rehabilitation: a narrative review

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Fragility fractures, particularly hip fractures, represent a major public health concern among older adults and are associated with high morbidity, mortality, functional decline, and socioeconomic burden. Cognitive impairment is common in older adults with hip fractures and contributes to increased fracture risk, poor postoperative outcomes, delayed recovery, and higher rates of institutionalization. This review aimed to examine rehabilitation strategies for older adults with hip fractures, with a specific focus on considerations for those with cognitive impairment. Evidence suggests that individuals with mild-to-moderate cognitive impairment can achieve meaningful functional gains through structured, intensive, multidisciplinary rehabilitation programs incorporating progressive resistance training, balance and mobility exercises, and individualized approaches tailored to cognitive and physical abilities. However, the implementation of such programs is often hindered by insufficient staff training and awareness in dementia-specific rehabilitation, limited resources, and the lack of standardized protocols defining eligibility, intensity, and adaptation. Optimizing outcomes requires structured, tailored rehabilitation protocols, enhanced staff education, interprofessional collaboration, and proactive management of delirium and secondary fracture prevention through fracture liaison services, while concurrently addressing systemic barriers such as resource constraints. Integrated, coordinated care across the continuum is essential to maximize recovery, independence, and quality of life in older adults with hip fractures and cognitive impairment.

Keywords: Aged; Cognition disorders; Dementia; Hip fractures; Rehabilitation

Introduction

Fragility fractures typically result from low-energy trauma, defined as a fall from standing height or less, or from spontaneous fractures occurring at common sites such as the vertebrae, proximal hip, wrist, or humerus [1]. Although osteoporosis is clinically significant primarily because of fragility fractures resulting from decreased bone strength [1,2], it is important to recognize that most fragility fractures occur in individuals with only modest reductions in bone mass or even normal bone mineral density (BMD) [2]. This observation highlights that factors beyond BMD, such as bone geometry, microarchitecture, and other clinical risk determinants, play crucial roles in fracture risk [2]. Ultimately, fragility fractures represent a major consequence of both osteoporosis and aging, irrespective of BMD status.

Among fragility fractures, hip fractures are the most severe because of their high mortality, profound functional decline, and substantial healthcare costs. The 1-year mortality rate ranges from 20% to 24%, and approximately one-third of patients require nursing home care [3]. Functionally, only 40%–60% of survivors regain their pre-fracture mobility, and about 60% continue to need assistance 1 year later, underscoring the persistent challenges of recovery [3]. With the rapidly aging global population, the incidence of hip fractures is projected to increase sharply, amplifying the socioeconomic burden. In 2019, 1.4 million hip fractures occurred worldwide among individuals aged ≥50 years, and this figure is expected to rise to 4.5 million by 2050 [4]. The total healthcare cost per patient—including hospitalization, medical treatment, and social care—exceeds US$50,000 within the first year following a hip fracture [5]. In South Korea, which is projected to

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become a super-aged society by 2025 [6], the increase in hip fracture incidence is anticipated to be approximately 2.64 times higher than the global average [7]. Nationwide data from 2022 reported an incidence of 16.9 per 10,000 persons, with a strikingly higher rate of 100.7 per 10,000 persons among those aged ≥80 years [8]. In 2021, the 1-year mortality rate after hip fracture in individuals aged ≥50 years was 18.2% [8]. Economically, compound fractures, including hip fractures, accounted for the highest average medical expenditures (US$8,100), followed by isolated hip fractures (US$6,100) [9]. Patients with hip fractures incurred significantly greater direct medical costs than those without fractures. During the first year post-fracture, additional direct medical costs averaged US$2,514 per patient, with an additional US$264 in the second year [10], illustrating the enduring financial burden in older adults.

Multiple factors, including cognitive impairment, contribute to poor outcomes after hip fractures, further exacerbating the socioeconomic impact [11]. Cognitive impairment—ranging from mild deficits to severe dementia—becomes increasingly prevalent with age and is influenced by cardiovascular and neurological conditions, genetics, frailty, lifestyle, education, social engagement, and nutrition [12]. It is particularly common among older adults with hip fractures, with approximately 19% of patients having dementia and up to 40% exhibiting some degree of cognitive impairment [13]. Cognitive impairment not only increases the risk of hip fractures [13,14] but also worsens postoperative outcomes [11], complicates rehabilitation, and hinders recovery [13,15].

Given the high prevalence and significant impact of cognitive impairment on outcomes following hip fractures, this review aimed to explore rehabilitation strategies for older adults with hip fractures, emphasizing the role of cognitive impairment. The discussion highlights the importance of early identification and standardized assessment of cognitive status to guide individualized management strategies and improve functional recovery.

Ethics statement

As this study is a literature review, it did not require institutional review board approval or individual consent.

Hip fractures and cognitive impairment

Cognitive impairment is a well-recognized risk factor for hip fractures in older adults because it is associated with reduced physical function, multiple comorbidities, and polypharmacy, including the use of medications that increase fracture risk [13]. Compared with cognitively intact individuals, those with cognitive impairment exhibit a higher prevalence of osteoporosis and reduced access to preventive care, both of which contribute to an elevated risk of hip fractures [13]. In addition to serving as a risk factor, cognitive impairment independently predicts poor outcomes after hip fractures, including high rates of nursing home admission, mortality, recurrent fractures, and impaired functional recovery [11,14,16]. Older adults with dementia are particularly vulnerable, with a markedly increased risk of loss of walking ability and greater limitations in activities of daily living (ADLs) after fracture than those without dementia [14].

Cognitive impairment often coexists with other geriatric syndromes such as sarcopenia, frailty, and malnutrition [17], which are closely interrelated and collectively worsen outcomes after hip fracture. Patients with sarcopenia are 2.85 times more likely to have cognitive impairment (95% confidence interval [CI], 2.19–3.72) [18]. Conversely, cognitive impairment is more prevalent among patients with sarcopenia (odds ratio, 2.50; 95% CI, 1.26–4.92) [19], and nearly one-third of adults aged ≥65 years with cognitive impairment are affected by sarcopenia [20]. Malnutrition frequently develops after hip fracture and is more common among those with cognitive impairment [11]. Frailty, defined as an age-related decline in physiological reserves, not only increases the risk of hip fracture but also is associated with a heightened risk of dementia [21]. Collectively, these interrelated conditions are consistently linked to poor pre-fracture function, multimorbidity, and adverse outcomes.

Cognitive impairment exacerbates poor outcomes after hip fracture by limiting mobility, reducing physical activity, and impairing nutritional intake, thereby accelerating muscle weakness and atrophy [17,22,23]. Conversely, muscle weakness and atrophy associated with sarcopenia, malnutrition, and frailty further reduce physical activity—an essential determinant of brain health that supports brain volume preservation and memory-related neural function—and contribute to cognitive decline through mechanisms such as chronic inflammation, impaired cerebral blood flow, and disruptions in the muscle–brain axis mediated by dysregulated myokine secretion [24]. Patients with cognitive impairment are generally less likely to achieve early mobilization after hip fracture surgery compared with those without such impairment [25]. Walking, the primary focus of post-surgical rehabilitation, is a complex process requiring not only muscle strength, joint flexibility, and proprioception, but also cognitive functions such as executive function, attention, motor planning, concentration, memory, and learning [26]. Therefore, cognitive impairment, whether alone or combined with sarcopenia, frailty, and malnutrition, substantially increases vulnerability to poor out-

comes after hip fracture.

Patients with cognitive impairment are often perceived as having limited or no rehabilitation potential, leading to fewer referrals, reduced opportunities for mobilization, lower therapy intensity, and premature discontinuation of treatment [15,25,27]. These challenges are compounded by systemic limitations, including inadequate inpatient and outpatient rehabilitation resources, insufficient provider training, and the absence of dementia-specific rehabilitation protocols [15,25]. In a cross-sectional survey of rehabilitation providers in Australia and New Zealand, only 10% of acute care facilities reported having a specific rehabilitation protocol for individuals with dementia [28]. Moreover, memory deficits can hinder adherence to therapy—not due to unwillingness but to difficulty recalling instructions [25]—further restricting participation and functional gains. Combined with underlying physical vulnerabilities, these barriers contribute to poor functional outcomes and delayed recovery.

Rehabilitation in older adults with hip fracture

Effective recovery after a hip fracture requires not only timely surgical intervention, postoperative stabilization, complication prevention, and initial pain management, but also early, intensive rehabilitation aimed at restoring physical function. Beyond the acute phase, long-term management, including re-fracture prevention, sustained exercise programs, medication management, nutritional support, chronic disease control, and quality-of-life improvement, is essential [29]. Throughout this process, a multidisciplinary team comprising rehabilitation specialists, physicians, physical and occupational therapists, nutritionists, clinical nurse specialists, and social workers collaborates to support recovery while providing psychological support for patients and their families and establishing continuing social support networks after discharge [29]. Continuous rehabilitation should be integrated with secondary prevention within a coordinated care framework to ensure a seamless transition from acute treatment to post-discharge recovery [29].

Multidisciplinary rehabilitation during the acute phase has proven particularly effective in improving functional outcomes, reducing nursing home admissions, lowering healthcare costs, and decreasing mortality among older adults with hip fractures; therefore, it serves as a cornerstone of hip fracture management [30-32]. Delivered through an interdisciplinary, coordinated team, this approach provides intensive and integrated orthogeriatric care that combines structured physical therapy, early mobilization, education, and goal setting to facilitate early supported discharge [32]. It also promotes continuity of care through structured post-discharge coordination, such as fracture liaison services (FLSs) [33]. Rehabilitation interventions should be intensive, structured, individualized, and guided by standardized functional assessments [32]. Structured exercise refers to carefully designed interventions that target impairments, activity limitations, and participation restrictions. Such programs typically combine multiple components—progressive resistance training, balance exercises, functional mobility training, and weight-bearing activities—delivered at high frequency along with early mobilization, rather than relying solely on simple gait training [32].

An expanding body of clinical evidence supports the superior effectiveness of multidisciplinary rehabilitation compared with usual orthogeriatric care or basic exercise programs in acute settings. A recent randomized controlled trial (RCT) in South Korea [34]—the first to directly compare distinct rehabilitation strategies in older adults with hip fractures—demonstrated that comprehensive multidisciplinary rehabilitation was superior to conventional rehabilitation in improving ambulation and other functional outcomes over a 12-month follow-up. The program provided structured, high-volume, high-intensity interventions, including physical therapy (two 30-minute sessions per day for 10 days) and occupational therapy (4 days), consistent with previously reported intensive rehabilitation protocols and aligned with current clinical guidelines (e.g., 2 hours per day, 3 days per week; three 90-minute sessions daily, 7 days per week; or 60 minutes per day, 6 days per week) [32]. Similarly, a review by Beaupre et al. [35] found that very intensive physiotherapy (extended inpatient therapy with a home exercise program), intensive outpatient center-based rehabilitation (e.g., 45–90 minutes, 3 times per week), and progressive resistance training improved physical performance and reduced falls. Multidisciplinary programs that integrate intensive exercise with comprehensive management provide additional benefits, including better ADL performance and lower risks of mortality, institutionalization, and disability. Collectively, these findings highlight that rehabilitation effectiveness depends not only on its availability but also on ensuring adequate intensity, structure, and multidisciplinary integration to maximize recovery after hip fracture.

Recovery of gait and balance in older adults with hip fractures typically occurs within 6–9 months, whereas instrumental ADLs may take up to 1 year [36]. However, many survivors fail to fully regain their pre-fracture mobility and continue to require assistance with daily activities, with a considerable proportion eventually needing nursing home care [3]. This underscores that older adults with hip fractures often require prolonged recovery periods, and many continue to experience persistent functional lim-

itations. Depending on individual recovery trajectories, patients should be connected to ongoing rehabilitation programs and community-based support services to optimize long-term outcomes.

The FLS is a coordinator-based integrated model designed to prevent secondary fractures in patients with fragility fractures. Initially developed in the United Kingdom to address the rising incidence of such fractures, the FLS has since expanded worldwide, with more than 1,142 programs implemented across multiple regions since 2012 [37]. The FLS encompasses both acute management and secondary prevention by coordinating evaluation of the index fracture, assessment of underlying comorbidities, and initiation of early postoperative rehabilitation in acute hospitals. It also ensures ongoing fracture risk assessment, targeted treatment, and coordinated care as patients transition through post-acute services toward completion of their rehabilitation continuum. Evidence indicates that the FLS increases osteoporosis diagnosis and treatment rates, decreases fall and re-fracture incidence, reduces fracture-related morbidity and mortality [38], and lowers healthcare costs [39]. Considering the poor outcomes often observed in hip fracture patients—such as delayed functional recovery, prolonged hospitalization, and elevated re-fracture risk—the FLS model represents a critical strategy for improving outcomes across the entire continuum of care, from the acute hospital phase through post-acute rehabilitation after discharge.

Rehabilitation in older adults with hip fracture and cognitive impairment

Older adults with hip fractures and cognitive impairment are less likely to regain their pre-fracture functional level, and delivering effective rehabilitation can be challenging. Nevertheless, multiple studies have demonstrated that these patients can benefit significantly from structured, intensive rehabilitation interventions. A systematic review by Allen et al. [40] examined rehabilitation interventions in older adults with hip fractures and compared outcomes between those with mild-to-moderate dementia and those without cognitive impairment. Thirteen secondary analyses (5 RCTs and 8 cohort studies) conducted in early postoperative inpatient settings were included. Interventions commonly involved strength, range-of-motion, gait, and transfer training, as well as self-care activities. Owing to heterogeneity in participants, interventions, and outcomes, a meta-analysis was not feasible. Functional outcomes, most frequently measured using the Functional Independence Measure and Barthel index, showed no significant effect of cognitive status on recovery. Individuals with cognitive impairment achieved functional improvements comparable to those without impairment. Similarly, across 5 studies assessing ambulation with various measures, patients with mild-to-moderate dementia demonstrated gains similar to those of cognitively intact patients.

A recent Cochrane review included 7 trials [41]. Three compared enhanced inpatient care with conventional care, 2 evaluated enhanced care spanning inpatient and home settings, and 2 compared geriatrician- versus orthopedic-led inpatient care. None of the interventions were designed specifically for individuals with dementia; thus, the review's data were derived from subgroups of participants with dementia or cognitive impairment enrolled in RCTs assessing care models for older adults after hip fracture. The outcomes evaluated included ADLs and functional performance (4 trials); mortality (5 trials); postoperative adverse events including delirium (6 trials); and health and social care utilization measures such as length of hospital stay, readmissions, emergency visits, discharge destination, and medication use (6 trials). The review suggested that enhanced inpatient models of rehabilitation and care may reduce postoperative delirium and hospital length of stay in patients with dementia following hip fracture, although the available evidence remains limited.

A review of 4 RCTs by Beaupre et al. [35] investigating approaches to maximize functional recovery after hip fracture evaluated intensive inpatient rehabilitation in community-dwelling older adults with cognitive impairment compared with usual postoperative care. Patients with mild-to-moderate cognitive impairment benefited from higher-intensity interventions, demonstrating greater improvements in walking speed, functional performance, pain reduction, ambulation, and likelihood of returning to their pre-fracture residence. Although patients without cognitive impairment generally achieved higher absolute functional levels, both groups exhibited significant functional gains, indicating that cognitive impairment does not preclude the benefits of intensive rehabilitation.

A recent scoping review identified 17 studies examining rehabilitation interventions for adults with hip fractures and cognitive impairment, most of which included older adults with a mean age of ≥75 years [42]. Six studies enrolled only participants with cognitive impairment, while the others included mixed populations. The interventions were broadly classified into physical rehabilitation (e.g., standing, walking, range of motion, balance, and strength training) and comprehensive programs that incorporated discharge planning, patient and family education, and nutritional support. Delivery was primarily led by interdisciplinary teams, although 2 studies involved physiotherapists alone, and approximately half tailored interventions to individual needs. All programs were initiated in hospital settings, with several extending to

home-based or cross-sectoral components. The outcomes most frequently targeted physical function and ADL performance, with some studies additionally assessing mortality, readmission, length of stay, and quality of life. The findings were mixed: several studies reported improvements in walking ability, ADL performance, and reduced hospital stay, whereas others found no significant differences. Mortality outcomes were inconsistent. Notably, comparative analyses indicated that patients with and without cognitive impairment achieved largely similar functional outcomes, although one study reported poorer fall and emergency visit outcomes among those with cognitive impairment. Overall, the evidence underscores the potential of rehabilitation interventions to facilitate recovery in this population, while the heterogeneity in study design and outcome measures highlights the need for further research to establish standardized, evidence-based protocols.

Many patients with hip fractures and cognitive impairment require prolonged, coordinated post-discharge rehabilitation to achieve optimal functional recovery. However, the most effective rehabilitation and care model for this population remains unclear. A Cochrane review by Smith et al. [41] and a review by Chu et al. [43] evaluated largely overlapping studies on community-based rehabilitation after hip fracture. Chu et al. [43] reported that post-discharge, community-based interventions produced promising effects on physical function, mobility, and ADLs in older adults with cognitive impairment. Similarly, the Cochrane review found that enhanced interdisciplinary inpatient and home-based rehabilitation models improved functional performance and ADLs and reduced falls at 12 months [41]. Nevertheless, the evidence remains insufficient to recommend these models over conventional rehabilitation specifically for individuals with dementia. A systematic review by Resnick et al. [44] included 7 heterogeneous studies conducted in post-acute care settings, comprising 4 RCTs, a single-group pre–post study, a descriptive comparison, a matched case–control trial, a non-equivalent group trial, and a case report. Across these studies, patients with and without cognitive impairment demonstrated functional gains, although cognitive function itself did not improve. Most interventions produced outcomes comparable to those of usual care in terms of functional recovery, length of stay, and discharge destination. However, specific models—such as the patient-centered rehabilitation model for individuals with cognitive impairment, the cognitive geriatric unit, and augmented exercise programs—were associated with a greater likelihood of returning home and with improvements in gait, balance, mobility, and quality of life. These findings suggest that post-acute rehabilitation targeting patients with cognitive impairment is feasible and that intensive, structured exercise combined with innovative engagement strategies can optimize functional outcomes in this population.

Although cognitive impairment may limit complete functional recovery after hip fracture, patients with mild-to-moderate dementia can still benefit substantially from structured rehabilitation and should not be excluded from participation. This recommendation is consistently supported by recent systematic reviews [35,40,42-44] and clinical guidelines [32]. Interventions incorporating progressive high-intensity resistance training, balance exercises, weight-bearing activities, and functional mobility training have been shown to enhance mobility, ADL performance, pain management, and the likelihood of returning to independent living [32]. Standardized cognitive assessment is essential, as modifiable factors—such as medication optimization, complication prevention, and early mobilization [44]—can influence outcomes and enable individualized treatment planning. Multidisciplinary, tailored programs that potentially integrate cognitive therapies or technology-assisted interventions are also promising. Older adults with cognitive impairment often struggle to maintain or regain mobility and functional abilities after discharge, frequently requiring long-term care, extended hospital stays, and experiencing higher readmission rates [13]. Beyond early rehabilitation and intensive exercise during the acute phase, extended post-acute rehabilitation is crucial for optimizing recovery. Integrating the FLS with prolonged rehabilitation, structured discharge planning, and coordinated post-discharge care may further enhance functional and clinical outcomes. The studies included in the reviews discussed in this section are summarized in Table 1 (Supplement 1).

Management considerations for older adults with hip fractures and cognitive impairment

Delirium

Delirium is particularly common among older adults with hip fractures and dementia. Its occurrence is primarily influenced by advanced age and cognitive impairment and is precipitated by perioperative stress, hospital-related factors, polypharmacy, nutritional and fluid deficiencies, and systemic inflammation [45]. Delirium at the onset of rehabilitation can hinder postoperative weight-bearing, delay mobility recovery, and complicate effective therapy [25,46]. Given its reversible nature and substantial impact on functional outcomes, early recognition and proactive management are essential [47]. Effective delirium management can enhance rehabilitation potential, reduce the risk of long-term care placement, and decrease mortality [48]. Therefore, prevention and early intervention are integral components of post-fracture rehabilitation strategies for older adults.

Table 1. Summary of studies on rehabilitation in older adults with hip fracture and cognitive impairment included in the reviewed literature

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Watne et al. [S52][a] (2013), Norway	Randomized controlled trial	329 patients; intervention (ortho-geriatric ward): 163 (42 men, 26%); control (orthopedic ward): 166 (38 men, 23%)	Intervention: 84 (55–99); control: 85 (46–101)	Conventional recovery intervention: a traditional orthopedic ward with conventional rehabilitation.	Ortho-geriatric intervention: intervention group participants were transferred as soon as possible to the ortho-geriatric ward, stabilized there preoperatively, and transferred back to the same ward postoperatively for further treatment and rehabilitation.	Cognition (CDR+CERAD), ADL, NEADL, IQCODE, mortality, SPPB, delirium, complications, dementia (4 & 12 months), LOS	No significant differences were found between acute geriatric and orthopedic ward care in cognitive function at 4 months, delirium rates, or 4-month mortality. In a subgroup analysis, patients living at home pre-fracture and treated in the geriatric ward had better mobility at 4 months (SPPB median 6 vs. 4, P = 0.04). Overall, orthogeriatric care did not reduce delirium or long-term cognitive impairment, but improved mobility in community-dwelling patients.
Huusko et al. [S53][a),b),c),d),e),f] (2000), Finland	Randomized controlled trial	243 independently living patients with dementia; intervention: 120 (79 with MMSE < 24); control: 123 (67 with MMSE < 24); overall: 174 women, 69 men	Intervention: 80 (67–92); control: 80 (66–97)	Usual care rehabilitation in local hospitals consisted mainly of treatment by general practitioners and physiotherapists, with variable input from occupational therapists and rehabilitation nurses; all participants were encouraged to mobilize from the first POD.	Patients were referred to a geriatric ward for intensive, multidisciplinary rehabilitation that included staff training, early mobilization from the first POD, twice-daily physiotherapy, and daily activity practice with nursing support. Individualized schedules, weekly team meetings, and input from occupational and physiotherapists ensured tailored care. Ongoing communication with families was supported by educational materials. Discharge planning was coordinated through weekly discussions, with up to 10 physiotherapy-led home visits provided for those returning to independent living.	LOS, mortality, and place of residence 3 months and 1 year after surgery for hip fracture	LOS did not significantly differ between those with normal cognition or severe dementia. However, the intervention group had shorter LOS in mild (29 days vs. 46.5 days, P = 0.002) and moderate dementia (47 days vs. 147 days, P = 0.04). At 3 months, more patients in the intervention group lived independently (mild: 91% vs. 67%, P = 0.009; moderate: 63% vs. 17%, P = 0.009). At 1 year, independence was maintained in 77% (mild) and 62% (moderate) of intervention patients versus 76% (P = 0.092) and 33% (P = 0.1) in controls. Mortality did not differ. Overall, active geriatric rehabilitation facilitated earlier discharge and greater return to independent living in mild-to-moderate dementia

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Naglie et al. [S54][c),e)] (2002), Canada	Randomized controlled trial	280 patients, of whom 74 (26%) had cognitive impairment	Interdisciplinary care: 83.8 (6.9); usual care: 84.6 (7.3)	Usual care	Inpatient interdisciplinary care with complication prevention (delirium, urinary issues, constipation, pressure ulcers, polypharmacy), early mobilization, twice-daily PT, and early discharge planning vs. usual postoperative care.	Recovery of ambulation and transfers (modified BI); return to pre-fracture residence at 3 and 6 months	At 6 months, 17/36 (47%) of the intervention group and 9/38 (24%) of the control group were alive with no decline in ambulation, transfers, or residential status (P = 0.03). Among patients with dementia, a greater proportion in the intervention group maintained ambulation, transfers, and residence compared with controls.
Jones et al. [S55] [b)] (2002), Canada	Prospective cohort study	100 patients (83 women, 17 men); mean MMSE 25.4 ± 4.7	81.7 (7.6)	NA	Intensive rehabilitation including PT (approximately 1.5 hr/day) and OT (approximately 1.0 hr/day), 5 days per week, for 3 to 6 wk.	Physical and cognitive functioning (motor and cognitive FIM); Rehabilitation outcome for locomotion (MRFS)	Total FIM scores improved after discharge (P < 0.001) with the improvement in motor function (P < 0.001) not cognitive function (P < 0.443). Rehabilitation efficacy (P < 0.001) and efficiency (P < 0.001) improved with regard to participant function.
McGilton et al. [S56][b),e)] (2009), Canada	Longitudinal retrospective feasibility study	31 community-dwelling patients (58% women); 17 with impaired cognition (MMSE < 23) and 14 with normal cognition	87	NA	ACTED model-based rehabilitation program—early initiation, individualized assessment (dementia/delirium/depression), patient-centered goals, tailored therapy, behavioral symptom management, staff education	FIM (motor, cognition), discharge location (community/institution/acute care/death), rehabilitation efficiency (functional gain per inpatient day)	There were no differences between patients with and without cognitive impairment in LOS, rehabilitation efficiency, or motor and cognitive FIM scores. The majority of patients in both groups were discharged home (80%), while 11.8% of cognitively impaired patients were discharged to continuing care facilities.
McGilton et al. [S57]b),f) (2013), Canada	Nonequivalent quasi-experimental pre-post design	149 community-dwelling patients; usual care: 76 (30% with cognitive impairment); intervention: 73 (33% with cognitive impairment)	Usual care: 80.1 (6.7); intervention group: 82.5 (8.8)	Usual care	PCRM-CI: integrates rehabilitation management, dementia care, delirium prevention/management, staff education/support, and family/caregiver education/support	Mobility & locomotion (FIM mobility/locomotion subscales); motor function (FIM motor subscale); living situation (interview)	No difference in mobility gains was observed between PCRM-CI and usual care groups; however, intervention patients were more likely to return home after discharge (P = 0.02), indicating that interdisciplinary PCRM-CI can support successful rehabilitation in older adults with cognitive impairment after hip fracture repair.

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Moseley et al. [S58][b),c),d)] (2009), Australia	Randomized controlled trial	160 patients; high intervention: 80 (37.5% with cognitive impairment); low intervention: 80 (30% with cognitive impairment); overall, 54 patients (34%) had cognitive impairment	High intervention: 84 (8); low intervention: 84 (7)	Lower-dose exercise (30 min/day, mostly seated/supine; limited walking with aids) for 4 weeks, followed by home-based self-directed program	Higher-dose exercise (60 min/day × 16 wk): standing, weight-bearing (multidirectional stepping, sit-to-stand), progressed via reduced support/height blocks; initiated inpatient, continued at home with walking program.	Knee extensor strength, 6MWT; functional ability (PPME, sit-to-stand, gait aid, BI); balance (6 tests, self-report); pain, fear of falling (FES), QoL (EQ-5D); LOS, residential status, community service use, adverse events, treatment adherence	At 4 and 16 weeks, cognitively impaired patients in the high group had greater improvements in walking speed (+0.20 m/sec; +0.24 m/sec) and BI (+9; +17); by 16 weeks, they also showed better FES and EQ-5D scores, were more likely to walk unaided, and reported less pain vs. low group.
Rosler et al. [S59][b)] (2012), Germany	Case-control study	96 patients—48 with proximal femur fracture (prospective) and 48 matched controls (cognitive status, age, sex, surgical treatment); mean MMSE 14.5 ± 6.3 in both groups; 73% women	84.1 (7.8)	Conventional rehabilitation (PT, OT)	Specialized cognitive geriatric unit with environmental modifications (e.g., open wandering areas), comprehensive geriatric assessment, staff training (integrative validation, gerontological-psychiatric care), and higher nurse staffing (18.5 nurses/23 beds ≈1:1.5) vs. control ward (14 nurses/28 beds ≈1:2).	BI (function); Tinetti scale (gait/balance); LOS; LTC placement; medication use	LOS was significantly longer in the cognitive geriatric unit than in the conventional rehabilitation group. No group differences were observed in functional status, medication use, or discharge location. However, the cognitive geriatric unit group demonstrated significantly greater improvement in balance ($P = 0.003$).
Stenvall et al. [S60][c),f)] (2012), Sweden	Randomized controlled trial (subgroup analysis)	64 patients; intervention: 28; control: 36	Intervention: 81.0 (5.8); control: 83.2 (6.4)	Usual care	Multidisciplinary program with complication prevention (pressure ulcers, delirium, falls), nutritional assessment, pain management, and early mobilization with daily PT during hospitalization vs. usual care.	Fall incidence rate, walking ability, ADL, MMSE, modified OBS scale	Fewer falls occurred in the intervention group than in the control group (4% vs. 31%, $P = 0.008$); at 4 months, more participants in the intervention group regained independent walking (67% vs. 6%, $P = 0.005$) and pre-fracture functional independence (53% vs. 21%, $P = 0.027$).
Giusti et al. [S61][e)] (2007), Italy	Prospective cohort study	96 patients with dementia; intervention (institution-based rehabilitation): 55; control (home-based rehabilitation): 41	Intervention: 84.4 (6.9); control: 84.1 (5.4)	Home rehabilitation program	Institution-based rehabilitation	Functional recovery (BI) at 3, 6, and 12 months	Comparable recovery of ADL in patients with dementia receiving either home-based rehabilitation or institutional rehabilitation.

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Goldstein et al. [S62][e] (1997), USA	Prospective cohort study	58 patients; 35 with cognitive impairment (18 mild, 9 moderate, 8 severe)	84.0 (6.7)	NA	In-patient geriatric rehabilitation unit	Functional recovery (FIM) and discharge location at 1 month	Patients with impaired and normal cognition showed similar gains in FIM scores, and rates of return to the community did not differ between the 2 groups.
Heruti et al. [S63][e] (1999), Israel	Prospective cohort study	204 patients; 119 with available MMSE data; 54 identified with cognitive impairment	80 (7.1)	NA	Comprehensive in-patient interdisciplinary rehabilitation	Functional recovery (FIM motor subscale) at 1 month	Motor FIM scores were lower in patients with cognitive impairment. While absolute motor FIM gains were similar between impaired and normal cognition, relative functional gain was significantly reduced in patients in the lowest MMSE quartile.
Frances Horgan and Cunningham [S64][e] (2003), Ireland	Prospective cohort study	59 patients	80 (73–87)	NA	In-patient PT	Ambulation (EMS), discharge location at discharge	Patients with mild to moderate dementia achieved functional gains comparable to those with normal cognition regardless of PT intensity, whereas those with more advanced dementia did not. Cognitively impaired patients were less often discharged home and more often to nursing facilities.
Lenze et al. [S65][e] (2007), USA	Prospective cohort study	97 patients; SNF: 20 (51% with impaired cognition); IRF: 18 (31% with impaired cognition)	81.7 (8.8)	SNF	IRF	Functional recovery (FIM) at 2 and 12 weeks	Cognitive impairment had no overall effect on functional outcomes and did not alter the superior results of inpatient rehabilitation facilities over skilled nursing facilities.
Penrod et al. [S66][e] (2004), USA	Prospective cohort study	443 patients; 93 with cognitive impairment, 350 with normal cognition	81.4 (8.7)	NA	PT from day of surgery to POD 3 (early PT); number and duration of PT/OT sessions from POD 4 to 8 weeks post-admission (later therapy)	Ambulation (FIM locomotion subscale) at 2 and 6months	More PT exposure in the early days after hip fracture surgery was associated with significantly improved locomotion at 2 months post-admission

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Rolland et al. [S67][e),f)] (2004), France	Prospective cohort study	61 patients; 8 with impaired cognition (MMSE < 20), 23 with possible impairment (MMSE 20–27), and 10 without impairment (MMSE > 27)	MMSE < 20: 87.6 (7.2); MMSE 20–27: 83.9 (6.8); MMSE > 27: 77.6 (7.4)	NA	Rehabilitation in geriatric in-patient unit	Functional recovery (FIM, MRFS) at 2 months	No difference in FIM score change was observed between patients with and without cognitive impairment. Absolute FIM scores and MRFS were lower in cognitively impaired patients.
Uy et al. [S68][a),e)] (2008), Australia	Randomized controlled trial	11 patients, all women with impaired cognition; 3 in-patient multidisciplinary rehabilitation; 7 conventional rehabilitation	Intervention 83; control 80	Standard hospital treatment. Nursing home residents and those with limited disability were discharged once deemed orthopedically appropriate.	The inpatient multidisciplinary program included early postoperative nursing care to promote mobility and self-care, with physician assessment within 24 hours to guide individualized rehabilitation. Mobilization began after postoperative X-ray, targeting sitting out of bed the next day and walking the following day. Nurses supervised mobilization with physiotherapy input, supported by daily weekday sessions (ideally twice daily). Patients were reviewed 3–4 times weekly by orthopedic and rehabilitation physicians, and discharged to nursing homes as soon as feasible, with ongoing follow-up from the rehabilitation physician.	Functional recovery (BI) and gait velocity (Timed 2.44 m walk) at 1 and 4 months	Non-significant improvements were observed in BI and gait velocity in the intervention group.
Vidan et al. [S69][e)] (2005), Spain	Randomized controlled trial	319 patients; 78 with impaired cognition, 241 with normal cognition. Intervention: 155 (39 with impaired cognition, 25%); Usual care: 164 (39 with impaired cognition, 24%)	Intervention: 81.7 (7.8); usual care: 82.6 (7.4)	Usual care	Intensive multidisciplinary geriatric intervention	Functional independence (Katz ADL; FAC) at 3, 6, and 12 months	Patients without dementia showed greater gains in function and ambulation than those with dementia, although both groups improved.

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Al-Ani et al. [S70][f] (2010), Sweden	Prospective cohort study	246 patients with cognitive impairment; 19 died before discharge	84 (6.0)	NA	Postoperative PT began immediately, with standing on day 1 and assisted walking thereafter. Transfer to rehabilitation units was jointly decided by the physician and ward staff. Rehabilitation care was provided under the Health and Medical Services Act, while residential care under the Social Services Act had limited PT resources. In rehabilitation units, typically run or affiliated with Stockholm County Council, physiotherapists and occupational therapists provided daily activities.	ADL and walking ability at 4 and 12 months	ADL and preserved walking ability were associated with discharge to rehabilitation.
Chammout et al. [S71][f] (2021), Sweden	Prospective cohort study	98 patients with cognitive dysfunction; intervention group: 38; control group: 60	Intervention: 85 (4.0); control: 86 (6.0)	After surgery, patients were discharged directly to nursing homes, where rehabilitation depended on PT availability and staff capacity, with many lacking structured programs for femoral neck fracture patients.	Rehabilitation in the geriatric ward was individually tailored to cognitive status, with the goal of restoring walking ability before discharge. The average stay was 10 days prior to return to the nursing home.	Main outcomes: hip-related complications and reoperations. Secondary outcomes: return to previous walking status, mortality, HRQoL (EQ-5D), hip function (modified HHS), ADL (Katz index), hip pain and adverse events	The lack of geriatric rehabilitation was correlated with poorer outcomes overall and those who receive geriatric rehabilitation were less likely to be confined to a wheelchair or bedridden at the 1-year follow-up.

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Karlsson et al. [S72][†] (2020), Sweden	Randomized controlled trial (subgroup analysis)	103 patients; 57 in the GIHR group and 46 in the control group	83.9 (6.8); intervention: 84.5 (47.1); control: 83.2 (6.4)	Interdisciplinary rehabilitation based on comprehensive geriatric assessment provided individualized plans, staff engagement in daily activities, and structured discharge planning, with emphasis on preventing and managing postoperative complications. Physiotherapists and occupational therapists retrained patients in PADL, transfers, and walking. After discharge, patients were referred to primary care or, at 3 months, to geriatric outpatient rehab, while rehabilitation needs in residential care were communicated to facility therapists.	GIHR: After hospital-based rehabilitation, medically stable patients able to manage basic transfers were discharged early to continue up to 10 weeks of home-based rehabilitation. The GIHR team (nurse, occupational therapist, 2 physiotherapists, geriatrician, with social worker and dietician available) delivered individualized care including fall prevention, home modifications, ADL and device training, walking, and progressive strength/balance training (HIFE program). Medical care addressed complications, pain, and medication safety, while nutrition was assessed and optimized. The team worked closely with families and home/residential care providers.	LOS, readmissions, falls, mortality, ADL performance, and walking ability at discharge, 3, and 12 months	Interdisciplinary home rehabilitation and in-hospital geriatric care showed comparable outcomes for falls, mortality, ADL, and walking ability at 3 and 12 months, with no differences observed between participants with and without dementia.
Kazuaki et al. [S73][†] (2019), Japan	Retrospective cohort study	43,206 patients with dementia	Age distribution (n, %): 65–74 yr: 1,913 (4.4%); 75–84 yr: 12,905 (29.9%); 85–94 yr: 24,339 (56.3%); ≥ 95 yr: 7,371 (17.1%)	NA	Postoperative rehabilitation: 1 rehabilitation unit = 20 minutes; patients could receive up to 9 units per day	ADL (BI), LOS, discharge location	Earlier, more frequent, and higher daily doses of postoperative rehabilitation in acute-care hospitals were independently associated with better ADL recovery at discharge after hip fracture surgery in patients with dementia.
Paul-Dan et al. [S74][†] (2019), Romania	Retrospective cohort study	178 patients with dementia (64 men, 114 women); partial weight-bearing: 72; total weight-bearing: 106	81.5 (74–96)	Early mobilization with assisted standing and walking using an assistive device; partial weight-bearing permitted.	Early mobilization with assisted standing and walking using an assistive device; full weight-bearing permitted.	1-year mortality	Patients with total weight-bearing who were discharged to a rehabilitation facility had a better recovery (pre-fracture level) and 1-year survival rate

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Raivio et al. [S75][f] (2004), Finland	Retrospective cohort study	98 patients with dementia (MMSE < 24); 72.4% women	80.2	NA	PT 30 min/day, 5 days/wk, with guided self-exercises on weekends. Nurses were rehabilitation-oriented. Therapy included strengthening, walking, and balance training	Independent walking ability (with or without aids) in the rehabilitation ward within 6 weeks, and total days of active rehabilitation with a physical therapist	Strict weight-bearing restrictions may impair rehabilitation outcomes and may be more severe for patients with dementia
Seitz et al. [S76][f] (2016), Canada	Retrospective cohort study	11,200 with dementia; no rehabilitation: 4,494; CCC: 2,492; HCR: 1,157; IPR: 3,075	No rehabilitation: 85.4 (6.7); CCC: 84.8 (6.4); HCR: 83.2 (6.8); IPR: 83.7 (6.3)	No rehabilitation	CCC: Low-intensity, long-duration inpatient rehabilitation (similar to US skilled nursing facilities); HCR: In-home physiotherapy and OT after hip fracture surgery; IPR: Highest-intensity rehabilitation	LTC admission, mortality, risk of repeat falls and fractures	Postoperative rehabilitation was associated with decreased risks of LTC placement and mortality
Shyu et al. [S77][a),d),f] (2013), Taiwan	Randomized controlled trial (post-hoc analysis)	160 patients; interdisciplinary rehabilitation: 79 (including 24 women and 3 men with probable dementia); conventional rehabilitation: 81 (including 16 women and 8 men with probable dementia)	Probable dementia (interdisciplinary 81.3; Conventional 81.7)	Non-interdisciplinary rehabilitation with no continuity of care between providers or across settings. Inpatient rehabilitation consisted of only 3 physical therapy sessions, with no in-home rehabilitation. No additional details on the conventional program were reported	Interdisciplinary recovery program: Geriatric consultation (preoperative and postoperative assessment of medical and functional issues, surgery timing, prophylaxis, nutrition, urinary and delirium management); Rehabilitation (individualized, starting day 1 post-surgery, daily inpatient sessions with nurse/physician plus twice-daily PT, followed by 3 months of home rehab with monthly nurse visits and PT follow-up); Discharge planning (nurse-led assessment, referrals, home safety evaluation, environmental modifications).	Walking ability (pre/post-fracture, Chinese BI), ADL (Chinese BI), falls, mortality, ER visits, readmissions, institutionalization—assessed at 1-, 3-, 6-, 12-, 18-, and 24-month post-discharge.	Cognitively impaired individuals benefited from our interdisciplinary intervention by improving their walking ability and physical function during the first 2 years following discharge.

