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Aims & Scope

Journal of Evidence-Based Practice (J Evid-Based Pract, JEBP) aims to present 1) Original evidence-based research on important issues in healthcare, 2) Methods, tools, and concepts essential for evidence-based medicine (EBM), education and practice,3) Perspectives, debates, analyses, and opinions on reliable evidence and related topics in evidence-based medicine.

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Calculating and extracting missing summary statistics for meta-analysis

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ABSTRACT

Systematic reviews and meta-analyses are pivotal for evidence-based decision-making but depend on the availability of precise statistical data. Researchers often encounter studies where essential statistics are missing or presented only in graphs, leading to potential data exclusion and selection bias. This study aims to provide specific methodologies for extracting or reconstructing the statistical parameters required for meta-analysis—specifically effect sizes (MD, OR, RR, HR) and their corresponding variance measures (SD, SE, variance)—from incomplete or graphically reported data. We describe calculation and extraction protocols for five specific scenarios encountered in medical literature: (1) continuous data missing standard deviations; (2) categorical data missing standard errors; (3) calculating risk estimates from frequency tables; (4) extracting continuous data presented solely in graphs; and (5) reconstructing hazard ratios from Kaplan-Meier survival curves. Valid meta-analysis requires both an effect size and a measure of variance. When these are not explicitly reported, they can often be derived from other available statistics or digital extraction from figures. While heterogeneity is inherent in meta-analysis, the methodology allows for error adjustment and robust synthesis. Therefore, preventing data loss via these extraction methods is preferable to excluding studies. Maximizing data inclusion enhances the comprehensive value and statistical power of the final analysis.

Keywords: meta-analysis; systematic review; missing data; data extraction; imputation

Introduction

With the explosive increase in research output on various clinical topics, academic focus has shifted beyond individual study findings toward the systematic integration of vast datasets to derive rational conclusions. Against this backdrop, meta-analysis emerged in the late 1980s as a cornerstone of research synthesis, quantitatively aggregating preceding studies to provide intuitive and consolidated results. Following continuous methodological evolution, meta-analysis has become an essential research tool not only in the social sciences, such as psychology and pedagogy, but also in the medical and health sciences [1]. By ensuring objectivity in literature selection and quantifying individual findings into pooled effect sizes, meta-analysis contributes decisively to decision-making in evidence-based medicine (EBM) [2,3].

Since the Cochrane Collaboration established the methodology for systematic reviews [2], pooled effect sizes in me-

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ta-analyses have typically been presented as mean differences (MD), odds ratios (OR), relative risks (RR), or hazard ratios (HR) [4-6]. Conducting such analyses requires the extraction of specific statistical information from individual studies. For instance, when effect sizes are reported as MD or risk ratios (OR, RR, or HR), both the point estimate and its corresponding 95% confidence interval (CI) or standard error (SE) must be retrieved [1]. Similarly, for proportion data expressed as percentages, most meta-analyses require the sample size, effect size, and 95% CI [1,3].

However, researchers often encounter difficulties calculating accurate summary statistics when individual papers fail to explicitly report these values. Excluding such studies can introduce selection bias; therefore, maximizing the utility of available statistical information is crucial. For continuous data, if the standard deviation (SD) is not directly stated, it can be calculated using sample sizes, variances, or SEs [7,8]. If the data remain insufficient for direct derivation, alternative methods, such as imputing the largest SD from other included studies, may be considered [9,10]. In the case of time-to-event data, when statistical information is presented only through graphs, data must be estimated directly from the visual representations. While some studies have reported using grid paper to visually estimate values from Kaplan-Meier survival curves (KMSC) [11], utilizing high-resolution digital tools is preferable for greater accuracy. To this end, methods for extracting survival data using Python-based programs have been developed [12].

Accordingly, this manuscript aims to explore methodologies for back-calculating or extracting the necessary statistical parameters for different data types when primary values are unreported in published literature.

Methods

Missing data can compromise the precision of pooled effect size estimates and introduce bias in meta-analyses. In this study, we operated under the assumption that missing data were missing at random (MAR), implying that the probability of missingness was not dependent on unobserved variables. Furthermore, we calculated estimates assuming that the 95% CIs were symmetrically distributed under a normal distribution.

Fundamentally, meta-analysis synthesizes findings by calculating study-specific weights. This process necessitates the extraction of effect sizes and SEs—or values from which these can be derived, such as variance and 95% CIs—from each individual study. Consequently, obtaining accurate effect sizes and SEs for the intervention in question is a critical priority for researchers.

For Randomized Controlled Trials (RCTs), particularly those conducted since approximately 2007, most studies have been prospectively registered in the web-based database ClinicalTrials.gov to mitigate research misconduct and ensure transparency regarding sponsorship and study background [13]. While not universally mandatory by law, this practice is largely driven by high-impact journals, which typically require a ClinicalTrials.gov registration number as a prerequisite for manuscript submission. Therefore, when including RCTs in a meta-analysis, researchers should prioritize consulting this database to identify potential unpublished but valuable data.

Practical Guidance for Missing Summary Statistics and Extracted Data

Calculation of summary statistics and effect sizes for continuous data

For continuous variables, we calculated the MD, SD, SE, Cohen's d, and Hedges' g for both paired groups (e.g., pre- vs. post-intervention; Table 1) and independent groups (Table 2) using the virtual data. While most statistical software automatically computes effect sizes (Cohen's d and Hedges' g) upon entry of the sample size, mean, and SD, specific manual adjustments were applied as follows.

In paired group designs (Table 1), in clinical medicine, improvement is typically indicated by a reduction in values (i.e., a negative direction). In this simulation study, change scores

Table 1. Paired Two Groups (Pre vs. Post)

Treatment								Control							
n_pre	m_pre	s_pre	n_post	m_post	s_post	S_{diff}	m1	n_pre	m_pre	s_pre	n_post	m_post	s_post	S_{diff}	m2
100	20	5	100	10	3	4.359	-10	100	19	4	100	17	3	3.606	-2

m1 = m_post-m_pre
S_{diff} = SQRT(s_pre^2+s_post^2-(2*r*s_pre*s_post)) *Since correlation (r) is generally unknown, treat it as 0.5.
n, sample size; m, mean; s, standard deviation; Sdiff, standard deviation of mean difference; m1, mean difference between pre- and post-treatment in the treatment group; m2, mean difference between pre- and post-treatment in the control group.
All values are virtual data.