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Tseng et al. [S78][f] (2021), Taiwan	Randomized controlled trial	152 patients with cognitive impairment; intervention: 76; control: 76	81.8 (7.13)	PT typically started on POD 3, focusing on walker use and bed transfers. Patients were discharged after 5–6 days without a home assessment, and follow-up needs were referred by the primary nurse to the hospital discharge nurse. No in-home rehabilitation or nursing care was provided post-discharge.	Modified family-centered model based on Interdisciplinary care model [S77] with a family caregiver-training component. Caregivers received 2 in-home training sessions (delivered by trained research nurses) during the fourth and fifth home visits (at 1- and 1.5-month post-discharge) to help identify and manage patients' behavioral problems and symptoms.	Self-care ability (Chinese BI), nutritional status, HRQoL, and self-rated health)—assessed 1, 3, 6, and 12 months	Physical recovery of patients with hip fracture and dementia did not improve, but caregivers' self-efficacy and competence was improved.
Freter et al. [S79][a] (2017), Canada	Pragmatic (quasi-randomized) clinical trial	283 patients; intervention: 144 (30 men, 21%); control: 139 (40 men, 29%). Probable dementia (intervention: 48; control: 29)	Intervention: 83.2 (7.0); control: 82.5 (10.0)	Regular postoperative care: admitted to control ward, not provided with delirium-friendly postoperative care	Delirium-friendly postoperative care: patients were admitted to the intervention ward and managed with PPOs including delirium-sensitive options and dosing for nighttime sedation, analgesia, and nausea, with attention to timely catheter removal and bowel management.	Delirium, haloperidol use, LOS, hospital mortality, discharge destination, complications—assessed POD 1–5 and at discharge	Orthopedic nurses adhered reasonably well to delirium-friendly postoperative care. Among 283 participants, 42% developed postoperative delirium, with significantly lower rates in the intervention group (33% vs. 51%, P = 0.001). The effect was more pronounced in those with preexisting dementia (60% vs. 97%, P < 0.001).

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Table 1. Continued

Article	Study design	Participants		Interventions		Outcomes	Results
		No.	Age (yr)	Control group	Intervention group		
Marcantonio et al. [S80][a] (2001), USA	Randomized controlled trial	126 patients; intervention (geriatrician-led): 62 (13 men, 49 women); control (orthopedic-led): 64 (14 men, 50 women)	Intervention: 78 (8.0); control: 80 (8.0)	Orthopedic-led recovery program, with pre- and postoperative management by the orthopedic team. Internal medicine or geriatric consultation was reactive, rather than proactive as in the geriatrician-led group	Geriatrician-led recovery program included consultation preoperatively or within 24 hours postoperatively, followed by daily visits. Protocol-based recommendations (max 5 initially, 3 at follow-up) addressed oxygenation, fluid/electrolyte balance, pain, medication review, bowel/bladder regulation, nutrition, early mobilization/rehabilitation, complication prevention/management (cardiac, embolic, respiratory, urinary), environmental optimization (glasses, hearing aids, clocks, calendars, radios, soft lighting), and delirium management.	Total cumulative incidence of delirium throughout the acute hospital stays	Delirium occurred in 32% of intervention patients vs. 50% of controls (RR, 0.64), with 1 case prevented per 5.6 patients. Severe delirium was reduced to 12% vs. 29% (RR, 0.40). LOS was similar (median 5±2 days). The greatest benefit was seen in patients without pre-fracture dementia or ADL impairment. Proactive geriatrics consultation was feasible, well-adhered to, and significantly reduced delirium but not hospital stay.
Bellelli et al. [S81][b] (2006), Italy	Case report	1 patient	An 82-year-old woman with severe Alzheimer's disease	NA	BWST training involving stepping on a motorized treadmill while unloading a percentage of a person's body weight using a counterweight harness system.	Function (BI); gait and balance (Tinetti scale)	The patient showed no functional or cognitive improvement with conventional training during the first 12 days. After initiating BWST, endurance and function (walking, chair rise, balance) improved, with a Tinetti score of 16/28 and BI of 49/100 at discharge on day 36, which was maintained at 6 months post-fracture.

Values are presented as number or mean (standard deviation or range) unless otherwise stated.

CDR, clinical dementia rating scale; CERAD, Consortium to Establish a Registry for Alzheimer's Disease battery; ADL, activities of daily living; NEADL, Nottingham extended ADL index; IQCODE, informant questionnaire on cognitive decline in the elderly; SPPB, short physical performance battery; LOS, length of stay; MMSE, Mini-Mental State Examination; POD, postoperative day; PT, physical therapy; BI, Barthel index; NA, data not available; FIM, Functional Independence Measure; MRFS, Montebello rehabilitation factor score; ACTED, Assessment, Patient-Centered Goals, Treatment, Evaluation, and Discharge; OT, occupational therapy; PCRM-CI, Patient-Centered Rehabilitation Model for Cognitive Impairment; 6MWT, 6-minute walking test; PPME, physical performance and mobility examination; FES, fall efficacy scale; QoL, quality of life; EQ-5D, EuroQol-5 Dimension; LTC, long-term care; OBS, organic brain syndrome; EMS, elderly mobility scale; SNF, skilled nursing facility; IRF, in-patient rehabilitation facility; FAC, functional ambulation category; HRQoL, health-related quality of life; HHS, Harris hip score; GIHR, Geriatric Interdisciplinary Home Rehabilitation; PADL, personal activities of daily living; HIFE, high-intensity functional exercise; CCC, Complex Continuing Care; HCR, Home-Care Rehabilitation; IPR, Inpatient Rehabilitation; ER, emergency room; PPOs, preprinted postoperative orders; RR, relative risk; BWST, body weight–supported treadmill.

References for the studies in this table are provided in Supplement 1: [a]Included in a review by Smith et al. [41]. [b]Included in a review by Resnick et al. [44]. [c]Included in a review by Beaupre et al. [35]. [d]Included in a review by Chu et al. [43]. [e]Included in a review by Allen et al. [40]. [f]Included in a review by Cadel et al. [42].

A high-quality clinical practice guideline reported moderate evidence supporting multicomponent, non-pharmacological interventions delivered by an interprofessional team trained in delirium management [49]. These programs emphasize assessing at-risk patients, monitoring behavioral changes or fluctuations, and referring to trained providers for diagnosis. Preventive strategies include adequate pain management, facilitated mobility through therapy, and engagement in meaningful activities. A Cochrane review also indicated that enhanced inpatient rehabilitation and care models may reduce postoperative delirium [41]. Physical therapists should actively participate in interprofessional, multicomponent programs throughout hospitalization for at-risk older adults undergoing hip fracture surgery to prevent delirium [32].

Prevention of secondary fractures

The occurrence of any fragility fracture, regardless of location, doubles the risk of subsequent fractures [38], with the highest risk observed within the first 2 years [50]. Anti-osteoporosis medications (AOMs) are effective in preventing recurrent fractures; however, only 10%–20% of patients with fragility fractures receive AOM therapy [50]. Individuals with mild cognitive impairment or dementia experience pronounced disparities in both the diagnosis and treatment of osteoporosis [25]. No clinical guidelines specifically address osteoporosis screening in this population, and although professional societies recommend screening for adults aged ≥65 years, implementation remains inconsistent. Challenges include the technical difficulty of performing dual-energy X-ray absorptiometry scans—which require patients to remain still in specific positions and may be unfeasible for those with cognitive impairment—and the limited applicability of most fracture risk prediction tools, which do not account for cognitive comorbidities. Treatment disparities are also evident: patients with cognitive impairment are less likely to receive pharmacologic therapy, including AOMs and vitamin D, and adherence to oral medication regimens is particularly challenging.

The FLS has been shown to promote and support adherence to AOMs. In a review by Cianferotti et al. [38], the FLS was associated with increased rates of BMD testing (relative risk [RR], 2.45; 95% CI, 1.86–3.23), therapy initiation (RR, 1.91; 95% CI, 1.58–2.29), and adherence (RR, 1.54; 95% CI, 1.03–2.31), as well as reduced risks of subsequent fractures (RR, 0.65; 95% CI, 0.53–0.79) and mortality (RR, 0.68; 95% CI, 0.48–0.96) compared with standard care or non-attenders. Although tailored guidelines are still needed to direct osteoporosis screening and simplify treatment regimens for patients with cognitive impairment—thereby reducing medication burden and improving therapeutic outcomes—the FLS remains an effective model for secondary prevention in older adults with hip fractures and cognitive impairment.

Optimizing post-hip-fracture rehabilitation in older adults with cognitive impairment

Patients with cognitive impairment should not be excluded from post-hip-fracture rehabilitation. Rehabilitation programs should be tailored to address both cognitive and functional needs through individualized strategies that incorporate clear communication, cueing, and task repetition. Qualitative evidence indicates that staff education, mentoring, and strong interdisciplinary collaboration are essential to equip healthcare professionals with the knowledge, skills, and confidence necessary to effectively rehabilitate this population [51]. Structured mentoring sessions, regular team huddles, and debriefings create opportunities to exchange strategies, sustain staff morale, and foster a supportive, patient-centered culture of care [51].

Individualized rehabilitation is critical; "one-size-fits-all" approaches are ineffective [51]. Comprehensive geriatric assessments, continuity of staffing, and flexible, creative engagement—such as incorporating meaningful activities or adapting therapy to align with patient preferences—enhance participation and functional progress [51]. Early and continuous discharge planning, involving patients, families, and community resources, further promotes safe transitions and empowers caregivers through education and trial home stays.

Effective clinical decision-making requires standardized criteria or protocols to determine rehabilitation eligibility, intensity, and adaptation; however, such guidance remains limited. Systemic barriers, including resource constraints, insufficient dementia-specific training, and inconsistent access criteria, must be addressed through targeted education initiatives and institutional support.

Cost and resource considerations are equally important. Although intensive, high-frequency exercise programs are demonstrably effective, they may not be feasible in all healthcare settings because of financial limitations and the high prevalence of older adults with hip fractures. The feasibility and acceptability of such interventions vary across institutions and patient populations, underscoring the need for resource-efficient, scalable, and adaptable models of care.

In summary, rehabilitation for older adults with cognitive impairment should be structured, adaptable, and well-supported—grounded in staff education, interprofessional collaboration, standardized protocols, and evidence-based guidelines. By tailoring interventions to cognitive and physical capacities and addressing

systemic barriers, meaningful functional recovery and improved quality of life are achievable even in this vulnerable population.

Conclusion

Older adults with hip fractures and cognitive impairment experience slower postoperative recovery, greater rehabilitation challenges, and accelerated long-term functional decline. Nevertheless, evidence consistently demonstrates that tailored, structured, intensive, and multidisciplinary rehabilitation can produce meaningful improvements in mobility, ADLs, and reintegration into community life. To optimize outcomes, rehabilitation programs must be strengthened through dementia-specific staff training, interprofessional collaboration, and proactive management of delirium and secondary fracture prevention. Addressing systemic barriers—such as limited resources, inconsistent protocols, and inequitable access—is essential for developing scalable, sustainable, and equitable models of care. Future research should focus on refining rehabilitation frameworks and secondary prevention strategies specifically designed for older adults with cognitive impairment, thereby reducing care disparities and improving long-term functional and quality-of-life outcomes.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

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Shifting from a provider-centered to a person-centered model of long-term care for older patients in Korea: a narrative review

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South Korea is experiencing a rapid demographic transition, with the proportion of older adults projected to exceed 20% by 2025. This unprecedented pace has intensified the demand for healthcare and social support, creating complex challenges in the management of multimorbidity, frailty, and functional dependency. Historically, Korea has relied on a rigid, provider-centered model, with healthcare financed through National Health Insurance and long-term care through long-term care insurance. Although these systems expanded service availability, they also entrenched fragmentation between long-term care hospitals and nursing homes. Recent reforms mark a paradigm shift toward person-centered, integrated care. The Community Care pilot programs (2019–2022) and the Integrated Community Care Support Act (2024) introduced coordinated models that link healthcare, housing, and social services under local government leadership. Evidence from domestic and international studies underscores the risks of prolonged institutionalization and highlights the benefits of integrated approaches, including reduced hospitalizations, improved functional independence, and higher satisfaction among older adults and their families. At the same time, experiences from Korea and Japan suggest that institutional care remains indispensable for individuals with high medical needs or at the end of life, emphasizing the need for balanced strategies. Successful implementation of the 2026 reforms will require redefining the role of institutions, expanding community-based alternatives, developing a professional care manager workforce, achieving interoperability of data systems, and undertaking financing reforms to align incentives. Beyond structural change, embedding a cultural ethos that values dignity, autonomy, and personhood will be essential. Korea's evolving model not only responds to urgent demographic challenges but also offers lessons for other aging societies.

Keywords: Aged; Long-term care; Community health services; Delivery of health care; Republic of Korea

Introduction

South Korea (hereinafter, Korea) is undergoing one of the most rapid and profound demographic transitions worldwide. In 2000, only 7% of the population was aged 65 years or older; by 2025, that figure is expected to exceed 20%, classifying the nation as a super-aged society [1]. This compressed aging trajectory, occurring far more quickly than the decades- or centuries-long processes observed in Western Europe, imposes immediate and substantial strain on policymakers, healthcare systems, and social structures, forcing rapid adaptation and reform [2]. The growing population of older adults is closely linked to an increased prevalence of chronic disease, multimorbidity, functional disability, and frailty, producing complex and overlapping needs that span healthcare and social support domains [3]. Korea's historical response to these challenges has been characterized by a rigid, provider-centered dichotomy. Medical services are primarily financed and delivered through the national health insurance (NHI) system, while custodial and functional care is provided under the separate long-term care insurance (LTCI) system, introduced in 2008 [4]. This dual financing and delivery structure expanded access but entrenched systemic fragmentation, particularly between long-term care hospitals (LTCHs) covered by NHI and nursing homes (NHs) funded by LTCI [5]. Importantly, this provider-centered model conflicts with the well-documented preference of older adults to age in place, maintaining independence and social ties within familiar communities [6]. In recent years, policy initiatives such as the Community Care pilot programs (2019–2022) and the landmark Integrated Community Care Support Act (2024) reflect a decisive shift toward integrated, person-centered, com-

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munity-based care [1,7].

This review analyzes the evolution of Korea's long-term care (LTC) system through a historical and policy lens. It explores the roots of institutional fragmentation, examines recent policy moves toward integration, and synthesizes supporting evidence from domestic research and international experience.

Ethics statement

This is a literature-based study; therefore, neither approval by the institutional review board nor the obtainment of informed consent was required.

Historical evolution and institutional fragmentation

The development of Korea's LTC system reflects both the nation's compressed socioeconomic modernization and the strong influence of policy-driven financial incentives. Unlike the gradual, organic evolution observed in many Western countries, Korea's system was constructed rapidly within just a few decades, shaped by cultural shifts, specific reimbursement mechanisms in its insurance schemes, and deliberate policy decisions [4]. During the 1980s and 1990s, eldercare facilities expanded in an unregulated fashion, often established by religious or private organizations to address growing unmet needs. The pivotal change, however, was the meteoric rise of LTCHs [8]. Fueled by NHI's generous per diem reimbursement model—which guaranteed stable and predictable revenue regardless of patient acuity or service intensity—LTCHs proliferated at an extraordinary pace [9]. Originally envisioned as facilities for post-acute rehabilitation and complex medical management, they quickly became the default long-stay option for medically stable but functionally dependent older adults. This trend led to widespread overutilization and the medicalization of normal aging [8,9]. By the 2000s, Korea had reached one of the highest per capita supplies of LTCH beds among Organization for Economic Cooperation and Development (OECD) countries, marking it as a striking international outlier [10]. The introduction of the LTCI system in 2008 represented a landmark social policy reform, designed to provide universal coverage for functional dependency and to expand alternatives to institutionalization [11]. It significantly increased access to formal services, particularly NHs and basic home-based helper programs. Yet, in a critical design flaw, the system inadvertently reinforced the very fragmentation it was intended to resolve. By establishing a separate financing and administrative stream for social care (LTCI for NHs and home care) while NHI continued to fund medical care, including LTCHs, the reform entrenched a rigid dual-track structure [5,12]. Unlike Japan, which embedded strong coordination mechanisms such as the care manager role, Korea's model lacked effective structures for integration [13]. The consequences quickly became evident: patients cycled between acute hospitals, LTCHs, and NHs, facing multiple handoffs and fragmented care planning; families were forced to navigate a confusing maze of eligibility criteria, benefit rules, and copayment requirements; and community-based services remained chronically underdeveloped and underfunded, starved of resources that flowed disproportionately to institutions [11,14].

Policy shifts toward integrated, person-centered care

By the early 2010s, there was a growing consensus among policymakers, academics, and civil society groups that the existing system was both financially unsustainable and ethically misaligned with the needs of an aging society. Policymakers, guided by critical reports from national research institutions such as the Korea Institute for Health and Social Affairs and recommendations from international bodies like the OECD and World Health Organization, began to acknowledge the urgency of developing models that could support aging in place [15,16]. The decisive turning point came in 2018 with the announcement of the "Community Care" initiative, introduced as part of the broader welfare reform agenda. This nationwide effort sought to build comprehensive local systems that would enable older adults and individuals with disabilities to remain in their own homes and communities while receiving integrated supports spanning healthcare, housing, and social services [7,17]. From 2019 to 2022, large-scale pilot programs were implemented in 16 strategically selected municipalities to test a range of coordinated approaches. These included integrated home-based medical and nursing services, housing-linked care models such as public rental housing with embedded care staff, and multidisciplinary teams tasked with coordinated care planning [18]. Early independent evaluations reported promising results, including significant reductions in unnecessary hospitalizations and emergency department visits, measurable improvements in functional independence, and higher satisfaction among both older adults and family caregivers [19,20]. Building on these outcomes, the Ministry of Health and Welfare's 3rd Basic Plan for Long-Term Care (2023) explicitly prioritized the expansion of community-based services, the technical integration of NHI and LTCI information systems for improved data sharing, and the strengthening of local government leadership and community workforce capacity [21]. The most signifi-

cant legislative milestone thus far was the passage of the Integrated Community Care Support Act in 2024, with full implementation scheduled for 2026 [22]. This Act establishes Korea's first comprehensive legal framework dedicated to community-based integrated care. Its core provisions mandate local governments to function as the primary coordinators and planners of care within their jurisdictions; introduce a certified and licensed care manager workforce responsible for conducting holistic needs assessments and developing individualized service plans; and create both physical and virtual integrated service platforms to connect users with providers. In addition, the Act pilots innovative outcome-based financing models designed to reward measurable improvements in quality of life and functional status, rather than the volume of services delivered [22,23]. This Act marks a decisive paradigm shift—from fragmented, provider-driven systems to coordinated, person-centered care—and draws explicit inspiration from successful international precedents, including Japan's Community-based Integrated Care System and Singapore's Agency for Integrated Care [24,25].

Evidence from domestic and global studies supporting integration

An expanding body of domestic and international research substantiates both the necessity and the anticipated benefits of Korea's policy shift toward integration. Recent studies provide critical and timely insights that directly inform the reform agenda. A consistent line of evidence highlights the risks associated with prolonged institutionalization. Multiple studies demonstrate that extended stays in LTC facilities are independently associated with accelerated functional decline, higher rates of depression, and a pervasive loss of autonomy, indicating that these settings—while ensuring basic safety and medical care—can inadvertently erode overall quality of life and personhood [26,27]. A Korean study further identified weakened social support as one of the strongest predictors of institutionalization [28]. At the same time, emerging evidence strongly supports the clinical and economic value of integrated, multidisciplinary approaches. Research on frailty management has shown that coordinated interventions—including nutritional support, tailored physical therapy, and cognitive engagement—can effectively slow progression among NH residents [29]. Yet the current siloed structures and staffing models of LTC facilities often impede the delivery of such holistic, person-centered care [30]. International experience underscores the benefits of integration: Japan's system, centrally organized around the care manager role, has achieved measurable success in reducing avoidable hospitalizations and supporting aging in place for millions of older adults [31,32]. Similarly, evaluations of the UK's National Health Service Integrated Care Systems show that, despite implementation challenges, integrated models are linked with higher satisfaction among both patients and caregivers [33]. Taken together, this body of evidence provides strong justification for Korea's reforms. It not only warns against perpetuating a fragmented, institution-centered model but also points to a clear, evidence-based path toward community-based, person-centered integration.

Future outlook and strategic recommendations

The passage of the Integrated Community Care Support Act positions Korea at a pivotal moment in the evolution of its social welfare system. Successful implementation from 2026 onward will demand meticulous planning, substantial investment, and a concerted focus on several key strategic priorities. First, the roles and functions of existing institutions must be clearly redefined and streamlined within an integrated continuum of care. LTCHs should be rigorously repositioned as primarily post-acute and rehabilitative facilities, with active and mandated discharge planning aimed directly at community reintegration. In parallel, NHs should focus on delivering high-quality custodial care, specialized dementia services, and palliative or end-of-life care. A fundamental component of this restructuring is the complete overhaul of reimbursement systems for both sectors. Payment models must incentivize time-limited, goal-oriented care in LTCHs and reward NHs for quality outcomes—such as functional maintenance, dementia-friendly environments, and caregiver support—rather than relying on bed-occupancy–based payments [1,34].

Second, the national scaling of a robust ecosystem of community-based alternatives must proceed with urgency. This requires sustained public investment in diverse services, including home healthcare, visiting nursing, respite programs for family caregivers, and innovative housing-linked care models. Third, the development of a new care manager workforce is arguably the most critical human resource factor for the Act's success. These professionals must receive rigorous, standardized training in geriatrics, social work, case management, and inter-sectoral coordination. Adequate compensation, professional recognition, and manageable caseloads will be essential to ensure effectiveness. Lessons from Japan's and Taiwan's case manager models provide valuable guidance [32,35]. Because municipal governments will serve as lead coordinators but currently vary greatly in capacity, strong national-level support—including conditional funding, technical assistance, and workforce development programs—will be vital to

prevent regional inequities.

Fourth, digital and technological integration must be prioritized as a central enabler of reform. Achieving full interoperability between NHI and LTCI data systems is a prerequisite for seamless information sharing, coordinated care planning, and effective outcome monitoring across providers. Moreover, the use of big data analytics and artificial intelligence for risk prediction, population health management, and resource optimization presents tremendous potential, provided it is pursued with robust safeguards for privacy and ethical use [36-38]. Finally, comprehensive financing reforms are indispensable for ensuring the system's long-term fiscal sustainability. The current dual financing structure fragments incentives and is widely acknowledged as inefficient. Long-term strategies should include serious consideration of partial or full integration of NHI and LTCI budgets into a unified funding pool, enabling flexible allocation across the medical-social care spectrum [31,39]. Ultimately, beyond technical and structural reforms, embedding a cultural ethos that honors older adults as individuals with unique goals, preferences, and dignity is essential to realizing the vision of truly person-centered care.

Balanced perspectives on institutional and community care

Although Korea's reform agenda emphasizes community-based, person-centered integration, institutional care retains an indispensable role within the continuum. Evidence from Korea shows divergence between older adults and their families regarding end-of-life preferences. One study found that 67.5% of care recipients preferred to die at home, whereas 59.6% of family caregivers favored hospitals, reflecting the caregiving burden and the sociocultural realities of declining fertility and shrinking family size [40-43]. These findings suggest that an exclusive focus on community-based care could unintentionally intensify pressures on families. Japan's policy trajectory underscores similar complexities. Although the Japanese government initially sought to eliminate LTC beds, it was compelled to revise this plan due to strong public demand for institutional options [44,45]. Such experiences highlight that effective integration requires a balanced approach—expanding community-based services while recognizing the continued necessity of LTC facilities for populations with high medical needs or those nearing the end of life.

The key developments and their impacts are summarized in Table 1.

Conclusion

Korea's complex journey in developing its LTC system encapsulates the profound challenges presented by ultra-rapid demographic change. The country moved from a tradition of family-based care to a heavily institutionalized, provider-centered model in a remarkably short time. LTCHs initially addressed an urgent need for beds, and the introduction of the LTCI system in 2008 expanded access to services but, in a critical oversight, ce-

Table 1. Timeline of healthcare and long-term care policy evolution in Korea and its impact on older adults

Year/period	Policy/development	Key features	Impact on older adults
1980s–1990s	Growth of eldercare facilities	Unregulated expansion, mostly private/religious sector	Limited quality control, variable access; reliance on families remained high
Late 1990s–2000s	Rapid expansion of long-term care hospitals	Driven by per diem NHI reimbursements	Increased institutionalization, medicalization of aging, overutilization of beds
2008	Introduction of LTCI	Coverage for nursing homes, home helpers, functional dependency	Improved access, but created a dual-track system (NHI vs. LTCI) and reinforced fragmentation
2010s	Recognition of system fragmentation	Growing consensus on unsustainability, KIHASA/OECD/WHO reports	Older adults cycled between institutions, families faced navigation burden
2019–2022	Community Care Pilot Programs	Integration of healthcare, housing, and social services at the local level	Reduced hospitalizations, better functional independence, higher satisfaction
2023	3rd Basic Plan for Long-Term Care	Expansion of community-based services, integration of NHI and LTCI data	Improved coordination, stronger local government leadership
2024	Integrated Community Care Support Act	Legal framework for community-based integrated care, care manager role	Paradigm shift toward person-centered care
2026 (planned)	Implementation of Integrated Community Care Act	Nationwide rollout, financing reform, data interoperability, workforce development	Opportunity for a sustainable, balanced system; focus on dignity, autonomy, quality of life

NHI, national health insurance; LTCI, long-term care insurance; KIHASA, Korea Institute for Health and Social Affairs; OECD, Organization for Economic Co-operation and Development; WHO, World Health Organization.

mented the problematic divide between healthcare and social care financing, perpetuating the siloed nature of service delivery. The recent series of policy shifts—the Community Care initiative, the 3rd Basic Plan for Long-Term Care, and the landmark Integrated Community Care Support Act—mark a decisive and welcome turn toward integration and person-centeredness.

The implementation challenges are significant and multifaceted, involving overcoming entrenched institutional interests, addressing fiscal constraints, and resolving workforce shortages. At the same time, evidence from Korea and Japan highlights that institutional settings, including LTCHs and LTC facilities, remain essential for certain populations, particularly those with high medical complexity or at the end of life. Effective reform therefore requires a balanced approach: one that strengthens community-based services while recognizing the indispensable role of institutions within the continuum of care.

By thoughtfully learning from international models and heeding the growing domestic evidence, Korea can navigate this complex transition successfully. By clearly redefining institutional roles, massively expanding community capacity, empowering a new generation of care managers, integrating data systems, and implementing comprehensive financing reforms, Korea has the potential to build a sustainable, equitable, and effective LTC system. If implemented with vision and determination, Korea's integration efforts will not only benefit its own aging population but also provide invaluable lessons and a roadmap for other nations facing similar demographic destinies. The integration of healthcare and LTC is more than a mere administrative restructuring; it is a necessary societal evolution to ensure that longer lives are also healthier, more dignified, autonomous, and fulfilling.

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Authors' contribution

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Conflict of interest

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Two paths, one goal–uniting regional and general anesthesia for optimal surgical care: a narrative review

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The integration of regional anesthesia (RA) with general anesthesia (GA) has become a central component of multimodal strategies to improve perioperative pain management. This approach not only enhances analgesic efficacy but also reduces opioid requirements and mitigates opioid-related adverse effects. By targeting peripheral or neuraxial nociceptive pathways, RA attenuates the surgical stress response and decreases central sensitization, complementing the systemic actions of GA. The combined application of RA and GA has shown substantial benefits across a wide range of surgical procedures, including abdominal, thoracic, orthopedic, and pediatric operations. Reported advantages include improved hemodynamic stability, enhanced pulmonary function, earlier ambulation, faster gastrointestinal recovery, and greater patient satisfaction. Moreover, recent evidence indicates a positive association between effective postoperative pain control and long-term outcomes, such as reduced incidence of persistent postsurgical pain, better functional independence, and even improved immune function and survival following cancer surgery. The development of sustained-release local anesthetic delivery systems, which provide localized and prolonged analgesia, further extends the benefits of RA-GA integration into the postoperative period. This review summarizes the mechanistic rationale, clinical applications, and future directions of RA-GA combinations in modern surgical care, with special emphasis on their role in enhanced recovery after surgery protocols.

Keywords: Analgesia; Conduction anesthesia; General anesthesia; Enhanced recovery after surgery; Postoperative pain

Introduction

Background

Surgical procedures elicit a complex physiological stress response involving nociceptive signaling, neuroendocrine activation, and inflammatory cascades, all of which can negatively affect postoperative recovery. General anesthesia (GA), although indispensable for inducing unconsciousness and immobility, provides limited site-specific analgesia and frequently necessitates the use of high-dose opioids. These opioids are associated with a broad range of adverse effects, including respiratory depression, nausea, ileus, urinary retention, and opioid-induced hyperalgesia, all of which may delay recovery and diminish patient satisfaction [1,2].

Regional anesthesia (RA), when integrated into anesthetic management, enables targeted blockade of nociceptive pathways at peripheral or neuraxial sites. When combined with GA, RA decreases intraoperative opioid and anesthetic requirements, improves hemodynamic stability, and facilitates early mobilization. For these reasons, RA has become a cornerstone of enhanced recovery after surgery (ERAS) protocols [3,4].

Recent pharmacological innovations have introduced sustained-release local anesthetic delivery systems designed to prolong analgesia while limiting systemic exposure [5]. Liposomal bupivacaine, for example, employs multivesicular liposomes to sustain peripheral nerve blockade for up to 72 hours [6]. Other investigational platforms, including polymeric microspheres, nanofiber scaffolds, and hydrogel-based carriers, aim to optimize controlled drug release at the target site. These systems are designed to maintain therapeutic concentrations locally, decrease central sensitization, and enhance the effectiveness of multimodal analgesia when combined with GA.

The quality of acute postoperative pain control is increasingly recognized as a determinant of long-term outcomes. Poorly managed acute pain is a known risk factor for persistent postsurgical pain (PPSP), which develops in 30%–50% of patients undergoing major surgery [7]. PPSP is associated with functional limitations,

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reduced quality of life, and psychological comorbidities such as depression and anxiety. Inadequate pain control also elevates the risk of complications, including venous thromboembolism, pulmonary dysfunction, and impaired wound healing, ultimately prolonging hospitalization and increasing healthcare costs.

Emerging evidence further suggests that optimized perioperative analgesia may improve long-term health outcomes, including cancer-related survival and reduced tumor recurrence [8]. These benefits are thought to arise from decreased systemic inflammation, preservation of immune surveillance—particularly through natural killer (NK) cell activity—and attenuation of the immunosuppressive effects of opioids and surgical stress [9,10].

Accordingly, the integration of RA with GA not only addresses the limitations of GA alone but also supports both immediate recovery and favorable long-term clinical outcomes.

Objectives

This review outlines the physiological rationale, clinical benefits, technical applications, and future directions of combining RA with GA as a comprehensive and evidence-based perioperative strategy.

Ethics statement

This was a literature-based study; therefore, neither approval by the institutional review board nor informed consent was required.

Mechanisms and rationale for combined use

RA exerts its principal analgesic effect by selectively blocking nociceptive signal transmission at the level of peripheral nerves, nerve plexuses, or the spinal cord—particularly the dorsal horn. This targeted interruption of afferent input prevents amplification of pain signals within the central nervous system, thereby lowering the risk of central sensitization and the development of hyperalgesia or allodynia [11]. A key mechanism involves attenuation of the wind-up phenomenon through inhibition of excitatory neurotransmitter release—such as glutamate and substance P—and downregulation of NMDA receptor activity. When combined with GA, which primarily acts at the cortical level to suppress pain perception and consciousness, this multimodal approach provides synergistic analgesia covering both peripheral and central pathways, thereby ensuring broad-spectrum antinociception throughout the perioperative period [12,13].

Beyond analgesia, the combined application of RA and GA offers additional physiological advantages. By blocking nociceptive input at its source, RA dampens activation of the hypothalamic-pituitary-adrenal axis and blunts perioperative surges in catecholamines (epinephrine and norepinephrine) and cortisol. This neuroendocrine modulation enhances intraoperative hemodynamic stability, decreases myocardial oxygen demand, and reduces the risk of arrhythmias and ischemia; these effects are particularly valuable in cardiac patients and older adults. Neuraxial techniques such as spinal or epidural anesthesia also improve pulmonary function by reducing systemic opioid requirements and preventing opioid-induced respiratory depression [14]. Consequently, diaphragmatic function is better preserved, atelectasis is minimized, and gas exchange is improved. In addition, RA has been associated with favorable immunomodulatory effects, including reduced leukocyte activation and attenuation of the inflammatory response, which may contribute to improved wound healing and preserved immune competence during the postoperative period [15].

One of the most consistently documented benefits of combining RA with GA is its opioid-sparing effect. Depending on the surgical procedure and block type (e.g., peripheral nerve block, epidural), intraoperative and postoperative opioid consumption may be reduced by 30%–50%. This reduction lowers the incidence of opioid-related side effects—including postoperative nausea and vomiting, ileus, urinary retention, and sedation—and may also decrease the risk of opioid-induced hyperalgesia and prolonged opioid use after discharge. For example, a systematic review and meta-analysis found that the erector spinae plane (ESP) block in laparoscopic abdominal surgery reduced opioid use (mean difference, –5.95 mg; 95% confidence interval [CI], –8.86 to –3.04 mg), as well as the incidence of nausea (relative risk [RR], 0.38; 95% CI, 0.25–0.60; $P < 0.001$) and vomiting (RR, 0.32; 95% CI, 0.17–0.63; $P = 0.0009$) [16]. Another study reported that ultrasound-guided posterior quadratus lumborum (QL) block in abdominal surgery decreased postoperative opioid consumption at 24 hours (standardized mean difference, –0.45; 95% CI, –0.86 to –0.03) [17].

Enhanced recovery is further supported by accelerated gastrointestinal function, earlier mobilization, and a lower incidence of postoperative delirium—particularly in geriatric patients [3]. Multimodal analgesic strategies incorporating RA have been linked to shorter hospital stays, quicker return to baseline functional status, and higher patient satisfaction scores [18]. Importantly, RA may also reduce the risk of chronic postsurgical pain by mitigating early central sensitization and interrupting ongoing nociceptive input during the perioperative period [19].

Techniques of regional anesthesia adjunct to general anesthesia

RA, when combined with GA, constitutes a cornerstone of multimodal analgesia and ERAS protocols [3,20]. RA techniques are broadly classified into neuraxial and peripheral blocks, each offering targeted analgesia, reducing systemic opioid requirements, and minimizing perioperative complications [21-24]. Table 1 summarizes regional anesthetic techniques applicable across surgical contexts.

Spinal anesthesia involves intrathecal injection of local anesthetics into the subarachnoid space, producing a rapid-onset, dense sensory and motor block. It is particularly suited for operations involving the lower abdomen, pelvis, and lower extremities. When combined with GA, spinal anesthesia enables substantial dose reduction of inhaled anesthetics and opioids, attenuates the neuroendocrine stress response, and improves hemodynamic stability [25].

Epidural anesthesia, achieved through catheter placement in the epidural space, allows continuous or intermittent administration of local anesthetics, providing prolonged and titratable analgesia. It is widely employed in thoracic, abdominal, and obstetric surgery, particularly for postoperative pain management.

The combined spinal-epidural technique merges the rapid onset of spinal anesthesia with the extended control of an epidural catheter, making it especially useful for prolonged or staged surgical procedures [26].

Peripheral nerve blocks deliver highly localized analgesia with minimal systemic effects. For upper extremity surgery, interscalene, supraclavicular, infraclavicular, and axillary blocks are commonly used to manage pain in procedures ranging from shoulder to hand, while preserving hemodynamic stability and reducing opioid use.

Lower extremity blocks, including femoral, adductor canal, sciatic, and interspace between popliteal artery and capsule of the knee (iPACK) blocks, play a key role in total joint arthroplasty and orthopedic trauma surgery. Motor-sparing approaches, such as the adductor canal block, are particularly advantageous in facilitating early ambulation and functional recovery after total knee replacement.

Truncal blocks—including transversus abdominis plane (TAP), QL, ESP, and paravertebral blocks (PVBs)—are highly effective for controlling both somatic and visceral pain during abdominal and thoracic operations [27,28]. Among these, ESP and serratus anterior plane blocks are increasingly preferred in patients with coagulopathies as safer alternatives to epidural anesthesia [29].

Local anesthetic infiltration at the surgical site remains a simple

Table 1. Regional anesthetic techniques applicable in surgical contexts

	Regional anesthetic techniques
Neuraxial anesthesia	Spinal anesthesia
	Epidural anesthesia
	Combined spinal-epidural
	Caudal epidural block
Paraspinal blocks	Erector spinae plane block
	Cervical
	Thoracic
	Lumbar
	Paravertebral block (thoracic, lumbar)
	Costotransverse foramen block
	Intertransverse process block
	Thoracolumbar interfascial plane block
Upper extremity–brachial plexus blocks	Interscalene block
	Supraclavicular block
	Infraclavicular block
	Axillary block
Upper extremity–terminal nerve blocks	Median nerve block
	Ulnar nerve block
	Radial nerve block
	Musculocutaneous nerve block
	Medial antebrachial cutaneous nerve block
	Lateral antebrachial cutaneous nerve block
	Suprascapular block
	Dorsal scapular nerve block
Lower extremity–lumbar plexus blocks	Lumbar plexus block
	Psoas compartment block
	Posterior lumbar plexus block
Lower extremity–lumbar plexus-related	Femoral nerve block
	Adductor canal block
	Obturator nerve block
	Lateral femoral cutaneous nerve block
	Genitofemoral nerve block
	Ilioinguinal/iliohypogastric nerve block
Lower extremity–sacral plexus-related	Sciatic nerve block (subgluteal, infragluteal, transgluteal)
	Popliteal sciatic nerve block (lateral, posterior)
	Posterior femoral cutaneous nerve block
Lower extremity–distal leg and ankle	Saphenous nerve block
	Ankle block

(Continued on the next page)

Table 1. Continued

	Regional anesthetic techniques
	Tibial nerve
	Deep peroneal nerve
	Superficial peroneal nerve
	Sural nerve
	Saphenous nerve
Truncal	TAP blocks
	Lateral TAP block
	Posterior TAP block
	Subcostal TAP block
	Dual TAP block
	Rectus sheath block
	Ilioinguinal/iliohypogastric block
	QL blocks
	QL1 (lateral)
	QL2 (posterior)
	QL3 (transmuscular)
	QL4 (intramuscular variant)
	Transversalis fascia plane block
Thoracic–interfascial plane blocks	PECS I block (pectoralis and serratus plane)
	PECS II block
	Serratus anterior plane block
	Clavipectoral fascial plane block
	Intercostal nerve block
	Transversus thoracic plane block
Head and neck–cervical plexus	Cervical plexus block
	Superficial
	Intermediate
	Deep
Head and neck	Scalp nerve block
	Supraorbital nerve block
	Supratrochlear nerve block
	Zygomaticotemporal nerve block
	Greater occipital nerve block
	Lesser occipital nerve block
	Auriculotemporal nerve block
Airway	Glossopharyngeal nerve block
	Superior laryngeal nerve block
	Recurrent laryngeal nerve block
	Translaryngeal block
Distal digital and penile blocks	Digital nerve block (4-point, 2-point)
	Penile block (dorsal nerve, ring block)
Intravenous regional anesthesia (bier block)	-
Wound infiltration	-

TAP, transverse abdominis plane; QL, quadratus lumborum.

yet effective technique, particularly in minimally invasive operations or as part of multimodal analgesia. Field blocks such as rectus sheath and ilioinguinal/iliohypogastric blocks are frequently employed in inguinal hernia repair and lower abdominal surgery.

The widespread adoption of ultrasound guidance has revolutionized RA practice by enabling real-time visualization of anatomical structures, thereby increasing accuracy and reducing complications such as vascular puncture or nerve injury.

Continuous catheter-based RA techniques extend analgesic coverage into the postoperative period, allowing titration of doses for sustained pain control. Furthermore, the use of sustained-release local anesthetic delivery systems and adjuvants, including dexamethasone, clonidine, and dexmedetomidine, can prolong block duration and enhance analgesic efficacy [5,30].

The choice of RA technique should be individualized based on surgical site, patient comorbidities, coagulation profile, and recovery goals. When optimally implemented, RA techniques improve pain control, enhance patient satisfaction, reduce opioid-related adverse effects, and accelerate functional recovery [21,22].