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Table 2. Independent Two Groups (Treatment vs. Control)

Treatment			Control			MD	S_p	SE_{md}	Cohen's d	V_d	SE_d	J	Hedges' g	V_g	SE_g
n1	m1	s1	n2	m2	s2										
100	-10	4.359	100	-2	3.606	-8	4.000	0.566	-2.000	0.030	0.173	0.996	-1.992	0.030	0.173

MD = m2-m1
S_p = SQRT(((n1-1)*s1^2+(n2-1)*s2^2)/(n1+n2-2))
SE_{md} = SQRT(1/n1+1/n2)*S_p
Cohen's d = MD/Sp
V_d = 1/n1+1/n2+Cohen's d^2/(2*(n1+n2))
SE_d = SQRT(V_d)
J = (1-(3/(4*(n1+n2)-9)))
Hedges' g = Cohen's d*J
V_g = Vd*J^2
SE_g = SQRT(Vg)
n, sample size; m, mean; s, standard deviation; MD, mean difference between treatment and control; Sp, standard deviation of MD (pooling standard deviation); SEmd, standard error of MD; Vd, variance of Cohen's d; SEd, standard error of Cohen's d; J, correction factor; Vg, variance of Hedges' g; SEg, standard error of Hedges' g.
All values are virtual data.

were calculated by subtracting baseline values from post-intervention values (Post - Pre), meaning that negative values represent improvement; however, this directionality was adjusted based on the specific research context. Regarding the calculation of the pre-post pooled SD, most individual studies do not report the correlation coefficient (r) between pre- and post-values, consequently, we assumed a conservative correlation coefficient of 0.5 for these calculations, a method explicitly be stated in the meta-analysis methodology [14,15]. Additionally, it is recommended to conduct a sensitivity analysis (Cochrane Handbook for Systematic Reviews of Interventions. Section 6.5.2.8 Imputing standard deviations for changes from baseline) [2].

For independent groups (Treatment vs. Control), we utilized Cohen's d as the standardized mean difference (SMD). In cases where sample sizes were small, we employed Hedges' g to correct for small-sample bias (Table 2). When summary statistics were not explicitly reported in individual studies, they were derived using relevant algebraic formulas. For instance, when only the pre- and post-test SDs were available, the pooled SD corresponding to the mean change was calculated (Table 1). Similarly, when the SDs of two independent groups were provided, the pooled SD for the mean difference between the groups was computed (Table 2).

Handling missing standard deviations in continuous data

When SDs were not reported, we derived the SE using the following formulas:

$$SE = SD/\sqrt{n} SE = \left(CIH - CIL\right)/\left(1.96*2\right)$$

For continuous outcomes presenting MD as the effect size, we extracted the sample size, mean, and SD. It is crucial to verify whether the extracted values correspond to independent or paired groups before applying the formulas. Generally, the SE is the SD divided by the square root of the sample size. Alternatively, if the 95% CI is provided, the SE can be calculated by subtracting the lower limit (CIL) from the upper limit (CIH) and dividing the result by 3.92.

In instances where these calculations were not feasible, we employed imputation strategies as described in Cochrane Handbook Chapter 6: Choosing effect measures and computing estimates of effect [2].

First, we excluded studies with missing data to calculate a pooled effect size and pooled SD from the remaining studies; this pooled SD was then imputed into the studies with missing values. Alternatively, we imputed the SD from a representative study with high methodological quality (e.g., rigorous design, large sample size) that closely resembled the study with missing data.

Importantly, these handling methods for missing data must be clearly defined in the methodology section. To enhance the robustness of the findings, we recommend conducting a sensitivity analysis comparing results that include imputed data against those that exclude studies with missing values.

Handling missing standard errors in categorical data

For categorical data where the effect size is presented as an OR, RR, or HR, the SE is the square root of the variance (V):

$$SE = \sqrt{V} SE = \left(\log\left(CIH\right) - \log\left(CIL\right)\right)/3.92$$

Studies often omit the SE and variance but provide the 95% CI. In such cases, the SE can be calculated using the log-transformed CI limits. Log transformation is essential

to normalize the data distribution. Furthermore, when conducting meta-analyses on categorical data, effect sizes are log-transformed to calculate the pooled effect size and then back-transformed (exponentiated) to report the final OR, RR, or HR.

Deriving Statistics from Frequency Tables (Categorical Data)

When effect sizes (OR, RR, HR) and related statistics were absent but frequency tables for specific treatments were available, we calculated crude unadjusted risks (Figure 1). OR and RR were calculated using standard statistical formulas, while HRs were estimated using the methodology described by Tierney et al. [16]. We calculated OR and RR based on the observed frequencies in the 2*2 contingency tables. To assess statistical significance, we computed test statistics (e.g., chi-square) by comparing the discrepancy between observed and expected frequencies, providing 95% CIs. In addition, following the method described by Tierney et al. [16], we calculated HR by rearranging the observed and expected frequencies from the patient groups only into the corresponding frequencies for the treatment and control arms.

Extracting continuous data from graphical presentations

While the aforementioned methods utilize numerical data, some studies present findings solely through graphs. Given that graphs in modern medical literature are generated by software with standardized axes and ratios, data can be accurately extracted using digital measurement tools such as Adobe Acrobat Reader, WebPlotDigitizer, Plot Digitizer, or Engauge Digitizer [12].

Observed frequency

	D+	D-	
Treatment	a	b	n1
Control	c	d	n2
total			N

Expected frequency

	D+	D-
Treatment	a' = ((a+b)*(a+c))/N	b' = ((a+b)*(b+d))/N
Control	c' = ((c+d)*(a+c))/N	d' = ((c+d)*(b+d))/N

Statistics

	D+	D-
Treatment	((a-a')^2)/a'	((b-b')^2)/b'
Control	((c-c')^2)/c'	((d-d')^2)/d'

▶ **Crude OR**

OR	95%CI
(a*d)/(b*c)	EXP(log(OR) ±1.96*(SQRT(1/a+1/b+1/c+1/d)))

▶ **Crude RR**

RR	95%CI
(a/n1)/(c/n2)	EXP(log(RR)±1.96*(SQRT((b/a)/n1+(d/c)/n2)))

▶ **Calculating HR by Tierney**

	Treatment	Control
Observed	a	c
Expected	a'	c'

HR	logrank variance	variance of HR	SE of HR	95% CI
(a/a')/(c/c')	1/((1/a')+(1/c'))	1/log rank variance	SQRT(variance of HR)	EXP(log(HR)-1.96*SE)

Fig. 1. Calculation of Odds Ratio (OR), Relative Risk (RR), or Hazard Ratio (HR) Using Frequencies.

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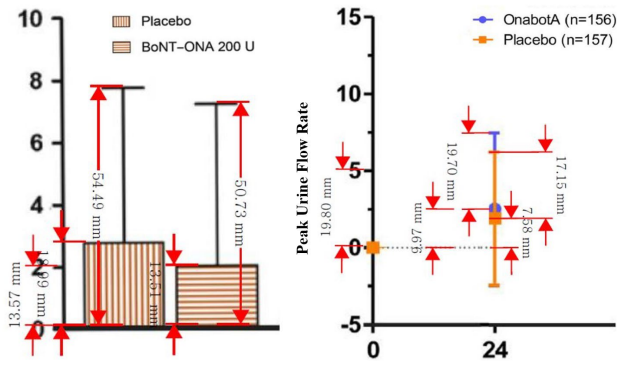

Fig. 2. Data extraction from graph Using Adobe Acrobat Reader. All values are virtual data. BoNT-ONA, Onabotulinum toxin A; OnabotA, Onabotulinum toxin A.

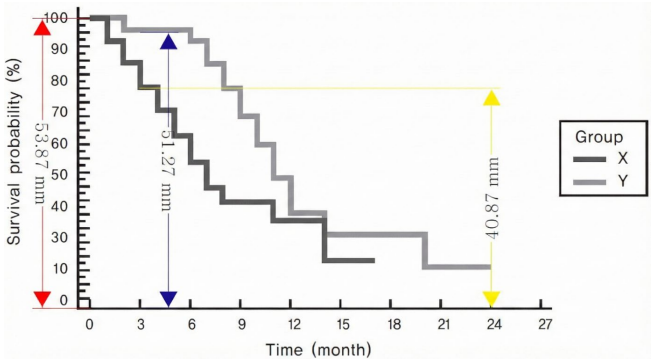

Fig. 3. Data extraction from Kaplan-Meier survival curve. All values are virtual data.

As shown in Figure 2, we extracted mean changes and SDs from bar graphs and box-and-whisker plots using the measurement tool in Adobe Acrobat Reader. By setting a specific segment of the Y-axis as a reference scale, we calculated the values of the target bars or boxes using proportional equations. For example, if a reference measurement of 0 to 5 on the Qmax axis corresponds to 19.80 mm in the software, and the placebo change bar measures 7.58 mm, the actual value is calculated as 1.91 (Calculation: 5 : 19.80 = x : 7.58, therefore x = 1.91).

Extracting survival data from graphical presentations

In survival analyses where only Kaplan-Meier survival curves were provided without explicit HRs, we extracted data points from the curves to calculate the HR (Figure 3). The fundamental principle involves determining interval-specific HRs, variance (V), and observed-minus-expected (O-E) events, then synthesizing these to derive a single pooled HR and SE [11,17]. Narrower time intervals typically yield results closer to the raw data.

However, our validity checks revealed significant discrepancies between summary statistics extracted via this method and actual values. This is likely because survival analysis inherently accounts for both time and censoring simultaneously. Inverse calculation from a final static graph cannot fully capture the dynamic censoring information present in the raw data, inevitably leading to deviations from the original effect sizes.

Conclusions

Despite the inherent heterogeneity across individual studies included in a meta-analysis, the methodological framework of this approach allows for the adjustment of various errors, thereby facilitating robust synthesis. Given that the primary objective of meta-analysis is to enable comprehensive decision-making based on a wide array of evidence [1,18-20], it is methodologically preferable to minimize data exclusion due to missing values rather than discarding potentially valuable information. This rigorous approach reflects the rationale behind the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, which employ a 27-item checklist to enhance the completeness and establish the transparency of systematic reviews and meta-analyses. [21]

However, this study is subject to certain limitations. We operated under the assumption that the missing data in individual studies were MAR. It is important to acknowledge that the MAR assumption is inherently untestable and cannot be empirically verified. Consequently, to address this uncertainty, we strongly recommend conducting sensitivity analyses that account for reasonable deviations. Comparing results derived from datasets that include imputed missing values against those that exclude them is essential to validate the robustness of the study's conclusions.

Furthermore, excluding studies solely due to missing summary statistics reduces the effective sample size and statistical power, potentially leading to Type II errors where significant effects are overlooked. By employing valid imputation strategies under the MAR assumption, researchers can preserve the integrity of the total sample, ensuring that the synthesized evidence reflects a more complete picture of the available data.

In addition, HRs reconstructed from Kaplan-Meier curves may not fully capture censoring information, potentially leading to discrepancies with the actual HRs. Therefore, this approach should be considered an approximation; priority

should be given to obtaining original summary statistics or contacting the study authors whenever possible.

Ultimately, the challenges associated with missing data highlight the critical need for improved reporting standards in primary research. Future clinical trials should strictly adhere to reporting guidelines, such as the CONSORT statement, ensuring that all summary statistics—including means, SD, and CIs—are explicitly reported or archived in public repositories. Such transparency would eliminate the need for post-hoc data extraction or imputation, thereby enhancing the accuracy and reliability of subsequent systematic reviews and meta-analyses.

Conflict of Interest

The author declares no conflict of interest.

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Data Availability Statement

Not applicable.

Ethics Approval and Consent to Participate

Not applicable.

Authors Contributions

Jieun Shin and Sung Ryul Shim had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Analysis and interpretation of data: Jieun Shin, Seong-Jang Kim and Sung Ryul Shim. Drafting of the manuscript: Jieun Shin, Taeho Greg Rhee and Sung Ryul Shim. Critical revision of the manuscript for important intellectual content: Jieun Shin, Taeho Greg Rhee and Sung Ryul Shim. Statistical analysis: Jieun Shin and Sung Ryul Shim.

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Review

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Patient values and preferences in guideline development

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ABSTRACT

Clinical practice guidelines (CPGs) are critical for translating research into clinical practice; however, high-quality evidence alone does not ensure optimal care. The integration of patient values and preferences is essential for developing recommendations that are both relevant and applicable, yet many guidelines continue to underrepresent patient perspectives and lack transparent incorporation of preference research. This review delineates the distinction between values and preferences, examines their influence on preference-sensitive decisions, and evaluates methods for eliciting patient input, such as utility-based measurements, discrete-choice experiments, and qualitative studies. Systematic integration of this evidence through guideline development enhances both credibility and patient-centeredness. Persistent challenges include issues of representativeness, methodological uncertainty, and cultural barriers. Implementing practical strategies to address these challenges will improve transparency, relevance, and acceptance of clinical practice guidelines.