Surgical applications

RA plays a pivotal role in optimizing perioperative analgesia across a broad range of surgical disciplines. In abdominal surgery, RA techniques have become integral to opioid-sparing multimodal strategies [23]. The TAP block, which targets the intercostal nerves (T6–L1) within the fascial plane between the internal oblique and transversus abdominis muscles, is widely used in both open and laparoscopic procedures. It provides effective somatic analgesia of the anterior abdominal wall, thereby reducing systemic opioid use, postoperative nausea, and ileus [24]. The QL block, a deeper posterior fascial plane block, offers broader analgesic spread into the thoracolumbar fascia and paravertebral space, potentially covering visceral pain pathways. Its application in colorectal, urological, and gynecological surgery has been associated with improved pain scores and enhanced recovery outcomes [31]. For major open abdominal procedures, thoracic or lumbar epidural analgesia remains the gold standard, providing both somatic and visceral pain relief. Epidural anesthesia also improves bowel motility, reduces postoperative ileus, and decreases pulmonary complications such as atelectasis and pneumonia, particularly in patients undergoing bowel resection or hepatobiliary surgery [32].

In thoracic surgery, effective analgesia is essential due to the high risk of respiratory complications and the severity of post-thoracotomy pain [22,29]. Even minimally invasive approaches such as video-assisted thoracoscopic surgery can cause significant dis-

comfort from intercostal nerve trauma. Thoracic epidural analgesia, which produces dense, multisegmental sympathetic and sensory blockade, has long been the standard for open thoracotomies and is associated with decreased pulmonary morbidity and lower rates of postoperative respiratory failure [33]. However, newer fascial plane blocks such as the PVB and erector spinae plane block (ESPB) provide safer alternatives with comparable efficacy. These techniques can be administered unilaterally, produce less hypotension, and are safer in patients requiring anticoagulation. Randomized trials have demonstrated that PVB and ESPB reduce opioid use, facilitate early mobilization, and lower the incidence of chronic post-thoracotomy pain syndrome [34,35].

RA is equally indispensable in orthopedic surgery, where functional recovery and early rehabilitation are critical to long-term outcomes [11]. Peripheral nerve blocks for major joint procedures provide targeted analgesia while enabling motor-sparing approaches. For instance, femoral and adductor canal blocks are frequently used in total knee arthroplasty (TKA), with the latter preferred for preserving quadriceps strength while maintaining analgesia of the anteromedial knee. The iPACK block, which targets posterior capsule innervation without affecting motor function, further complements analgesic coverage in TKA [36]. Continuous catheter techniques are particularly beneficial in major joint surgery by delivering titratable, extended analgesia, thereby supporting early ambulation, reducing systemic opioid needs, and lowering the risk of chronic stiffness [37,38]. In upper limb procedures, interscalene and supraclavicular brachial plexus blocks provide profound analgesia for shoulder and arm surgery, facilitating same-day discharge and shorter hospital stays.

In pediatric populations, the use of RA is expanding due to its effectiveness in minimizing perioperative opioid exposure, reducing emergence delirium, and improving overall comfort [39]. Caudal epidural blocks remain one of the most frequently employed techniques for subumbilical procedures in infants and children [40]. Ultrasound-guided TAP and QL blocks have been safely adapted to pediatric practice, demonstrating efficacy in laparoscopic appendectomies, herniorrhaphies, and urological operations. In thoracic and cardiac surgery, fascial plane blocks such as parasternal and ESP blocks serve as alternatives when neuraxial techniques are contraindicated by anticoagulation or anatomical limitations. Additionally, RA in children has been associated with fewer postoperative behavioral disturbances, shorter post-anesthesia care unit stays, and reduced incidence of postoperative nausea and vomiting [39,41].

The use of RA should be tailored to the surgical procedure, patient comorbidities, and recovery objectives. By limiting systemic opioid exposure and providing targeted pain relief, RA facilitates early mobilization, reduces perioperative complications, and supports improved long-term functional outcomes. As surgical techniques and patient expectations evolve, the integration of RA into individualized perioperative care pathways continues to be a cornerstone of high-quality surgical management.

Role in ERAS protocols

The ERAS program is a multimodal, evidence-based perioperative pathway designed to reduce surgical stress, accelerate recovery, and shorten hospital stays [3,42,43]. Regional anesthesia is central to ERAS protocols because of its ability to attenuate neuroendocrine responses, provide superior analgesia, and enable early mobilization.

Effective pain management is a cornerstone of ERAS, and the use of regional techniques—such as neuraxial blocks, fascial plane blocks, and peripheral nerve blocks—substantially reduces reliance on systemic opioids [42]. This opioid-sparing effect decreases the incidence of nausea, vomiting, ileus, sedation, urinary retention, and respiratory depression, all of which can delay recovery.

In abdominal surgery, thoracic epidural analgesia or TAP/QL blocks are frequently incorporated into ERAS protocols to facilitate earlier ambulation and faster resumption of enteral nutrition [23]. In orthopedic procedures, adductor canal and iPACK blocks are emphasized for their ability to preserve motor strength and optimize postoperative physiotherapy [21]. Pediatric ERAS adaptations also increasingly incorporate regional techniques to improve comfort, reduce anxiety, and minimize opioid exposure [39].

Clinical evidence demonstrates that integrating RA into ERAS reduces postoperative pain scores, opioid use, complications, and hospital length of stay. Furthermore, the physiological benefits of RA, including improved pulmonary function and modulation of inflammatory responses, contribute to better surgical outcomes [3,20,43].

Successful implementation of RA within ERAS requires close interdisciplinary collaboration, careful patient selection, adherence to standardized protocols, and investment in both training and equipment. As ERAS protocols evolve, RA remains central to advancing perioperative care by aligning safety, recovery optimization, and patient-centered outcomes.

Safety and limitations

Although RA provides substantial benefits when combined with GA, its application must be carefully weighed against associated

risks and procedural limitations [44]. Table 2 summarizes potential complications following RA. The most serious complications include local anesthetic systemic toxicity (LAST), bleeding, infection, nerve injury, and inadvertent dural puncture. LAST, although rare, with estimates around 0.03% or 0.27 episodes per 1,000 nerve blocks, is potentially fatal—particularly in high-volume blocks or accidental intravascular injection—and necessitates early recognition and immediate treatment with lipid emulsion therapy [44]. The incidence of neurological complications after regional anesthesia is reported to be between 1/1,000 and 1/1,000,000. Bleeding risk is especially pertinent in neuraxial and deep peripheral blocks, particularly in patients on antithrombotic therapy. The incidence of epidural or spinal hematoma has been reported to be approximately 1:150,000 for epidural blocks and 1:220,000 for spinal anesthetics. To mitigate these risks, strict adherence to anticoagulation management guidelines, such as those established by the American Society of Regional Anesthesia and Pain Medicine, is mandatory [45]. Nerve injury, though uncommon, may result from direct mechanical trauma, intraneural injection, or ischemia, and can range from transient paresthesia to long-term sensorimotor deficits.

Table 2. Possible complications of regional anesthesia

Possible complications of regional anesthesia
Nerve injury (transient or permanent)
Spinal cord injury
Radiculitis and nerve root irritation
Arachnoiditis
Cauda equina syndrome
Conus medullaris syndrome
Spinal or epidural hematoma
Local bleeding or bruising at puncture site
Epidural abscess
Meningitis
Local infection at needle or catheter site
Post-dural puncture headache
Hypotension
Bradycardia
Arrhythmias
Respiratory depression
LAST
Seizures due to LAST
Cardiac arrest due to LAST
Allergic reactions to local anesthetics or preservatives
Failed or incomplete block
Unintentional high block
Needle or catheter breakage
Back pain at injection site
Fibrosis or scarring of neuraxis
Meningeal deformities
Pseudomeningocele
Syringomyelia
Polyradiculopathy
Block failure
Pseudoaneurysm
Vascular puncture

LAST, local anesthetic systemic toxicity.

The use of ultrasound guidance and refined injection techniques plays a critical role in minimizing neural complications [21]. However, successful execution of RA requires highly trained personnel, specialized equipment such as ultrasound machines and nerve stimulators, and institutional infrastructure to support perioperative analgesia services. Variability in provider expertise and limited resource availability, particularly in low-resource settings, remain significant barriers to widespread adoption.

In addition to procedural risks, clinical challenges such as rebound hyperalgesia and limited block duration must be addressed. Single-shot RA typically provides analgesia for 12–24 hours, after which patients may experience rebound pain. This limitation can be mitigated by incorporating preemptive multimodal analgesia, sustained-release local anesthetic formulations, adjuvants such as dexamethasone or clonidine, or continuous catheter-based techniques [5,30,46]. Not all patients are suitable candidates for RA. Contraindications include patient refusal, local infection, coagulopathy, hypersensitivity to local anesthetics, and anatomical abnormalities that compromise safe block placement. Careful preoperative assessment and interdisciplinary consultation are essential to identify appropriate candidates. In addition, standardized documentation—including informed consent, block details (site, technique, drug, and dose), and vigilant post-procedural monitoring—is necessary to ensure quality, detect complications early, and manage delayed adverse events [11]. In summary, RA is a powerful component of multimodal analgesia, but its safety and efficacy depend on meticulous planning, clinical expertise, and ongoing monitoring. Broader adoption will require overcoming current barriers through enhanced clinician education, standardized institutional protocols, and the integration of enabling technologies.

Future perspectives

The rapidly evolving field of perioperative medicine offers significant opportunities to expand and refine the role of RA in combination with GA. Anticipated advancements encompass pharmacological innovation, digital technologies, personalized medicine, educational reform, and health system integration, all directed to-

ward improving patient outcomes, enhancing safety, and optimizing resource utilization.

Recent developments in long-acting local anesthetic formulations, such as liposomal bupivacaine and polymer-based drug carriers, have the potential to extend the duration of single-injection RA while minimizing systemic toxicity [5,47]. Ongoing research is also investigating nanoparticle-based platforms, pH-responsive release mechanisms, and perineural adjuvants, all designed to increase selectivity, improve safety, and enhance the efficacy of local anesthetic administration [30,46].

The integration of artificial intelligence, machine learning, and predictive analytics holds promise for developing personalized RA strategies. Algorithms that incorporate patient-specific variables, including demographics, comorbidities, surgical characteristics, and pain sensitivity, may support tailored decisions on block selection, anesthetic dosing, and catheter management, ultimately optimizing analgesia and recovery trajectories.

Emerging technologies such as perineural pressure sensors, ultrasound elastography, and sensor-equipped needles are expected to improve the precision and safety of RA by providing real-time feedback during block placement. Furthermore, embedding clinical decision-support tools within anesthesia information management systems could enhance consistency in RA delivery, reduce errors, and promote adherence to evidence-based best practices.

Discussion

In addition to its well-documented benefits for perioperative pain management, recent evidence has linked RA with improved neurocognitive outcomes, particularly in older patients. The pathogenesis of postoperative cognitive dysfunction is multifactorial, involving mechanisms such as hypotension-induced cerebral ischemia, systemic inflammation, and neurotoxicity from anesthetic agents [48,49]. Epidural analgesia may provide a protective effect by attenuating inflammatory responses and reducing intraoperative hemodynamic fluctuations [50]. However, findings from meta-analyses remain mixed, suggesting that RA should be regarded as one component of a broader neuroprotective strategy rather than as a stand-alone intervention. Complementary measures—including strict intraoperative blood pressure control and multimodal neuroprotective protocols—are equally important.

The immunomodulatory effects of RA are another area of growing interest, particularly in oncological surgery. By blunting the surgical stress response and preserving NK cell activity, RA may influence tumor recurrence and metastasis [9,10]. Although causal relationships are still under investigation, retrospective analyses have suggested improved recurrence-free survival among patients receiving RA during cancer resection procedures.

Pharmacological innovations continue to expand the clinical utility of RA. Long-acting local anesthetic formulations such as liposomal bupivacaine extend the duration of single-shot blocks, while adjuvants including dexamethasone, clonidine, and dexmedetomidine enhance both block quality and duration [30,46]. These adjuncts are increasingly incorporated into practice to optimize analgesia and tailor regimens to patient needs.

RA also demonstrates particular value in high-risk populations. For patients with significant cardiovascular or pulmonary comorbidities, RA reduces the requirement for systemic medications and mitigates sympathetic activation. In patients with chronic kidney disease, RA may help avoid nephrotoxic systemic analgesics and maintain renal perfusion by minimizing opioid use and reducing hypotensive episodes.

Ultimately, the success of RA-GA integration relies not only on technical proficiency but also on comprehensive interdisciplinary planning, thoughtful patient selection, and adherence to standardized protocols. As the evidence base continues to expand, anesthesiologists are uniquely positioned to lead multimodal strategies that integrate RA to improve both short- and long-term surgical outcomes.

Conclusion

The integration of RA with GA provides a robust multimodal approach to address the complex and multifactorial nature of postoperative pain. Supported by a growing body of clinical evidence and closely aligned with the ERAS paradigm, this strategy should be routinely considered across diverse surgical populations. Widespread adoption, however, will depend on continued research, equitable dissemination, and comprehensive education to ensure safe and effective implementation. Importantly, the long-term benefits of RA-GA integration extend beyond perioperative analgesia. Reduced chronic pain, enhanced functional independence, improved immune recovery, and even favorable oncological outcomes underscore the need to prioritize perioperative pain control as an essential component of comprehensive surgical care.

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Personalized perioperative pain management: a narrative review

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Perioperative pain management has shifted from standardized, procedure-based protocols toward individualized, patient-centered approaches. Inadequate pain control can result in short-term adverse outcomes, including delayed ambulation, prolonged hospitalization, and increased complications, as well as long-term sequelae such as chronic persistent postsurgical pain. Early models of preemptive and preventive analgesia emphasized pain relief primarily through the use of opioids. Growing concern about opioid-related adverse effects established the basis for multimodal and opioid-sparing strategies. Nevertheless, with the onset of the global opioid crisis, heightened awareness of the risks of opioid overuse has fueled interest in opioid-free techniques. However, evidence does not demonstrate that opioid-free methods are superior to opioid-sparing approaches. This underscores the importance of returning to the central goals of enhanced recovery after surgery: early restoration of function and reduction of complications. Within this framework, personalized pain management has emerged as a practical paradigm that tailors interventions to individual characteristics, including comorbidities, psychological status, pain sensitivity, and recovery objectives. This review outlines the rationale, current practices, and future directions of personalized perioperative pain management and proposes a framework for integrating new strategies into clinical care.

Keywords: Analgesia; Enhanced recovery after surgery; Pain management; Personalized medicine

Introduction

Background

Over the past decade, surgical trends have evolved significantly, ranging from major inpatient operations to minimally invasive techniques and an increasing number of day care surgeries [1]. These developments have improved surgical efficiency, shortened hospital stays, and broadened treatment options for diverse patient populations. At the same time, they have intensified the need for more advanced perioperative pain management strategies [2].

Pain characteristics, including intensity and duration, vary considerably depending on the type and invasiveness of surgery. Day care procedures in particular demand careful attention, as inadequate analgesia can delay discharge, hinder early mobilization, lower patient satisfaction, and increase the likelihood of readmission. More broadly, poorly controlled perioperative pain compromises respiratory function, restricts ambulation, amplifies physiological stress responses, and raises the risk of long-term complications such as delayed psychological recovery and the development of chronic persistent postsurgical pain (CPSP) [3,4].

These changes in surgical practice highlight the limitations of standardized, procedure-based analgesic regimens. Uniform protocols often fail to incorporate key determinants of pain experience, including individual pain sensitivity, baseline functional status, comorbidities, and recovery goals. As minimally invasive techniques, enhanced recovery pathways, and the continued expansion of outpatient operations become more common, recognition of the importance of personalized perioperative pain management is growing.

This patient-centered approach adapts analgesic strategies to individual needs, surgical characteristics, and expected recovery trajectories. Recent studies indicate that individualized pain assessment combined with multimodal interventions reduces postoperative pain severity, lowers opioid consumption, and shortens hospital stays [5,6]. At the same time, advances in pharmacogenomics hold promise for guiding analgesic choice and dosing

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based on genetic profiles, thereby improving efficacy while limiting adverse effects.

Objectives

The aim of this narrative review is to present the rationale, current practices, and emerging directions in personalized perioperative pain management, and to explore strategies for translating these concepts into effective clinical protocols.

Ethics statement

As this study is a narrative review, it did not require institutional review board approval or individual consent.

Historical evolution of perioperative pain management

The conceptual framework of perioperative pain management has undergone profound transformation over the past 4 decades (Fig. 1). Each period has been shaped by new insights into pain physiology, evolving clinical practices, and broader societal forces.

The 1980s: preemptive analgesia

A major conceptual advance occurred in the 1980s when Clifford Woolf introduced the idea of preemptive analgesia. His work demonstrated that surgical injury could trigger central sensitization, a process in which repeated or sustained noxious input amplifies pain signaling in the central nervous system [7,8]. Based on this mechanism, it was hypothesized that administering analgesic interventions before surgical incision could attenuate sensitization and thereby reduce postoperative pain. Although groundbreaking, clinical trials yielded inconsistent results, in part because preemptive analgesia focused narrowly on the timing of drug administration without ensuring continuous pain control throughout the perioperative period.

The 1990s: preventive analgesia

In the 1990s, the concept of preventive analgesia emerged. Unlike strategies confined to the pre-incision phase, preventive analgesia sought to maintain continuous suppression of nociceptive input throughout the entire perioperative period [9,10]. This broader approach addressed the shortcomings of strictly preemptive methods and laid the foundation for more integrated, multimodal strategies.

The late 1990s to early 2000s: multimodal analgesia

By the late 1990s and early 2000s, the principle of multimodal analgesia had become well established. This approach emphasized combining multiple classes of pharmacologic agents with regional anesthesia techniques to achieve additive or synergistic effects while reducing reliance on any single drug [11]. Typical combinations included nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, gabapentinoids, local anesthetics, and, in selected cases, low-dose opioids. Multimodal analgesia represented a paradigm shift away from opioid-dominant regimens toward individualized combinations designed to maximize efficacy while minimizing adverse effects.

The 2000s to 2010s: opioid-sparing analgesia and enhanced recovery after surgery

During the 2000s and 2010s, opioid-sparing strategies gained momentum, largely driven by the global adoption of enhanced recovery after surgery (ERAS) programs [12]. These pathways promoted early mobilization, reduced hospital stays, and decreased complication rates, all supported by minimizing opioid use. The rationale was twofold: (1) to accelerate recovery by reducing opioid-related adverse events such as nausea, sedation, and ileus, and (2) to mitigate the growing public health threat of opioid misuse and dependence.

The opioid crisis and the emergence of opioid-free analgesia

In parallel, the early 2000s saw a dramatic escalation in oral opi-

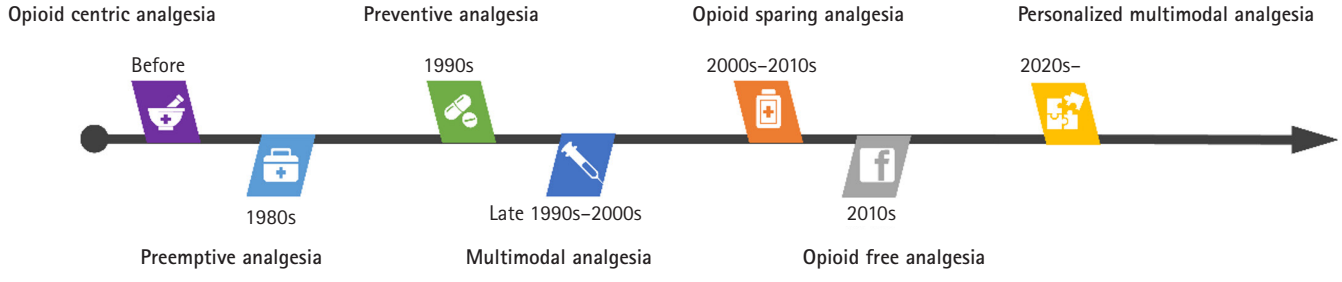

Fig. 1. Pain management concepts.

oid prescribing in the United States, fueled by aggressive pharmaceutical marketing, permissive prescribing practices, and supportive policy frameworks [13,14]. Excessive postoperative prescriptions were often issued without consideration of surgical invasiveness or actual pain severity, leading to widespread availability of unused medications [15,16]. At the same time, socioeconomic stressors such as rising unemployment exacerbated misuse, and opioid overdose deaths increased by more than 180% during this period [14,17].

Heightened concern over misuse and dependence reframed the epidemic as both a public health and social crisis. In this context, opioid-free analgesia (OFA) emerged, aiming to eliminate opioids by substituting agents such as dexmedetomidine, ketamine, and intravenous lidocaine [18,19]. Despite its appeal during the opioid epidemic, OFA has not achieved broad clinical adoption because supporting evidence remains limited, protocols are inconsistent, and questions regarding safety and efficacy persist [17,20,21].

In sum, the historical trajectory of perioperative pain management reflects a progressive departure from opioid-centered strategies toward integrated, multimodal, and increasingly individualized approaches. These developments have laid the foundation for the current paradigm of personalized perioperative pain management.

The advent of personalized pain management

Concerns about opioid overuse have been heightened not only by the clinical adverse effects of opioids—including over-sedation, respiratory depression, tolerance, and opioid-induced hyperalgesia—but also by the wider societal consequences of the opioid crisis. In this context, OFA has drawn increasing attention. However, current evidence does not demonstrate clear superiority of OFA over opioid-sparing strategies in either analgesic efficacy or reduction of excessive prescribing [17]. Accordingly, rather than focusing exclusively on eliminating opioids, it is more appropriate to return to the central aim of ERAS: restoring patients to baseline functional status as rapidly as possible while minimizing perioperative complications.

Personalized perioperative pain management has therefore emerged as a pragmatic, patient-centered strategy. Instead of framing the debate as opioid versus non-opioid, this approach emphasizes tailoring the analgesic plan to each patient's individual characteristics, the surgical context, and specific recovery goals [22-25].

Pain perception and treatment response are influenced by many factors. These include demographic variables (such as age and sex), comorbidities (e.g., diabetes, cardiovascular disease, chronic pain conditions), baseline functional capacity, and psychological factors such as anxiety, depression, and catastrophizing tendencies. Biological and genetic variability, differences in pain sensitivity, and circadian rhythms also shape analgesic requirements and outcomes [25-29].

The overarching aim of personalized perioperative pain management is to provide effective analgesia while preserving functional capacity, reducing adverse drug effects, and promoting early mobilization and recovery. This is achieved through a combination of multimodal analgesia, advanced regional anesthesia techniques, and technology-enabled monitoring tools, including wearable sensors and digital pain assessment platforms [27,30,31].

This approach aligns closely with the broader objectives of ERAS protocols. Beyond promoting rapid recovery, it seeks to improve long-term functional outcomes and quality of life. Perioperative pain management must therefore extend its scope beyond the immediate postoperative period to include the prevention of CPSP. CPSP can have lasting consequences, including physical disability, psychological distress, and reduced social participation [32,33]. Consequently, early recognition of patient- and procedure-specific risk factors is essential for developing individualized preventive strategies (Table 1).

Multimodal approach for personalized pain management

A multimodal approach forms the cornerstone of personalized perioperative pain management, integrating pharmacologic, non-pharmacologic, regional anesthesia, and technology-based strategies in a phase- and risk-specific manner. Patients with pre-

Table 1. Reported risk factors for chronic persistent postsurgical pain

Category	Risk factors
Preoperative	Pre-existing painful condition; long-term opioid use; psychological comorbidities (e.g., depression, anxiety); young adult age; female sex; high body mass index (> 30 kg/m^2)
Surgical	Type of surgery (e.g., thoracotomy, amputation, mastectomy)
Postoperative	Severe acute postoperative pain; postoperative neuropathic pain

operative risk factors such as chronic pain, prolonged opioid exposure, or psychological comorbidities benefit from early multidisciplinary consultation. Such consultation can optimize analgesic planning, provide psychological support, and, when appropriate, initiate prehabilitation to enhance resilience and postoperative outcomes. For surgeries with high anticipated nociceptive input, regional anesthesia techniques—including epidural analgesia, peripheral nerve blocks, and fascial plane blocks—can reduce central sensitization, limit intraoperative opioid use, and facilitate recovery. In the postoperative phase, clinicians must escalate therapy promptly in patients with severe acute pain or neuropathic features, using targeted pharmacologic agents, repeat or rescue nerve blocks, and adjuvant medications that address neuropathic pain. Organizing multimodal strategies within this phase-specific framework helps translate personalized pain management into evidence-based practice, improving acute pain control, accelerating recovery, and enhancing long-term quality of life.

Pharmacological approach

Pharmacological strategies in personalized perioperative pain management center on multimodal analgesia: combining agents with complementary mechanisms to achieve additive or synergistic pain relief while limiting opioid use. Non-opioid agents—acetaminophen, NSAIDs, and gabapentinoids—serve as the foundation and should be selected and dosed based on comorbidities, renal and hepatic function, and the expected pain phenotype (somatic, visceral, or neuropathic) [23]. In patients at high risk of respiratory complications (e.g., obstructive sleep apnea, severe chronic obstructive pulmonary disease, obesity hypoventilation), opioid-sparing regimens should be prioritized, reserving only short courses of the lowest effective opioid doses when unavoidable. In renal dysfunction, nephrotoxic agents—especially NSAIDs—should be avoided, and renally cleared drugs such as gabapentinoids should be dose-adjusted or substituted [24,34]. In hepatic impairment and older adults, therapy should begin with lower doses and be titrated cautiously, accounting for altered pharmacokinetics and pharmacodynamics, as well as heightened susceptibility to sedation, delirium, and hypotension [35,36]. For patients with neuropathic features or a high risk of CPSP, mechanism-based adjuvants—such as NMDA-receptor antagonists (e.g., low-dose ketamine), gabapentinoids, and serotonin–noradrenaline reuptake inhibitors—should be integrated into structured, time-limited protocols with clear goals and monitoring for side effects such as dizziness, somnolence, and hemodynamic instability [27,37].

Pharmacogenomics provides another dimension of personalization. *CYP2D6* polymorphisms affect bioactivation of codeine and tramadol, producing poor or ultrarapid metabolizer phenotypes that result in either loss of efficacy or increased toxicity [23,38]. Variants in *OPRM1* (μ-opioid receptor) influence opioid sensitivity, while *COMT* and *ABCB1* polymorphisms may further contribute to variability in analgesic response and central nervous system exposure [39,40]. Although not yet routine, targeted pharmacogenomic testing can inform drug selection and dosing in specific scenarios, reducing variability and minimizing adverse outcomes.

Emerging evidence also highlights the role of circadian biology in modulating nociception and analgesic response. Diurnal variations in pain thresholds and time-dependent differences in pharmacokinetics and pharmacodynamics (chronopharmacology) have been observed for several analgesics [28,41,42]. Incorporating timing into perioperative regimens—such as aligning scheduled non-opioids with periods of heightened pain or activity and avoiding sedative loading during nocturnal vulnerability—may optimize efficacy and reduce side effects [43].

Together, these biological determinants—clinical phenotype, organ function, pharmacogenomic variability, and circadian rhythms—support moving beyond "one-size-fits-all" multimodal regimens toward more precise, patient-specific pharmacological strategies. Integrating these factors with established perioperative principles advances effective analgesia, preserves function, accelerates recovery, and reduces variability and adverse outcomes.

Regional anesthesia

Regional anesthesia, which provides targeted analgesia by blocking nociceptive transmission, is a central component of personalized perioperative pain management. Advances in imaging, particularly the widespread adoption of ultrasound guidance, have transformed regional anesthesia from landmark-based blocks to more precise peripheral nerve and fascial plane techniques. These advances allow clinicians to deliver effective analgesia while avoiding complications traditionally associated with neuraxial approaches, such as hypotension, urinary retention, or unnecessary motor impairment.

In thoracic surgery, analgesic strategies must be adapted to the degree of invasiveness. Thoracotomy produces severe acute pain and is a risk factor for CPSP, making potent analgesia essential. Thoracic epidural analgesia (TEA) has long been regarded as the gold standard, providing excellent static and dynamic pain control with substantial opioid-sparing benefits, though its use may be constrained by adverse effects such as hypotension or urinary retention. Thoracic paravertebral block (TPVB) has emerged as an

effective alternative, producing unilateral somatic and sympathetic blockade with comparable efficacy to TEA but a more favorable safety profile. Although intercostal nerve block (ICNB) offers better analgesia than systemic opioids, its short duration limits its role as a primary modality [44,45].

In contrast, video-assisted thoracic surgery (VATS) is less invasive, and postoperative pain is less intense than after thoracotomy. In this context, TPVB may provide non-inferior analgesia compared with TEA while avoiding neuraxial risks [45]. The erector spinae plane block (ESPB) has gained popularity due to its technical simplicity, wide dermatomal coverage, and favorable safety profile. Similarly, the serratus anterior plane block is particularly effective for VATS, lateral chest wall, and breast surgery [46]. ICNB remains widely used and reduces both intraoperative and postoperative opioid consumption, but its relatively short duration and potential systemic toxicity when administered at multiple levels restrict its role as a stand-alone technique. The development of liposomal bupivacaine has renewed interest in ICNB by potentially prolonging its effects, though current evidence is inconsistent, with some studies demonstrating improved analgesia and others finding no advantage over conventional agents [45]. As a result, ICNB in VATS is increasingly regarded as an element of multimodal analgesia rather than a sole technique.

Personalized regional anesthesia also emphasizes motor-sparing and risk-adapted techniques. For example, the adductor canal block in knee surgery provides effective analgesia while preserving quadriceps strength, enabling early mobilization and rehabilitation, and is now frequently favored over femoral nerve block in this setting [22,33]. In patients at high risk of respiratory depression, effective shoulder analgesia can be achieved while reducing phrenic nerve involvement through newer approaches such as selective upper trunk block or combined suprascapular and axillary nerve blocks, rather than traditional interscalene block [47].

By tailoring block selection to surgical invasiveness, expected pain patterns, and patient-specific risk factors, clinicians can enhance analgesic efficacy, reduce opioid requirements, and support early ambulation. Regional anesthesia may also contribute to the prevention of CPSP by mitigating central sensitization. Thus, it exemplifies the principles of personalized pain management, integrating technological advances with individualized decision-making to improve both short- and long-term outcomes.

Technology-enabled monitoring

Recent advances in digital health technologies have expanded opportunities for personalized pain monitoring and management. Smartphone applications for acute pain services allow real-time reporting of pain scores, medication use, and side effects, enabling clinicians to respond promptly and adjust treatment regimens in patient-specific ways [48]. Wearable devices that measure physiologic parameters such as heart rate variability, skin conductance, or movement patterns provide continuous, objective data that complement traditional subjective pain scores. Furthermore, high-resolution perioperative datasets such as VitalDB and the MOVER (Medical Informatics Operating Room Vitals and Events Repository) create a foundation for AI-driven predictive analytics. These systems can anticipate analgesic requirements, identify patients at risk of inadequate pain control, and support real-time decision-making [49,50]. Emerging perspectives also suggest that artificial intelligence applied to large, heterogeneous datasets could help identify pain subtypes, predict treatment responses, and guide individualized strategies, further reinforcing the role of precision medicine in perioperative care [5].

Although still in the early stages of adoption, these technologies illustrate the potential for integrating digital tools into routine perioperative management to achieve more consistent, patient-centered outcomes. Significant challenges remain, including data standardization, integration into clinical workflows, and concerns over privacy and security. Nevertheless, technology-enabled monitoring represents a promising frontier in personalized perioperative pain management. By bridging the gap between conventional clinical assessment and precision medicine, digital tools may help establish the next generation of individualized pain strategies. The integration of pharmacological approaches, regional anesthesia, and digital health innovations highlights how personalized models can reshape perioperative pain management, and future research should lay the foundation for broader clinical application.

Conclusion

Perioperative pain management is shifting from standardized, procedure-based regimens to individualized, patient-centered strategies. Rather than concentrating exclusively on opioid-free concepts, improving patient outcomes should be prioritized through optimized multimodal pharmacological regimens, tailored regional anesthesia, and non-pharmacological interventions, all aligned with ERAS protocols. By considering patient-specific factors—such as comorbidities, psychological status, and functional goals—clinicians can reduce opioid dependence, facilitate early mobilization, and prevent CPSP. Clinical decision-making should not be guided merely by technical feasibility but should instead be anchored in patient-centered values, with functional recovery and patient satisfaction as primary goals. Ultimately, the

safe and efficient restoration of preoperative functional status, while minimizing complications and improving quality of life, represents the highest objective of perioperative pain management.

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Authors' contribution

Conceptualization: MKK, HK. Data curation: MKK, HK. Methodology/formal analysis/validation: MKK, HK. Project administration: MKK, HK. Writing–original draft: MKK. Writing–review & editing: MKK, HK.

Conflict of interest

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Supplementary materials

None.

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Not just small adults–practical pearls in pediatric anesthesia: a narrative review

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Pediatric anesthesia presents unique challenges due to children's distinct physiological and anatomical characteristics, including variations in drug metabolism, airway structure, and respiratory and circulatory regulation. Despite significant advances in patient safety that have reduced anesthesia-related mortality over recent decades, the declining pediatric population has made specialized training and clinical practice increasingly difficult. This narrative review addresses practical aspects of pediatric anesthesia, emphasizing patient monitoring, airway management, and recent clinical advances. Oxygen supply targets in children require careful titration to ensure adequate tissue oxygenation while avoiding oxygen toxicity and its associated complications, such as bronchopulmonary dysplasia and retinopathy of prematurity. Quantitative monitoring of neuromuscular blockade, such as with train-of-four stimulation, is essential to prevent postoperative respiratory complications. Temperature monitoring is equally critical in pediatric surgery because children and neonates are highly susceptible to intraoperative hypothermia. Airway management in infants and young children is complicated by anatomical differences, and while video laryngoscopy offers advantages, evidence for its benefits in neonates remains inconclusive. Extubation strategies must be individualized, taking into account risks such as laryngospasm and airway obstruction, as both deep and awake extubation have demonstrated comparable safety profiles. Emerging modalities, such as transfontanelle ultrasonography, provide real-time cerebral blood flow assessment and enhance perioperative brain monitoring. Regional anesthesia techniques in neonates and infants reduce exposure to general anesthetics and facilitate faster recovery but require meticulous technique and monitoring to ensure safety. Multidisciplinary collaboration and effective communication with parents are essential to achieving optimal outcomes.

Keywords: Airway management; Child; Neuromuscular monitoring; Oxygen; Regional anesthesia

Introduction

Background

Children exhibit distinctive physiological and anatomical features—including differences in drug metabolism and responses, airway anatomy, and respiratory and circulatory regulatory mechanisms—that distinguish them markedly from adults. It is widely recognized that "pediatric patients are not simply small adults" [1,2]. Through continuous improvements in patient safety, anesthesia-related mortality has declined substantially, from 1:2,500 to 1:13,000 over the past 50 years [3-5]. However, the global total fertility rate (TFR) in 2021 was 2.3 children per woman, continuing its decline from 3.3 in 1990 and 2.8 in 2000 [6]. In South Korea, the TFR dropped to 0.72 in 2023, the lowest among Organization for Economic Co-operation and Development countries [7].

As the number of pediatric patients decreases, specialized training in pediatric anesthesia has become increasingly complex. Even after achieving board certification, pediatric anesthesia continues to pose significant technical and clinical challenges for anesthesiologists.

Objectives

This narrative review aims to provide practical guidance drawn from recent literature to support clinicians in their daily practice, focusing on patient monitoring, airway management, and recent advances that can be directly implemented in pediatric anesthesia.

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Ethics statement

Because this is a literature-based study, neither approval from an institutional review board nor informed consent was required.

Monitoring

Setting oxygen supply targets

Various equipment and techniques have been developed to optimize oxygen use, improving survival rates in pediatric patients with difficult airways [8-10]. However, the optimal target oxygen concentration during anesthesia in children remains uncertain. Several studies have explored complications related to oxygen concentration and use [11-13], underscoring the need to consider individualized oxygenation goals rather than simply maintaining a peripheral oxygen saturation (SpO_2) of 100%. An appropriate oxygen concentration enhances tissue oxygenation and tolerance to hypoxia while reducing the risk of surgical site infection [14]. Conversely, excessive oxygen concentrations can cause absorption atelectasis due to airway closure and collapse, elevate pulmonary vascular resistance and pulmonary circulation, and decrease cerebral blood flow through systemic and cerebral vasoconstriction [15-17]. Moreover, oxygen toxicity resulting from reactive oxygen species may trigger inflammation and edema, leading to bronchopulmonary dysplasia and retinopathy of prematurity [18-21]. A recent review emphasized that no single universal range can define the optimal oxygen target during general anesthesia in pediatric patients. Anesthesiologists must determine oxygen concentration carefully, considering patient-specific factors before, during, and after surgery—such as lung function, oxygen consumption, and the presence of heart disease—to achieve optimal oxygenation [14]. Additionally, pulse oximetry measures arterial oxygen saturation but not arterial oxygen partial pressure (PaO_2). While pulse oximetry is effective for detecting hypoxia, it does not reduce mortality or accurately identify hyperoxia [22]. The oxygen reserve index (ORi) quantifies oxygen reserves when SpO_2 is near 100%, providing an early warning of impending hypoxia. Balancing the risks of hypoxia and hyperoxia is especially critical in neonates, who are at increased risk for retinopathy of prematurity, bronchopulmonary dysplasia, and mortality. Although studies on ORi in pediatric populations remain limited, it may support an individualized approach to defining safe oxygenation thresholds [23]. However, because ORi is not equivalent to PaO_2, arterial blood gas analysis remains necessary to determine the optimal oxygen concentration [24].

Neuromuscular blockade monitoring

Neuromuscular blocking agents (NMBAs) facilitate tracheal intubation and immobility during pediatric anesthesia; however, inadequate reversal or excessive blockade can result in serious complications, including respiratory failure and aspiration pneumonia [25,26]. Therefore, neuromuscular monitoring (NMM) is crucial for assessing the degree of neuromuscular blockade in pediatric patients. NMM is essential for maintaining an appropriate depth of blockade during anesthesia, ensuring timely recovery after surgery, and minimizing postoperative complications.

NMM methods include clinical observation, qualitative assessment (nerve stimulator), and quantitative assessment techniques such as electromyography, mechanomyography, acceleromyography (AMG), and kinemyography. Among these, the train-of-four (TOF) stimulation method is the most widely used standard. TOF evaluates the depth of blockade and recovery by measuring muscle responses to 4 consecutive stimuli, and a TOF ratio ≥ 0.9 is generally considered indicative of sufficient recovery. In pediatric patients, NMM poses unique challenges due to anatomical and physiological differences, as well as variable drug responses. The absence of standardized guidelines, limited availability of monitoring equipment, inadequate user proficiency, and concerns about device reliability have contributed to the inconsistent application of NMM in clinical practice [27]. Nevertheless, to prevent postoperative respiratory complications caused by residual neuromuscular blockade, quantitative NMM and documentation of TOF are essential whenever nondepolarizing muscle relaxants are administered. The consistent use of practical monitoring tools that can be easily applied and interpreted by clinicians is also critical [28].

Accurate skin preparation, proper electrode placement, and the use of appropriately sized and spaced electrodes are vital for improving the accuracy of pediatric NMM. The cathode should be positioned distally, and electrode spacing should be adjusted in consideration of children's smaller arm size and shorter nerve distances. The arm should be stabilized to prevent unnecessary movement, and baseline calibration (before NMBA administration) should be performed [26,29]. Because temperature changes can alter NMBA pharmacodynamics, maintaining a core temperature above 35°C and a peripheral temperature above 32°C is recommended [30]. When using AMG, normalization of the TOF ratio after calibration is required, and applying a 5-second, 50 Hz tetanic stimulation before measurement can help stabilize the signal [31].

Temperature monitoring

Temperature monitoring is an essential perioperative parameter, enabling the detection of both hypothermia and hyperther-

mia, each of which requires prompt intervention. Intraoperative hypothermia occurs in approximately 50% of pediatric patients [32,33], and the incidence in neonates has been reported to exceed 80% [34]. Children are more susceptible to heat loss because their thermoregulatory capacity is less effective than that of adults, their weight-to-surface-area ratio is lower, heat loss from the head is greater, and subcutaneous fat stores that provide thermal insulation are limited [35]. Moreover, hypothermia can cause numerous adverse effects, including altered pharmacokinetics and pharmacodynamics (particularly of NMBAs), impaired platelet function, coagulation abnormalities, increased bleeding tendency, cardiocirculatory and respiratory complications, delayed wound healing, and an elevated risk of surgical site infection [36]. Accordingly, accurate temperature measurement is essential for appropriate intraoperative temperature management.