Keywords: Clinical practice guideline; Patient preference; Patient values; Decision Making, Shared; Evidence-based medicine

Introduction

Clinical practice guidelines (CPGs) are systematically developed statements intended to support optimal clinical decision-making by translating appraised and synthesized evidence into actionable recommendations. With the growing emphasis on patient-centered care within health systems, guideline developers are increasingly expected to involve patients in priority setting and to ensure that recommendations reflect patient priorities in both everyday life and clinical practice.

Incorporating patient values and preferences into guidelines can enhance their feasibility and acceptability in clinical practice [1,2]. Excluding patient perspectives may result in recommendations that overlook individual circumstances and trade-offs, potentially leading to reduced adherence [3]. Mirza et al. emphasized that involving patient panels through structured approaches can help guideline developers prioritize outcomes that matter to patients, extending beyond traditional clinical endpoints [4].

Contemporary guideline development standards increasingly recognize patient values and preferences as a core component of trustworthy recommendations [5]. However, empirical evaluations indicate that patient involvement and the systematic use of preference research remain inconsistent and are frequently inadequately documented in final guideline products [6]. This inconsistency is partly due to the tendency to treat preferences as subjective inputs rather than as an evidence domain that can be systematically identified, appraised, and synthesized, as well as the lack of practical guidance on integrating preference evidence. To provide a clear framework for readers, this review will first clarify the conceptual distinction between values and preferences, then explain the pivotal role of preference evidence in pref-

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erence-sensitive decisions and finally summarize feasible methods and stage-specific strategies for integrating patient perspectives into guideline development.

Conceptual Definitions of Patient Values and Preferences

The term ‘patient preferences’ is applied heterogeneously, encompassing at least two levels: (1) individual choices made during clinical encounters and (2) aggregate evidence about preferences derived from population-based studies. Failure to distinguish between these levels can lead to confusion when searching for, synthesizing, and reporting preference-related evidence.

Patient values are defined as the relative importance patients assign to outcomes, health states, and treatment attributes, such as symptom relief, survival, adverse effects, cost, and burden. Patient preferences are defined as expressed choices or rankings among reasonable alternatives, reflecting how patients weigh these valued outcomes and attributes in specific contexts. Preferences thus operationalize values into concrete decisions.

Although values and preferences are conceptually distinct—with values describing the importance of outcomes and preferences describing choices among alternatives—the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach often integrates these constructs. Within GRADE, 'patient values and preferences' are typically operationalized as the relative importance assigned to outcomes or health states of interest [7]. Whether an intervention is preferred depends on how patients weigh benefits, harms, costs, and treatment burden [8]. Even when population-level evidence indicates general trends, individual contexts and goals may differ. Therefore, guidelines should clearly distinguish between typical patterns in the target population and the necessity for individualized application in clinical practice [9].

Importance of Incorporating Patient Values in Guideline Development

Incorporating patient values and preferences into CPGs is fundamental to patient-centered care and enhances the reception and implementation of recommendations. In individual clinical encounters, explicit consideration of patient priorities supports more tailored and higher-quality decisions [10]. Even when clinical effectiveness evidence is equivalent, the preferred option may differ based on a patient’s priorities and tolerance for risk or burden.

Clinicians' preferred treatments, chosen for their effectiveness, may not always align with patients' priorities. Owens et al. demonstrated that patient preferences could alter recommendations for spinal disease treatment, as patients and clinicians may assess risks and benefits differently [3]. Uniform recommendations that disregard preference heterogeneity may therefore result in suboptimal outcomes. When a recommendation conflicts with a patient’s values, intentional non-adherence may occur; such decisions should not be automatically interpreted as poor-quality care, as they may represent value-concordant choices [11].

Guidelines that transparently articulate value judgments can reduce expectation gaps between patients and clinicians, thereby facilitating more effective shared decision-making (SDM) by clarifying which outcomes and trade-offs should be discussed during consultations [12]. When appropriate, supplementing recommendations with plain-language summaries and decision aids can further enhance understanding and support implementation.

Preference-sensitive Decisions

As used here, values refer to the relative importance patients assign to outcomes and attributes, whereas preferences refer to expressed choices or rankings among reasonable alternatives that follow from those values.

Within the GRADE methodology, the strength of a recommendation is determined not only by the certainty of evidence but also by the balance between benefits and harms and the degree of variability in patient values and preferences (Fig. 1). When patient values are broadly consistent and the benefit–harm balance is clear, strong recommendations are justified. Conversely, when the balance is closely matched or values vary substantially, conditional recommendations are more appropriate. In these cases, guidelines should explicitly indicate the need to elicit individual preferences through SDM in clinical practice.

Many clinical choices are preference-sensitive decisions, characterized by the existence of multiple reasonable alternatives and meaningful trade-offs in burden, risks, or quality of life, such that the optimal option depends on patient value judgments [13]. In these contexts, even with sufficient effectiveness evidence, different conclusions may be reasonable depending on which outcomes are prioritized [14]. Guideline developers should therefore actively seek and incorporate preference evidence during development and reflect anticipated variability in the rationale and wording of recommendations.

Evidence suggests that clinicians frequently have difficulty

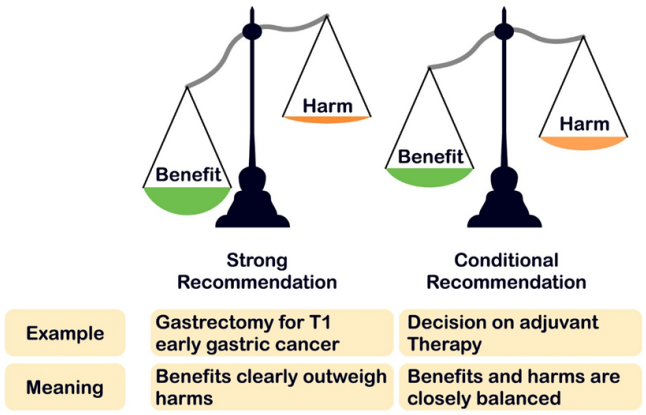

Fig. 1. Interpretation of recommendation strength within the GRADE framework. Strong recommendations are appropriate when expected benefits clearly outweigh harms and patient values and preferences are relatively consistent. Conditional recommendations are appropriate when benefits and harms are closely balanced and/or when values and preferences are expected to vary, signaling the need for shared decision-making. Examples shown are illustrative and not intended to be prescriptive: gastrectomy for T1 early gastric cancer (strong) and decision on adjuvant therapy (conditional).

accurately predicting which outcomes patients prioritize, such as quality of life versus survival duration or tolerance of specific risks [15,16]. Therefore, guidelines should move beyond reporting general trends and provide concrete prompts to facilitate preference elicitation at key decision points, such as suggested questions to explore patient goals, concerns, and acceptable trade-offs.

Gartner et al. analyzed oncology CPGs modules in the Netherlands and found that 18 of 32 recommendations were preference-sensitive; notably, 3 of 14 recommendations presented as strong would have been more appropriately classified as conditional based on the underlying text [17]. They argued that standard guideline phrasing may be insufficient to foster choice awareness or to encourage neutral presentation of options in clinical discussions [17]. These findings support the recommendation that guideline wording should explicitly acknowledge legitimate alternatives where preference sensitivity is anticipated and direct clinicians to verify patient values, even when recommendations are strongly framed.

The presence of a strong recommendation does not eliminate the need for SDM. Even when a strong recommendation is issued, an alternative option may be rational if the patient's context and goals differ. The perspective that patient participation is only necessary for conditional recommendations has been criticized as inconsistent with patient-centered care [9].

Current Status of Patient Involvement in Guidelines and Gaps

Despite broad consensus on the importance of patient values and preferences, evaluations repeatedly show that patient/public involvement and the systematic use of preference evidence remain limited and inconsistently applied in guideline development. International reviews suggest that approximately half of major guideline organizations report routine patient involvement, indicating substantial variability in practice.

Armstrong et al. reviewed 101 independent recommendation-developing organizations in the United States (2011–2015) using websites, methodology manuals, and guideline documents and found that only 8% required patient/public participation in guideline development groups, while 15% described it as optional or occasional [18].

Evidence also suggests that patient participation can materially change the scope and content of guidelines. For example, parallel guideline development groups, with and without patient representatives, identified additional outcomes important to patients (e.g., trajectories of cognitive decline and the speed of disease progression) and shifted discussion toward a patient-centered framing [19]. Such involvement may influence outcome selection, the direction and strength of recommendations, and dissemination strategies, ultimately strengthening acceptability and implementability [19].

In an earlier survey of 31 international guideline developers, 58% reported including patients on panels and 45% reported using surveys to assess patient preferences [20]. Even after influential recommendations by the Institute of Medicine (now the National Academy of Medicine), subsequent analyses indicate that meaningful patient participation remains suboptimal in many guideline programmes [18,21].

Beyond direct participation, available analyses reveal persistent gaps in the use and reporting of preference research evidence in both pharmaceutical coverage decisions and CPGs development [22]. Content analyses underscore this issue, showing that guideline documents allocate substantially less attention to patient preferences than to clinical effectiveness evidence. For instance, Chong et al. observed that effectiveness evidence comprised 24.2% of guideline text, whereas patient preference content comprised only 4.6%, with preference studies rarely cited [23]. Similarly, Sale et al. reported that among 70 international osteoporosis guidelines, only 39% explicitly mentioned patient beliefs, values, or preferences, and most of these did not support their recommendations with evidence from primary studies or systematic reviews [24]. Taken together, these studies highlight a consistent

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gap: guidelines often acknowledge the relevance of patient preferences yet fall short of systematically incorporating and reporting empirical preference evidence in decision-making.

Finally, guideline documents often fail to report concretely how panels weighed patient values and preferences when judging benefit–harm trade-offs [25]. Armstrong et al. noted that many studies focus on exploratory descriptions of methods; few empirically evaluate how patient participation affects question formulation and recommendation development [19].

Barriers to Patient Involvement in Guideline Development

Commonly reported barriers to meaningful patient participation include resource constraints (time, budget, personnel), recruitment challenges, concerns about representativeness, limited health literacy and difficulties understanding technical evidence, resistance from developers or panel members, and inadequate facilitation and communication capacity [14,18].

Additional barriers arise from conceptual ambiguity. Terminology around “patient preference” is used inconsistently across stakeholders, complicating evidence searching and synthesis. Moreover, panels often lack explicit guidance on how much weight preference evidence should receive relative to other decision criteria such as effectiveness, cost, feasibility, and equity [26]. Methodology manuals frequently do not provide sufficient operational procedures or reporting templates for integrating preference evidence into deliberations and documenting its influence on recommendations [6,27].

Structural inequities and culture can further limit participation. Socioeconomic constraints, educational disparities, and persistent expert-centric norms may exclude underrepresented groups and marginalized patient input even when involvement is formally encouraged [5]. Addressing these barriers requires both procedural improvements (e.g., recruitment strategies, support and training, compensation) and cultural change that treats patient perspectives as essential evidence for trustworthy guidance.

Types of Patient Preference Evidence and Measurement Methodologies

Approaches for incorporating patient perspectives in guidelines can be grouped into (1) direct patient and public involvement (e.g., Guideline Development Group (GDG) membership, focus groups, public comment, patient panels) and (2) the use of preference evidence derived from research on patient values and preferences (Table 1), which can be used as a quick reference to match research methods with specific guideline development needs.

Regarding the latter, research methodologies are commonly distinguished into four categories. Qualitative methods (e.g., in-depth interviews) are valuable for identifying outcomes and explaining the decision factors important to patients [28]. Quantitative surveys (e.g., Likert scales, visual analogue scales (VAS)) help quantify relative importance but may limit the assessment of complex trade-offs. To explicitly model these trade-offs, preference elicitation techniques such as Discrete Choice Experiments (DCE) are essential; for instance, Mühlbacher et al. (2021) used a DCE to identify avoidance of severe hypoglycemia as a dominant preference relative to other attributes [29]. Finally, utility measurements (e.g., Standard Gamble) derive values required for economic evaluations.

Since preferences may concern care processes as well as outcomes [26], mixed-methods designs are often recommended. These approaches allow researchers to generate candidate attributes through qualitative work and then estimate weights and explore heterogeneity through quantitative studies [28,30].

Incorporating Patient Values and Preferences at Each Guideline Development Stage

Integrating patient values and preferences at each stage of the CPGs development process involves a sequence of coordinated steps. Begin by identifying "questions/outcomes important to patients" during the scoping phase. Then, conduct a targeted search for preference evidence to connect with Evidence-to-Decision (EtD) discussions. Structurally reflect patient perspectives during the consensus process and explicitly state preference sensitivity, with supporting materials, in the final product. This systematic approach embeds patient perspectives at every key stage.