Because extremity and skin temperatures are typically lower than core body temperature [37,38], the esophagus is most commonly used for core temperature monitoring [39]. Although the pulmonary artery provides the most accurate single-site core temperature measurement, it is highly invasive and thus unsuitable for non-cardiac surgical patients [40]. Correct placement of an esophageal temperature probe between the left atrium and the descending aorta minimizes exposure to airway cooling and allows for accurate measurement of core temperature. In pediatric patients, insertion depth can be estimated using formulas such as that proposed by Hong et al. [41] (height/5+5 cm from the incisors), which assists in determining the appropriate probe depth for accurate temperature assessment.

Airway management: from intubation to extubation

Efficiency of intubation techniques

Airway management in infants and young children is particularly challenging because of their anatomical and physiological differences from adults. In children, the larynx is positioned more anteriorly and superiorly, forming a sharper angle between the larynx and tongue during tracheal intubation. In addition, a proportionally larger tongue further limits endotracheal tube manipulation [42,43]. Recently, the use of video laryngoscopes (VLs) in pediatric anesthesia has increased, and multiple studies have examined their efficacy. VLs enable direct or indirect visualization of airway structures without requiring alignment of the oral, pharyngeal, and tracheal axes, thereby providing higher glottic exposure scores and reducing the need for airway manipulation during intubation [44]. Furthermore, in less experienced users, VLs have been shown to improve first-attempt success rates compared to direct laryngoscopes (88% vs. 63%) [45]. Rahendra et al. [43] compared the effectiveness of spiral endotracheal tubes (spiral ETTs) with standard endotracheal tubes during intubation using a McGrath VL in children aged 1 month to 6 years. Although no significant differences were observed in total intubation time or first-attempt success rates, the spiral ETT achieved significantly shorter total tube handling time and greater accuracy in central positioning of the tube tip at the glottic opening compared with the standard ETT. However, when VLs were compared with direct laryngoscopy for routine tracheal intubation, intubation times and numbers of attempts were similar; thus, current evidence remains insufficient to either recommend or discourage the use of VLs for neonatal intubation [46].

Timing and methods for endotracheal tube removal

Extubation poses a substantial risk of complications in both adults and children; however, in pediatric patients, adverse respiratory events such as airway obstruction, laryngospasm, and oxygen desaturation occur more frequently [47]. Tham and Lim [48] reported that early extubation after pediatric cardiac surgery is feasible and associated with shorter intensive care unit stays and fewer mechanical ventilation–related complications. Nevertheless, in patients with pulmonary hypertension, impaired cardiac function, or a high risk of intraoperative bleeding, early extubation should be approached cautiously.

Post-extubation airway complications in children are primarily respiratory in nature. Laryngospasm, in particular, is associated with risk factors such as younger age, recent upper respiratory tract infection, and asthma. It may be triggered by laryngeal stimulation from the endotracheal tube, airway manipulation, secretions, or blood. Because pediatric airways are structurally delicate and highly sensitive to stimulation, 2 principal approaches are used for tube removal: deep extubation, performed under a deep plane of anesthesia, and awake extubation, performed when the patient is fully conscious. Although many pediatric anesthesiologists prefer awake extubation, studies have shown no significant difference in the incidence of serious complications between the 2 techniques [49,50]. Therefore, the choice of method should be based on the patient's condition and the anesthesiologist's experience. Deep extubation is often selected for patients with recent upper respiratory infections, asthma, or when postoperative coughing could be detrimental. Conversely, awake extubation is generally recommended for patients with a potentially difficult airway or a high likelihood of requiring reintubation.

According to Igarashi [47], the timing of airway removal at the conclusion of surgery should take into account the patient's respiratory and circulatory status, type of surgery, and risk of airway

edema. The most critical consideration is the accurate assessment of anesthetic depth and the patient's ability to maintain airway patency at the time of extubation. However, owing to the wide variation in age and physiological condition among pediatric patients, establishing standardized objective criteria remains difficult, and current practice primarily depends on clinical judgment and observation. Some studies have proposed awake extubation criteria—including facial grimacing, eye opening, purposeful movement, and adequate tidal volume—but no definitive criteria exist for deep extubation [3]. The laryngeal stimulation test provides an objective means of assessing anesthetic depth before extubation. It involves gently moving the endotracheal tube and observing the laryngeal response. In stage 1 (awake), stimulation elicits coughing and brief apnea; in stage 2 (light anesthesia), it produces repetitive coughing and apnea lasting longer than 5 seconds, during which the risk of laryngospasm is high; and in stage 3 (deep anesthesia), there is no response to stimulation [51].

Expanding the horizons

Transfontanelle ultrasound

Cerebral blood flow velocity can be assessed using transcranial Doppler; however, in pediatric patients, the small size of cerebral vessels makes it difficult to maintain proper probe positioning, thereby limiting its clinical application. In contrast, transfontanelle ultrasonography (TFU) enables the evaluation of blood flow in major cerebral vessels using standard ultrasound equipment and probes, making it particularly valuable in children (Fig. 1). TFU allows real-time visualization of key intracranial anatomical structures, including the ventricles, cerebral arteries, and overall cerebral circulation, while also providing hemodynamic parameters such as blood flow velocity and resistance indices [52]. TFU has been employed for real-time monitoring of cerebral blood flow during cardiac and neurosurgical procedures, enabling the assessment of hemodynamic changes before and after surgery and throughout cardiopulmonary bypass [53]. It also aids in detecting intraoperative abnormalities such as flow reversal or vascular occlusion. When TFU indicates decreased cerebral blood flow during surgery, it can be combined with near-infrared spectroscopy to confirm cerebral perfusion status. This multimodal approach is especially critical in neonates and infants who are at high risk of brain injury. Overall, TFU provides a noninvasive, real-time means of assessing cerebral blood flow in pediatric surgical patients. However, further studies are needed to expand its clinical

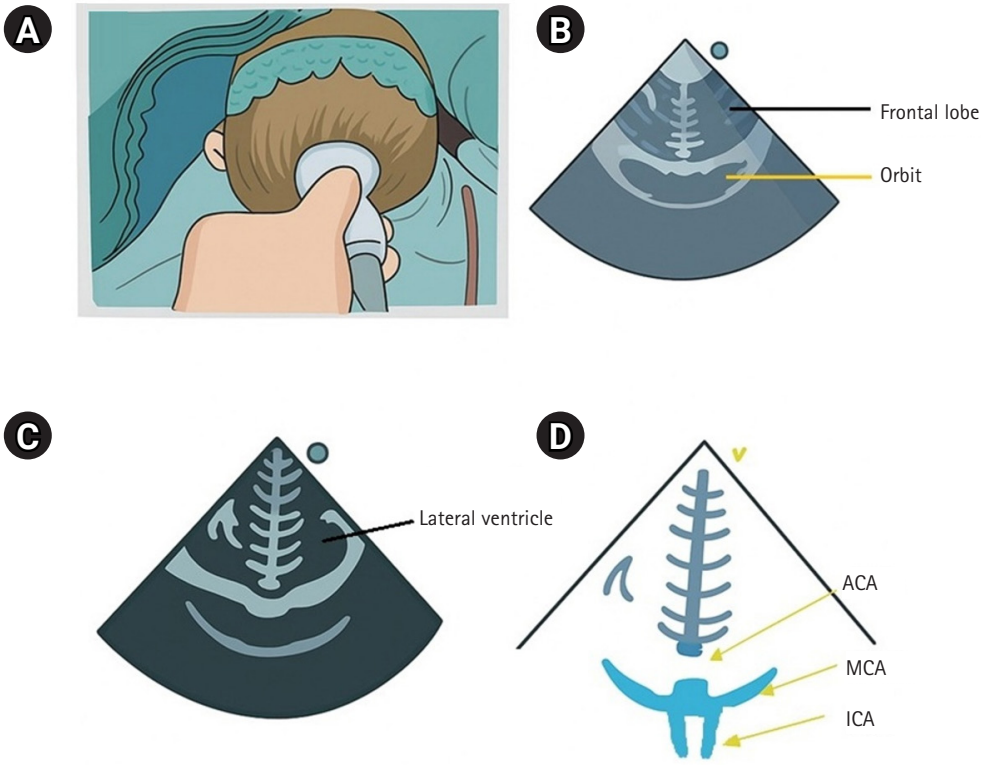

Fig. 1. Coronal section of transfontanelle ultrasonography. (A) Probe placement on the anterior fontanelle of the infant, (B) coronal frontal image, (C) coronal image at Monro levels, and (D) coronal sections of the anterior cerebral artery (ACA), middle cerebral artery (MCA), and both internal carotid arteries (ICAs).

Table 1. Dosages of various common local anesthetics

	Bupivacaine	Ropivacaine	Levobupivacaine	Lidocaine with adrenaline
Allowable dose (mg/kg)	2.5	2.5	2.5	7
Bolus for peripheral and truncal blocks (mL/kg)	0.25	0.2	0.25	0.125
For infusion concentration (%)	0.2 or 0.1	0.2 or 0.1	0.2 or 0.1	0.2 or 0.1
For infusion rate (mg/kg/hr)	0.2	0.2	0.2	-

applications and to establish standardized protocols for its routine use [52].

Regional blocks in neonates and infants

In neonates and infants, general anesthesia carries a higher risk of adverse effects such as hypoxemia, bradycardia, and postoperative apnea. Because hepatic and renal functions are immature, drug metabolism is delayed, potentially prolonging anesthetic effects. Furthermore, concerns have been raised regarding the possible long-term impact of general anesthesia on neurodevelopment. Regional anesthesia (RA) reduces the need for general anesthetics and systemic analgesics, thereby promoting faster recovery and improving postoperative safety [54].

Safe administration of RA requires continuous monitoring, precise drug dosing, and accurate injection techniques. Among central neuraxial blocks, caudal epidural anesthesia is the most frequently performed and can be guided by anatomical landmarks, nerve stimulators, or ultrasound, of which ultrasound guidance significantly enhances the accuracy of catheter placement. Bupivacaine (0.25%) is the most commonly used local anesthetic, with dosage adjusted according to the surgical site (Table 1) [55]. In neonates, the needle insertion depth beyond the sacrococcygeal membrane should be limited based on body weight to prevent injury. When an indwelling catheter is placed, its position should be confirmed and carefully managed throughout the procedure. Adherence to these technical precautions ensures safe and effective anesthesia in neonates and infants. Peripheral nerve blocks are widely used in both upper- and lower-limb surgeries and are typically performed under ultrasound guidance to increase precision and safety. For upper limbs, the supraclavicular, infraclavicular, and axillary approaches are most commonly employed, whereas femoral and sciatic nerve blocks are standard for lower-limb procedures. Although RA offers numerous benefits, Ponde et al. emphasized the importance of recognizing and managing local anesthetic systemic toxicity, integrating multimodal analgesia before and after surgery, maintaining vigilant monitoring, fostering multidisciplinary collaboration, and providing thorough explanations to parents [56].

Conclusion

Pediatric anesthesia requires individualized approaches that reflect the unique physiological and anatomical characteristics of children. Optimization of oxygen delivery, precise monitoring of neuromuscular blockade and temperature, and individualized airway management are essential to minimize perioperative risks. Emerging modalities such as TFU enhance cerebral monitoring, while RA offers an effective alternative to general anesthesia, potentially reducing neurodevelopmental risks. Despite these advancements, challenges persist in standardizing practices and training due to patient variability and declining pediatric case volumes. Ongoing research, education, and multidisciplinary collaboration remain essential to further improve the safety and efficacy of pediatric anesthesia care.

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Authors' contribution

Conceptualization: HYK. Data curation: HYK. Methodology/formal analysis/validation: HYK. Project administration: HYK. Funding acquisition: HYK. Writing–original draft: HYK. Writing–review & editing: HYK.

Conflict of interest

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Case report

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The Ewha Medical Journal

Raising awareness through a case of recurrent fractures in a child with congenital insensitivity to pain and anhidrosis in Saudi Arabia

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Patients with congenital insensitivity to pain and anhidrosis (CIPA) exhibit an inability to perceive pain, recurrent fractures, self-mutilation, and impaired thermoregulation, which lead to severe complications and high morbidity. Children with CIPA often sustain multiple unnoticed fractures that may be mistaken for child abuse because of the presence of fractures at different stages of healing. If unrecognized or inadequately managed, these injuries can cause permanent damage. We report the case of a 9-year-old boy who presented with recurrent fractures, chronic osteomyelitis, heterotrophic ossification, and gangrene. This case underscores the need for heightened awareness among healthcare providers regarding the clinical manifestations and management challenges of CIPA. It also emphasizes the importance of early diagnosis, meticulous follow-up, and a multidisciplinary approach to optimize outcomes and prevent severe complications in affected children.

Keywords: Child; Congenital pain insensitivity; Hypohidrosis; Multiple fractures; Osteogenesis; Case reports

Introduction

Background

Congenital insensitivity to pain with anhidrosis (CIPA), classified as hereditary sensory and autonomic neuropathy type IV, is a rare autosomal recessive disorder [1]. Clinically, patients with CIPA present with a distinct spectrum of symptoms, including congenital insensitivity to pain, anhidrosis, frequent injuries, and varying degrees of autonomic dysfunction [2].

The inability to perceive pain predisposes patients to repeated trauma, fractures, and self-inflicted injuries, often resulting in severe orthopedic complications such as malunion and chronic osteomyelitis [3].

Orthopedic complications in CIPA are a major cause of morbidity. Recurrent fractures, joint deformities, and heterotrophic ossification (HO) frequently require surgical intervention and long-term management [4]. Chronic infections such as osteomyelitis are also common, arising from trauma-related open wounds, poor healing, and impaired immune responses. These infections are often resistant to standard therapies and necessitate a multidisciplinary management approach [5]. The rarity of CIPA presents considerable challenges in developing evidence-based treatment protocols [6].

Objectives

We report a child with recurrent fractures originating from CIPA in Saudi Arabia to raise awareness of differentiating such cases from child abuse.

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Case presentation

Ethics statement

Ethical approval was obtained from the Research Ethics Committee of the Makkah Region Health–Ministry of Health (20/05/2025, IRB: H-02-K-076-0425-1340). The patient's parents provided written informed consent for the publication of this case and the accompanying images.

Patient information/clinical findings

A 9-year-old boy presented to the emergency department with a chief complaint of painless limping. Radiographic evaluation revealed a non-displaced fracture of the right distal tibia. Conservative management was initiated with an above-knee back slab, analgesia, and close follow-up. Within 3 months, the patient developed swelling in the left leg, and imaging revealed a new painless fracture of the left distal tibia with malunion of the proximal tibia, requiring immobilization with a full above-knee cast.

Diagnostic assessment

A pediatrician was consulted and referred the patient for genetic testing, which confirmed mutations in the NTRK1 gene, establishing the diagnosis of CIPA.

Therapeutic intervention

After 5 months, the patient sustained a left femur fracture and was initially stabilized with a temporary back slab, later undergoing surgical intervention with elastic nailing. Persistent concerns regarding abnormal bone healing and possible infection prompted advanced imaging 3 months postoperatively. A Tc99m bone scan revealed active lesions in the femur and tibia (Fig. 1). Computed tomography confirmed chronic osteomyelitis (Fig. 2) and demonstrated extensive HO. Subsequent management included joint aspirations and scheduled procedures, such as nail removal and bone biopsy.

Follow-up and outcomes

During follow-up, the patient developed additional complications. He was referred to the plastic surgery team and eventually underwent amputation of the right index finger due to gangrene following necrosis (Fig. 3).

Discussion

Fractures in patients with CIPA often present atypically because of the absence of pain, and they may go unnoticed until secondary complications such as deformity or swelling occur. Because child abuse is far more prevalent than CIPA, it is crucial to raise awareness among healthcare providers to differentiate CIPA from abuse when evaluating children with recurrent or unexplained fractures [6].

Our case highlights the multifaceted clinical challenges associated with managing CIPA, including recurrent fractures, chronic infections, and the psychosocial burden of the condition. The patient experienced repeated fractures involving the tibia and femur, frequently accompanied by delayed healing and malunion. Immobilization using above-knee casts remains a cornerstone of fracture management, although surgical interventions such as elastic nailing may be necessary in cases of instability or delayed union [7,8].

HO, a rare but recognized complication of CIPA, is characterized by abnormal bone formation in soft tissues, which likely contributed to joint stiffness and impaired mobility in our patient [9].

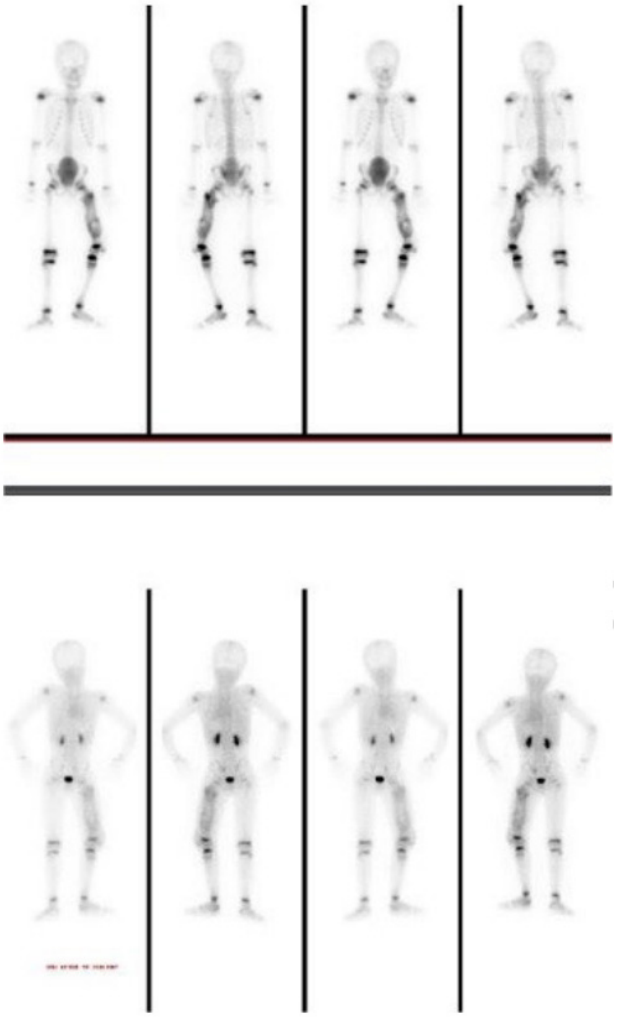

Fig. 1. Tc99m MDP bone scan (triple-phase bone scan). Written informed consent for the publication of this image was obtained from the patient.

Fig. 2. Noncontrast computed tomography of the left thigh with multiplanar re-formations showing post-nailing fixators in the left femur. Written informed consent for the publication of this image was obtained from the patient.

Fig. 3. Index finger amputation. Written informed consent for the publication of this image was obtained from the patient.

Chronic osteomyelitis poses a major concern in CIPA due to recurrent fractures, impaired wound healing, and the absence of pain as a protective mechanism. In this case, repeated infections required bone biopsies, surgical debridement, and, in severe situations, amputation to control disease progression. Multidisciplinary collaboration, including infectious disease specialists, is essential for achieving optimal outcomes. Psychological support and behavioral therapy, supplemented by pharmacological management such as risperidone, are also crucial for addressing behavioral and psychosocial challenges [10].

These challenges emphasize the need for vigilant monitoring, early imaging, and individualized treatment plans to minimize long-term complications. Current management focuses on symptom control and prevention of secondary sequelae, with regular follow-up to ensure early detection of fractures, infections, and joint deformities [1,2]. Early diagnosis and coordinated multidisciplinary care are vital for improving quality of life and functional outcomes in affected individuals.

Since multiple fractures and limb deformities are key orthopedic manifestations of CIPA [11-14], it is reasonable for concerns to arise regarding child abuse. Nonetheless, we aim to increase awareness among orthopedic surgeons and healthcare professionals regarding children with recurrent fractures arising from CIPA.

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Authors' contribution

Conceptualization, methodology, and design of the case report and management of the patient: AMA. Project administration and the important intellectual content: AAA. Manuscript editing, critical revision, and approval of the final version: HAB, KMA. Patient management, imaging interpretation, and follow-up of the case: RMS. Funding acquisition: none. Writing–original draft: AAA. Writing–review & editing: AMA, AAA, HAB, RMS, KMA. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Data availability

Not applicable.

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Supplementary materials

None.

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이화의 정신, 세계의 무대에서 빛나다: 장명주 선배 인터뷰

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Ewha spirit shines on the global stage: an interview with Dr. Myung-Joo Jang

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이 인터뷰는 해외에서 활동한 선배의 경험을 통하여 현 의대생이 국제적인 활동을 할 수 있는 지혜를 얻는 과정의 하나로 진행하였다. 대담자로 초빙을 받아 장명주 선생님과 줌을 통하여 면담을 진행하였다(Fig. 1). 장명주 선생님은 1977년 1월에 이화의대를 졸업하고 그해 3월에 미국으로 이주하여, Northwestern 대학에서 인턴을 시작하였다. 동 병원 재활의학과 레지던트를 마친 후, South Dakota의 Sioux Falls에 있는 병원에서 medical director로 활약하며 통증 전문의 경력을 이어왔다. 현재 북미주 이화동창회 이사장으로서 활동하며 서울병원 설립 기금 기부를 비롯하여 다방면에서 모교 발전에 기여하고 있다. 본 대담은 2023년 입학생 정서화 학생기자가 진행하였고, 2024년 입학생 김지윤 학생기자가 정리하고, 기사를 작성하였다.

이화의대지(*Ewha Medical Journal*, EMJ): 선배님 안녕하세요. 인터뷰를 수락해 주심에 감사드립니다. 간단한 자기소개 부탁드립니다.

장명주 이화의대 북미주 동창회 이사장(이하 장): 안녕하세요? 저는 이화의대 북미주 의과대학 동창회 이사장 장명주라고 합니다. 이화의대를 졸업하고 재활의학과 의사로 긴 시간을 활동하였습니다.

EMJ: 선배님께서는 의과대학을 졸업하시고 곧바로 미국에 오셨다고 들었습니다. 당시 어떤 계기로 미국행을 결심하시게 되었는지, 또 처음 의사로서의 삶은 어떠셨는지 궁금합니다.

장: 사실 유학을 결심하고 온 것이 아니었어요. 공부하려고 온 게 아니라 연애를 해서, 사랑을 따라 미국에 오게 된 것이죠. 한국과 미국의 의료환경 차이를 처음부터 의식하고 온 건 아니었지만, 막상 와 보니 전혀 다른 환경이 눈에 들어왔습니다. 의대를 졸업하고 겨우 한 달 만에 미국에 와서 인턴 과정을 시작하게 되었는데, 그때부터 제 인생이 크게 바뀌었어요.

EMJ: 많은 이민자들이 해외 생활 초창기에 낯선 환경에 적응하는 데에 어려움을 겪는다고 알고 있습니다. 선배님께서도 문화적 차이나 언어적 차이에서 장벽이 있으셨을 것 같은데요, 어떤 방식으로 극복하셨는지 궁금합니다. 또한 이러한 적응과정에서 이화의대에서 공부하신 내용들이 어떤 도움이 되셨는지도 듣고 싶습니다.

장: 이화의대에서 의사로서 성장하는 데 배운 지식은 도움이 많이 되었습니다. 덕분에 처음 인턴을 시작할 때에 지식적으로는 큰 문제가 없었습니다. 하지만 언어, 그게 가장 큰 어려움이었죠. TV를 켜면 광고만 겨우 알아들을 수 있었고, 동료들이 하는 말은 잘 따라잡을 수가 없었어요. 논문을 읽고 이해하는 건 쉬웠는데, 의학적 지식을 영어로 설명하고 논리적으로 풀어내는 게 어려웠으니 이를 공부하느라 시간이 두세 배 더 걸렸죠. 그래서 저는 늘 정리하고 준비하면서 극복했습니다. 당직을 서다가 통화로는 영어를 알아들을 수 없는 상황도 있어서, 해결이 안 되면 직접 환자 곁으로 달려가서 상황을 파악하는 일도 많았습니다.

그러나 이 역시 시간이 지나니까 어느 부분 해결되는 게 있었습니다. 생활 속에서 몸으로 부딪치다 보니 조금씩 귀가 트이고, 어느 날은 갑자기 들리기 시작하더라고요. 따로 공부를 한 게 아니라, 살면서 스며든 거예요. 언어라는 건 결국 '생활'이라고 생각합니다. 생활 속에서 내가 어떻게든 생존하려고 열심히 노력하다보면 장벽을 극복하는 순간이 옵니다. 그리고 제가 언어가 미숙해도, 제 노력을 알아주는 동료와 교수님들이 있었기에 끝까지 버티고 서서히 적응을 해나갈 수 있었습니다.

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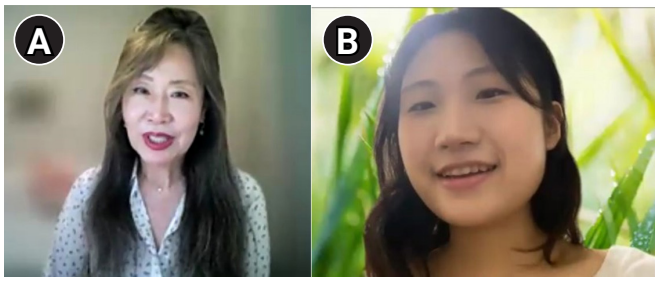

Fig. 1. Screenshot during Zoom interview with Dr. Myung-Joo Jang (A) by student reporter, Seohwa Jeong (B) on October 1, 2025.

EMJ: 재활의학이라는 분야를 선택하신 것도 미국에서의 경험이 큰 계기가 되었다고요.

장: 당시 한국에서 여성 의사들은 내과나 소아과를 많이들 택했습니다. 그런데 미국에 오니 특별한 것을 하고 싶은 마음이 들었습니다. Northwestern 대학에서 인턴을 돌다가 재활의학을 처음 제대로 보게 되었어요. 그 병원이 세계적으로도 재활의학이 앞서 있었거든요. 병을 고치는 차원을 넘어, 환자가 다시 살아갈 수 있도록 돕는 분야라는 점이 굉장히 특별하게 다가왔습니다. 저는 재활의학에 대한 지식이 거의 없었기에 오히려 더 매료되었고, 이 길을 가야겠다고 마음먹었습니다.

EMJ: 미국에서 인턴과 레지던트 과정을 거치며 힘든 순간도 많으셨을 텐데, 의사로서 환자들을 대하면서 기억에 남는 장면이나, 환자가 있으신가요?

장: 저는 시카고에서 인턴과 레지던트를 마친 후에 사우스 다코타의 병원에서 메디컬 디렉터로 초청되어 일을 하게 되었습니다. 사우스 다코타의 병원에서 메디컬 디렉터로 근무하던 도중, 중증 뇌손상을 입은 환자를 치료한 적이 있었습니다. 병원에서의 처치가 끝났다고 생각하고 있었는데, 어느 날 그 환자의 가족들이 저를 따로 만나고 싶다고 하셨습니다. 상황이 위독해지자, 아버지의 치료를 중단하는 것이 맞을지 아니면 연명치료를 계속할지 제 의견을 듣고 싶다고요. 신경외과나 심장외과의 의견을 듣는 게 맞지 않을까 싶었는데, 그분들은 오히려 재활의학과 의사인 제가 환자의 삶의 질에 대해서 보다 더 통찰력 있는 조언을 줄 수 있을 거라고 믿고 계셨습니다. 제 한마디가 한 사람의 삶과 가족의 미래를 좌우한다는 사실이 너무 무겁게 다가왔습니다. 하지만 저는 제 자리에서 할 수 있는 말을 드렸고, 그 가족은 치료를 중단하기로 결정을 내렸습니다. 그 이후 한동안 저의 말을 곱씹어 보며 그 조언이 가족들과 환자에게 잘한 것일까 하는 고민에 휩싸여 있었는데, 감사하도 가족들이 이후 손편지와 선물을 보내오시며 잘 지내고 있다고 소식을 전해주셨습니다. 그때 깨달았어요. 의사는 병만 고치는 사람이 아니라, 사람의 인생에 관여하는 존재라는 것을요. 그 경험이 제 가치관을 완전히 바꿔놓았습니다.

EMJ: 여성 의사로서 차별이나 편견을 경험하시지는 않으셨을지도 궁금합니다.

장: 시카고에서는 인종도 다양하고 사람도 많아서 크게 이질감을 느끼지 않았습니다. 그런데 사우스 다코타의 Sioux Falls로 갔을 때는 상황이 달랐습니다. 주민의 대부분이 북유럽계 백인이었고, 저는 그곳에서 유일한 동양인 여성 의사였습니다. 걱정이 좀 들었지만, 차별은 없었습니다. 오히려 재활의학이 꼭 필요한 분야였기에 협조적이었고, 다들 저를 필요로 했습니다. 저의 정체성 덕분에 재미있는 일도 있었죠. 티벳에서 온 환자가 있었는데, 다른 의사와는 커뮤니케이션이 잘 되지 않아 동양인 의사를 만나고 싶다며 저를 찾더군요. 미국 음식이 맞지 않는다기에 제 집으로 모셔와 라면을 끓여드렸는데, 너무 맛있다고 하시던 모습이 아직도 기억에 남습니다.

EMJ: 동문회 활동이나 한인 사회와의 교류는 어떻게 이루어졌나요? 그리고 그것이 선배님의 커리어에 어떤 의미가 있었나요?

장: 처음 시카고에 왔을 때, 이화 동창회와 한인의사회를 통해 많은 선배님들을 만날 수 있었는데, 그것이 제게 정말 큰 힘이 되었습니다. 이후 사우스 다코타로 옮기면서 교류가 끊기기도 했지만, 우연히 시카고 동창회 모임에 참석하면서 다시금 이화의 인연을 이어갈 수 있었습니다. 그 자리에서 만나 뵌 선배님들은 각자 다른 전공과 수련 경로를 밟아왔지만, 모두가 자신만의 뚜렷한 정체성과 소명을 가지고 계셨습니다. 그분들을 보면서 이화에서 배운 것이 단지 지식만이 아니라, 자기 자신을 굳건히 세우는 힘이라는 것을 새삼 깨닫게 되었습니다.

지금 되돌아보면 이화의대 동문회는 제게 늘 '친정 같은 곳'이었습니다. 남녀가 함께 다니는 학교에서는 여자들만의 끈끈한 공동체를 만들기 쉽지 않은데, 미국에서의 이화의대 동문회는 마치 집에 돌아온 듯한 편안함과 연대감을 주었습니다. 거기에서 나눈 대화들은 단순한 추억담을 넘어, 삶의 가치와 인간다움(humanity)에 대해 다시금 생각하게 하는 건설적인 자리이기도 했습니다. 지금 제가 북미주 의과대학 동창회 이사장으로서, 동문들과 함께 이대 서울병원 기금 마련 등과 같은 뜻깊은 일을 이어갈 수 있는 것도 그 연대의 힘 덕분입니다. 결국 동문회와 한인 사회의 교류는 저의 가치관을 형성하는 데 중요한 밑거름이 되었고, 외국에서 의사로 살아가는 긴 시간 동안 저를 지탱해 준 가장 든든한 울타리였습니다.

EMJ: 굉장히 의미 있는 경험을 하신 것 같습니다. 그렇다면 선배님께서는 중요하게 꼽으시는 의사의 역량은 무엇인지 듣고싶습니다. 그러한 가치관을 어떻게 형성하셨는지, 또 오랜 시간 동안 한 분야에서 최고의 전문가로 인정받기까지 어떤 노력이 가장 중요했다고 생각하시는지 궁금합니다.

장: 제가 미국에서 다양한 시행착오를 경험하면서 가장 크게 배운 것은, 환자의 배경과 삶을 이해하는 것이 진료의 질을 좌우한다는 점이었습니다. 미국에 와서 전혀 다른 문화 속에서 환자들을 만나며, 단순히 병만 보는 것이 아니라 그 사람의 삶 전체를 바라봐야 한다는 것을 알게 되었죠. 그렇게 하기 위해서는 의학적 지식만으로는 충분하지 않았습니다. 미국이라는 환경에서의 생활 그 자체에 대한 이해가

너무나도 필요했습니다. 환자가 어떤 환경에서 살아왔는지, 어떤 문화적 배경을 가지고 있는지를 아는 것이 결국 환자를 진정으로 치료하는 길이라는 것을 깨달았습니다. 미국인들의 생활과 문화적 배경에 대한 관심을 소홀히 하지 않으려고 노력하다보니까 자연스럽게 의학적 지식과 삶에 대한 이해가 결합되어 가치관이 형성된 것 같습니다.

동시에, 무엇보다 중요한 것은 커뮤니케이션의 힘이었습니다. 수련 시절 지도교수께서 "의사로 인정받는 것보다 더 중요한 건 환자와 어떻게 대화할 수 있느냐"라고 말씀하셨는데, 시간이 흐를수록 그 말의 의미를 절실히 알게 되었어요. 환자를 설득하고 공감하며, 환자의 삶의 질을 함께 고민하는 것이야말로 의사의 가장 중요한 역량이었습니다. 의료진뿐 아니라 다른 직종과도 소통하며 함께 환자를 케어하는 태도가 필요하다는 말이었던 것 같습니다.

현실적인 측면에서는, 재활의학과 전공을 선택하고 전문가로서 성장하는 과정에서는 훈련 환경의 선택이 큰 역할을 했습니다. 다양한 환자와 수많은 사례를 접할 수 있는 좋은 수련 프로그램 덕분에 재활의학에 대한 경험을 폭넓게 쌓을 수 있었고, 이는 훗날 제 진로를 결정짓는 데 큰 밑거름이 되었습니다.

EMJ: 긴 세월 동안 의사로 살아오면서 후배들에게 꼭 전하고 싶은 메시지가 있다면 무엇일까요?

장: 무엇보다 열정(passion)을 잃지 말라고 말해주고 싶습니다. 그리고 자신만을 위한 시간을 꼭 가지라고 권하고 싶어요. 우리는 환자를 돌보다 보면 너무 쉽게 나 자신을 잊어버립니다. 학생 때부터 스스로를 힐링할 수 있는 습관을 갖는 게 중요합니다. 또 국제무대에서 활동하고 싶다면 언어와 문화를 깊이 익혀야 합니다. 단순히 영어를 공부하는 것을 넘어서, 다른 문화와 삶을 이해하는 노력이 필요합니다. 그래야 환자와 제대로 소통할 수 있습니다.

EMJ: 의사가 되기 위해서는 힘든 의과대학 과정을 거쳐야 하는데, 이 과정에서 흔들리는 학생들이 더러 있는 것 같습니다. 선배님께서는 어떻게 이 길을 걸어오셨는지, 또 어떤 방식으로 의미를 되새기며 긴 세월동안 최선을 다할 수 있었는지 궁금합니다. 이와 관련하여 후학들에게 전하고 싶은 조언이 있다면 무엇일까요?

장: 사실 저는 의사가 되고 싶다는 강한 의지가 있었던 건 아니었습니다. 아버지의 권유로 시작했는데, 시간이 지나고 보니 그 선택이 얼마나 귀한 조언이었는지를 알게 되었어요. 환자들의 고통을 매일 마주하면서, 한 인간의 삶을 책임지고 돌보는 일이 단순히 그들을 위한 것만이 아니라 결국 저를 돌보며 스스로를 성장시키는 일이 된다는 걸 깨달았습니다. 그래서 후회는 없었습니다.

이 길에서 중요한 것은 매 순간에 대한 열정과 자기 돌봄의 균형이라고 생각합니다. 환자들을 돕는다는 자부심은 큰 힘이 되지만, 그 과정에서 자신을 잃어버리기 쉽습니다. 학생 때부터라도 스스로를 위한 시간을 꼭 마련하고, 작은 방식으로라도 자신을 치유하는 습관을 가져야 합니다. 그래야 오래 버틸 수 있습니다. 또, 인간에게는 할 수 있는 일이 있는 만큼 할 수 없는 일도 있기 때문에, 때로는 영적인 지침(spiritual guidance)을 통해 한계를 받아들이는 마음도 개인적으로는 도움이 많이 되었습니다.

EMJ: 긴 인터뷰에 감사드립니다. 끝으로 EMJ 독자들에게 한 말씀 부탁드립니다.

장: 재미있게, 열정을 다해 살아가시길 바랍니다. 인생은 멋이 있어야 하고, 남을 존중하면서도 자신만의 삶을 즐길 줄 아는 태도가 필요합니다. 의사라는 직업은 분명 힘들지만, 동시에 남을 도울 수 있는 가장 보람 있는 길입니다. 그 보람을 잊지 않고 자신을 돌본다면, 분명히 끝까지 흔들림 없이 걸어갈 수 있을 것입니다.

장명주 선배님의 의사로서의 가치관과 삶의 가치관이 매우 감명깊게 다가온 인터뷰 였다. 특히 "의사는 타인의 삶을 'care' 하는 직업이지만 이 과정에서 최선을 다하다 보면 결국 자신의 삶을 'care' 하게 되는 직업"이라는 말씀이 참 인상적이었다. 이화 의대가 세계로까지 연결이 되어 네트워크를 형성하며 서로 도움을 주고 받으며 활약하시는 모습을 보니, 나도 자랑스러운 이화의대 후배로 성장하기 위해서 매순간 최선을 다하며 노력해야겠다고 생각했다.

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The Ewha Medical Journal

Life as a pediatrician in the United States: an interview with Dr. Jeong-Ok A. Lee

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Jeong-Ok A. Lee, M.D.(안정옥) is a distinguished graduate of the Ewha Womans University College of Medicine in 1973 who has worked as a pediatrician in the United States since 1975. The interview with Dr. Lee was conducted online on September 30, 2025 (Fig. 1). Here, we will share the story of Dr. Lee's life as a Korean physician in the United States, along with her thoughtful and heartfelt advice for future generations of doctors.

Ewha Medical Journal (EMJ): Hello, Dr. Jeong-Ok A. Lee. Thank you so much for joining us for this interview. It is truly an honor to have this time with you, and I believe your insights will inspire and encourage our readers. To start, let's talk about your early experiences settling in the United States and life as a physician. Could you share what motivated you to move to the United States and start practicing medicine there?

Dr. Jeong-Ok A. Lee (Dr. Lee): I was in pediatrics, and back then in Korea, pediatrics wasn't very developed. I thought if I went to the United States, I could learn more and teach future generations. My husband had graduated from law school, so he also wanted to study law further in the United States. These were the 2 main reasons we decided to move.

EMJ: How did you overcome language barriers as a doctor in the United States?

Dr. Lee: Honestly, I didn't have time to study English separately. I went straight into my internship, working around 80 hours a week. The more I worked and the less I slept, the more I picked up. It was a matter of survival, and I learned on the job. After residency, when I finally had more time, I realized communication was just as important as medical knowledge. That's when I started taking classes and practicing, and my English improved over time.

EMJ: What were the most challenging and rewarding moments during your internship and residency in the United States?

Dr. Lee: The most difficult part was the physical demand. Americans tend to be bigger, and I'm small, so keeping up was tough. It was even harder when I had a baby while working 80 hours a week as a resident—I wondered if I could manage it all. But making it through residency gave me a deep sense of accomplishment. I realized that strength and stamina are just as important as skills.

EMJ: Could you share a memorable case and what you learned from it?

Dr. Lee: I completed a 2-year pediatric hematology-oncology fellowship after finishing my pediatrics residency. Back then, acute lymphoblastic leukemia was very common, with survival rates of about 50% compared to 80%–90% today. One 10-year-old patient relapsed a second time. Since the relapse was dangerous and we had little more to offer, we were preparing to stop treatment. But he said, "I survived the first relapse, and I'll survive this one too. Don't ever give up on me." Hearing that from a child shocked me. It taught me that doctors should never give up before their patients do, as patients often hold on to hope until the very end.

EMJ: Do you have any special experience as a Korean doctor?

Dr. Lee: I work in the Korean community. About half of our patients are Korean, and I treat them as if they were my own children. I want to help them grow into leaders while keeping their cultural roots. In our office, we guide kids not just medically, but also in life—teaching them how to be responsible adults and leaders. For those preparing for medical school, we help them gain the experiences they need and get good recommendations from our hospital.