Scoping and question formulation

Early incorporation of patient input is critical to prevent guideline priorities from diverging from lived experiences. Needs assessments, public surveys, and focus group interviews can identify outcomes and decision factors that patients consider most important [31]. Using this information to refine Population–Intervention–Comparator–Outcome (PICO) questions and to prioritize key outcomes reduces the risk of overlooking quality-of-life outcomes or longer-term

Table 1. Types and Characteristics of Patient Values and Preferences Research Methods

Category	Method	Characteristics & Description	Key Outcome / Measure
Qualitative Methods	In-depth Interview	Explores individual experiences, values, and contextual backgrounds in detail. Useful for discovering novel value drivers.	Key concepts and value categories (Thematic analysis)
	Focus Group Discussion (FGD)	Identifies shared opinions or conflicting views through group interaction. Often used for instrument development.	Group dynamics, consensus, and spectrum of perspectives
Quantitative Survey	Likert Scale	Measures level of agreement or importance using an ordinal ranking scale. Low cognitive burden and intuitive.	Mean scores, frequency distribution, response rates
	Visual Analogue Scale (VAS)	Quantifies subjective value by asking respondents to mark their preference state on a continuous line (e.g., 0–100).	Mean score (0–100 scale), median values
Preference Elicitation	Discrete Choice Experiment (DCE)	Analyzes trade-offs by requiring respondents to choose between hypothetical scenarios defined by varying attributes and levels.	Part-worth utility, relative importance, marginal rates of substitution
	Best-Worst Scaling (BWS)	Measures preference intensity by asking respondents to select the "best" (most important) and "worst" (least important) items.	Preference scores, relative importance rankings
Utility Measurement	Standard Gamble (SG)	Measures health state utility based on decision-making under uncertainty (risk).	Utility values (0–1), basis for quality-adjusted life year (QALY) calculation
	Time Trade-Off (TTO)	Measures utility by determining the indifference point between a duration in a specific health state and a shorter duration in perfect health.	Utility values, weights for quality-adjusted life year (QALY) calculation

concerns. Including patients or patient representatives in the GDG further increases the likelihood that outcomes clinicians may underweight are incorporated into the scope [19].

Evidence review stage – collection of preference-related evidence

In the evidence review stage, panels should use explicit procedures to identify and appraise preference-related evidence separately from clinical effectiveness evidence [10]. The GRADE EtD framework includes a values and preferences domain, encompassing outcome importance, risk acceptance, and perspectives on treatment burden [32]. Zhang et al. described guideline development processes in which additional searches were performed for preference literature (e.g., utility values, quality of life data, treatment preference surveys, qualitative research) for each PICO question and were then incorporated into EtD discussions with input from clinicians and patient representatives [10]. Because preference evidence may be sparse for specific subpopulations or regions, developers may need to prioritize local evidence and, where feasible, complement gaps with targeted qualitative studies or surveys.

Recommendation formulation stage – patient panel involvement and panel surveys

During recommendation formulation and consensus, governance structures should enable patient perspectives to influence deliberations substantively. Direct patient or patient-representative membership on GDGs is the most transparent approach, while a separate patient panel can provide structured input at critical decision points [27,31]. Meaningful participation requires clear recruitment criteria, attention to representativeness, preparatory education and support, appropriate compensation, and skilled facilitation. Providing plain-language materials and flexible participation modalities (e.g., online or asynchronous formats) can help mitigate barriers associated with educational and socioeconomic disparities [5].

Goodman et al. illustrated that a rheumatoid arthritis patient panel's prioritization of trade-offs between infection risk and relapse risk could shift the direction and strength of recommendations toward conditional recommendations [14]. When direct participation is infeasible, structured procedures such as panel surveys can supplement deliberations. Zeng et al. proposed a survey framework to elicit and share patient perspectives (e.g., minimum acceptable benefit, risk

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tolerance) before meetings [30]. Because expert estimation may not fully reflect patient experience, such approaches should be triangulated with empirical patient data whenever possible.

Recommendation wording & supplementary materials – explicit statement of preference information

In drafting recommendations and accompanying materials, panels should: (1) explicitly indicate when decisions are preference-sensitive and specify reasonable exceptions; (2) summarize the key preference evidence and its variability; and (3) provide tools that support SDM (e.g., plain-language summaries, decision aids). Brief summaries of what patients value most (and the extent of variability) can facilitate evidence-based dialogue during consultations. Citing preference instruments or primary preference studies in recommendation rationales can also make transparent how patient perspectives were considered [33]. As Gartner et al. argued, recommendation phrasing should promote choice awareness when multiple reasonable options exist [17].

Remaining Challenges and Potential Solutions

Despite the emerging methodologies for integrating patient values and preferences into CPGs, several impediments remain. Implementing these concepts requires overcoming concerns regarding representativeness, resource constraints, methodological uncertainties, cultural resistance, and the need for patient empowerment.

A primary concern is the representativeness of patient opinions. Since individual preferences vary significantly by disease stage, age, socioeconomic background, and culture, a limited number of patient panelists may not adequately reflect the universal values of the target population. To mitigate this limitation, guideline developers should strive to include patients from diverse backgrounds and utilize multiple channels, such as surveys and focus groups, to gather a broader range of perspectives. Furthermore, integrating large-scale survey data and systematic literature reviews can supplement direct participation. As demonstrated by Goodman et al., while acknowledging the constraints of small panels, triangulating panel discussions with existing literature evidence can lead to more persuasive and representative value judgments [14].

Practical constraints—including time, budget, and personnel—can hinder implementation. Overcoming these barriers requires early planning and resource allocation. Securing funds for recruitment, travel, and honoraria, as well as providing facilitators, patient coordinators, and educational resources, supports meaningful participation [5]. While these steps require investment, they increase the long-term acceptability and usefulness of guidelines. Institutional support, such as dedicated budget items for patient involvement, is also essential.

Methodological uncertainty further complicates the integration process [26]. As noted by Kim et al., there is a lack of consensus on the optimal methods for integrating and reporting preference evidence, and relevant studies remain scarce [27]. To bridge this gap, it is essential to systematically document and evaluate the success and failure factors of various engagement strategies in guideline development. Sharing these experiences through international platforms such as the Guidelines International Network (GIN) and conducting local primary research—both quantitative and qualitative—will strengthen the evidence base. For instance, discrepancies in attitudes toward end-of-life care planning among patients, families, and physicians highlight the need for region-specific data to inform policy and guideline development.