EMJ: How did you balance family time and leisure with your

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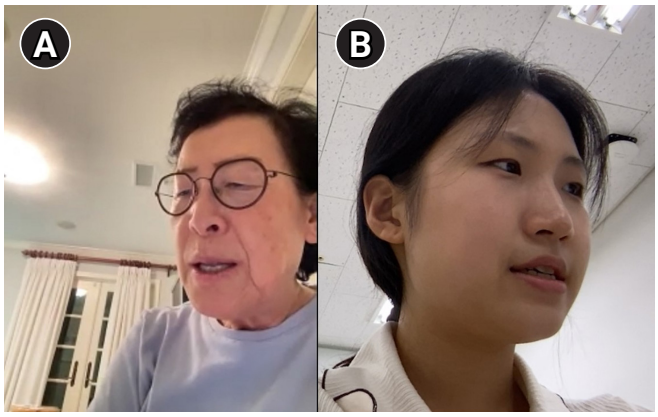

Fig. 1. Screenshot during a Zoom interview conducted on September 30, 2025. (A) Jeong-Ok A. Lee, M.D.(안정옥), graduate of the Ewha Womans University College of Medicine in 1973. (B) Student reporter Seohwa Jung.

medical career?

Dr. Lee: Raising children is a big responsibility as a mother. I tried to take them on trips whenever I could, but later they told me what mattered more wasn't those few trips a year—it was the time I spent with them every day. I think this holds true in Korea too, as Korean society tends to place additional expectations on female doctors in their role as mothers.

EMJ: Having learned about your life in the United States, we would now like to focus on your professional growth and the values you hold as a physician. What motivated you to pursue your current path in medicine?

Dr. Lee: I've always loved children. Being the fifth of 9 siblings, I saw how much it hurt when kids were sick and wanted to help. With several doctors in my family, I thought, "If they can do it, so can I." Growing up in a large family naturally led me to a career in pediatrics.

EMJ: What do you think was the most important factor in becoming recognized as a top expert in your field?

Dr. Lee: At Ewha, I learned that achieving goals requires giving your utmost effort. My faith also guides me—I believe that if God gives me work, He will provide support. Combining faith with Ewha's values, I've always tried my best in everything, from studying to building stamina. Without that dedication, reaching this point wouldn't have been possible.

EMJ: Were there any people or experiences that shaped your values or beliefs as a doctor?

Dr. Lee: Jesus has been the greatest influence on me. Growing up in a Christian family, I learned He came to teach, heal, and spread the gospel, which inspired me to do my best for every patient. Even when outcomes are not perfect, my faith sustains me with hope and humility. If a patient recovers well, I see it as God's work, not my own, which keeps me humble. Following Jesus has been my greatest source of strength as a doctor.

EMJ: How do you think the roles or qualities required of doctors have changed over time?

Dr. Lee: In the past, doctors mainly told patients what to do. Today, it's more about guidance and respect. Giving patients options helps them feel some control over their health, which is crucial—except in life-threatening situations.

EMJ: How have you dealt with ethical conflicts in clinical practice?

Dr. Lee: Ethical challenges, such as issues with vaccine management, sometimes tempted us to take shortcuts. I've learned that honesty and addressing problems directly are always better in the long run. Mistakes happen, and admitting them is part of being a responsible doctor. My faith helps me stay humble and handle challenges with integrity.

EMJ: How have alumni activities or interactions with the Korean community influenced your career and life?

Dr. Lee: Being connected to alumni and the Korean community has been invaluable. In LA, we support and encourage each other, which helps us grow as doctors and as individuals. The network strengthens both our professional and personal lives.

EMJ: What has been the greatest meaning of being a doctor over the years?

Dr. Lee: In pediatrics, our goal isn't just treating illness—it's helping children grow into healthy, capable adults, maximizing their physical, emotional, and spiritual potential. Supporting a child from birth to adulthood and watching them thrive is the greatest meaning of my work.

EMJ: What principles do you emphasize when mentoring young doctors?

Dr. Lee: When mentoring students, I emphasize cooperation over competition. They should discover and nurture each other's strengths and support one another's growth. Once they enter medical school and residency, they need to fully commit to mastering their specialty. Physical stamina, faith, and a strong support network are essential for success. Students should enjoy some leisure during their school years, but once in residency, it's all about dedication.

EMJ: Thank you for sharing your insights on your career. Let's now move on to the messages you would like to share with the next generation of doctors. What message would you like to deliver to current Ewha Womans University students?

Dr. Lee: Enjoy your undergraduate years—have fun, build skills, strengthen your faith, and gain diverse experiences. Make friends, encourage one another, and help each other discover strengths. For example, someone with strong hands-on skills

might thrive in surgery, while those who think deeply and carefully might do well in internal medicine or pediatrics. Once in residency, give your absolute best—study hard, conduct research, and gain experience.

EMJ: In today's rapidly advancing medical field, what core competencies should future doctors have?

Dr. Lee: Future doctors must keep up with advances as they happen. AI and genetics are rapidly revealing new diseases, and in the United States, artificial intelligence (AI) can now do in a year what used to take a decade. Young doctors should be ready to explore these fields and adapt quickly, even in pediatrics, where AI is beginning to be applied to patient care.

EMJ: What should students do now if they want to compete on the international stage?

Dr. Lee: To compete globally, you must study hard and gain research experience now. Being a top professional requires preparation and dedication from the start.

EMJ: How can young doctors overcome challenging periods in their careers?

Dr. Lee: Always remember why you became a doctor. Reflect on your purpose and mission. If you lose sight of it, you may falter. Difficulties are opportunities for growth—use them to strengthen your skills and resolve.

EMJ: Finally, what life wisdom would you like to share with your juniors, as both a doctor and a mentor?

Dr. Lee: Medicine is about doing your absolute best for patients—making accurate diagnoses, providing the right treatments, and preventing disease. I hope our junior doctors begin with prayer, drawing strength and guidance from God, and then care for their patients with compassion, humanity, and dedication.

Dr. Lee's sincere story revealed not only her warmth and deep sense of responsibility toward her young patients but also her thoughtful guidance for junior doctors. Through her experiences, I gained a deeper understanding of what it means to live and work as a Korean pediatrician in the United States. Listening to her story made me reflect on the values and mindset a doctor should embody. As a pre-med student, it also encouraged me to think more deeply about the kind of doctor I aspire to become. I will keep her words close to my heart and commit myself to putting them into practice, starting now.

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The Ewha Medical Journal

Approach patients with warmth and respect: an interview with Dr. Chung Hur, graduate of the Ewha Womans University College of Medicine

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How have the graduates of Ewha Womans University, who worked as doctors abroad after graduation, lived? Why did they decide to go abroad and work? This interview article was prepared as part of a project where current medical students seek wisdom from seniors through these questions, and I participated as an interviewer. An interview with Dr. Chung Hur(박정욱) was conducted on September 26, 2025, via Zoom (Fig. 1). Dr. Hur graduated from the Ewha Womans University College of Medicine in 1971 and moved to the United States in 1972.

Ewha Medical Journal (EMJ): Hello, Dr. Hur. Thank you for agreeing to this interview. We are truly grateful for your time, and we hope your insights will be of great help to our readers. To begin, could you share what motivated you to start your medical career in the United States?

Chung Hur, M.D. (Dr. Hur): In the decades following the Korean War, Korea remained in a very difficult state, both economically and politically unstable. So I decided to leave Korea while doing my internship after graduation. At that time, almost half of my classmates also went abroad.

EMJ: What made you choose your current specialty?

Dr. Hur: At first, I chose pathology. However, I realized I was quite good at carefully reviewing patients' medical histories. While examining specimens, I often found myself going back to the medical records, and at times even speaking directly with patients to clarify details. Through this process, I became increasingly interested in direct communication and patient care, which eventually led me to switch my specialty to internal medicine.

EMJ: From a medical perspective, what differences did you notice between Korea and the United States?

Dr. Hur: At that time, the United States was undoubtedly more technologically advanced. But what struck me even more was the culture of referral. General practitioners readily referred patients to specialists rather than trying to manage everything themselves. This practice was closely tied to the strong legal liability in the United States—patients could sue very easily, and physicians minimized their risk by referring cases. As an internist, I still tried to treat as many as I could myself, but I recognized this as a significant cultural difference.

I would also like to highlight another important point: the approach to end-of-life care. In the United States, for the past 2 decades, there has been extensive education for both physicians and patients about making decisions in advance. Patients are encouraged to document their wishes while they are still capable of sound judgment, often through living wills, medical powers of attorney, or advance healthcare directives. In my own case, I clearly stated my choices—no cardiopulmonary resuscitation, no tube feeding, no intubation, and no respirator.

Such planning was not part of my medical training in Korea, but I understand that Korean society has recently begun to pay attention to these issues. I view this as a very positive and meaningful development.

EMJ: Working as a physician in the United States, you must have faced many difficulties. Could you share an episode where cultural differences created challenges?

Dr. Hur: One experience in the emergency room remains vivid. A 14-year-old girl presented with vaginal bleeding. At that time, I

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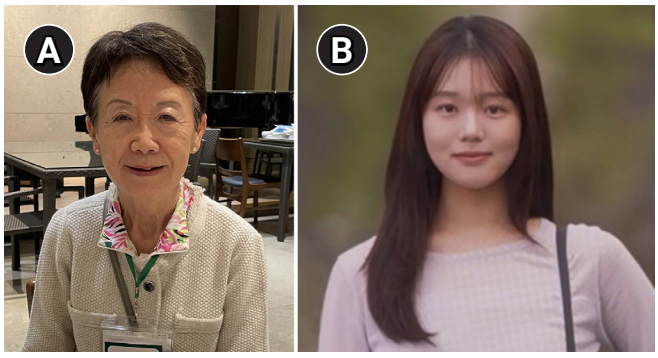

Fig. 1. On September 26, 2025, an online interview was conducted via Zoom with Dr. Chung Hur(박정옥), a graduate of Ewha Womans University College of Medicine, Class of 1971. (A) Dr. Chung Hur(박정옥, Photograph provided by Dr. Hur). (B) Kyungmin Kim, student editor. (Photograph provided by Kim).

could not imagine someone so young being sexually active, and therefore, I failed to consider the possibility of pregnancy and miscarriage as the cause. This mistake taught me an important lesson about cultural differences in clinical practice.

EMJ: How did you overcome cultural and language barriers?

Dr. Hur: Language was my biggest challenge. In Korea, I studied medicine using English textbooks, so academically I was fine, but conversation was very difficult. In particular, when a nurse asked about an order over the phone, I often struggled to understand and had to go to the ward to communicate in person. At that time, international trainees were provided with English lessons. A Polish professor gave me the most valuable advice for learning English: never separate your daily life from it. I immersed myself in reading newspapers, listening to the radio, and repeating what I heard. I have continued this habit to this day.

EMJ: Beyond language, how did you improve communication skills with patients?

Dr. Hur: I always tried to listen carefully and ask thoughtful, appropriate questions. Simple inquiries about family or work often provided me with very important clinical insights.

EMJ: That is admirable. At Ewha, we place a strong emphasis on the humanities, incorporating a 6-year curriculum that includes courses in related fields. I am currently taking a class on communication skills, and your emphasis on listening attentively and asking the right questions resonates strongly with me.

Dr. Hur: I think it's wonderful that communication training is being emphasized.

EMJ: How did your medical education at Ewha help you in the United States?

Dr. Hur: The knowledge I gained at Ewha Medical School was more than sufficient for working in the United States. Additionally, since I had completed an internship in Korea, I was already proficient in basic clinical procedures such as IV sampling. That proved helpful whenever such tasks were needed.

EMJ: How did the values you learned at Ewha blend with your experience in the United States?

Dr. Hur: Over the years, I came to believe that our bodies are created according to the design of the creator, and there are aspects science cannot fully explain. Medicine and technology are vital, but I emphasized to patients that their bodies also possess the intrinsic ability to heal, and that they must actively participate in the process.

EMJ: Did you work alongside your classmates abroad?

Dr. Hur: Not with my exact classmates, but I did work with other Korean doctors. We supported each other a great deal, whether by sharing meals, exchanging food, or helping with daily practical matters. Since I had no car at first, others gave me rides to church or shopping.

EMJ: Did you experience prejudice as a Korean or as a woman?

Dr. Hur: I am sure discrimination existed, but I did not dwell on it. During the internship, I was under such tension I hardly noticed. As a resident, I did hear insulting remarks from patients, and sometimes people assumed I was a hospital worker rather than a physician because of my petite frame as an Asian woman. To make my role clear, I wore my white coat wherever I go.

EMJ: How did you cope with such situations?

Dr. Hur: I reminded myself of my clear goal, which is to be a competent physician. "You work towards the goal. You don't waste time or energy worrying about discrimination." That mindset carried me through.

EMJ: Your strong mindset is truly inspiring. What do you think was the most important effort behind your recognition as a physician?

Dr. Hur: Integrity is crucial. But above all, physicians must continually update their knowledge. Medicine evolves rapidly, and staying current is essential.

EMJ: Then, do you feel the qualities expected of physicians have changed over time?

Dr. Hur: Yes, physicians today must be fast. In the past, test results might have taken a week, but now results and communication are expected almost immediately. Therefore, physicians must adapt to these changes.

EMJ: Were there particular figures or events that shaped your convictions?

Dr. Hur: Reading Albert Einstein's autobiography inspired me to pursue medicine. Influenced by that inspiration, I went to Africa and treated indigenous patients in the mountains. Throughout my career, I also sought to live faithfully according to the teachings of Jesus.

EMJ: Those stories are truly fascinating. In one of my classes, we

discuss ethical dilemmas in medical settings, but we often conclude that you can only truly understand them through real-life experience. Could you share how you handled conflicts in practice?

Dr. Hur: Conflicts occurred often. For instance, patients with mild colds sometimes demanded antibiotics, which I considered inappropriate, or some might angrily request a different doctor. In those cases, I treated them kindly but followed my medical standards. Even if emotions ran high, a physician should never argue with patients.

EMJ: Could you tell us about your personal life in the United States?

Dr. Hur: I first went alone, but later I married and started a family. On weekends and holidays, I spent as much time as I could with my children.

EMJ: You also served as President of the Ewha Womans University Alumnae Association of North America. How did alumni activities influence you?

Dr. Hur: Interacting with diverse people helped shape my character, just like an artist sculpting. I added positive traits and tried to carve away the deficient ones.

EMJ: Over the years, what has being a physician meant to you?

Dr. Hur: I have always felt deep pride and gratitude for being a physician. To alleviate suffering and care for the beautifully designed human body has been profoundly meaningful to me. I retired from full-time practice in 2016, continued part-time until 2020, and worked as locum tenens until October 2024, when I fully retired. I wanted to keep working, but I realized my physical limits so decided to stop for the sake of patients.

EMJ: I've been most eager to ask this question. What principles do you emphasize when mentoring young doctors?

Dr. Hur: Patients come to us in distress. Approach them with warmth and respect. Listen carefully, make a plan, and treat them with dignity. Always honor their autonomy and allow them to choose.

EMJ: So, a good physician ensures that patients retain decision-making power over their own bodies. Looking back on your career, what advice would you give your younger self as a medical student?

Dr. Hur: Study hard, of course, but also cultivate the soft side—music, literature, and social relationships. I engaged in spiritual education that helped me appreciate how much I had been given. It is important to develop eyes and ears that recognize those blessings.

EMJ: Then, what should Korean students preparing for international careers keep in mind?

Dr. Hur: They must become comfortable with artificial intelligence and languages, and expose themselves to diverse cultures. Korea has improved since, but the United States, as a multicultural society with more diversity and greater recognition of women's rights, requires adaptability. Those who embrace diversity will succeed.

EMJ: Finally, could you share one piece of wisdom for future generations?

Dr. Hur: One must have a clear life goal. For me, it was my faith. My guiding principle was to always give my best in every moment.

EMJ: Thank you, Dr. Hur, for your generosity in sharing your experiences. We have learned an incredible amount from you.

Dr. Hur's life illustrates what it means to be a "complete physician." She is a communicator who deeply empathizes with patients' suffering, a principled professional grounded in the most current knowledge, and a pioneer whose resilience turns every hardship into an opportunity for growth. She is also a leader marked by humanistic depth and a vocation to serve humanity, guided by a steadfast life purpose that integrates these commitments. I, too, resolve to embrace the wisdom her life imparts and to grow into a physician who heals those suffering from disease.

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The Ewha Medical Journal

멘델리안 무작위화를 활용한 관찰연구 보고지침(STROBE-MR): 설명 및 해설

Strengthening the reporting of observational studies in epidemiology using Mendelian randomization (STROBE-MR): a Korean translation of explanation and elaboration

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멘델 무작위화(Mendelian randomization, MR) 연구는 조절 가능한 노출(modifiable exposure)이 건강결과에 미치는 인과효과(causal effect)를 더 잘 이해하게 해 주지만, 그 근거는 종종 보고가 불충분함으로 인하여연구 결과의 해석과 적용에 한계가 있을 수 있다. 보고지침은 흔히 무슨 연구를 하고 무엇을 발견했는지 독자가 쉽게 이해하도록 돕는다. STROBE-MR(관찰연구의 멘델 무작위화를 활용한 보고지침)은 MR 연구를 명확하고 투명하게 보고하도록 돕는다. STROBE-MR을 논문 작성에 활용하면 독자, 심사자, 학술지 편집인이 MR 연구의 보고 품질과 완성도를 평가하는 데 도움이 될 것이다. 이 글은 STROBE-MR 체크리스트 20개 항목의 의미와 근거를 설명하고, 각 항목마다 사례를 제시해 독자가 잘 이해할 수 있는 논문 작성법을 설명하려고 하였다.

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요약

관찰연구에서 멘델 무작위화(Mendelian randomization, MR) 연구는 편향(bias)의 위험을 줄이면서 노출과 결과 간 인과적 관련성을 알 수 있게 한다. MR 연구 보고에 관한 합의가 부족하고, 보고의 질도 일관되지 않았다. 다수의 MR 논문은 MR의 각 가정을 명시하거나 점검하지 않았고, 자료 출처에 대한 세부 정보도 불충분하게 보고하였다. STROBE-MR(관찰연구의 멘델 무작위화를 활용한 보고지침)은 MR 연구를 쉽게 이해하도록 20개 보고 항목으로 구성된 체크리스트를 제시하였다. 이 논문은 각 체크리스트 항목의 근거를 설명하고, 명확한 보고 예를 들었다. MR 연구의 저자, 심사자, 학술지 편집인은 STROBE-MR을 활용하여 MR 연구 보고의 질을 높이기를 권한다.

서론

관찰연구는 흔히 노출과 건강결과 간의 관련성을 다룬다. 그러나 역학 연구에서 보고되는 이러한 관련성은 인과적 추론을 하기에는 충분하지 않은 경우가 많으며, 결과와 노출 모두에 영향을 미치는 제3의 요인에 의한 교란 또는 다른 형태의 편향으로 생성될 수 있다[1-3]. 예를 들어, 알코올 섭취는 흡연, 권장하지 않는 식습관, 운동 부족 등 많은 잠재적 교란요인과 관련될 수 있다. 반대로 건강이 좋지 않으면 알코올 섭취의 감소나 중단이 뒤따를 수 있어, 알코올 섭취가 이후 건강에 미치는 영향을 연구할 때 역인과(reverse causality)로 인한 편향 가능성이 생긴다[4,5]. 이러한 편향을 완화하려는 여러 접근법이 개발되어 왔다[6]. 예컨대 도구변수 분석(instrumental variable methods)은 노출과 관련되어 있으나, 노출을 통하지 않고는 결과에 영향을 미치지 않는다[6,7].

지난 10여 년간의 유전체 분석 기술의 발전은 유전변이와 관련 노출, 형질, 건강결과 사이의 수천 개 재현 가능한 관련성을 확인하게 하였다. 이러한 유전변이는 멘델 무작위화(Mendelian randomization, MR)라 불리는 연구방법을 통해, 조절 가능한 노출이 질병에 미치는 영향을 분석하는 도구변수로 사용할 수 있다[8]. MR 연구는 조절 가능한 노출과 깊이 관련된 유전변이를 이용해, 노출이 다양한 건강 · 사회 · 경제적 결과에 미치는 영향을 이해하도록 한다. 유전변이는 부모로부터 무작위로 자식에게 유전되므로, 노출-결과 관련성을 교란할 수 있는 많은 요인이 유전변이에 영향을 미치지 못한다. 유전변이는 일반적으로 결과에 의해 영향을 받지 않으므로 역인과의 영향에서도 비교적 자유롭다. 따라서 MR은 교란과 역인과에서 비롯될 수 있는 잠재적 편향을 줄이면서 노출과 결과의 관련성을 연구할 기회를 제공한다[9].

이러한 특성은 유전변이를 도구변수의 적절한 후보로 만들며, 조절 가능한 노출이 결과에 미치는 인과효과 추정에 기여한다[7]. 예를 들어, 알코올 탈수소효소 1B 유전자(ADH1B)의 rs1229984 변이는 심혈관질환에서 알코올의 인과적 역할을 조사하는 도구로 사용되어 왔다[10]. 이러한 장점에 힘입어 MR 연구는 빠르게 확산되었으며, 질병 원인을 보다 정확히 이해하고 예방, 치료 저략 수립에 기여하기 시작하였다. MR은 유전변이를 사용해 도구변수 추정을 생성하는 연구(Box 1, Table 1)로만 국한되지 않지만, 현재 문헌에서는 이러한 유형의 연구가 대다수를 이룬다. MR에서 흔히 사용되는 용어의 용어집은 Table 2에 제시되어 있으며, 추가 용어와 설명은 오픈 액세스 MR 사전에 수록되어 있다[21].

Box 1. 멘델 무작위화(MR)의 범위와 STROBE-MR 체크리스트

MR은 일반적으로 유전 변이를 도구변수로 사용하지만, 그러한 연구에만 한정되지 않는다. 실제로 "멘델 무작위화"라는 용어는 소아 악성종양 치료에서의 골수이식 연구를 위해 1991년에 도입되었다[11,12]. 기본 개념은 human leukocyte antigen (HLA)가 일치하는 형제자매가 있는 아동은 그렇지 않은 아동보다 골수이식을 받을 가능성이 높다는 점이었다. 형제자매의 유무(이상적으로는 형제자매 수까지 고려하여)에 따라 결과를 분석하는 것은 무작위배정 임상시험에서 치료 의도(intention-to-treat) 분석과 유사하다[11,12]. HLA 일치 형제자매를 "우연히" 가질 수 있다는 사실은 골수이식의 유전적 도구로도 기능할 수 있으므로, 이식이 암 결과에 미치는 효과를 추론하는 데 활용될 수 있다. 이러한 접근은 이후에도 계속 사용되어 왔다

Table 1. STROBE-MR 체크리스트가 다루는(또는 다루지 않는) 연구설계

STROBE-MR이 다루는 연구 유형	STROBE-MR이 다루지 않는 연구 유형
단일 표본(집단)(one-sample) MR 연구	전장유전체 관련성 분석(GWAS)
두 표본(집단)(two-sample) MR 연구	시퀀싱 연구
동일 논문에서 GWAS 이후 수행되어 함께 보고된 MR 연구	유전자 발현 연구
단일 또는 두 표본 MR 중 다중 노출[a] · 다중 결과(또는 둘 다)를 다루는 연구	전통적 관찰연구

STROBE-MR, strengthening the reporting of observational studies in epidemiology using Mendelian randomization; MR, Mendelian randomisation; GWAS, Genome-Wide Association Study(전장유전체 관련성 분석).

[a]예를 들어, 순환 단백질(circulating protein) 수준에 대한 MR 연구에서는 고속 분석법을 통해 측정된 수백 가지의 순환 단백질 수준과 특정 결과 간의 관련성을 검정하는 경우가 많다.

Table 2. 멘델 무작위화(MR)에서 흔히 쓰는 용어

용어	설명
MR	유전 변이를 이용해 조절 가능한 노출(예: 체질량지수, 알코올 섭취, 혈중 지질단백, 교육시간, C-반응단백, 혈청 25-하이드록시 비타민 D)이 질병 위험이나 다른 결과에 미치는 인과적 관계를 추정하는 방법론적 접근이다. 대부분의 MR 연구는 유전변이를 도구변수로 사용하는 도구변수 분석의 형태로 수행된다.
단일 표본(one-sample) MR	동일한 연구 표본에서 유전 변이(SNP), 노출, 결과가 모두 측정되어, SNP 노출(G X) 및 SNP 결과 (G Y) 연관을 같은 개별 수준 자료 (individual level data) 에서 추정하는 연구 설계이다. 유전도구변수 (genetic instrumental variable)는 MR 의 3 가지 가정(①노출과 연관, ② 노출을 통한 경로만으로 결과에 영향, ③ 교란 요인과 독립 을 충족해야 한다. 단일 표본 MR은 일반적으로 2 단계 최소제곱법(two stage least squares, 2SLS) 을 통해 구현된다. 1 단계에서는 유전변이로부터 노출을 예측하고, 2 단계에서는 예측된 노출값과 결과의 관계를 분석하여 인과효과를 추정한다. 개별 수준 자료를 이용하므로, 교란 요인과의 연관 검증, 상호작용(interaction), 비선형성(nonlinearity), 하위표본 분석(subgroupanalysis)이 가능하다. 단일 표본 MR에서는 약한 도구로 인한 편향이 전통적 회귀분석의 교란된 추정치 방향으로 치우치는 경향이 있다.
두 표본(two-sample) MR	서로 다른 독립 표본에서 G X, G Y 연관을 추정하고, 이를 메타분석 혹은 Wald ratio 방식으로 결합하는 연구 설계이다. 각 표본에서 유전 변이별 요약 통계(summary level data)가 필요하며, 개별 수준 자료는 요구되지 않는다. 이 방법은 역인과(reverse causality) 가능성을 점검하고, 인과방향(direction of causality)을 명확히 하기 위해 활용된다. 각 변수의 유전 도구변수는 MR의 3 가지 기본 가정 관련성 · 독립성 · 배제 제한을 각각 충족해야 하며, 양 방향의 분석간 통계적 검정력(statistical 차이와 도구의 유효성 차이를 고려하여 해석해야 한다.
양방향(bidirectional) MR	한 집합의 도구변수로 '노출→결과' 효과를, 다른 독립 집합으로 '결과→노출' 효과를 시험해 인과방향성을 더 잘 파악하는 접근이다.
도구변수(instrumental variables)	관심있는 노출과 통계적으로 유의미한 연관을 가지며, 교란 요인과는 독립적이고, 노출을 통한 경로 외에는 결과에 영향을 미치지 않는 변수이다.
도구변수 가정(핵심 MR 가정)	관련성(relevance: 유전변이가 관심 노출과 관련성), 독립성(independence: 유전변이가 결과와 공유하는 미측정 원인이 없음), 배제 제한(exclusion restriction: 유전변이가 관심 노출의 효과 경로 외에는 결과에 영향 없음)의 가정을 포함한다.
도구변수 가정 평가	가정의 개연성은 여러 가지 방법으로 점검할 수 있다. 관련성은 유전 변이와 관심 노출 간의 연관을 검증하고, 배제 제한 가정은 다면발현이나 교란 요인과의 관계를 검정하여 정황 증거를 제시할 수 있다. 배제 제한 가정은 위반 여부를 직접적으로 검증할 수 없지만, MR Egger 회귀, weighted median 방법 등으로 위반 가능성을 평가할 수 있다.
유전자-환경 등가성(gene-environment equivalence)	유전변이에 의해 유도된 노출 차이가 환경 요인에 의해 유도된 노출 차이와 건강 결과에 미치는 하위 효과가 동일하다는 개념이다. 이 가정이 충족되어야 MR 추정치를 정책적 개입 효과로 해석 가능하다.
유전변이(genetic variant)	한 집단 내에서 관찰되는 DNA 서열의 변이를 말한다. 전형적으로 단일염기다형성(SNP)을 가리킨다.
단일염기다형성(SNP)	DNA의 단일 염기가 의미 있는 빈도로 집단 내에서 변이를 보이는 유전변이다. 보통 두 개의 대립유전자(예: A, C, G, T)를 가지며, 형질과 관련된 경우 하나는 형질 증가, 다른 하나는 감소와 관련된다. MR에서는 조절 가능한 노출의 도구변수로 가장 흔히 사용된다.
가닥 정렬(strand alignment)	노출 GWAS와 결과 GWAS에서 보고된 대립유전자가 동일한 DNA 가닥 기준으로 일치하도록 맞추는 절차이다. 팔린드롬(palindromic) SNP(G/C, A/T)는 두 가닥에서 동일하게 보여 혼동을 유발할 수 있어 주의가 필요하다. 가닥을 일치시키지 않으면 효과대립유전자 식별의 모호성이 생긴다. MR 또는 메타분석 수행 시, 노출 GWAS 와 결과 GWAS 에서 보고된 대립유전자가 동일한 DNA 가닥 기준으로 일치하도록 맞추는 절차이다.
대립유전자 점수(allele score)	여러 SNP의 정보를 결합해 하나의 변수로 만든 것으로, 특정 형질(예: 혈압)과 관련된 SNP들을 합성해 MR에서 노출을 예측하는 데 쓴다. 유전위험점수(genetic risk score), 다유전자 점수(polygenic score), 유전 예측점수라고도 한다.

(Continued on the next page)

Table 2. Continued

용어	설명
관련성불평형(LD)	두 개 이상의 좌위에서 대립유전자가 무작위가 아닌 방식으로 공동 분포하는 현상이다. 일반 인구에서 보통 좁은 유전체 구간 내에서 관찰되며, MR에서 편향의 잠재 원인이 될 수 있다.
r^2	두 유전 좌위 간 LD의 상관을 정량화하는 지표이다(r^2 =1은 완전 상관). 노출 변이의 분산 설명력을 나타내는 R^2 (도구 강도 계산에 쓰임)와 혼동하지 않도록 한다. LD는 보통 인접한 염색체 구간 내의 유전변이들 수 킬로베이스 수십 킬로베이스 범위 에서 관찰되며, 이는 재조합(recombination)이 세대를 거듭해도 완전히 무작위화되지 않기 때문에 발생한다. MR 연구에서는 LD가 독립적 도구변수(independent instrumental variables) 가정의 위반을 초래할 수 있다. 즉, 선택된 SNP들이 서로 높은 LD에 있다면, 각각의 SNP가 동일한 인과 신호를 중복 반영하거나, 다른 유전자의 효과를 혼합(reflection)함으로써 함으로써 효과 추정치의 편향(bias) 또는 과대평가(overestimation)가 발생한다.
도구 강도 검정(test of instrument strength)	유전변이와 노출 간 관련성의 크기를 평가한다. 부분 F 통계량(partial F)이나 R^2 가 흔히 사용된다.
차이 검정(test for difference)	다변량 보정 관찰연구 추정치와 MR 추정치의 차이가 단순 추정오차를 넘어서는지 평가한다(예: 하우스만 검정). 일반최소제곱법(ordinar y least squares, OLS 에서 얻은 추정치와 2단계 최소제곱법(two stage least squares, 2SLS)에서 얻은 추정치의 차이를 그 분산 차이로 나누어(statistical ratio of their variance difference) 통계적으로 평가한다. 차이가 통계적으로 유의하면(P<0.05), 관찰연구 추정치가 교란(confounding)이나 역인과(reverse causality)의 영향을 받을 가능성 이 있거나, MR 의 핵심 가정(예: 배제 제한)이 위배되었을 가능성을 시사한다.
수평 다면발현(horizontal pleiotropy)	유전변이가 관심 노출과 무관한 경로로 결과에 영향을 미치는 현상이다. 배제 제한 가정 위반이며 MR 편향의 원인이다.
약한 도구 편향(weak instrument bias)	도구로 사용한 유전변이가 관심 노출과의 관련성이 약할 때 발생하는 편향이다. 단일 표본 분석에서 부분 F<10이면 약한 도구 가능성이 높다는 경험법칙이 있으나, 10을 넘어도 편향이 생길 수 있다(이는 P=0.05의 이분법과 유사한 경험적 기준일 뿐이다)[20].
콜라이더 편향(collider bias)	유전변이와 또 다른 핵심 변수(예: 결과)의 공통 효과에 대해 조건부화할 때 생길 수 있는 편향이다. 통계적 조정(변이와 결과 모두에 의해 생성된 공변량을 모형에 포함)이나 표본추출 과정(예: 입원이 변이와 다른 요인에 의해 좌우되는 병원 환자 표본 분석)에서 발생할 수 있다.
승자의 저주(winner's curse)	가장 유의한 SNP의 효과가 실제보다 과대 추정되는 현상이다. 일반적으로 P값 문턱으로 가장 강한 관련성만 선택할 때 발생한다.
데이터(data)	참가자의 개별 수준 자료(예: 표현형·유전형) 또는 SNP 수준의 표현형–관련성 요약치(요약수준 자료)를 가리킨다.

MR, Mendelian randomization; SNP, single nucleotide polymorphism; GWAS, Genome-Wide Association Study(전장유전체 관련성 분석); LD, linkage disequilibrium.

[13-15]. 초기에는 MR을 "질병 위험 또는 기타 결과에 영향을 미치는 조절 가능한 노출의 인과추론을 강화하기 위해 생식계열(germline) 유전변이를 사용하는 것"으로 정의하였다[16]. 이러한 광의의 정의에는 예를 들어 유전자-공변량 상호작용 연구(종종 환경을 공변량으로 함)가 포함되며, 여기서 상호작용은 관심 노출에 대한 도구변수로 간주될 수 없다[17,18]. 또한 쌍생아 연구와 같이 멘델 유전의 기본 원리를 사용하는 다른 연구설계도 MR의 한 형태로 간주할 수 있다. 이러한 사례 중 하나는 (평균적으로) 태아기 테스토스테론 수치가 더 높음을 나타내는 지표로 남자 쌍생아를 대상으로 하여 테스토스테론이 신경발달적 특성에 미치는 영향을 평가하였다[19]. MR 연구는 단일염기다형성과 결과 간 관련성을 단순히 시험해 특정 노출이 질병에 영향을 미치는지에 대한 근거를 제공하는 수준부터, 도구변수 분석으로부터 특정 효과 추정치를 산출하는 수준까지 폭넓다.

STROBE-MR 현재 도구변수 체계 내에서 수행되는 대다수 MR 연구를 주된 대상으로 한다. 노출에 대한 도구를 사용하지 않는 MR 연구(예: 유전자-환경 상호작용 연구)나, 유전변이를 도구변수 체계에서 사용하지만 도구변수 추정치를 보고하지 않는 MR 연구(예: 이식에서의 형제자매 적합성 연구)의 경우, STROBE-MR 항목 중 일부는 적용되지 않을 수 있다. 그렇지만 체크리스트는 여전히 유용한 지침을 제공한다. Table 1은 STROBE-MR이 다루는 연구설계와 다루지 않는 연구설계 설명이다.

MR 연구 보고의 강화

MR 적용과 방법이 성장하고 MR 결과의 중요성이 커졌음에도, MR 연구 보고방식에 대한 합의는 부족하다. 그 결과, MR 연구의 보고 질은 일관되지 않았다. 실증적 근거에 따르면[22-

24], 많은 MR 연구 보고가 MR 방법의 다양한 가정을 명확히 기술하거나 점검하지 않았고, 자료 출처에 대한 세부 정보를 불충분하게 보고하여 결과의 질과 신뢰성을 평가하기 어렵게 만든다.

관찰연구를 위한 STROBE (strengthening the reporting of observational studies in epidemiology) 지침은 역학의 세 가지 주요 연구설계(코호트, 환자-대조군, 단면연구)를 대상으로 개발되었다[25,26]. 그러나 STROBE의 일부 항목은 지나치게 일반적이거나 MR 연구에 적용되지 않으며, MR 연구에 중요한 항목이 누락되어 있기도 하다. MR 연구 보고를 개선하기 위해, 우리는 STROBE 지침에 기반을 두되 MR 연구설계에 초점을 맞춘 별도의 체크리스트를 개발하였고, 그 결과가 STROBE-MR 보고지침(strengthening the reporting of observational studies in epidemiology using Mendelian randomization)이다[27] (Table 3). STROBE 체크리스트와 유사하게, STROBE-MR 항목은 논문의 제목, 초록, 서론, 방법, 결과, 고찰에 해당한다.

STROBE-MR의 개발, 범위, 활용

자세한 내용은 다른 곳에 기술되어 있으며[27], 우리는 의학연구 보고지침 개발을 위한 권고를 따라[28], 2018년에 작업을 시작하였다. MR 방법론 전문가, 기존 보고지침의 저자, MR 연구설계를 자주 사용하는 연구자, 학술지 편집인 등으로 구성된 전문가 그룹을 워크숍에 초청하였다. 이 그룹은 2019년 5월 영국 브리스톨에서 이틀간 대면으로 만나 MR 연구의 보고 질에 관한 실증적 근거를 논의하고 체크리스트 초안을 마련하였다. 초안은 2019년 7월 프리프린트로 공개되었고[29], 프리프린트 플랫폼, 소셜 미디어, 제4회 국제 멘델 무작위화 학술대회 전용 세션에서 논의되었다[30]. 우리는 의견을 반영해 체크리스트를 수정하고 STROBE-MR 성명서를 제시하는 논문을 작성하였다[27].

STROBE-MR 보고지침은 생식계열(germline) 유전변이의 특성을 이용해 조절 가능한 노출의 잠재적 효과가 결과에 미치는 인과추론을 강화하는 연구에 적용된다. MR의 주요 유형은 단일 표본(one-sample)과 두 표본(two-sample)이다. 단일 표본 MR에서는 유전변이-노출 관련성과 유전변이-결과 관련성을 동일 표본에서 모두 측정한다. 두 표본 MR에서는 두 관련성을 서로 다른 표본에서 측정한다. MR 연구는 단일염기다형성(SNP)별 가중치를 도출·적용할 때 개별 수준 자료 또는 요약 수준 자료를 사용할 수 있다. 두 표본 MR은 대개 요약 수준 자료로 수행되며, 첫 번째 표본에서 도출한 가중치를 두 번째 표본에 적용해 유전자-결과 관련성을 추정한다. 노출과의 관련성에 대한 요약 가중치는, 이들 변이와 결과의 관련성을 개별 수준 분석에 적용하는 데도 사용할 수 있다. STROBE-MR이 다루는/다루지 않는 연구설계 개요는 Box 1의 Table 1에 제시되어 있다.

이 논문의 목적

이 설명 및 해설(explanation and elaboration, E&E) 문서는 STROBE-MR 성명서를 보완한다[27]. 형식은 STROBE E&E 문서[26] 등 기존 보고지침을 따르며, 체크리스트 20개 항목 각각을 뒷받침하는 상세 설명과 투명한 보고 사례를 제공하는 데 목적이 있다. 각 항목의 우수한 보고 사례는 출판된 MR 연구에서 선정하였다.

이 문서는 저자가 체크리스트의 각 항목을 더 잘 이해하도록 돕는 참고자료로 보아야 한다. 제시한 예시는 각 항목의 '이상적' 진술을 뜻하지 않으며, 해당 항목이 다루려는 쟁점을 부각하는 데 목적이 있다. 본문의 Box와 Table은 MR 연구설계에 관한 이론적 배경을 담아 보고 권고사항을 보완한다. MR 수행에 관한 추가 지침은 다른 자료에 제시되어 있다[31].

일부 예시는 해당 항목과 무관한 인용·문단을 제거해 편집하였다. 항목은 제목·초록(항목 1), 서론(항목 2–3), 방법(항목 4–9), 결과(항목 10–13), 고찰(항목 14–17), 기타 정보(항목 18–20)로 구분된다(Table 3). 일부 항목은 동일 주제의 하위 항목을 가진다(예: 항목 10d는 두 표본 MR에만 해당). 추가 예시는 Supplement 2에 있다. 지면 제약으로 일부 정보를 보충자료에 보고했더라도, 저자는 체크리스트의 모든 항목을 논문에서 다루는 것이 바람직하다.

제목과 초록(항목 1)

연구의 주요 목적이 MR일 때, 제목 및/또는 초록에 MR을 연구설계로 명시한다.

제목

예시

"BMI as a Modifiable Risk Factor for Type 2 Diabetes: Refining and Understanding Causal Estimates Using Mendelian Randomization [32]."

"Genome Wide Analyses of >200,000 Individuals Identify 58 Loci for Chronic Inflammation and Highlight Pathways that Link Inflammation and Complex Disorders [33]."

설명

MR이 연구설계에서 핵심적 역할을 하였다면, 제목에 "Men-

Table 3. 멘델 무작위화(MR) 연구 보고에서 다뤄야 할 권장 항목(STROBE-MR 체크리스트)

항목 번호	구역	체크리스트 항목
1	제목과 초록	연구의 주요 목적이 MR일 때, 제목 및/또는 초록에 MR을 연구설계로 명시한다.
	서론	
2	배경	보고하는 연구의 과학적 배경과 근거를 설명한다. 노출은 무엇인가? 노출과 결과 간 잠재적 인과 관련성은 개연적인가? MR이 연구질문을 다루는 데 유용한 이유를 제시한다.
3	목적	사전에 규정된 인과 가설(있다면)을 포함하여 구체적 목적을 명확히 기술한다. MR은 특정 가정하에서 인과효과를 추정하려는 방법임을 명시한다.
	방법	
4	연구설계와 데이터 출처	논문 서두에 연구설계의 핵심 요소를 제시한다. 연구의 모든 단계에 대한 데이터 출처를 나열한 표를 포함하는 것을 고려한다. 분석에 기여한 각 데이터 출처에 대해 다음을 기술한다: a) **환경(Setting)**: 가능하면 연구설계와 기반 모집단을 설명한다. 이용 가능한 경우 모집·노출·추적·자료수집 기간을 포함해 장소·위치·관련 날짜를 기술한다. b) **참가자:** 선정기준, 선정의 원천과 방법을 제시한다. 표본 수, 본 분석 이전에 수행한 검정력/표본 수 계산 여부를 보고한다. c) **유전변이의 측정·품질관리·선정**을 기술한다. d) **각 노출·결과·기타 변수**의 평가방법과 질병의 진단기준을 기술한다. e) 해당 시 **윤리 심의 승인**과 **연구참여 동의**의 세부를 제시한다.
5	가정	본 분석의 세 가지 핵심 도구변수 가정(관련성, 독립성, 배제 제한)과 추가/민감도 분석에 필요한 가정을 명시한다.
6	통계방법: 본 분석	사용한 통계방법과 통계치를 기술한다. a) **정량 변수 처리**(척도, 단위, 모형)를 기술한다. b) **유전변이 처리**와 가중치 선택(해당 시)을 기술한다. 유전변이 전처리(품질 관리, LD 클럼핑, 가닥 정렬 팔린드롬 처리)와 분석 절차를 기술한다.c) **MR 추정량**(예: 2단계 최소제곱, Wald 비)과 관련 통계, 포함 공변량, 두 표본 MR의 경우 두 표본에서 동일 공변량 세트를 사용해 보정했는지 기술한다. 도구 강도 평가(F 통계량), 2 단계 최소제곱법 (2SLS) 또는 요약통계 기반 MR(IVW, MR Egger 등) 방법을 명시한다 d) **결측치 처리**방법을 명확히 한다. e) 해당 시 **다중 검정**처리 방법을 기술한다. 유전 변이 노출 (G X), 유전 변이 결과 (G Y) 연관 산출법과 다중 검정 보정을 기술한다.
7	가정의 평가	가정의 타당성을 평가하거나 근거를 제시하기 위해 사용한 방법 또는 사전 지식을 기술한다.
8	민감도 분석 및 추가 분석	수행한 민감도/추가 분석을 기술한다(예: 방법 간 효과추정 비교, 독립 재현, 편향 분석 기법, 도구 검증, 시뮬레이션).
9	소프트웨어 및 사전 등록	a) 사용한 통계 소프트웨어와 패키지(버전·설정 포함)를 명시한다. b) 연구 프로토콜과 세부가 **사전 등록**되었는지(언제·어디에) 기술한다.
	결과	
10	기술 통계	a) 포함된 연구의 각 단계에서 개인 수와 제외 사유를 보고한다(플로우 다이어그램 사용 고려). b) 표현형 노출·결과·기타 변수의 요약통계(예: 평균, 표준편차, 비율)를 보고한다. c) 데이터 출처에 기존 메타분석이 포함되면, 연구 간 이질성 평가를 제시한다. d) **두 표본 MR**의 경우: i. 노출 표본과 결과 표본에서 **유전변이-노출**관련성의 유사성에 대한 근거를 제시한다. ii. 두 표본에 **중복 포함된 개인 수**를 보고한다.
11	주요 결과	a) **유전변이-노출, 유전변이-결과** 관련성을 해석 가능한 척도로 보고한다. b) **MR 추정치**와 불확실성 지표를 해석 가능한 척도로 보고한다(예: 표준편차 1단위당 OR 또는 RR). c) 해당 시, 상대위험을 임상적으로 의미 있는 기간의 **절대위험**으로 변환하는 것을 고려한다. d) 결과 시각화를 위한 도표를 고려한다(예: 포레스트 플롯, 유전변이-결과 대 유전변이-노출 산점도).
12	가정의 평가(결과)	a) 가정 타당성 평가결과를 보고한다. b) 추가 통계(예: 유전변이 간 이질성 평가: I^2, Q 통계, E-value)를 보고한다.
13	민감도 분석 및 추가 분석(결과)	a) 가정 위반에 대한 주요 결과의 견고성을 평가하기 위해 수행한 민감도 분석을 보고한다. b) 기타 민감도/추가 분석결과를 보고한다. c) 인과 방향성 평가(예: 양방향 MR)를 보고한다. d) 관련될 때 비-MR 분석 추정치와 비교·보고한다. e) 추가 시각화(예: leave-one-out 분석)를 고려한다.
	고찰	
14	핵심 결과	연구목적에 비추어 핵심 결과를 요약한다.
15	한계	도구변수 가정의 타당성, 기타 잠재적 편향원, 불정확성을 고려해 연구의 한계를 논의한다. 잠재적 편향의 **방향과 크기**, 이를 줄이려 한 노력을 함께 기술한다.

(Continued on the next page)

Table 3. Continued

항목 번호	구역	체크리스트 항목
16	해석	a) **의미:** 한계와 타 연구와의 비교 맥락에서 결과를 신중하게 종합 해석한다. b) **기전:** 노출-결과 인과 관련성을 매개할 수 있는 생물학적 기전을 논의하고, 유전자-환경 등가성 가정의 개연성을 검토한다. 인과 언어는 신중히 사용하며, 도구변수 추정치는 특정 가정하에서만 인과효과를 제공할 수 있음을 명확히 한다. c) **임상적 관련성:** 결과가 임상·정책에 갖는 함의와, 잠재적 중재의 효과크기 추정에 어느 정도 기여하는지 논의한다.
17	일반화 가능성	연구결과의 일반화 가능성을 (a) 다른 인구집단, (b) 다른 노출 기간/시점, (c) 다른 노출 수준으로 논의한다.
	기타 정보	
18	연구비	본 연구(및 해당 시, 기반 데이터베이스·원연구)의 **연구비 출처**와 연구비 제공자의 역할을 기술한다.
19	데이터 및 데이터 공유	분석에 사용한 데이터를 제공하거나 접근 위치·방법을 명시하고, 논문 내에서 이를 인용한다. 결과 재현에 필요한 **통계 코드**를 제공하거나, 공개 접근 가능 여부와 위치를 보고한다.
20	이해관계	모든 저자는 **잠재적 이해관계**를 모두 선언한다.

이 체크리스트는 Supplement 1에도 있음.
MR, Mendelian randomization; STROBE-MR, strengthening the reporting of observational studies in epidemiology using Mendelian randomization.

delian randomization"을 포함하는 것이 바람직하다. 1차 분석이 MR이 아니고 MR이 후속 분석기법으로 사용된 경우에는 제목에 MR을 직접 포함하지 않고 논문의 주목적에 초점을 유지할 수 있다.

초록

예시

"Importance: 인간 유전 연구는 혈장 지단백(a)(Lp[a])가 관상동맥질환(coronary heart diseases, CHD) 위험과 인과적으로 관련됨을 시사해 왔다. 그러나 Lp(a)를 25%-35% 낮추는 여러 치료의 무작위배정시험은 Lp(a) 저하가 CHD 위험을 감소시킨다는 근거를 제공하지 못하였다.

Objective: LDL-C 1 mmol/L (38.67 mg/dL) 변화가 CHD 위험을 의미 있게 낮추는 효과와 동등한 근거를 보이기 위해 필요한 Lp(a) 농도 변화의 크기를 추정한다.

Design, setting, and participants: 5개 연구의 개별자료로 MR 분석을 수행하고, 48개 연구의 요약자료로 외부 검증을 하였다. 코호트·환자-대조군 연구에 포함된 개별자료는 CHD 20,793명과 대조군 27,540명이며, 요약자료는 CHD 62,240명과 대조군 127,299명을 포함한다. 분석기간은 2016년 11월-2018년 3월이다.

Exposures: 유전적 LPA 점수와 혈장 Lp(a) 질량 농도.

Main outcomes and measures: 관상동맥질환.

Results: 참가자의 53%는 남성이었고, 모두 백인 유럽계였으며, 평균 연령은 57.5세였다. 유전적으로 예측된 Lp(a)와 CHD 위험의 관련성은 Lp(a) 절대 변화에 선형적으로 비례하였다. 유전적으로 예측된 Lp(a) 10 mg/dL 감소는 CHD 위험 5.8% 감소(odds ratio [OR], 0.942; 95% confidence interval [CI], 0.933-0.951; $P=3\times10^{-37}$)와 관련성되었고, LDL-C 유전 점수로 추정한 LDL-C 10 mg/dL 감소는 CHD 위험 14.5% 감소(OR, 0.855; 95% CI, 0.818-0.893; $P=2\times10^{-12}$)와 관련되었다. 따라서 Lp(a) 농도 101.5 mg/dL 변화(95% CI, 71.0-137.0)가 LDL-C 38.67 mg/dL 변화와 동등한 CHD 위험 감소와 관련성되었다. 유전적으로 예측된 Lp(a)와 CHD 위험의 관련성은 스타틴, PCSK9 억제제, 에제티미브를 모사하는 변이에 의해 매개되는 LDL-C 변화와 독립적으로 보였다.

Conclusions and relevance: Lp(a) 저하의 임상적 이득은 Lp(a) 절대 감소량에 비례할 가능성이 크다. CHD 위험을 LDL-C 38.67 mg/dL 저하와 유사한 크기로 낮추려면 약 100 mg/dL 규모의 Lp(a) 절대 감소가 필요할 수 있다[34]." (추가 예시는 Supplement 2 참조)

설명

초록은 수행 내용과 발견 내용을 균형 있게 요약해야 하며, 자료 출처, 노출·결과, 개별/요약자료 사용 등 설계의 핵심 이슈와 함께(가능하면) "Mendelian randomization"을 포함해 검색 용이성을 높이는 것이 바람직하다. 결과는 적용한 접근 전반에 걸쳐 점추정치와 불확실성(오차) 정보를 함께 제시해야 하며, P값만을 보고하는 것은 피한다. "인과적"이라는 표현은 신중히 사용해야 하며, MR이 특정 가정하에서 인과 관련성을 이해하도록 고안된 추정임을 분명히 해야 한다. 가능하면 구조화 초록을 사용해 관련 정보를 빠짐없이 담는 것이 좋다. Supplement 2에는 단일·두 표본·내재형(embedded) MR 초록의 추가 예시가 있다.

서론

배경(항목 2)

보고하는 연구의 과학적 배경과 근거를 설명한다. 노출은 무엇인가? 노출-결과 간 인과성이 개연적인가? MR이 연구질문에 유용한 이유를 정당화한다.

예시

"역학 연구는 특히 여성에서 사춘기 연령이 이를수록 다발성 경화증(multiple sclerosis, MS) 위험이 증가한다는 결과를 보고해 왔다. 그러나 이를 재현하지 못한 연구도 있다. 사춘기 시기는 체중 상태와 복잡하게 상호작용하며, 소아기의 높은 체지방은 이른 사춘기로 이어지고, 이는 다시 성인기의 높은 body mass index (BMI)와 관련된다. 증가한 BMI가 MS 병태생리에 기여한다는 근거가 있으므로, 관찰된 '사춘기 시기-MS' 관련성의 일부는 BMI로 설명될 수 있다. 관찰연구의 일부 한계는 도구변수 방법으로 완화할 수 있는데, 이는 노출의 효과를 결과에서 탐색하기 위해 노출의 대리변수를 사용하는 접근이다. 멘델 무작위화(MR)에서는 유전변이를 도구변수로 사용해 위험요인과 결과 간 인과 관련성을 검정한다[35]."

"비선형 관계는 의생명과학 전반에서 위험요인-결과 사이에 존재한다. BMI와 심혈관질환과 같은 노출 간 비선형 관계를 추정하는 방법이 개발되었다. 유전 성분을 제거한 BMI(도구변수 비포함 BMI)의 분위 오분위별로 BMI가 각 위험요인에 미치는 국소 평균 인과효과를 추정하고, 이 값들에 대해 이질성 및 추세 검정을 수행하였다[36]."

설명

가설 없이 다양한 결과에 대한 노출의 효과를 탐색적으로 시험한 MR도 있으나[37], 다수의 MR 연구는 선행 근거에서 도출된 구체적 가설을 평가하도록 설계된다. 특정 가설을 사용하는 경우, 현 가설을 평가하는 사전 기대 효과크기 포함한 근거를 제시해야 한다. MR은 인과 영가설 검정 또는 점 · 기간 · 평생 효과 추정에 쓰일 수 있다. MR이 연구가설을 평가하는 데 어떤 역할을 하는지 명확히 하여, MR 적용이 문헌의 어떤 공백을 메우는지 독자가 이해하도록 해야 한다.

목적(항목 3)

사전 규정된 인과 가설(있다면) 포함하여 구체적 목적을 명확히 기술한다. MR이 특정 가정하에서 인과효과 추정을 목적으로 하는 방법임을 명시한다.

예시

"목적: 혈청 칼슘 상승과 관련된 유전변이가 관상동맥질환(coronary artery disease, CAD) 및 심근경색 위험과 잠재적 인과 관련성을 갖는지 멘델 무작위화를 이용해 평가한다[38]."

설명

연구가 특정 노출이 특정 결과에 미치는 인과효과 추정을 목표로 함을 명확히 밝혀야 한다. 이 부분에서 관심 노출 · 결과를 정의해 독자가 맥락을 파악하게 하고, 전체 연구목적을 제시한다.

방법

연구설계와 데이터 출처(항목 4)

논문 서두에 연구설계의 핵심 요소를 제시하고, 연구의 모든 단계에 대한 데이터 출처를 나열한 표를 포함하는 것을 고려한다.

예시

"기여한 GWAS 컨소시엄의 세부는 Table 4에 제시하였다. 연구는 심혈관 · 대사 건강 관련 형질을 조사하고, 표본 수가 가장 크며, 표본 중복을 최소화하면서 인구 구성이 가장 유사한 것을 기준으로 선택하였다. 표본 중복 비율은 보충표 S1에 제시하였다. 주관적 웰빙은 행복 · 긍정정서 · 전반적 삶의 만족과 관련된 항목으로 측정하였다. 각 구성요소의 GWAS를 메타분석해 주관적 웰빙을 포착하였다. 모든 형질의 표현형 정의와 GWAS 방법에 관한 추가 정보는 보충표 S2를 참조하라. 혈압을 제외한 모든 표현형 점수는 z-점수로 표준화하였다[39]."

설명

STROBE와 마찬가지로[26], 논문 서두에서 연구설계의 핵심 요소를 제시하면 독자가 연구의 기본 구도를 빠르게 파악할 수 있다. 저자는 MR 연구가 개별 수준 참가자 자료를 사용했는지, 아니면 SNP 수준 요약자료를 사용했는지, 그리고 단일 표본설계인지 두 표본설계인지 명확히 해야 한다. 두 표본 MR에서는 한 단계는 요약자료, 다른 단계는 개별자료를 사용할 수도 있다. 일부 MR 연구는 여러 데이터 출처를 결합한다(예: 유전변이-노출 관련성은 한 출처, 유전변이-결과 관련성은 다른 출처). 또한 데이터 출처가 여러 표본의 메타분석일 수도 있다. 그러므로 전체 설계와 데이터 출처를 명확히 밝혀야 한다.

우리는 MR 연구에서 유전변이 수준 정보의 출처를 명확히 기록한 표(예: Table 4)를 제시할 것을 권장한다. 예컨대 노출을 추정하는 데 사용한 유전변이는 한 연구에서 확인되었지만, 이 유전변이가 노출에 미치는 효과크기(또는 가중치)는 다른 연구에서 가져왔을 수 있다. 이런 경우 두 정보의 출처를 모두 보고하는 것이 바람직하다. 필요에 따라 표를 확장한다. 예를 들어,

Table 4. 각 표현형에 사용된 GWAS 컨소시엄 개요(도표는 Wootton 등, 2018에서 허가 받아 재수록함[39])

변수	제1저자(연도)	컨소시엄	표본 수	인구집단[a]	성별[a]
주관적 웰빙	Okbay (2016)	SSGAC	298,420	유럽계 100%	혼합[b]
체질량지수(BMI)	Locke (2015)	GIANT	339,224	유럽계 95%	여성 53%
허리-엉덩이둘레비(WHR)	Shungin (2015)	GIANT	210,088	유럽계 100%	여성 56%
허리둘레	Shungin (2015)	GIANT	232,101	유럽계 100%	여성 55%
체지방률	Lu (2016)	보고 없음	100,716	유럽계 89%	여성 48%
HDL 콜레스테롤	Willer (2013)	GLGC	92,860	유럽계 100%	혼합[b]
LDL 콜레스테롤	Willer (2013)	GLGC	83,198	유럽계 100%	혼합[b]
총 콜레스테롤	Willer (2013)	GLGC	92,260	유럽계 100%	혼합[b]
관상동맥질환(CAD)	Nikpay (2015)	CARDIoGRAMplusC4D	사례 60,801; 대조 123,504	유럽계 77%	혼합[b]
심근경색(MI)	Nikpay (2015)	CARDIoGRAMplusC4D	사례 43,676; 대조 128,199	혼합[b]	혼합[b]
이완기 혈압	Wain (2017)	보고 없음	150,134	유럽계 100%	여성 60%
수축기 혈압	Wain (2017)	보고 없음	150,134	유럽계 100%	여성 60%

GWAS, genome-wide association study; SSGAC, Social Science Genetics Association Consortium; BMI, body mass index; GIANT, Genetic Investigation of Anthropometric Traits consortium; WHR, waist to hip ratio; HDL, high-density lipoprotein; GLGC, Global Lipids Genetics Consortium; LDL, low-density lipoprotein; CAD, coronary artery disease; MI, myocardial infarction.

[a]보고가 없는 경우, 성별 비율과 유럽계 비율은 보충자료의 기여 코호트 정보를 바탕으로 계산하였다. 모든 GWAS는 유사한 성비와 조상을 포함하였다. 가장 큰 차이는 관상동맥질환과 주관적 웰빙 컨소시엄 사이에서 관찰되었고, 각각 유럽계 77%와 100%를 사용하였다. 두 표본의 인구 구성이 다르더라도 두 표본 멘델 무작위화로 인과효과 검정은 가능하지만, 효과 크기의 정밀도는 떨어질 수 있다[32]. [b]CARDIoGRAMplusC4D, GLGC, SSGAC 컨소시엄에서는 전체 표본의 성비와 조상 구성 비율을 보고하지 않았거나 계산이 불가능하였다.

서로 다른 결과를 갖는 추가 MR 연구를 포함한다면 표에 열을 더하고, 추가 노출을 다룬다면 행을 추가한다.

자료가 기존 연구에서 추출되었다면, 데이터가 어떻게 수집·획득되었는지 기술한다. 데이터가 공개 접근 가능하다면, 가능한 경우 출처의 하이퍼링크를 제공한다. 요약자료를 사용하는 경우, 이러한 세부가 추적 가능해야 하며 데이터 출처 간 이질성을 정성적으로 평가할 수 있어야 한다. 분석에 기여한 각 데이터 출처에 대해서는 항목 4a-4e의 요소를 기술한다.

환경(Setting, 항목 4a)

가능하면 연구설계와 기반 모집단을 설명한다. 가능하면, 장소, 위치, 관련 시기(모집, 노출, 추적, 자료수집 기간 포함)를 기술한다.

예시

"이 연구는 21개 코호트(총 42,024명)에서 직접 유전형 분석 및 보간(imputation)된 SNP를 대상으로 한 메타분석으로 구성되었다(Table 1). 참여 연구의 확장 설명은 Supplement 2에 제시하였다."[40]

"전장유전체 유전형과 골절 자료를 보유한 총 23개 코호트가 GEFOS 컨소시엄(http://www.gefos.org/)을 통해 전 세계에서 모집되었다. 이들 코호트는 주로 유럽계였으며, 유럽(n=13), 북미(n=8), 호주(n=1), 동아시아(n=1)에 분포했고(표 S1A, S2A), 골절 사례 20,439명과 대조 78,843명이 포함되었다[41]."

설명

연구 인구, 환경, 위치에 대한 정보는 결과의 맥락과 일반화 가능성을 평가하는 데 필요하다. 환경 요인이나 치료 같은 노출은 시간이 지나며 변할 수 있고, 연구방법 또한 진화한다. 연구가 언제 수행되었는지, 참가자가 어느 기간에 모집·추적되었는지를 아는 것은 결과 해석에 필요한 역사 정보를 제공한다. 이러한 정보가 선행 논문에 이미 기술된 경우, 명확한 인용만으로 충분할 수 있다. 참가자의 조상(ancestry) 정보를 제공하면 잠재적 이질성과 일반화 가능성을 이해하는 데 도움이 된다. 기존 연구의 요약 수준 자료를 사용하는 경우, 자료 출처 간 환경의 이질성을 정성적으로 평가할 수 있도록 세부 사항을 추적 가능하게 제시해야 한다.

참가자(Participants, 항목 4b)

선정기준, 참가자 출처, 선정방법을 제시한다. 표본 수와, 본 분석 전에 검정력/표본 수 계산을 수행했는지 여부도 보고한다.

예시

"UK Biobank는 2006-2010년에 영국 전역에서 37-73세(99.5%는 40-69세) 성인 50만 명 이상을 모집하였다. 참가자는 설문 및 인터뷰로 인구학, 건강상태, 생활습관을 제공했고, 인체계측, 혈압, 혈액·뇨·타액 검체를 채취하였다. 자세한 내용은 다른 문헌에 기술되어 있다. 우리는 초기 UK Biobank 데이터셋에서 백인 영국계 120,286명을 사용했으며, 이 중 119,669명은 유전 자료와 BMI 및 키 측정값이 모두 유효하였다. 다른

인종 집단은 개별적으로는 검정력이 부족하여 포함하지 않았다[42].” (추가 예시는 Supplement 2 참조)

설명

참가자와 표집방법에 대한 상세 기술은 결과의 적용 가능성을 이해하는 데 도움이 된다. 모든 선정기준, 참가자 출처 · 선정방법, 해당될 경우 추적방법, 그리고 모집방식을 제시한다. 선행 연구에 기술된 경우에는 명확한 인용으로 대체할 수 있다. 요약 수준 자료를 사용하는 경우에도 출처별 참가자 이질성을 정성적으로 평가할 수 있도록 세부 사안을 추적 가능하게 기술해야 한다.

환자-대조군 연구에서는 사례 · 대조 선택이 결과 해석의 핵심이며, 선택 · 방법이 타당성에 큰 영향을 준다. 일반적으로 대조군은 사례가 발생한 모집단을 반영해야 한다.

주요 분석 전에 표본수/검정력 계산을 수행하였다면 설계나 통계방법 부분에 보고한다. 연구 기획 · 해석에서 표본 수 정보는 필수다. 검정력은 효과 추정치의 원하는 정밀도에 적합한 검정력을 얻기 위해 필요한 표본크기에 대한 정보를 제공한다[43,44]. 검정력 분석을 수행할 경우 연구 수행 전에 실시해야 한다. 통계적 검정력은 실험 전 검정력 계산보다 가정이 적게 필요하므로, 추정치의 95% 신뢰구간을 검토함으로써 가장 잘 확인할 수 있다.

유전변이(항목 4c)

유전변이의 측정, 품질관리(quality control, QC), 선정을 기술한다.

예시

“유전형 분석은 Affymetrix UK Biobank Array로 수행하였다. 상염색체 분석은 HRC 보간 변이 중 MAF >0.05%, 소수대립유전자 수 >5, info 점수 >0.3, 하드 콜률(call rate) >0.95, Hardy-Weinberg $P>1\times10^{-6}$의 고품질 변이(최대 13,977,204개)로 제한하였다.”[45]

“다양한 비만 관련 위험요인에 대한 유전 표지는 유럽계 참가자에서 관심 위험요인과 관련된 SNP ($P<5\times10^{-8}$)를 포함하였다. LD R^2 <0.1 기준으로 상관된 SNP는 제외하였다… 가닥이 모호한 SNP (A/T 또는 C/G)는 proxy snps R 패키지(유럽 인구)를 이용해 관련된 대체 SNP (R^2 >0.8)로 치환하거나, 소수대립유전자 빈도가 0.4를 초과하면 분석에서 제거하였다[46].”

설명

유전형 확인 및 QC정보를 제공하면 사용된 유전변이의 질을 평가할 수 있다. 두 표본 MR에서는 종종 선행 논문의 보충자료를 인용해야 한다.

방법론 섹션에서는 분석에 포함된 특정 유전 변이체의 선정 및 포함기준을 명확히 설명해야 한다. 관심 노출(역 MR인 경우 결과)에 할당된 변이를 기술하고, 각 변이에 대해 rsID 또는 염색체 기반좌표를 제시하며, 선정 이유, 참조 패널을 명확히 한다. 선정 이유에는 관심 노출/결과와의 관련성 근거, 대리지표(proxy) 사용할 때, 관련성불균형(linkage disequilibrium) 특성 등이 포함될 수 있다. 강한 관련성불균형에 있는 변이를 다수 포함하면 인과효과 추정에 추가 정보를 주지 못할 수 있고, 상관구조를 고려하지 않으면 표준오차 추정에 편향을 유발할 수 있다[47]. 독립 변이 선정 임계치(예: r^2), 참조 패널, 조사 인구를 명시한다. 다만 특정 유전자 영역의 생물학적 관련성이 분명한 경우, 관련성불균형이 있어도 포함할 수 있으며, 이때는 해당 변이가 관여하는 생물학적 경로, 포함 r^2 임계치, 상관구조 모형화 방법을 제시한다.

연구에서는 분석에 사용된 단일염기다형성(SNP)에 대한 품질 관리 매개변수 추정값도 제공해야 한다. 이 정보에는 정보점수(대입 품질 지표), 콜률(특정 SNP에서 대립유전자가 확인된 개체 비율), 하디-와인버그 평형 검정 P값(대입 또는 유전자형 분석 문제, 집단 분화, 비무작위 교배를 나타낼 수 있음)이 포함된다.

두 표본 MR 분석에서 유전 변이체 관리 및 데이터셋 조화를 도출하기 위해서는 추가 정보가 필요하다. 이 정보에는 양 데이터셋에 동일한 변이체가 존재하지 않을 경우 대리 변이체를 식별하는 데 사용된 조건(예: 관련성 불균형 임계값), 가닥 정렬의 유무 및 처리 방법, 효과 대립유전자와 비효과 대립유전자의 방향 등이 포함된다. 관련성의 시간적 안정성, 표본 특이성 또는 생물학적 타당성과 같은 다른 측면들은 선택된 유전 변이체가 도구변수로 사용될 수 있는 타당성을 이해하는 데 도움이 될 수 있다.

질병의 평가와 진단기준(항목 4d)

각 노출, 결과, 기타 관련 변수의 평가방법과 질병 진단기준을 기술한다.

예시—연속형 노출/결과

“연구 결과변수는 WHR(1 · 2b단계), 엉덩이 · 허리둘레(2a단계), 신체 구획별 지방량(3단계)… WHR은 허리둘레/엉덩이둘레 비로 정의했고, 둘레는 Seca 200 cm 줄자를 사용해 센티미터로 추정하였다… 구획별 지방량은 전신 저선량 X선 스캔인 DEXA로 그램 단위로 측정했으며, Lunar Prodigy 팬빔 스캐너(GE Healthcare)를 사용하였다. 훈련된 담당자가 표준 영상 · 자세 프로토콜에 따라 스캔했고, 모든 이미지는 훈련된 한 연구자가 표준화 절차로 DEXA 경계를 교정하였다[48].” (추가 예시는 Supplement 2 참조)

설명

분석에 사용한 핵심 노출 · 결과 · 혼란요인의 선택과 정의를 제시한다. 결과가 여러 개이거나 가설-비제한 접근(hypothesis-free)을 썼다면, 다중 검정을 처리하는 방법과 함께 명확히 밝혀야 한다. 메타분석의 경우 연구별 정의를 포함하거나, 선행 보고가 있다면 간단 요약+명확한 인용으로 대체할 수 있다. 독자는 사례 정의의 민감도 · 특이도를 고려해 적합성과 일반화 가능성을 평가할 수 있다.

윤리 승인과 동의(항목 4e)

해당될 경우, 윤리위원회 승인과 연구참여 동의의 세부를 제공한다.

예시

"모든 참가자로부터 사전 동의를 얻었고, 연구 프로토콜은 지역 · 기관 윤리위원회의 승인을 받았다[49]."

설명

모든 연구자는 2013년 개정 헬싱키 선언을 준수해 사람 대상 연구를 기획 · 수행 · 보고해야 한다[50]. 책임 윤리위원회의 승인과 동의 획득에 관한 정보를 제공해야 하며, 공개 데이터나 기존 연구의 데이터를 사용하는 경우에도 이를 명시한다. 연구가 원 윤리 승인 범위에 부합하고, 원 동의 조건을 위반하지 않도록 해야 한다.

가정(항목 5)

본 분석의 세 가지 핵심 도구변수 가정(관련성, 독립성, 배제제한)과 추가/민감도 분석에 필요한 추가 가정을 명시한다.

예시

"모든 MR 분석과 마찬가지로, 이 연구는 유전 도구가 관심 위험요인과 관련되고, 잠재 혼란요인과 독립이며, 대체 경로(다면발현)를 통해서가 아니라 위험요인을 통해서만 결과에 영향을 미친다는 가정을 전제하였다[51]."

"추가로, MR-Egger 회귀의 기울기는 다면발현을 보정한 인과추정치를 제공할 수 있다… 이 접근의 중요한 조건은 SNP의 노출과의 관련성이 그 SNP의 결과에 대한 직접효과와 독립적이어야 한다는 것으로, 이전에 InSIDE 가정으로 불렸다[52]."

설명

세 가지 핵심 가정을(이상적으로는 방법 파트에서) 명시하면 MR의 전제와 그 타당성 판단을 독자가 이해하는 데 도움이 된다. 가정은 연구 맥락에 맞는 직관적 언어로 풀어 쓰는 것이 바람직하다. 가정을 명확히 하면, 가정 점검과 민감도 분석의 설계 근거도 함께 제시된다.

도구변수 추정으로 효과추정치를 제시할 때는 네 번째 가정—보통 효과 균질성[53] 또는 단조성[54]—도 명시해야 한다. 많은 MR 연구는 전통적 도구변수 추정기(2SLS, Wald 등)를 보강하기 위해 다른 방법을 병행하며, 이 방법들의 고유 가정도 기술해야 한다. 예를 들어 MR-Egger 회귀[55]나 가중 중앙값 추정[56,57]은 다수 변이를 포함할 때 보조적으로 쓰인다. Box 2, Fig. 1, Box 3에서 도구변수 가정, 흔한 위반, 평가법을 더 자세히 제시한다.

Box 2. 멘델 무작위화(MR)의 범위와 STROBE-MR 체크리스트

핵심 IV 추정 가정과 추가 가정

대부분의 MR 연구는 노출이 결과에 미치는 인과효과를 검정하기 위해 세 가지 핵심 IV 가정—관련성, 독립성, 배제 제한—에 의존한다(Fig. 1, Box 3) [16]. 도구변수 접근으로 효과크기를 추정하려면 네 번째 가정, 보통 효과의 균질성(homogeneity)을 추가로 둔다[16,58-60]. 균질성 가정은 단조성(monotonicity) 가정—위험 대립유전자 수가 증가해도 어떤 개인에서도 노출

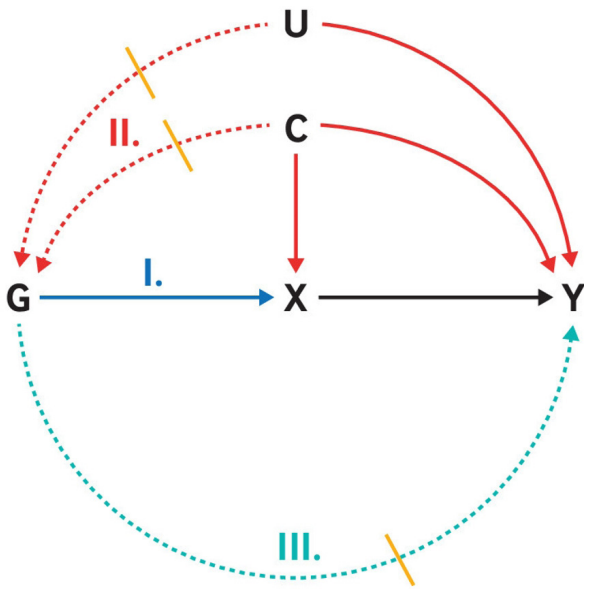

Fig. 1. 도구변수(IV) 분석의 가정을 보여 주는 표준 인과도. 유전변이 G를 노출 X의 도구변수(대리변수)로 사용해, 결과 Y에 대한 X의 인과효과를 평가한다. IV 가정은 다음과 같다: I. 관련성: 유전변이 G는 관심 노출 X와 관련되어 있다. II. 독립성: 유전변이 G는 결과 Y와 공유하는 미측정 원인이 없다. III. 배제 제한: 유전변이 G는 관심 노출 X에 대한 잠재적 효과를 통한 경우를 제외하고는 결과 Y에 영향을 미치지 않는다. 실선 화살표=인과효과; 점선 화살표=IV 가정에 의해 금지되는 인과효과. 참고로, IV 가정을 만족하는 인과도는 다른 방식으로도 그릴 수 있다(예: 유전변이 G가 노출 X를 직접 원인으로 하지 않아도 된다). 반대로, 도식에 그려지지 않은 다른 경로는 IV 가정을 위반할 수 있다(예: 선택 편향은 독립성 가정을 위반할 수 있음).

가능성이 낮아지지 않는다는 가정—으로 대체할 수도 있으며, 이 경우 연구 집단의 한 부분집단에 대한 효과를 추정하게 된다[61].

가정 위반

배제 제한은 때때로 "수평 다면발현 없음" 가정(Box 3)으로도 불리지만, 다음과 같은 여러 방식으로 위반될 수 있다: 유전자-노출 상호작용, 시간가변 노출, 도구와 관련된 노출 측정오차, 다성분 노출등[59]. 독립성 가정에 대한 우려는 흔히 조상/인구층화에 의한 교란에 초점이 맞춰지지만, 선택 · 콜라이더 편향, 가계(세대) 효과, 선택적 짝짓기(assortative mating)등으로도 위반될 수 있다[62-64]. 다수의 변이를 사용하는 분석에서는 이 가정들이 각 변이에 대해 성립해야 한다. 아래에 서술하듯, 일부 방법은 이러한 가정들을 완화할 수 있다.

추가 분석을 위한 가정

많은 MR 연구에서 도구변수 방법은 여러 방식으로 확장되어 왔다. 예를 들어 다수의 유전변이를 사용할 때, MR-Egger 회귀[55], 가중 중앙값[56], 가중 최빈값[57] 추정기를 보조적으로 쓰는 경우가 흔하다. MR-Egger 회귀는 배제 제한가정을 완화하는 대신, 노출을 통하지 않는 직접효과의 크기가 변이의 노출효과크기와 독립이어야 한다는 InSIDE 가정을 부과한다. 또한 두 표본 MR접근은 유전변이-노출 관련성이 두 표본에서 동일하다고 가정하는데, 표본이 성별 · 연령 · 민족 등 서로 다른 하위집단에서 추출된 경우에는 이 가정이 성립하지 않을 수 있다.

Box 3. 멘델 무작위화의 가정 평가와 민감도 분석

관련성(Relevance)

관련성 가정에 대해, 저자는 도구 강도를 어떻게 측정했는지 보고해야 한다. 개별 수준 자료가 있을 때 F 통계량을 보고하면 약한 도구 편향 위험을 이해하는 데 여러 이점이 있다[65]. 요약수준 자료만 있어도 F 통계량을 근사할 수 있다. 제안된 도구 강도가 낮다면, 약한 도구에 강한 접근법을 사용했는지 여부를 함께 보고해야 한다.

배제 제한(Exclusion restriction)

배제 제한 가정의 경우, MR-Egger 회귀[55]를 사용하면 특정 유형의 다면발현을 탐지할 수 있어, 배제 제한 위반의 정황증거를 제공한다. 다만 이 방법은 위에서 기술한 추가 가정(InSIDE)에 의존하고, 독립 변이 다수가 필요하다. 배제 제한을 점검하는 다른 접근으로 가중 중앙값[56]과 가중 최빈값[57] 방법이 있다. 음성 대조 결과/집단을 사용하는 것도 이 가정 평가에 도움될 수 있다[70]. 아울러 SNP의 알려진 생물학적 효과를 활용해 이 가정의 위반 가능성을 낮출 수 있다.

균질성(Homogeneity)

균질성 가정은 모든 개인에서 노출의 효과가 동일하다는 것을 요구하며, 직접 검증할 수 없다. 이를 뒷받침할 하나의 가능성은, 효과 추정치(또는 유전변이의 노출에 대한 효과)가 하위집단 간에 동일한지 확인하는 것이다[67,71]. 서로 다른 하위집단에서 의미 있는 차이가 관측되면, 층화 분석이나 보정 분석으로 이 가정을 완화할 수 있다[72]. 더 나아가, 연속형 결과의 분산이 유전 도구 수준에 따라 달라지는지 전반적으로 탐색해, 그 차이의 크기로 균질성 가정 위반의 정도를 가늠할 수 있다

공동 반증 전략(Joint falsification strategies)

일부 반증 전략은 가정들을 공동으로 평가한다. 다수의 유전변이를 도구로 사용할 때는, 개별 변이별 효과추정치의 이질성이 존재하는지 시험할 수 있다(Table 2의 '차이 검정' 참조). 이 검정은 흔히 배제 제한 평가로 이해되지만, 실제로는 배제 제한, 독립성, 균질성을 동시에 시험한다. 또 다른 비교적 단순한 공동검정은, 전통적 보정 접근으로 얻은 효과추정치와 MR 추정치를 비교하는 것이다[73]. 전통적 접근이 미측정 교란으로 편향되었고 그 방향이 예상 가능하다고 가정하면, MR 추정치가 그 예상 방향과 어떻게 부합하는지를 점검함으로써 MR 추정치의 기초 가정들의 공동 타당성을 뒷받침할 수 있다.

민감도 분석(Sensitivity analyses)

다수 변이를 사용하는 여러 추정기는 도구변수 가정을 서로 다른 방식으로 완화/적응한다(예: MR-Egger, 중앙값 기반, 최빈값 기반추정기). 따라서 각 접근으로 얻은 효과추정치들을 비교하면, 각 방법의 서로 겹치지 않는 가정들에 대한 결과의 민감도를 파악할 수 있다[74]. 필요에 따라 MR 추정치와 비-MR 추정치를 비교할 수도 있다. 결과의 견고성을 평가하기 위해, 독립 데이터셋이나 다른 설계(단일 표본, 두 표본)로 독립 재현을 수행하는 것을 권장한다.
역학의 전통적 편향 분석 기법도 MR에 쉽게 응용할 수 있다. 예컨대 교란 편향의 크기와 방향을 이해하기 위한 공식 기반 계산[59,67-69,75], 배제 제한 위반을 정량화하는 절차[59,76] 등이 있다. 선택 편향이 우려될 때는 가능한 편향의 크기·방향을 이해하기 위해 시뮬레이션을 자주 수행한다[64]. 또한 선택적 짝짓기[62], 가계(세대) 효과[9,63], 시간가변 효과[77]로 인해 유발될 수 있는 편향의 크기 · 방향을 파악하는 데도 시뮬레이션이 유용하다.

통계방법: 본 분석(항목 6)

사용한 통계방법과 통계치를 기술한다.

정량 변수(항목 6a)

분석에서 정량 변수를 어떻게 다루었는지(척도, 단위, 모형)를 기술한다.

예시

"각 메타분석의 효과크기는 주결과에서 25OHD[25-하이드록시비타민 D] 농도의 자연로그 변환 값 1표준편차(1-SD) 변화에 대한 효과로 보고하였다. 이 지표가 임의 차이보다 해석에 더 적합하기 때문이다… 1-SD 로그변환 25OHD 변화의 임상적 해석을 돕기 위해 비타민 D 상태의 세 임상 역치(<25 nmol/L 결핍, <50 nmol/L 불충분, >75 nmol/L 충분)를 선택하였다[78]."