Cultural barriers and the need for a paradigm shift present another formidable challenge. In medical cultures where expert opinion is traditionally prioritized, patient preferences may be marginalized even if their consideration is mandated by guidelines. Overcoming this requires continuous education for healthcare professionals to reinforce that respecting patient values is central to high-quality care. Armstrong et al. argue that patient participation should be regarded as a prerequisite for the trustworthiness of guidelines [19].

Finally, effective integration depends on patient empowerment. Patients must be able to voice their opinions and participate meaningfully in the decision-making process. This can be achieved by improving health literacy and access to information. Furthermore, structured training programs for patient representatives, like those operated by the National Institute for Health and Care Excellence (NICE), can significantly enhance the quality of patient contributions. Ultimately, establishing a "co-production" model where patients and clinicians act as partners will be instrumental in fostering a truly patient-centered medical culture.

Conclusion

Systematically integrating patient values and preferences into CPGs development can strengthen the relevance, acceptance, and practical implementation of recommendations.

To achieve this, guideline developers should: (1) distinguish values (outcome and attribute importance) from preferences (choices and trade-offs); (2) identify, appraise, and synthesize preference evidence alongside effectiveness evidence; and (3) transparently document how preference evidence informed EtD deliberations, recommendation wording, and the need for SDM at preference-sensitive decision points. In practical terms, developers can apply a stepwise approach by beginning with patient inclusion on guideline panels and progressively incorporating broader surveys, focus groups, or mixed-methods preference studies as resources permit. By tailoring the level of patient involvement to the specific context and available resources, guideline developers can more effectively ensure that recommendations are both feasible to implement and closely aligned with the lived experiences and priorities of the patient population.

Conflict of Interest

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Big data–driven observational evidence in Korea: challenges in interpreting non-randomized studies

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ABSTRACT

Big data–driven non-randomized studies (NRS) are an increasingly important source of observational evidence in evidence-based medicine, particularly when randomized controlled trials are limited, infeasible, or insufficiently generalizable to routine clinical practice. In Korea, this shift is especially pronounced because a single-payer national health insurance system enables near-complete population coverage, longitudinal follow-up, and linkage of healthcare utilization, prescriptions, and mortality data. These structural advantages, however, also create distinctive interpretative challenges. In big data–based NRS, key design elements—such as population definition, exposure classification, index dates, follow-up windows, and outcome specification—are inherently flexible. This flexibility, while analytically advantageous, increases vulnerability to residual confounding and overinterpretation. Advanced analytic approaches may improve internal validity, but they cannot fully resolve ambiguities related to population specification, temporal structure, or unmeasured contextual factors. This review discusses how to interpret big data–driven NRS using the Korean healthcare system as a representative example. We summarize the strengths that make large-scale observational research indispensable, delineate structural, institutional, and temporal factors that complicate causal inference, and propose practical principles for responsible interpretation. We emphasize the complementary responsibilities of researchers, reviewers and editors, and guideline developers in supporting transparent design, clinically plausible interpretation, and calibrated use of observational evidence in recommendations. A context-aware and proportionate approach is essential to ensure that expanding observational evidence strengthens—rather than distorts—evidence-based clinical and policy decision-making in rapidly evolving healthcare systems with complex institutional incentives.

Keywords: Observational studies as topic; Retrospective studies; Big data; Insurance, health; Confounding factors, Epidemiologic; Data interpretation, statistical

Introduction

Evidence-based medicine (EBM) has traditionally placed randomized controlled trials (RCTs) at the center of evidence generation, owing to their strong internal validity and ability to minimize bias [1,2]. However, in contemporary clinical practice, many important questions cannot be adequately addressed by RCTs alone. Ethical constraints, feasibility limitations, long follow-up requirements, rapidly evolving standards of care, and the growing need to evaluate real-world effectiveness have increasingly highlighted the limitations of an RCT-only paradigm [3,4].

In this context, large-scale, big data–driven non-randomized studies (NRS)—including cohort studies, registry-based analyses, and administrative claims data research—have assumed an expanding role in informing clinical decision-mak-

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ing, guideline development, and health policy [5-7]. Advances in data availability and statistical methodology have accelerated this trend, enabling observational analyses at a scale and longitudinal depth that were previously impractical [8]. As a result, observational evidence derived from big data–based NRS now constitutes a substantial component of the evidence base in many areas of medicine.

Korea represents a particularly distinctive environment for big data–driven observational research. A single-payer national health insurance system enables near-complete population coverage, longitudinal follow-up, and linkage across healthcare utilization, prescription, and mortality data [9,10]. These features have facilitated an extraordinary volume of large-scale NRS across a wide range of clinical and public health domains, extending beyond pharmacotherapy to disease epidemiology, risk stratification, screening strategies, and policy evaluation [9,11,12]. Consequently, big data–derived observational evidence plays a prominent role in clinical interpretation, guideline formulation, and health policy decisions in Korea.

However, the very conditions that make Korea an attractive setting for big data–based NRS also introduce substantial interpretative challenges. The flexibility inherent in observational study design, combined with complex reimbursement rules, policy-driven healthcare utilization patterns, rapid demographic transitions, and fast-paced changes in clinical practice, creates fertile ground for residual confounding and overinterpretation [13-16]. Although sophisticated statistical techniques can improve internal validity, they cannot fully compensate for ambiguities in population definition, exposure classification, time structure, or unmeasured contextual factors inherent to administrative data [17,18]. When these limitations are insufficiently acknowledged, findings from large-scale observational studies may be implicitly treated as causal evidence, leading to exaggerated conclusions or inappropriate translation into guidelines and policy.

Therefore, the central challenge is not whether NRS should be used, but how big data–driven observational evidence should be interpreted. Particularly in settings such as Korea, where such evidence is abundant and influential, a balanced framework is required—one that recognizes the strengths of large-scale NRS while applying rigorous scrutiny to their limitations. This review provides a context-specific framework for interpreting big data–driven observational evidence in modern EBM, with a focus on the Korean healthcare system. We discuss the methodological strengths that have made these studies indispensable, the structural and contextual factors that complicate their interpretation, and practical principles for researchers, reviewers/editors, and guideline developers to avoid overestimation and misuse of observational evidence.

What Are Non-Randomized Studies in Evidence-Based Medicine?

NRS are investigations in which exposures or interventions are not assigned through randomization, but instead arise from routine clinical practice, patient characteristics, or healthcare system factors [7]. Unlike RCTs, which are defined by experimental allocation, NRS are defined by their observational nature, regardless of whether the underlying data originate from cohort studies, case–control designs, registries, administrative claims, or electronic health records [5,19].