설명

정량 변수(노출, 결과, 관련 공변량)에 가한 변환은 결과 해석과 타 연구와의 비교가능성에 영향을 주므로 명시해야 한다. 생물학적 지식이나 선행 근거를 근거로 군집화 · 범주화의 타당성을 제시하라. 가능하다면 추정치를 역변환해 일반적 단위로도 보고해 재현을 돕는다. 예를 들어, 효과 크기를 표준편차 변화로 보고하는 경우 명확성을 위해 표준편차의 크기를 함께 보고할 것을 권장한다.

유전변이(항목 6b)

유전변이를 분석에서 어떻게 다루었는지, 해당 시 가중치를 어떻게 선택했는지 기술한다.

예시

"우리는 GIANT 컨소시엄의 최신 GWAS 메타분석에서 BMI와 관련된 97개 유전변이를 기반으로 대립유전자 점수를 만들었다. 점수는 BMI-증가 대립유전자 개수의 합을, GIANT GWAS에서 보고된 효과크기(대립유전자 용량 1단위 증가당 BMI의 SD 변화)로 가중해 계산했고, 평균 0, SD 1이 되도록 표준화하였다. 점수가 높을수록 BMI가 높다[79]."

설명

대립유전자 점수(=유전위험점수, 다유전자 점수, 유전 예측점수)는 여러 변이를 하나로 요약한 변수다. 점수에 많은 변이를 포함할 경우, 도구변수 추정값의 편향 및 포괄 확률(coverage probability)은 2단계 최소제곱법 접근법(2 stage least squares approach)으로 얻은 추정값에 비해 개선된다[80]. 점수에 포함할 변이의 선정기준(외부 데이터 기반 여부 포함)을 명시한다. 점수는 가중/비가중일 수 있으며, 가중치가 있다면 동일 표본 산출인지 또는 독립 표본에서 가져왔는지 밝힌다. 변이-노출/변이-결과 관련성을 추정할 때 어떤 유전 모형(가산/승산)을 가정했는지도 보고한다. 가중치를 같은 표본(예: 단일 표본 MR)에서 추정하였다면, 과적합을 줄이기 위한 교차검증 · 잭나이프(jackknife) 등 절차를 보고한다.

MR 추정량(항목 6c)

사용한 MR 추정량(예: 2단계 최소제곱, Wald 비)과 관련 통계를 기술한다. 포함 공변량을 상세히 적고, 두 표본 MR이라면 두 표본에서 동일 공변량을 사용했는지도 보고한다.

예시

"모든 노출에 대한 유전 관련성은 당뇨병이 없는 유럽계 성인(n=108,557; 평균 50.6세; 남성 약 53%)을 대상으로 한 대규모 GWAS 메타분석에서 가져왔고, 연령 · 성별 · 연구지 · 지리 공변량을 보정한 가산 유전 모형을 사용하였다… MI(심근경색), 협심증, 심부전에 대한 유전 관련성은 성별별 분석에서는 연령 · 칩 종류 · 주성분 10개를 보정한 로지스틱 회귀, 전체 분석에서는 여기에 성별을 추가 보정하여 추정하였다. SNP별 Wald 추정치(결과에 대한 유전 관련성÷인슐린에 대한 유전 관련성)를 구한 뒤, 가법 랜덤효과 IVW로 메타분석하였다[81]."

설명

도구변수 추정량의 계산과 표준오차추정(정규근사, 부트스트랩 등)을 명확히 제시해야 한다. MR 분석에 사용한 공변량을 상세히 쓰고, 두 표본 MR에서는 변이-노출과 변이-결과 관련성의 보정 공변량 차이가 편향을 유발할 수 있음을 고려하여 이를 보고해야 한다.

결측자료(항목 6d)

결측자료를 어떻게 다뤘는지 설명한다.

예시

"분석은 베이지안 체계에서 수행해 자료 대치가 자연스럽게 가능하도록 하였다. 먼저 베이지안 완전사례 분석방법을 제시하고, 무작위결측 가정하에서 베이지안 모형에 통합 가능한 4가지 대치방법을 제안하였다… 우리는 CRP, 피브리노겐, 3개 SNP의 완전 또는 부분 자료가 있는 3,693명의 단면 기저선 자료를 사용하였다. 결측은 CRP 2.1%, 피브리노겐 2.4%, rs1205 10.8%, rs1130864 1.9%, rs1800947 2.6%였다[82]."

설명

여러 변이에 결측이 있으면 인과효과 추정의 정밀도가 저하

될 수 있다. 변수별 결측 비율과 대치 수행 여부, 대치 시 패널과 방법을 보고한다.

다중 검정(항목 6e)

해당하는 경우, 다중 검정을 어떻게 처리했는지 명시한다.

예시

"모든 암의 위험·사망에 대한 유의수준은 0.004로 설정하였다(6개 PUFA×2개 결과이므로 0.05를 12검정으로 보정)… 6개 개별 암을 추가로 고려할 때는 유의수준을 0.004/36=0.0001로 설정하였다[83]."

설명

다중 노출 또는 다중 결과를 포함하는 MR 분석에서 저자는 다중 검정 문제를 고려했는지 여부와 그 방법을 명시하고 그 근거를 제시해야 한다. 또한 통계적으로 독립적인 모든 노출 변수 또는 결과 변수에 대한 총 검정 횟수에 대한 보정이었는지 여부를 명시해야 한다. 이러한 보정에는 위 예시에서 설명한 바와 같이 거짓 발견률(false discovery rates), 본페로니 보정 또는 기타 기법의 보고가 포함될 수 있다.

가정의 평가(항목 7)

가정을 평가하거나 타당성을 정당화하기 위해 사용한 방법 또는 선행 지식을 기술한다.

예시 1

"MR은 R 패키지 ivpack의 2단계 최소제곱법으로 구현하였다. 공변량으로 연령과 성별을 포함하였다. 약한 도구 편향 위험을 평가하기 위해 1단계 회귀에서 대립유전자 점수–노출 관련성의 F 검정을 사용하였다… 표준 다변량 회귀와 비교해 도구변수 추정의 상대 편향을 평가하기 위해 confounding bias plot을 사용하였다… 초기 인과추정의 다면발현에 의한 편향 정도를 조사하기 위해 MR-Egger와 가중 중앙값 MR 두 가지 민감도 분석을 수행하였다… MR-Egger와 가중 중앙값 방법은 R 패키지 TwoSampleMR로 구현하였다[84]."

예시 2

"단백질 약물표적에 대한 MR은 구별되는 범주로 볼 이유가 있다… mRNA 발현을 제외하면, 단백질 발현이나 기능의 차이가 자연 유전변이의 가장 근접한 결과다. 이로 인해 표적 유전자 주변 변이는 다른 형질과 비교해 단백질 발현에 큰 효과를 보일 수 있고, 또한 전장유전체 다른 위치의 변이보다 수평 다면발현가정 위반에 덜 취약할 수 있다… 단백질 MR의 경우 크릭의 '중심원리'(gene→mRNA→protein)가 유전정보의 흐름 방향을 규정하며, 이는 질병 위험으로 이어지는 인과사슬의 더 먼 생물학적 형질에는 확장되지 않는다. 마지막으로, cis-MR은 유전자→암호화 단백질→질병 경로가 유전자→질병→단백질 경로보다 항상 우세하다는 점에서 역인과위험을 크게 줄인다(대개 유전자→단백질 관련성은 질병 없는 모집단에서 얻어지기 때문). 따라서 MR 관점에서 단백질은 다른 범주의 위험요인보다 특권적 위치에 있고, cis-MR은 질병에 대한 단백질의 인과효과를 도구화하는 최적 접근을 제공한다[85]."

설명

MR의 각 기초 가정에 대해, 이를 평가하거나 타당성을 뒷받침하기 위해 사용한 방법을 보고해야 한다. 주제 관련 배경지식으로 가정의 개연성을 뒷받침할 수 있다. 많은 가정은 검증은 어렵지만 반증을 시도할 방법이 있다. 관련성 가정에 따라, 저자들은 도구 강도를 어떻게 평가했는지 보고할 수 있다. 가능한 방법은 많지만 일부는 특정 상황(예: 이분형 노출)에만 적용 가능하다. Box 3은 흔하고 유용한 접근을 요약하고, Table 5는 가정 점검과 민감도 분석에 흔히 쓰이는 통계를 정리하였다. 처음 세 가지 핵심 가정은 단일 도구MR에도 해당하며, 도구변수 추정을 위해서는 추가 가정이 필요하다. 배제 제한은 MR-Egger와 같은 민감도 분석에서 완화될 수 있다.

이들 평가는 가능한 전략의 전부가 아니며, 모든 MR에 모든 민감도 분석이 필요한 것도 아니다. 예를 들어 F 통계는 본질적으로 도구변수 분석에서 중요하며, GWAS 산출물 기반 두 표본 MR에서는 설명분산과 근사적으로 일치한다. 측정된 공변량(연령, 성별, 인종/민족)과 하위집단별 효과추정은 단일 표본 MR에서 보고할 수 있으나, 두 표본 MR에서는 일반적으로 어렵다. 다만 성별 · 조상 특이 GWAS 요약통계가 점점 더 이용 가능해지고 있다. 더 포괄적인 검토는 Glymour 등[73], Labrecque와 Swanson [86]을 참조한다.

민감도 분석 및 추가 분석(항목 8)

수행한 민감도 분석 또는 추가 분석(예: 서로 다른 접근 간 효과추정 비교, 독립 재현, 편향 분석 기법, 도구 검증, 시뮬레이션 등)을 기술한다.

예시

교란(Confounding): "우리는 표준 다변량 회귀와 비교해 도구변수 추정의 상대 편향을 평가하기 위해 confounding bias plot을 사용하였다. 이 분석은 표준 회귀에서 특정 교란변수를 보정하는 경우와 보정하지 않는 경우의 차이를 살피듯, MR 분석에 내재한 편향의 크기를 정량화하도록 고안되었다. 추가로 보충분석에서 의심 교란요인을 공변량으로 포함하였다(Table 4). 고려한 교란변수는 유전 주성분 1–10, Townsend 박탈지수,

Table 5. 멘델 무작위화에서 가장 흔한 도구변수 가정과 가능한 평가 · 민감도 분석 예시

가정	가능한 평가 예시
관련성(Relevance): 유전변이는 관심 노출과 관련되어 있다	F 통계량을 보고한다.
독립성(Independence): 유전변이는 결과와 공유하는 미측정 원인이 없다	가능한 교란변수가 유전변이(들)과 결과 모두와 어떤 관련성을 보이는지 보고한다; 모집단 층화를 어떻게 보정했는지(예: 주성분 보정) 기술한다; 변이-결과 관련성에 대한 미측정 교란 민감도 지표를 제시한다[59,68,69,75].
배제 제한(Exclusion restriction): 유전변이는 관심 노출을 통한 경로를 제외하고는 결과에 영향을 미치지 않는다	MR-Egger 회귀의 기울기 추정치, 절편 및 그 95% 신뢰구간을 보고한다; 음성 대조 결과 또는 음성 대조 집단을 이용한 결과를 함께 제시한다.
균질성(Homogeneity, 2단계 최소제곱): 관심 노출의 인과효과는 결과에 대해 모든 개인에서 일정하다	서로 다른 측정 가능한 하위집단(예: 연령, 인종/민족, 성별, 사회경제적 지위)에 대한 도구변수 효과추정치를 보고한다; 연속형 결과의 경우, 도구 수준별 분산을 보고한다[72].
InSIDE (MR-Egger): 유전변이의 노출과의 관련성은 그 변이의 결과에 대한 직접효과와 독립적이어야 한다	이 가정을 요구하지 않는 다른 추정기(예: 중앙값 기반, 최빈값 기반검정)의 효과추정치도 함께 보고한다.

출생체중, 모유수유 여부, 출생지(북위 · 동경 좌표)였다."

수평(유전) 다면발현: "초기 인과추정의 다면발현에 따른 편향 정도를 확인하기 위해 MR-Egger와 가중 중앙값 MR 두 가지 민감도 분석을 수행하였다. MR-Egger는 도구-노출 관련성과 도구-결과 관련성을 같은 표본에서 계산한 연구(본 연구 주 분석과 같음)에는 타당하지 않다. 따라서 표본을 임의로 반분해 'A/B' 분할 표본 분석으로 MR-Egger를 수행하였다. 보충표에는 각 군에서 변이와 교육기간, 굴절이상의 관련성이 제시되어 있다. MR-Egger와 가중 중앙값 방법은 R 패키지 TwoSampleMR (https://github.com/MRCIEU/TwoSampleMR)로 구현하였다."

측정오차: "교육을 마친 연령 변수의 비정규 분포가 '교육기간-근시' 관련성을 인위적으로 만든 것이 아님을 확인하려고, 교육기간을 두 가지 방식으로 재부호화하였다: (1) 교육 종료 연령 >16세 vs. ≤16세로 이분화, (2) 대학(교)진학자 제외. 그런 다음 원래의 연속형 연령 변수를 쓴 분석과 결과를 비교하였다[87]."

다른 추가 분석 예시: "개별 변이 관련성 검정은 유전자 단위 검정과 S-PrediXcan 분석으로 보완하였다. 후자는 대마 사용군과 비사용군의 차등 유전자 발현을 확인하는 데 사용하였다. 또한 평생 대마 사용과 다른 형질(다른 물질 사용, 조현병 등 정신건강 형질) 간 유전 상관을 추정하였다. 마지막으로, 쌍방향 두 표본 MR을 수행해 '대마 사용→조현병 위험'과 '조현병 소인→대마 사용'의 인과 방향성에 대한 근거를 검토하였다[88]." (추가 예시는 Supplement 2 참조)

설명

민감도 분석은 기저 가정의 현실적 위반에 대해 견고성을 시험하고, 가능한 편향의 크기 · 방향을 가늠하게 해준다. 수행한 민감도 분석은 모두 보고해야 한다. 흔한 전략은 Box 3에 정리되어 있고, 추가 정보는 다른 자료에 제시되어 있다[55,74,86].

소프트웨어와 사전등록(항목 9)

통계 소프트웨어(항목 9a)

사용한 통계 소프트웨어와 패키지(버전 · 설정 포함)를 명시한다.

예시

"분석은 Stata v14 (StataCorp LP)와 R v3.4.3 (R Foundation)으로 수행하였다. MR 분석에는 Stata의 mrrobust패키지와 R의 TwoSampleMR 패키지를 사용하였다[89]."

설명

통계방법 · 소프트웨어는, 원자료에 접근 가능한 숙련 독자가 결과를 재현 검증할 수 있을 정도의 세부로 기술하는 것이 바람직하다. 가능한 경우, 사용한 분석코드를 온라인 저장소에 제공하는 것이 좋다.

사전등록(항목 9b)

연구 프로토콜의 사전등록 여부(언제 · 어디에)를 명시한다.

설명

사전등록을 하였다면 그 사실과 프로토콜 링크를 제시해야 한다. MR에서 사전등록은 아직 드물며, 2차 자료 분석의 특성상 어려움이 있다. 연구자 편향을 줄이기 위한 대안으로, "연구의 근거 · 가설 · 방법 · 분석계획을 사전 명세하고, 이를 제3자 레지스트리(예: OSF, https://osf.io/)나 학술지 Registered Report 형식으로 제출"하는 방안이 제안되어 왔다[90]. 이러한 방식의 넓은 채택은 MR 연구의 정확성 · 투명성 · 견고성을 높일 것이다.

결과

서술적 자료(항목 10)

참가자 수(항목 10a)

포함 연구의 각 단계에서 개체 수와 제외 사유를 보고한다. 흐름도 사용을 고려한다.

예시

"UK Biobank는 영국 전역 22개 평가센터에서 40–69세 502,664명을 모집하였다… 모든 참가자는 과거 교육 · 직업 자격을 포함하는 사회인구학 설문을 완료하였다. 모집 후반에는 안과 평가가 도입되었고, 전체의 약 23%가 이를 완료하였다… 최종적으로 69,798명이 유효한 교육, 굴절이상, 유전자료를 보유하였다[87] (Fig. 2)."

설명

연구 참가자 정보는 표적 모집단을 이해하고 결과의 타당성과 일반화 가능성을 평가하는 데 도움이 된다. 또한 연구 재현에 필요한 정보를 제공하고, 연구가 콜라이더 편향을 보일 가능성이 있는지 판단하는 데 유용하다. 데이터 출처에 개별 수준 자료가 포함되어 있다면, 저자는 연구에 포함된 참가자 정보를 보고해야 한다. 구체적으로, 연구 각 단계의 개인 수와 추가 분석에서 제외된 사유를 제시한다. 제외 사유의 예로는 추적 손실, 자료 부재로 인한 제외, 품질관리(QC) 등이 있다. 연구 표본이 어떻게 선정되었는지 신속히 보여 주기 위해, 가능한 경우 STROBE 흐름도를 포함하는 것이 좋다[26]. 또한 가능하면 변수별 결측값을 보고한다.

요약 통계(항목 10b)

표현형 노출, 결과, 기타 관련 변수에 대한 요약 통계(예: 평균, 표준편차, 비율)를 보고한다.

예시

"UK Biobank 표본은 여성이 53.7%였고(Table 1), 모집 당시 중앙연령은 58.0세(사분위범위, 51.0–63.0)였다. UK Biobank 표본에서 체지방(노출)과 흡연행태(결과) 변수의 분포는 Table 6과 Table 7에 제시하였다. 선행 연구와 같이, 현재 흡연자는 비흡연자에 비해 BMI가 낮았고(–0.22; 95% 신뢰구간, –0.27 to –0.16), 반대로 과거 흡연자는 현재 흡연자보다 BMI가 높았다(1.04; 95% 신뢰구간, 0.98 to 1.09) [51]."

노출, 결과, 그리고 기타 변수의 분포에 대한 정보는 집단 간

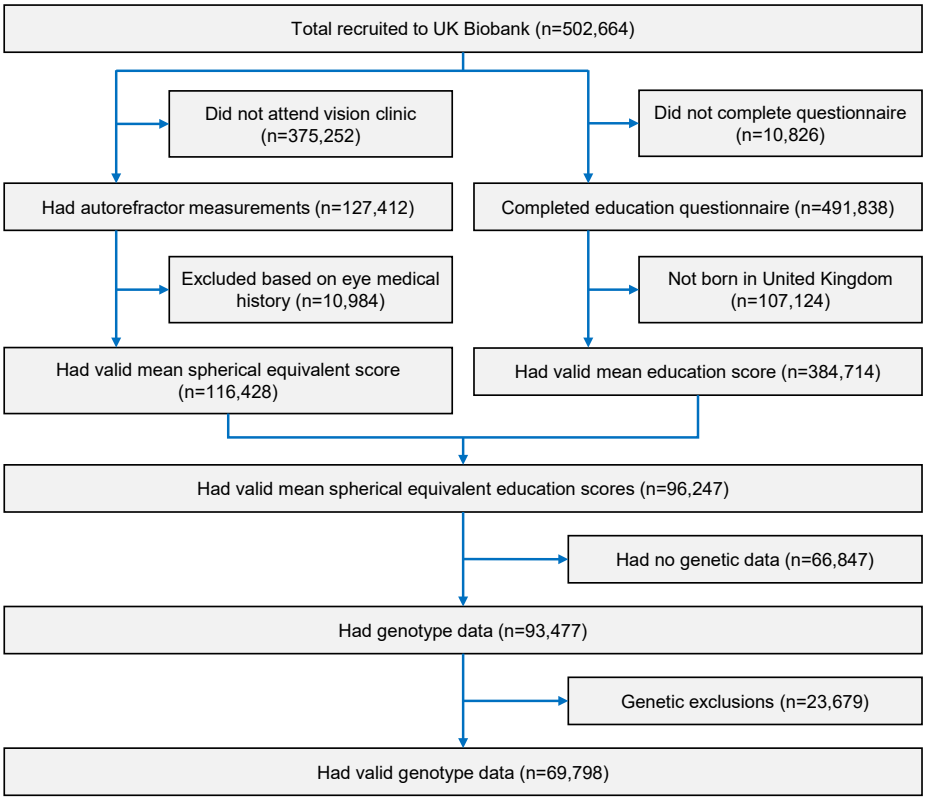

Fig. 2. 멘델 무작위화 연구 유효성 검증을 통과한 UK Biobank 참가자 수. 그림은 Mountjoy 등, 2018에서 허가받아 재수록함[87].

Table 6. UK 바이오뱅크에서 흡연 및 성별 범주별 신체 크기 매개변수의 표본 특성

신체지표	전체 (n=372,791)	비흡연 (n=203,735)	과거 흡연 (n=131,537)	현재 흡연 (n=37,519)	여성 (n=200,247)	남성 (n=172,544)
체질량지수(BMI)	27.4 (4.8)	27.1 (4.7)	28.0 (4.7)	27.0 (4.8)	27.0 (5.1)	27.9 (4.2)
체중(kg)	78.3 (15.9)	77.0 (15.6)	80.5 (16.0)	78.0 (16.3)	71.5 (13.9)	86.2 (14.3)
신장(cm)	168.8 (9.2)	168.3 (9.3)	169.4 (9.1)	169.5 (9.2)	162.7 (6.2)	175.9 (6.7)
허리둘레(cm)	90.4 (13.5)	88.8 (13.2)	92.6 (13.6)	91.2 (13.5)	84.6 (12.5)	97.1 (11.3)
체지방률(%)	31.4 (8.5)	31.5 (8.6)	31.7 (8.2)	29.9 (8.6)	36.6 (6.9)	25.3 (5.8)

데이터는 평균(표준편차)이다. Carreras-Torres 등, 2018 [51]으로부터 허가를 받아 재수록된 표.

Table 7. UK 바이오뱅크 평생 흡연자(현재 흡연자+이전 흡연자)의 체질량지수 및 성별 범주별 흡연 매개변수의 표본 특성

흡연 지표	전체 (n=169,056)	체질량지수(BMI) 범주				성별	
		저체중 (<18.5; n=816)	정상 (18.5-25.0; n=49,017)	과체중 (25.0-30.0; n=74,439)	비만 (>30.0; n=44,784)	여성 (n=81,091)	남성 (n=87,965)
흡연 시작 연령(세)	17.3 (4.2)	17.5 (4.8)	17.6 (4.2)	17.3 (4.2)	17.1 (4.3)	17.8 (4.4)	16.9 (4.0)
하루 평균 흡연 개비수—평생 흡연자(ever smokers)	18.4 (10.1)	16.6 (10.5)	15.9 (8.6)	18.2 (9.6)	21.1 (11.5)	16.1 (8.2)	20.5 (11.2)
하루 평균 흡연 개비수—현재 흡연자(current smokers)[a]	15.8 (8.4)	16.8 (11.1)	15.0 (8.2)	15.6 (8.1)	17.3 (9.0)	14.2 (7.3)	

데이터는 평균 (표준 편차)이다. Carreras-Torres 등, 2018 [51]으로부터 허가를 받아 재수록된 표.
BMI, body mass index.
[a]N=37519 현재 흡연자.

비교 가능성과 연구결과의 일반화 가능성을 판단하는 데 도움이 된다. 연속형 변수의 분포는 평균과 표준편차로 쉽게 요약할 수 있으며, 분포가 비대칭인 경우에는 중앙값과 분위수 범위(예: 25백분위수와 75백분위수)로 제시하는 것이 적절하다. 범주형 변수는 수와 백분율로 기술하는 것이 가장 적합하다. 기술통계는 각 범주별로 따로 제시할 때 독자가 집단 차이를 더 잘 평가할 수 있다. 집단 간 차이에 대한 통계적 추론은 본 분석에서 다루는 것이 바람직하다[26].

코호트 연구에서 결과가 사건(event)일 때, 연구자는 사건 수와 필요하다면 사건률(예: 인년당 사건 수)도 함께 보고해야 한다. 또한 평균, 중앙값, 총 추적기간 등 추적기간의 요약지표를 제시하여 사건이 기록된 기간을 이해할 수 있게 하는 것이 중요하다.

시간에 따라 변하는 결과(time-varying outcome)로 생존시간 자료가 있을 때는, 요약지표를 시간에 따라 제시해야 하며, 그림을 활용하면 전달에 도움이 된다. 환자-대조군 연구에서는 보통 요약지표를 환자군과 대조군에 분리하여 제시한다. 연속형 노출이나 결과를 범주별로 나누어 표로 제시하는 것도 유용할 수 있다[26].

이질성 평가(item 10c)

자료원에 기존 연구의 메타분석이 포함되어 있다면, 연구들 간 이질성에 대한 평가결과를 제공해야 한다.

예시

Table 8은 I^2 검정 통계량을 제시하여, 유전 변이가 결과에 미치는 효과의 이질성을 평가할 수 있게 한다.

설명

유전변이와 노출 또는 결과의 관련성이 일관되는지에 대한 근거는 효과의 이질성 정도를 이해하는 데 도움이 된다. 추정이 메타분석에 기반한다면, 포함된 연구 수를 함께 제시하여 이질성 검정이 그 존재를 탐지할 충분한 검정력을 가졌는지 판단할 수 있게 하는 것이 바람직하다. I^2 통계와 함께 95% 신뢰구간을 제시하는 것을 권장한다[91,92].

두 표본 멘델 무작위화(two-sample MR) (항목 10d)

두 표본 MR에서는 (1) 노출 표본과 결과 표본에서의 "유전변이-노출" 관련성이 유사하다는 근거를 제시하고, (2) 두 표본에 동시에 포함된 개인 수(노출 기준, 결과 기준)를 보고해야 한다.

Table 8. 골절과 관련된 전장유의(genome-wide significant) 단일염기다형성(SNP)

염색체 위치(locus)	후보 유전자 (candidate gene)	SNP	유전자까지 거리(kb)	EA	EAF	Odds ratio (95% CI), P			골절 사례 수 (no. of fracture cases)	I^2
						발견 단계[a)]	검증 단계[a)]	통합[a)]		
2p16.2	SPTBN1	rs4233949	-23.21	G	0.61	1.03 (1.02–1.05), 6.9×10^{-5}	1.04 (1.05–1.05), 8.9×10^{-11}	1.03 (1.02–1.04), 2.8×10^{-14}	185,057	22.4
3p22.1	CTNNB1	rs430727	107.2	T	0.45	1.03 (1.02–1.05), 1.0×10^{-4}	1.03 (1.02–1.04), 1.1×10^{-8}	1.03 (1.02–1.04), 5.0×10^{-12}	185,057	0
6q22.33	RSPO3	rs10457487	0	C	0.51	1.06 (1.05–1.08), 2.3×10^{-15}	1.04 (1.03–1.05), 1.7×10^{-15}	1.05 (1.04–1.06), 4.8×10^{-28}	185,057	5
6q25.1	ESR1	rs2982570	0	C	0.58	1.05 (1.04–1.07), 8.1×10^{-12}	1.03 (1.02–1.04), 5.2×10^{-10}	1.04 (1.03–1.05), 4.5×10^{-19}	185,057	23
7q31.31	WNT16, CPED1	rs2908007	-3.25, 24.67	A	0.60	1.08 (1.06–1.10), 1.2×10^{-20}	1.05 (1.04–1.06), 5.6×10^{-22}	1.06 (1.05–1.07), 2.3×10^{-39}	185,055	0
7q21.3	C7orf76, SHFM1	rs6465508	0, 0	G	0.34	1.05 (1.03–1.07), 4.0×10^{-9}	1.04 (1.03–1.05), 4.1×10^{-12}	1.04 (1.03–1.05), 2.0×10^{-19}	185,056	35
7p14.1	STARD3NL	rs6959212	-89.01	T	0.34	1.04 (1.02–1.06), 6.9×10^{-6}	1.02 (1.01–1.04), 1.1×10^{-5}	1.03 (1.02–1.04), 8.8×10^{-10}	185,057	15.6
7p12.1	GRB10, COBL	rs1548607	40.33, -182.4	G	0.32	1.05 (1.03–1.07), 3.2×10^{-8}	1.02 (1.01–1.04), 2.1×10^{-4}	1.03 (1.02–1.05), 4.7×10^{-10}	185,052	40
9q34.11	FUBP3	rs7851693	0	G	0.35	1.03 (1.01–1.06), 1.3×10^{-4}	1.05 (1.06–1.06), 4.8×10^{-16}	1.04 (1.03–1.05), 5.0×10^{-19}	185,057	23.5
10q21.1	MBL2/DKK1	rs11003047	-90.63	G	0.11	1.09 (1.07–1.12), 6.2×10^{-12}	1.08 (1.07–1.10), 1.4×10^{-21}	1.09 (1.07–1.10), 9.5×10^{-33}	185,057	0
11q13.2	LRP5	rs3736228	0	T	0.15	1.05 (1.03–1.07), 3.0×10^{-5}	1.07 (1.05–1.08), 2.8×10^{-18}	1.06 (1.05–1.08), 1.0×10^{-21}	185,056	24.6
14q32.12	RPS6KA5	rs1286083	0	T	0.82	1.04 (1.02–1.06), 8.8×10^{-5}	1.05 (1.04–1.07), 3.0×10^{-14}	1.05 (1.04–1.06), 1.6×10^{-17}	185,085	43.3
17q21.31	SOST, DUSP3, MEOX1	rs2741856	-4.26, -16.65, 88.02	G	0.92	1.11 (1.08–1.14), 2.4×10^{-12}	1.08 (1.06–1.11), 5.3×10^{-15}	1.10 (1.07–1.11), 3.1×10^{-25}	184,977	0
18p11.21	FAM210A, RNMT	rs4635400	0, -7.149	A	0.36	1.06 (1.04–1.07), 1.5×10^{-12}	1.03 (1.02–1.04), 2.7×10^{-9}	1.04 (1.03–1.05), 1.1×10^{-18}	185,057	22
21q22.2	ETS2	rs9980072	141.9	G	0.73	1.06 (1.04–1.08), 8.4×10^{-12}	1.03 (1.01–1.04), 1.8×10^{-5}	1.04 (1.03–1.05), 3.4×10^{-13}	185,057	36

Trajanoska 등(2018)의 자료를 허가를 받아 재인용한 것이다[41].

SNP, single nucleotide polymorphism; EA, effect allele(효과 대립유전자); EAF, effect allele frequency(효과 대립유전자 빈도); I^2, 이질성 지수(index of heterogeneity).

[a)]발견 단계(discovery stage): 사례 37,857명, 대조군 227,116명; 검증 단계(replication stage): 사례 147,200명, 대조군 150,085명; 통합(Combined): 사례 185,057명, 대조군 377,201명.

예시 1

"MR에 사용된 유전변이는 유럽인에서 수행된 담석증 GWAS에서 얻었다. 인도 인구와 유럽 인구 간에 해당 변이들의 대립유전자 빈도, 담석증 및 담낭암(gallbladder cancer, GBC) 위험을 비교했으며, 결과는 보충표 1에 제시하였다. 두 인구의 대립유전자 빈도는 전반적으로 유사하였으나, 일부 SNP에서는 뚜렷한 차이를 보였다(예: rs601338, rs1260326, rs174567, rs2469991, rs2290846; 소수 대립유전자 빈도 차이 >15%). 인도 인구에서의 담석증 및 GBC 위험 방향은 대체로 유사했으며, 담석증 관련 SNP의 80%, GBC 관련 SNP의 70%에서 위험 증가 방향이 일치하였다[93]."

설명 1

두 표본 MR 분석은 두 표본에서의 SNP-노출 관련성이 유사하다는 가정을 전제한다. 이는 두 표본이 동일한 기반 모집단에서 추출되었다는 가정과 유사하다. 다만 인종과 같은 특성만이 유일한 고려 요소는 아니다. 예를 들어 폐경 전 여성과 폐경 후 여성 간, 또는 지역사회 기반 표본과 고위험 표본 간에 유전 관련성이 추정되었다면, 표본 유사성이 깨질 수 있다. 이러한 가정을 단정하기 어렵다면, 가능한 경우 두 표본에서의 SNP-노출 및 SNP-결과 관련성을 비교하여 평가해야 한다. 두 표본에서 관련성이 유사하다면, SNP-노출/결과 관련성의 이질성이 편향을 일으킬 가능성은 낮아진다. 또한 저자는 노출과 결과 각각에 대해 두 표본에 중복 포함된 개인 수를 보고해야 한다.

예시 2

"이들 GWAS 추정치는 참가자 중복을 피하기 위해 UK Biobank 참여자를 포함하지 않은 연구에서 선택하였고, 그 결과 앞서 기술한 두 표본 멘델 무작위화에 사용된 GWAS 및 도구 변수가 일부 경우에서 상이하였다[89]."

설명 2

동일하거나 유사한 개인을 사용해 SNP-노출과 SNP-결과 관련성을 동시에 추정하면, 발견 표본에서 통계적으로 가장 강한 관련성(대개 P값 기준)을 선택하는 과정에서 '승자의 저주'로 인한 편향이 발생할 수 있다[94,95]. 이 편향은 SNP 선택과 SNP-결과 추정을 완전히 분리된 표본에서 수행함으로써 줄일 수 있다. 편향의 크기는 두 집단에 중복 포함된 개인 수에 선형적으로 비례하므로, 중복이 소량이면 영향이 크지 않을 수 있다[94].

주요 결과(항목 11)

유전변이 관련성(항목 11a)

유전변이와 노출, 그리고 유전변이와 결과 간의 관련성을 해석 가능한 척도로 보고하는 것이 바람직하다.

예시

"12개의 BMI 관련 SNP로 구성한 BMI 대립유전자 점수는 BMI와 용량-반응 양의 관련성을 보였다(점수 1단위 증가당 0.14% [0.12%–0.16%], $P=6.30\times10^{-62}$). 이 점수는 25(OH)D 농도와도 관련되었다(점수 1단위 증가당 −0.06% [−0.20% to −0.02%], P=0.004) [40]."

설명

유전변이와 노출 간 관련성 보고는 관련성 가정(항목 8b)을 평가하는 데 필수이다. 유전자형 분포에 따른 노출 수준 비교는 유전 효과의 단조성과 선형성을 가늠하는 데도 도움이 된다. 유전변이와 결과의 관련성 보고는 노출-결과 간 인과 관련 가능성에 대한 초기 단서를 제공할 수 있다.

멘델 무작위화 추정치(항목 11b)

노출과 결과 간 관련성에 대한 MR 추정치와 불확실성 지표를, 표준편차 1단위당 오즈비 또는 상대위험도처럼 해석 가능한 척도로 보고한다.

예시

"유전적으로 예측된 BMI가 1표준편차 증가할 때 관상동맥질환(coronary artery disease, CAD)의 오즈비는 1.49 (95% CI, 1.39–1.60)였다[96]."

설명

도구변수 가정이 반증되지 않고 전반적으로 지지되거나(항목 8b), 민감도 분석이 가정 위반에 견고하다면, MR 추정치는 상대위험도나 위험차 등 직관적 척도로 의미 있게 보고할 수 있다. 반면 균질성 및 단조성 가정이 성립하지 않으면, 추정치 보고를 지양하고 비영(非零) 효과에 대한 검정으로 대체하는 것이 바람직할 수 있다.

절대위험 계산(항목 11c)

적절하다면, 상대위험 추정치를 임상적으로 의미 있는 기간의 절대위험으로 변환하여 제시하는 것을 고려한다.

예시

"NPC1L1 좌위의 LDL 콜레스테롤 저하 대립유전자는 관상동맥질환과 역의 관련성을 보였다(유전적으로 예측된 LDL-C 1 mmol/L [38.7 mg/dL] 감소당 OR, 0.61; 95% CI, 0.42–0.88; P=0.008). 반면, 제2형 당뇨병과는 개별-집합 모두에서 양의 관련성을 보였다(동일 감소당 OR, 2.42; 95% CI, 1.70–3.43; P<0.001;

절대위험차 추정치, 1,000인-연당 5.3건 증가) [97]."

설명

기저위험을 고려하면, 상대위험보다 절대위험(또는 위험차)으로 제시하는 편이 임상적으로 더 해석 가능할 때가 있다. 절대위험은 특정 기간 동안 노출로 귀속 가능한 초과질환량을 추정하게 하며, 이를 통해 노출을 줄이는 중재의 절대 이득을 산출할 수 있다.

결과 시각화(항목 11d)

포레스트 플롯, 유전변이-노출 관련성 대비 유전변이-결과 관련성 산점도 등 도표를 활용해 결과를 시각화하는 것을 고려한다[98] (Fig. 3).

예시

예시는 Fig. 3에 제시되어 있다.

설명

도구변수 가정 위반 가능성을 살피는 데 도표가 유용하다. 특히 배제 제한(exclusion restriction) 가정 점검에 도움이 된다. 저자는 유전변이별로 노출 및 결과와의 관련성을 각각 보고해야 하며, 산점도나 퍼널 플롯(funnel plot)으로 제시할 수 있다[55]. 산점도는 유전효과와 노출의 관련성 대비 유전효과와 결과의 관련성을 나타내며, 직선의 기울기는 추정된 인과효과를, 절편은 원점에 고정된다(단, MR-Egger 회귀는 예외; 항목 8b). 퍼널 플롯은 변이별 인과효과 추정치를 정밀도에 대비해 그려 비대칭성을 시각적으로 점검하는 데 쓰이며, 비대칭성은 수평 다면발현의 단서일 수 있다[55]. 각 유전변인으로부터 얻은 인과추정치를 나열하는 포레스트 플롯은 전체 인과추정치 주변의 이질성을 시각적으로 점검하게 한다[84].

가정 평가(항목 12)

가정의 타당성(항목 12a)

가정의 타당성 평가결과를 보고한다.

예시—관련성(relevance) 가정

"근시 대립유전자 점수는 영국 바이오뱅크 참가자의 평균 구면 굴절오차 분산의 4.32% (F=3155)를 설명했고, 교육 대립유전자 점수는 교육에 사용한 시간의 분산 0.71% (F=464)를 설명하였다. 두 점수는 각각 교육시간과 근시와의 강한 관련성을 보여, 멘델 무작위화 추론에 쓸 수 있는 강한 집합 도구변수로 구성할 수 있었다. 큰 F 통계량은 약한 도구 편향이 문제되지 않을 것임을 시사하였다[87]."

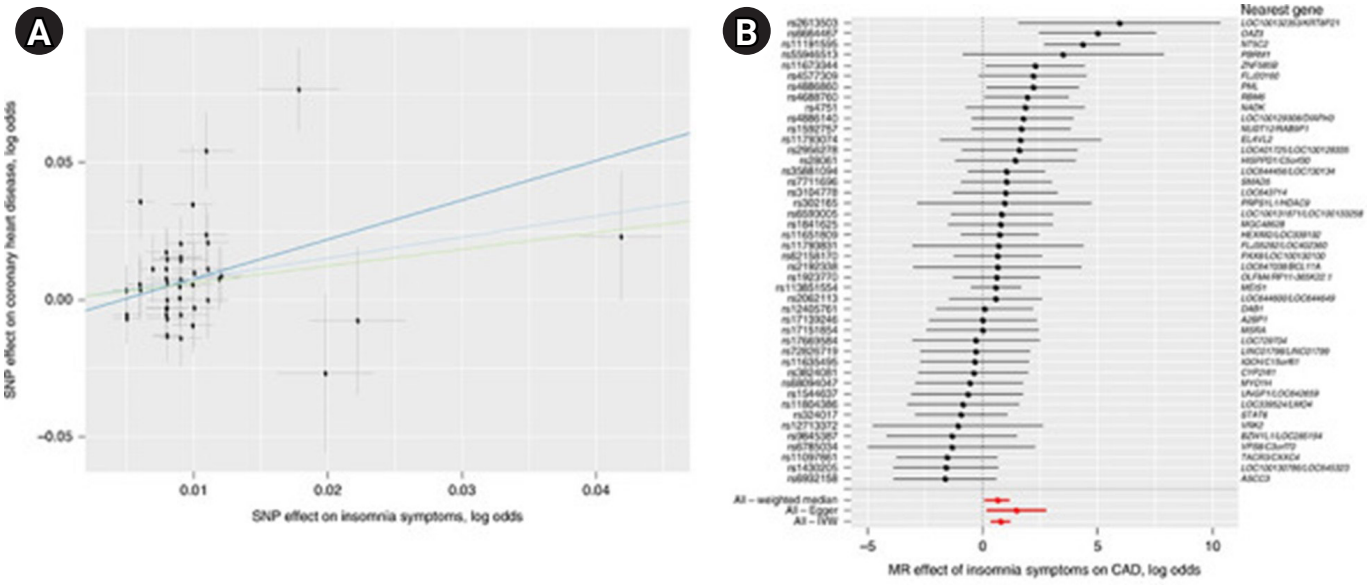

Fig. 3. "불면 증상의 인과적 관계. (A) 잦은 불면 증상과 관련된 SNP와 관상동맥질환(CAD) 간의 관련성을 제시한다. 각 대립유전자(allele)당 잦은 불면 증상 위험과의 관련성(가로축) 대비, 각 대립유전자당 CAD 위험과의 관련성(세로축)을 산점도로 표시하였으며, 각 점을 둘러싼 검은색 세로 · 가로 선은 각 다형성의 95% 신뢰구간(CI)을 나타낸다. 세 가지 서로 다른 MR 관련성 검정결과를 함께 제시한다. (B) 유전적으로 증가한 불면 위험이 CAD에 미치는 효과 추정치를 포레스트 플롯으로 제시한다. 가장 가까운 유전자는 플롯 오른쪽에 표시한다. 각 SNP에 대해 추정치의 95% CI(회색 선분)와 IVW MR, MR-Egger, 가중 중앙값(weighted-median) MR 결과(빨간색)를 함께 제시한다. MR 분석에 사용한 각 GWAS의 표본 크기는 다음과 같다: 잦은 불면 증상(사례 n=129,270; 대조군 n=108,352), CAD(사례 n=60,801; 대조군 n=123,504)." 도판은 Lane 등(2019)에서 허가를 받아 재인용하였다[98].

예시—독립성(independence) 가정

"교육시간과 근시에 대한 대립유전자 점수와 잠재 혼란요인 간 관련성을 시험한 결과, 영국 북향 거리(northing) 좌표는 교육시간과 음의 관련성(β=−1.6e−6; 95% CI, −1.8e−6 to −1.5e−6), 굴절오차와 양의 관련성(β=1.2e−6; 95% CI, 9.8e−7 to 1.3e−6)을 보였다. 노딩은 교육시간(P=7e−5)과 근시(P=6e−3) 대립유전자 점수와도 관련되었다(보충표 2 참조). 표준 회귀와 비교했을 때, 혼란 편향 플롯은 도구변수 분석에 노딩을 포함하면 교육 점수에서는 더 큰 편향을, 근시 점수에서는 그렇지 않을 것을 시사하였다[87]."

예시—배제 제한(exclusion restriction) 가정

"MR-Egger, 가중 모드, 가중 중앙값 방법은 모두 크기와 방향에서 유사한 인과추정치를 보였고, 교육시간이 증가할수록 근시 굴절오차가 더 근시 방향으로 이동하였다(−0.17 to −0.40 디옵터/년). 반면, 근시가 교육시간을 늘린다는 근거는 적었다… Egger 절편은 교육→근시(절편=0.007, SE=0.006, P=0.2)나 근시→교육(절편=−0.002, SE=0.007, P=0.8) 모두에서 0과 유의하게 다르지 않았고, 방향성 유전 다면발현의 근거가 적음을 시사하였다[87]."

예시—균질성(homogeneity)

"유전적으로 예측된 BMI와 전체 사망률 사이에서 J자 형태의 관계를 관찰하였다. 이 곡선은 영국 바이오뱅크에서 더 뚜렷했고, 저체중과 과체중/비만에서 위험이 높았다. 전체 인구에서 최소 위험은 HUNT 연구에서는 BMI 약 22–23 kg/m^2, 영국 바이오뱅크에서는 약 25 kg/m^{2}였다[99]."

설명

저자는 항목 7과 Box 3에서 기술한 바와 같이 도구변수 가정의 타당성 평가결과를 보고해야 한다. 위 예시는 가능한 평가의 일부일 뿐이며, 모든 평가 또는 가정을 포괄하지는 않는다.

추가 통계(항목 12b)

이질성(I^2, Q 통계량)이나 E-value 등 추가 통계를 보고한다.

예시

"이질성(각 SNP 효과의 분산) 존재 여부를 점검하기 위해 Cochran의 Q와 I^2 통계를 계산하였다. BMI와 웰빙 간 관련성에서는 이질성의 근거가 적었다(자세한 내용은 보충표 S8) [39]."

"Chen 등은 ALDH2 유전자의 단일 변이를 이용해 음주가 고혈압 위험에 미치는 영향을 연구하였다. 남성에서 변이–고혈압 관련성에 대한 오즈비는 2.42였고, E-value는 4.27이었다. 신뢰구간 하한(1.66)에 대한 E-value는 2.71이었다. 분석이 민족적으로 동질적인 아시아 인구에서 수행되었으므로, 이 E-value는 잔여 인종 혼란이 효과를 소거할 가능성이 낮음을 합리적으로 시사한다[69]."

설명

Cochran의 Q와 I^2 통계는 각 유전변인으로 추정한 인과효과의 이질성을 평가하는 데 쓰인다[100]. 이질성이 관찰되면, 제안된 도구 중 하나 이상에서 도구변수 가정이 성립하지 않을 수 있음을 의미한다. E-value는 미측정 혼란이 결과를 설명할 수 있는 정도를 정량화한다[69]. E-value가 크면, 특히 조상효과에 의한 혼란이 비영효과를 설명할 가능성이 낮음을 보강한다.

민감도 분석 및 추가 분석(항목 13)

주요 결과에 대한 민감도 분석(항목 13a)

가정 위반에 대한 결과의 견고성을 평가하기 위해 수행한 민감도 분석을 보고한다.

예시

"고정효과 역분산가중 및 Egger 회귀 추정치는 CRP가 CAD 위험에 역의 인과효과를 시사한다(표 1). 그러나 대응하는 랜덤효과 분석은 설득력 있는 인과효과의 근거가 없음을 시사한다. 더 나아가 단순 중앙값 추정치는 반대 방향이었다. 이는 가장 강한 유전변이는 음의 인과추정치를 보였지만, 다수의 유전변이는 양의 인과추정치를 보였기 때문이다. 방법 간 불일치는 CRP의 전장유의 변이들이 모두 유효한 도구가 아님을 시사하며, 이에 근거한 인과결론은 신뢰하기 어렵다[74]."

설명

Box 3과 7장에서 설명한 다양한 접근으로 얻은 결과를 보고·비교해, 도구변수 가정 위반에 대한 결론의 견고성을 평가해야 한다. 모든 접근의 결과가 대체로 일치하면, 효과의 존재와 크기에 대한 결론에 더 큰 확신을 가질 수 있다.

기타 분석(항목 13b)

독립 재현, 도구 검증, 시뮬레이션 등 수행한 추가 분석의 결과를 보고한다.

예시—독립 재현

"유전적으로 예측된 체질량지수와 허리둘레의 '흡연자일 위험'과의 관련성은 TAG 데이터에서 재현되었다(각각 1.19 [1.06–1.33], 1.32 [1.15–1.52]) [51]."

예시—도구 검증

"MR-PRESSO는 심부전에서 1개, 관상동맥질환에서 6개, 동맥성 고혈압에서 11개의 이상치(outlier) SNP를 확인하였다. 이상치 보정은 심부전(1.13; 95% CI, 1.08–1.17), 관상동맥질환(1.08; 95% CI, 1.06–1.10), 동맥성 고혈압(1.10; 95% CI, 1.08–1.12)의 OR 추정치를 실질적으로 변화시키지 않았다. 다른 결과에 대한 MR-PRESSO 분석에서는 이상치 SNP가 확인되지 않았다[101]."

예시—시뮬레이션

"그림 2는 X와 Y에 대해 양의 교형질 특성 짝짓기(cross-trait assortative mating)가 있을 때 two-stage least squares regression methods (TSLS)가 양의 편향을 보임을 보여준다. 편향은 짝짓기 정도가 커질수록 비례해 증가하였다. 반면, TSLS (2)(부모 대립유전자 점수 보정)와 TSLS (3)(개인 · 부모 효과를 공동 모형화하고 비전달[parental non-transmitted] 대립유전자 점수를 부모 표현형의 도구로 사용)은 편향이 없었고, 위양성률은 약 5%였다[62]."

설명

독립 재현, 도구 검증, 시뮬레이션 연구 등 수행한 민감도 · 추가 분석결과는 항목 8에서 설명한 바에 따라 보고해야 한다.

인과 방향성(항목 13c)

인과 방향성 평가(예: 양방향 MR)를 보고한다.

예시

"BMI 대립유전자 점수는 25(OH)D 농도와도 관련되었다(점수 1단위 증가당 −0.06% [−0.10% to −0.02%], P=0.004). 반면, 비타민 D 합성 또는 대사 대립유전자 점수는 BMI와 관련성을 보이지 않았다(합성 점수: 대립유전자 1단위당 0.01% [−0.17% to 0.20%], P=0.88; 대사 점수: 0.17% [−0.02% to 0.35%], P=0.08) [40]."

설명

양방향 MR은 노출과 결과 각각에 관련된 독립 유전변이 집합을 사용해 양방향의 인과성을 평가하는 방법이다[102].

비-MR 분석과의 비교(항목 13d)

관련될 때, 비-MR 분석의 추정치와 비교 · 보고한다.

예시

"Durbin-Wu-Hausman 내생성(endogeneity) 검정에서, 교육시간 대립유전자 점수를 이용한 도구변수 추정치는 관찰연구의 점추정치와 차이가 있다는 약한 근거가 있었다(P=0.06). 도구변수 추정치는 더 큰 음의 관련성을 시사하였다[87]."

설명

MR 추정치와 비-MR 추정치 사이의 중요한 차이를 기술해야 한다. 연구설계마다 편향의 종류와 통계적 검정력이 다르다. MR 결과를 기존 연구 맥락과 함께 제시하면, 독자들이 MR의 장단점이 기존 증거를 지지하거나 반박하는 결과를 도출할 수 있는지 이해하는 데 도움이 될 것이다. 일반적으로 인과추론은 삼각측량(triangulation) 틀에서, 여러 접근의 근거를 종합해 제시할 수 있다[103,104].

결과의 추가 시각화(항목 13e)

추가 도표(예: leave-one-out 분석)를 고려한다.

예시

"Leave-one-out 분석: 각 행은 Locke 등에서 이용 가능한 전장유의 SNP 중 y축에 표시한 SNP 1개를 제외하고 수행한 'BMI→주관적 웰빙' 두 표본 MR 분석을 나타낸다. 점은 해당 SNP를 제외했을 때의 효과크기, 선은 표준오차를 나타낸다. MR-Base를 사용해 특정 SNP가 BMI–웰빙 관련성을 주도하는지 확인하였다… 가장 큰 공헌을 보인 SNP는 염색체 16, fat mass and obesity associated (FTO) 유전자의 두 번째 인트론에 위치한 rs1421085였다. FTO는 여러 인구에서 비만과 반복적으로 관련되었으나, 인트론 SNP의 생물학적 결과는 아직 불확실하다. 현재로서는 시상하부에서 FTO 발현을 조절하는 역할을 하는 것으로 여겨진다. FTO의 큰 효과크기와 견고한 관련성은, 이 유전자가 다면발현 때문이 아니라 BMI 효과크기 때문에 두 표본 MR에서 가장 큰 영향을 주었음을 시사한다[39]." (Fig. 4, Supplement 2).

설명

추가 도표는 결과를 시각화하고, 가정 위반을 평가하며, 영향력이 큰 점이나 이상치를 탐지하는 데에도 도움이 된다. 여기에 한 개 제외법 플롯(leave-one-out plot) [84], 방사형플롯 (radial plot) [105], 그리고 각 유전변이에 대해 스튜던타이즈 잔차(studentized residuals)나 Cook 거리 플롯(Cook's distance for outlier assessment) [32]이 포함된다.

고찰(Discussion)

고찰은 연구 해석과 타당성에 관한 핵심 이슈를 다루어야 한다[106]. 구조화된 고찰은 저자가 결과를 과도하게 해석하는 것을 피하게 하고, 독자에게 안내 역할을 할 수 있다[107,108].

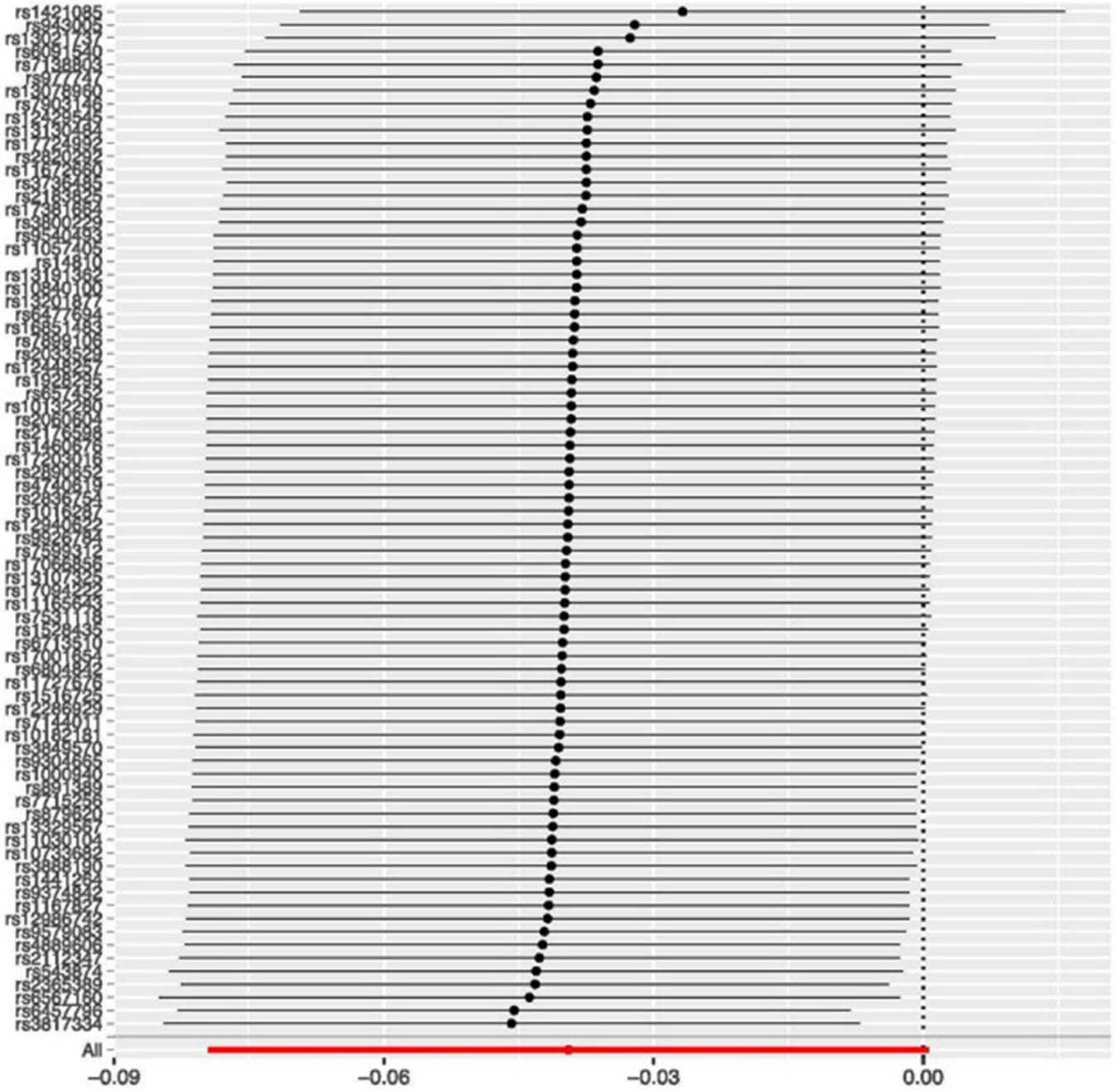

Fig. 4. Leave-one-out 분석. 도판은 Wootton 등(2018)에서 허가를 받아 재인용하였다[39].

핵심 결과(항목 14)

연구목적과 연계하여 핵심 결과를 요약한다.

예시

"약 45만 명의 포괄적 유전 자료를 바탕으로, 이 연구는 체질량지수와 체지방 분포의 차이가 흡연 행동의 여러 측면(흡연 시작 위험, 흡연 강도, 금연)에 인과적으로 영향을 준다는 근거를 제시한다. 이 결과는 비만이 흡연 시작과 금연에 미치는 역할을 부각하며, 관련 위험요인의 중요성을 낮추려는 공중보건 중재에 시사점을 제공한다[51]."

설명

고찰은 주요 결과 요약과 그 중요성에 대한 진술로 시작하는 것이 바람직하다. 이 부분은 연구질문과 1차 결과를 상기시켜 주고, 이어지는 해석이 결과와 일관적인지 독자가 평가하게 돕는다. 요약은 주요 연구목적의 관점에서 작성하고, 사전에 설정

한 가설에 초점을 맞추며, 해당 모집단에서 조사한 인과 관련성의 추정치를 보고하는 것이 바람직하다[107].

한계(항목 15)

도구변수 가정의 타당성, 기타 잠재적 편향원, 불정확성을 고려하여 연구의 한계를 논의한다. 잠재적 편향의 방향과 크기, 이를 완화하려 한 노력도 함께 기술한다.

예시

"모든 MR 분석과 마찬가지로, 이 연구도 유전도구가 관심 위험요인과 관련되고, 잠재 혼란요인과 독립이며, 대체경로(다면발현)를 통하지 않고 위험요인을 통해서만 결과에 영향을 준다는 가정을 전제하였다. 첫 번째 가정은 각 비만지표에 대해 가장 큰 GWAS에서 강건하게 관련된 변이를 사용함으로써 충족되었다. 나머지 두 가정의 충족 여부는 직접 검증하기 어렵지만, 광범위한 민감도 분석에서 뚜렷한 위반의 근거는 없었다. 둘째, 사회인구학적 요인에 의한 모집단 층화가 잠재 혼란요인이 될 수 있었다. 실제로 이전 연구에서 BMI 도구는 여성에서 사회계층 관련 요인(가계소득 낮음, 박탈감 높음 등)과 관련되었다. 그러나 남성에서는 그러한 관련성이 관찰되지 않았다. 우리 연구에서는 비만도구와 '흡연 시작' 및 '흡연 강도'의 관련성이 남녀 각각에서, 그리고 사회적 박탈감과 연결되었을 가능성이 있는 SNP를 제외했을 때에도 일관되게 관찰되었다. 따라서 여성에서만 관찰된 '체지방률–금연' 역관련성을 제외하면, 사회인구학적 요인에 의한 층화가 이러한 결과를 설명할 가능성은 낮아 보인다(추가 예시는 Supplement 2 참조) [51]."

설명

저자는 경험적으로 완전히 검증하기 어려운 가정이 많다는 점을 고려하여, 모든 도구변수 가정의 개연성을 다루어야 한다. 예를 들어, (잔차) 유전체–표현형 혼란(모집단 구조, genetic nurture, 짝짓기 등)이 독립성 가정을 위반할 가능성을 논의할 수 있다. 위반 가능성을 평가할 때는 결과에 영향을 줄 수 있는 위반의 근원을 식별하고, 그 상대적 중요성, 유발 가능한 편향의 방향과 크기를 논의해야 한다.

또한 결과의 정밀도도 논의해야 한다. 부정확성은 연구설계의 여러 요소에서 기인할 수 있다. 예컨대 다수 SNP의 메타분석으로 얻은 도구변수 추정은 단일 SNP에 비해 보통 더 정밀하다. SNP를 발견 GWAS의 P값 기준으로 선택하였다면, 표본크기, 측정오차 등 그 GWAS의 검정력에 영향을 주는 요인을 고려해야 한다. 더 큰 데이터에서 추정할수록 SNP 효과 추정의 표준오차가 작아지므로 도구변수 추정의 정밀도는 높아진다.

해석(항목 16)

의미(항목 16a)

한계와 타 연구와의 비교를 고려하여, 결과를 신중하게 종합해석한다.

예시

"본 멘델 무작위화 분석은 CETP (cholesteryl ester transfer protein) 억제가 심혈관 사건 위험에 미치는 인과효과가 LDL-C 또는 HDL-C 수준의 변화보다는 apoB 함유 지질단백 농도의 변화에 의해 결정될 가능성을 시사한다[109]."

설명

전체 결과를 신중하게 해석한다. 타 연구와 비교할 때는 추정치의 차이가 왜 발생하는지 가능한 이유(도구변수 가정 위반, 불정확성, 추정방법 차이, 연구집단 차이 등)를 논의한다. 전반적 결과는 같은 질문을 다른 연구설계로 다룬 선행연구들과의 비교 맥락에서 해석해야 한다. 이렇게 하면 결과를 삼각검증(triangulation)해 해석의 신뢰도를 높일 수 있다(항목 13d 참조). 효과크기를 해석할 때는 외삽의 전제와 그것이 결과에 미친 영향을 논의한다.

기전(항목 16b)

노출과 결과 간 잠재적 인과 관련성을 매개할 수 있는 생물학적 기전을 논의하고, 유전자–환경 등가성 가정의 개연성을 검토한다. 도구변수 추정치는 특정 가정 하에서만 인과효과를 줄 수 있음을 명확히 하여 인과 언어를 신중히 사용한다.

예시

"사춘기 시기와 체중상태의 관련성은 복잡하고 양방향일 가능성이 있다. 소아의 체지방 증가는 사춘기 성숙의 조기화를 유발할 수 있으며, 남아에서는 비선형일 수 있다. 또한 여러 연구가 이른 사춘기와 이후 비만 사이의 관련성 근거를 보고하였다. 따라서 우리는 유전적으로 예측된 성인 · 소아 BMI를 모두 보정하려고 했고, 사춘기 시기와 다발성경화증(MS) 위험의 관련성에서 유사한 정도의 약화 현상을 관찰하였다. 다만 소아와 성인 BMI 간 강한 관련성 때문에 연령별 효과 탐색에는 한계가 있다. 그럼에도 소아 비만보다는 사춘기 이후 비만이 대사증후군(MS) 발병 위험과 가장 명확한 관련성을 보이며, 이는 사춘기 시기와 성인 비만 사이의 관련성이 사춘기 연령이 MS 위험에 미치는 효과의 가장 유력한 매개임을 시사한다. BMI와 사춘기 시기가 동일한 인과적 생물학적 경로에 속하는 것으로 보이기 때문에, 선별된 유전 변이체들이 두 노출 요인과 모두 관련되는 현상은 공유된 생물학적 기반에 기인한 수직적 다면발현

(vertical pleiotropy)의 사례를 나타내며, 따라서 MR 추정값에 편향을 일으키지 않는다[35]."

설명

유전변이를 도구로 사용될 수 있게 하는 생물학적 기전은 종종 불명확하지만, 가능한 메커니즘을 고려해 제시하는 것이 바람직하다. 이렇게 하면 MR 결과를 생물학적 기전의 맥락에서 해석할 수 있어, 인과 관련성에 대한 이해를 높일 수 있다.

MR 추정치를 인과적으로 단순 해석하기 어려운 흔한 이유는 유전자–환경 등가성 가정(Table 2)의 타당성이 불명확하기 때문이다. 이 가정은 인구 내 유전적으로 정의된 하위집단 간 노출 차이가 중재로 인해 발생한 노출 차이와 동등하다는 것, 즉 일관성 가정(consistency assumption)의 MR 형태를 의미한다[110]. 유전변이의 효과는 수정 시점부터 복잡하고 가변적일 수 있고, 성장 · 발달의 다양한 요소에 영향을 미칠 수 있다. 반면, 유전관련성 연구는 흔히 단일 시점의 표현형과의 관련성으로 변이를 확인한다. 유전변이의 일생효과는, 대개 생애 후반 특정 시점에 경험되는 환경 영향과 다를 수 있다. 이러한 생애경로 차이는 MR 추정의 유용성을 약화시키지 않는다. 예를 들어, 서로 다른 도구를 사용해 소아기와 성인기의 BMI가 다양한 건강결과에 미치는 효과를 구분할 수 있다[111]. 반면, 저밀도 지단백(LDL) 콜레스테롤 수치 저하의 장기적 효과는 생애 초기부터 MR을 통해 추정할 수 있으며, 무작위 대조 시험에서 도출된 효과 추정치의 두 배에 달한다. 이러한 차이는 MR이 평생효과를 추정하는 반면, 임상시험은 콜레스테롤 저하 무작위 임상시험에서 불과 몇 년에 불과한 무작위 배정 기간에 대한 효과 추정치만을 제공하기 때문일 것이다. 평생 차이와 단기 콜레스테롤 저하 관련 추정치 간에 관찰되는 이러한 차이는 지질이 동맥경화성 관상동맥질환에 미치는 알려진 누적효과로부터 예상한다[112]. 이러한 측면에서 LDL 콜레스테롤 저하를 위한 약제와 일치하도록 구성된 다양한 비중복 도구 집합들에서도 유사한 추정값이 관찰된다는 사실은 해석을 더 신뢰할 수 있도록 한다[112]. 도구효과의 시간의존성은 MR 해석에서 중요한 이슈이며, 유전자–환경 등가성의 맥락에서 고려하는 것이 바람직하다.

임상적 관련성(항목 16c)

결과가 임상 또는 공공정책에 어떤 의미를 가질 수 있는지, 그리고 잠재적 중재의 효과크기 추정에 어느 정도 기여하는지 논의한다.

예시

"162개 SNP 각각의 정확한 기능, 심장 관련 형질과의 다면발현 정도, 그리고 이 유전변이가 심장보호 효과를 나타내는 기전에는 여전히 불확실성이 남아 있지만, 다음과 같은 결론은 가능하다… 중재는 예기치 않은 부작용에 대한 면밀한 모니터링과 함께 이루어져야 하며, 특히 장기 교육환경에 억지로 놓였을 때 적응하지 못해 건강불평등을 악화시킬 수 있는 사람들에게서 그러하다[113]."

설명

무작위배정시험으로 검증하기 어려운 중재가 많기 때문에, MR 근거는 노출이 결과에 미치는 인과효과를 더 잘 이해하는 데 기여할 수 있다(Box 4). 다만 이러한 진술은 다른 관찰 · 실험 근거를 함께 고려하여 신중히 제시해야 한다. 임상 · 정책적 중재의 효과크기는 MR 연구에 사용된 유전변이의 효과와 다를 수 있으므로, 근거의 외삽은 명확하고 신중해야 한다.

Box 4. 멘델 무작위화의 가정 평가와 민감도 분석

인과 추정치를 해석할 때는 여러 가지를 고려해야 한다. 균질성(homogeneity) 가정이 다른 가정들(Box 2)과 함께 개연적이라면, 인과 추정치는 연구된 집단에서 노출이 결과에 미치는 평균 인과효과를 나타낸다. 균질성 가정을 둘 수 없지만 단조성(monotonicity) 가정이 개연적이라면, 인과 추정치는 국소 평균 처치효과(local average treatment effect)를 나타내는 데 사용할 수 있다[86].

이진 노출(binary exposure)에 대한 효과 추정치를 해석할 때는 특히 주의가 필요하다[114]. 이 경우에는 균질성과 단조성 가정이 성립할 가능성이 낮다. 또한 노출이 연속형 위험요인을 이분화한 것이라면, 배제 제한(exclusion restriction) 가정 위반의 추가 위험을 초래한다[114].

두 집단 MR 환경에서 특히 중요한 또 하나의 고려사항은, 인과효과가 정말로 그 이진 노출에 귀속될 수 있는지 여부이다. 예를 들어, 관심 노출을 실제로 경험한 참가자가 매우 적은 노출 표본에서 두 표본 MR이 수행된 경우, 그 효과를 노출 자체의 효과로 해석하는 것은 오해를 불러일으킬 수 있다. 이때 인과 추정치는 노출에 대한 유전적 성향(genetic liability)의 효과를 반영하는 것으로 해석하는 것이 타당하다[115,116].

마지막으로, 해석의 중요한 요소는 시간 구간을 명확히 하는 일이다[60]. MR 연구는 대개 노출의 '평생 효과(lifetime effect)'로 해석되지만, 임신부에서의 MR처럼 산전 노출을 다루는 일부 연구 설정에서는 특정 기간효과(period effect)를 연구하는 것이 더 적절할 수 있다.

일반화 가능성(항목 17)

연구결과의 일반화 가능성을 (a) 다른 인구집단, (b) 다른 노출 기간이나 시점, (c) 다른 노출 강도로 논의한다.

예시

"우리의 멘델 무작위화 연구는 비타민 D 수치와 골절 위험 사이의 선형 관계를 검토하였다. 우리는 문턱값 의존적 관계, 즉 매우 낮은 수준의 비타민 D에서만 존재할 수 있는 효과 가능성은 시험하지 않았다… 마지막으로, 비타민 D가 골절 위험 증가와 관련될 수 있다는 비유의적 경향은 건강한 사람의 선택에 기인할 수 있다(즉 매우 낮은 비타민 D 수준과 골절을 가진 참가자, 고령 · 허약 · 신체기능 저하 참가자가 GWAS 메타분석에 포함된 연구들에서 과소대표되었을 수 있다). 따라서 이 연구의 비타민 D 추정치는 이러한 고령 집단에 일반화할 수 없다[41]."

설명

연구의 일반화 가능성은 연구가 수행된 상황과 다른 상황에 결과가 어느 정도 적용될 수 있는지를 의미한다[117]. 예를 들어, 과거에 특정 연령대 코호트에서 수집한 결과가 현재 동일 연령대의 사람들에게 적용되지 않을 수 있다[118].

MR 연구는 다른 방식으로도 일반화에 실패할 수 있다. 유전변이의 효과가 전 생애에 걸쳐 일정하지 않을 수 있으므로, 연구에서 산출된 효과 추정이 다른 노출 시기로 일반화될 수 있는지 고려해야 한다. 예컨대 노출의 결과에 대한 효과가 시간의존적이거나 특정 결정적 시기에만 나타난다면, 해당 기간을 벗어난 중재에 MR 추정을 적용하는 것은 오해를 낳을 수 있다. 반대로, 노출의 결과에 대한 효과가 수년에 걸쳐 누적된다면, MR은 단기 중재에 비해 효과를 과대추정할 수 있다[60,119].

또한 MR 추정은 대립유전자 차이에 의해 유발되는 노출범위에서만 직접 계산된다. 따라서 MR 결과의 적용은 더 넓은 노출범위에는 일반화되지 않을 수 있다. 더 나아가 MR 추정이 특정 인구 하위집단에서 도출된 것이라면, 그 범위를 넘어 일반화하기 어려울 수 있다.

기타 정보

연구비(항목 18)

이 연구와(해당되는 경우) 이 연구의 근간이 되는 데이터베이스 및 원(기) 연구의 연구비 출처와 연구비 제공자의 역할을 기술한다.

예시

"연구비: 유방암 전장유전체관련성 분석은 캐나다 정부(Genome Canada 및 Canadian Institutes of Health Research), 퀘벡주 경제 · 과학 · 혁신부(Genome Québec 및 PSR-SIIRI-701 과제), 미국 국립보건원(U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710), 유럽연합(HEALTH-F2-2009-223175, H2020 633784, 634935)의 지원을 받았다. 모든 연구와 연구비 제공자는 Michailidou 등에서 목록화되어 있다[25]. RCR, ELA, BMB, CLR, RMM, MM, DAL, GDS는 브리스톨대학교 MRC 통합역학연구소 소속으로, Medical Research Council의 지원(과제번호 MM_UU_00011/1, MC_UU_00011/2, MC_UU_00011/5, MC_UU_00011/6, MC_UU_00011/7)을 받는다. RCR은 브리스톨대학교 de Pass VC 연구 펠로우이다. 이 연구는 브리스톨 대학병원 NHS 재단 신탁과 브리스톨대학교 NIHR 생의학연구센터의 지원을 받았다. 이 출판물의 견해는 저자 개인의 것이며, National Health Service, National Institute for Health Research, Department of Health and Social Care의 공식 입장과 일치하지 않을 수 있다. 이 연구는 Cancer Research UK(과제 C18281/A19169)와 Economic and Social Research Council (과제 ES/N000498/1)의 지원도 받았다. SEJ는 Medical Research Council(과제 MR/M005070/1)의 지원을 받는다. TMF는 유럽연구위원회(과제 323195: GLUCOSEGENES-FP7-IDEAS-ERC)의 지원을 받는다. MNW는 Wellcome Trust Institutional Strategic Support Award(과제 WT097835MF)의 지원을 받는다[120]."

설명

연구비 출처는 연구의 설계 · 수행 · 해석에서 편향 또는 편향 인식을 유발할 수 있다[121,122]. 특히 연구비 제공자가 자사의 상업적 · 학문적 · 기타 이해관계에 유리한 결과에 이해관계를 가지는 경우 그러하다[123]. 저자는 모든 연구비 출처를 공개하고, 연구질문 개발, 자료 수집 · 분석, 연구자 선정, 결과 검토, 원고 작성, 투고 승인 등에서 연구비 제공자의 역할을 상세히 기술해야 한다. 고용주, 정치 임명자, 정부 연구자 등의 영향도 있을 수 있다. 연구비 출처를 기술하면 독자가 연구비 제공자의 잠재적 영향하에서 작업의 신뢰성을 평가할 수 있다. 바이오뱅크 등 저장소 · 데이터베이스의 연구비 출처도 공개해야 하며, 이들 기관 역시 연구의 무결성에 영향을 미칠 수 있는 상업적 이해를 가질 수 있다[124,125].

데이터 및 데이터 공유(항목 19)

모든 분석에 사용한 데이터를 제공하거나, 데이터 접근 위치와 방법을 논문에 명시하고, 해당 출처를 참고문헌에 제시한다. 재현을 위한 통계코드를 제공하거나, 공개 접근이 가능한지 여부와 위치를 보고한다.

예시

"데이터 공유: 이 논문에 보고된 데이터는 UK Biobank에 직접 신청하여 이용할 수 있다. UK Biobank 및 CARDIoGRAMplusC4D 컨소시엄에서의 결과와의 유전관련성은 보충자료에

제공되어 있다. 주성분분석을 포함한 멘델 무작위화 분석 구현을 위한 R 소프트웨어 코드는 보충노트에 제공되어 있다[126]."

설명

원자료는 분석을 평가하거나 복제하려는 독자 · 연구자에게 필요하다. 많은 연구비 제공자와 학술지는 데이터 공유를 장려 · 요구하며, 저자가 제출해야 할 데이터 공유 성명 내용에 대한 지침을 제공한다. 데이터 공유는 "연구과정의 불가분의 일부"라는 합의가 형성되고 있다[127]. 이상적으로는 연구기획 단계에서 데이터 공유계획을 수립하여 연구계획서와 논문에 기술해야 한다. 최소한 어떤 데이터가 이용 가능한지(개별 참가자 자료, 통계분석계획, 연구 관련 문서, 바이오뱅크 또는 데이터베이스 정보 등), 데이터 접근방법, 데이터 보유 주체의 연락처, 공유 메커니즘을 제시해야 한다. 또한 데이터 이용 가능 기간 제한, 요청 심사절차 · 기준(예: 연구계획 요구, 심의위원회 검토), 비용 부과 여부 등을 기술해야 한다. 데이터가 연합분석(federated analyses)으로만 이용 가능하다면 이를 명확히 밝혀야 한다. 데이터 출처가 다수이고 조건이 상이할 때는 서술문 대신 표 형식을 고려할 수 있다.

이해관계(항목 20)

모든 저자는 잠재적 이해관계를 모두 선언해야 한다.

예시

"이해관계: 모든 저자는 ICMJE 통합 공개 양식(www.icmje.org/coi_disclosure.pdf)을 작성하였다. ARC, DG, TT, JV, REW, GH, RM, SS, SB, GDS, MVH, IT, AD는 제출 작업에 대해 어떤 기관의 지원도 받지 않았고, 지난 3년간 제출 작업에 이해관계를 가질 수 있는 기관과의 재정적 관계가 없었으며, 제출 작업에 영향을 미칠 수 있는 기타 관계나 활동도 없다. MRM은 Pfizer의 연구비, GlaxoSmithKline의 비재정적 지원을(제출 작업 외) 보고하였다. NMD는 연구 수행 중 ESRC와 MRC의 연구비, 제출 작업 외의 관련 없는 연구에 대해 GRAND/Pfizer의 연구비를 보고하였다. AET는 제출 작업 외 Pfizer의 연구비를 보고하였다. LDH는 연구 수행 중 MRC의 연구비를 보고하였다. DW는 연구 수행 중 NIH의 연구비를 보고하였다[89]."

설명

연구자와 상업적 · 기타 기관 간 재정적 연결, 강한 이념 · 지적 신념은 연구설계 · 수행 · 보고에서 편향을 유발할 수 있다. 이러한 이해관계를 공개하지 않으면 연구에 대한 공적 신뢰가 약화된다[128]. ICMJE에 따르면, "이해관계는 1차 관심사(예: 환자 복지 또는 연구의 타당성)에 관한 전문가적 판단이 2차 관심사(예: 금전적 이익)에 의해 영향을 받을 수 있을 때 존재한다. 이해관계에 대한 인식은 실제 이해관계만큼 중요하다[129]." 저자는 독자가 관련하다고 볼 수 있는 모든 사항을 공개하는 쪽으로 판단해야 한다.

결론

STROBE-MR 보고지침은 MR 연구에서 '무엇을 계획했고, 무엇을 수행했으며, 무엇을 발견했는지'를 명확히 소통하도록 돕는 최소 항목 집합을 제시한다. 고전적 역학 연구설계(코호트, 환자-대조군, 단면연구)에 대한 STROBE 지침과 유사하게[25,26], 이 지침의 목표는 연구 수행을 규정하거나 창의성을 제한하는 것이 아니라, 명료하고 포괄적인 보고를 촉진하여 연구의 질, 한계, 결과의 일반화 가능성에 대한 평가를 가능하게 하는 데 있다. 체크리스트는 MR 연구의 방법론적 · 보고 질을 평가하는 공식 도구가 아니며, 질 척도로 변환되어서는 안 된다[130,131]. STROBE-MR은 MR 연구의 설계 · 수행을 위한 공식 가이드라인으로 보아서는 안 된다. 다만 일부 항목과 이 E&E 문서는 특히 MR 연구 경험이 적은 연구자에게 방법론적 의사결정을 알리는 데 유용할 수 있다.

독자의 의견을 환영하며, 체크리스트 · 설명 · 예시 개선 제안을 부탁한다. 체크리스트와 E&E 문서는 전용 웹사이트(https://www.strobe-mr.org/)에서 지속적으로 최신 상태로 유지될 것이다. 학술지는 저자 지침에 저자에게 기대하는 바를 명확한 언어로 포함하여 본 지침 채택을 권장한다. 예를 들어, 학술지는 저자에게 완성된 체크리스트 제출을 요구하고, 심사자에게 이를 심사의 일부로 활용하도록 요청할 수 있다[28]. STROBE-MR은 보고지침과 자원을 모아 제공하는 EQUATOR Network 웹사이트(https://www.equator-network.org/)에도 포함될 것이다[132]. 또한 우리는 체크리스트와 E&E 문서의 타국어 번역 시도에 참여하기를 희망한다.

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Authors' contribution

ME, GDS, and JBR contributed equally to this manuscript. GDS, NMD, ND, ME, Valentina Gallo, RMG, JPTH, CL, EWL, JBR, RCR, VWS, SAS, NJT, Anne Tybjaerg-Hansen, TJV, BARW, and James Yarmolinsky contributed to the content and elaboration of the STROBE-MR checklist. All authors contributed to the writing of the article and approved of its final version. VWS, RCR, and BARW prepared the first draft of the checklist and discussion material for the workshop. VWS and JBR undertook the practical coordination of STROBE-MR. ME and GDS initiated STROBE-MR and organized the workshop; ME obtained the funding. ME, GDS, and JBR oversaw the project. JBR is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the SNSF, NIHR Biomedical Research Centre at University Hospitals Bristol, Weston NHS Foundation Trust, and University of Bristol for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; EWL (head of research at *The BMJ*) played no part in the peer review or decision making of this paper at the editorial level, and contributed solely as an author; no other relationships or activities that could appear to have influenced the submitted work.

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Data availability

Not applicable.

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Supplementary materials

Supplementary files are available from https://doi.org/10.7910/DVN/QCIYG0

Supplement 1. STROBE-MR checklist of recommended items to address in reports of Mendelian randomization studies; skrv065837.ww1.pdf (101.5KB, pdf).

Supplement 2. Additional examples; skrv065837.ww2.pdf (307.6KB, pdf).

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