The defining methodological feature of NRS is that comparability between study groups is not ensured by design, but must be approximated analytically [20]. Whereas randomization in RCTs aims to balance both measured and unmeasured confounders, NRS must explicitly confront the possibility of systematic differences between exposed and unexposed groups [21]. As a result, NRS are inherently vulnerable to confounding, selection bias, and time-related biases, and their validity depends critically on how these issues are anticipated, addressed, and transparently reported [18,22].

Within EBM, NRS should therefore be understood not as failed attempts at experimentation, but as a fundamentally different class of evidence. Their interpretation requires a shift in emphasis—from whether bias exists to whether potential biases are sufficiently explicit, plausible, and consistent with the observed findings. As the scale and influence of observational research have expanded through the increasing use of large administrative and registry-based datasets, these interpretative challenges have become more consequential. In healthcare systems where big data–driven NRS play a central role in informing clinical and policy decisions, careful attention to context and design assumptions is particularly essential.

Why Large-Scale Observational Studies Matter: Questions Beyond the Reach of RCTs

While RCTs remain central to evidence-based medicine, their design is optimized for a specific subset of clinical questions, typically focusing on short- to medium-term efficacy under controlled conditions. Many clinically and policy-relevant questions fall outside this scope. In such contexts, large-scale, big data–driven observational studies, rather than

NRS in general, often represent the primary or only feasible source of evidence.

Big data–based observational research is particularly valuable when long-term outcomes are of interest. Extended follow-up, delayed adverse effects, and infrequent outcomes are difficult to capture within the constraints of randomized trials. In contrast, longitudinal administrative and registry data allow sustained observation over years or decades, making them indispensable for evaluating long-term safety, prognosis, and patterns of care. These strengths are most evident in healthcare systems with comprehensive population coverage, where loss to follow-up is minimized and outcome ascertainment is relatively complete [13,23].

Another critical role of large-scale observational evidence lies in evaluating care delivered to populations that are poorly represented in RCTs. Older adults, patients with multiple comorbidities, and individuals receiving complex or evolving treatment regimens often differ substantially from trial populations [24]. In such settings, big data–driven observational evidence does not merely complement randomized trials but increasingly shapes clinical interpretation and policy discourse. Moreover, many real-world clinical questions concern patterns and strategies of care rather than isolated interventions. Treatment sequencing, switching, discontinuation, adherence, and comparative effectiveness among commonly used options are rarely addressed through randomization, yet they are central to everyday clinical decision-making [25,26].

Finally, large-scale observational studies play a pivotal role in informing health policy and system-level decisions. Evaluations of screening programs, reimbursement policies, and healthcare delivery models typically rely on observational evidence, as randomized experimentation at the population level is often infeasible [27,28]. In these contexts, big data–driven observational evidence does not merely complement randomized trials but shapes policy discourse directly—underscoring the need for careful interpretation of its strengths and limitations.

The Korean Context: Why Big Data–Driven Observational Evidence Has Become Exceptionally Influential

Korea represents a distinctive environment in which big data–driven observational evidence plays an unusually prominent role within EBM. This is largely attributable to the structure of its healthcare system, which enables near-complete population coverage through a single-payer national health insurance framework. As a result, healthcare utilization, prescription records, diagnostic codes, and mortality data can be longitudinally captured and linked for the vast majority of the population.

Such comprehensive data infrastructure provides several methodological advantages for large-scale observational research. Large sample sizes allow the study of relatively uncommon diseases, subpopulations, and outcomes that would be difficult to examine in smaller or fragmented healthcare systems [29]. Longitudinal follow-up facilitates the evaluation of disease trajectories, treatment patterns, and long-term outcomes across extended periods [8,12]. In addition, population-level data reduce selection bias related to healthcare access, enhancing the relevance of findings to routine clinical practice [12,24]. These features have enabled the rapid expansion of big data–based NRS across diverse clinical and public health domains.

Importantly, the influence of Korean observational evidence extends beyond research volume. Findings from large-scale administrative and registry-based studies are frequently cited in clinical reviews, inform guideline discussions, and shape health policy decisions [5,26,30]. In areas where randomized evidence is limited or slow to emerge, big data–driven observational studies often function as de facto reference points for clinical interpretation [26]. While this prominence reflects the strengths of the Korean data environment, it also magnifies the consequences of misinterpretation. As observational evidence becomes increasingly visible and influential, careful attention to its contextual foundations becomes essential—a theme that underlies the challenges discussed in the following sections.

The Other Side of the Coin: Structural Pitfalls of Extensive Big Data–Driven Observational Research in Korea

The same structural conditions that have strengthened the role of big data–driven observational evidence in Korea also introduce important vulnerabilities. As large-scale NRS become increasingly abundant, influential, and methodologically sophisticated, the primary risk shifts from a lack of evidence to the uncritical acceptance of results that appear robust while resting on fragile assumptions. In this setting, the challenge is not the existence of bias per se, but the growing distance between analytical complexity and interpretative caution.

One major source of vulnerability arises from the high degree of flexibility inherent in large-scale observational study design and analysis. Population definitions, exposure classifications, index dates, follow-up windows, and outcome spec-

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ifications can often be modified in multiple plausible ways using the same underlying datasets. While such flexibility enables tailored analyses, it also increases the likelihood that analytically favorable results may emerge without sufficient consideration of alternative specifications that could lead to different conclusions [31,32].

Advanced statistical techniques further contribute to this tension. Methods such as multivariable adjustment, propensity score–based approaches, and time-dependent modeling can meaningfully reduce bias when appropriately applied [18]. However, in big data–driven NRS, methodological sophistication may inadvertently convey a false sense of causal certainty, particularly when statistical refinement is emphasized more than clinical plausibility or contextual coherence [8,33]. Statistical adjustment cannot compensate for ambiguities in population selection, exposure timing, or outcome ascertainment, nor can it fully address confounding by factors that are poorly measured or absent in administrative data [8,18].

Another important concern is the progressive blurring of association and causation in the interpretation of findings from large observational datasets [34]. Large sample sizes and narrow confidence intervals can yield statistically compelling results even when residual confounding remains substantial [35,36]. When similar associations are repeatedly reported across multiple studies using overlapping data sources, they may be perceived as confirmatory evidence despite sharing the same structural limitations [32]. In Korea, where the volume and visibility of big data–based NRS are particularly high, this accumulation effect amplifies the risk of interpretative drift—where observational associations are implicitly treated as causal effects.

Distortion of Healthcare Utilization by Reimbursement Rules and Health Policy

In Korea, patterns of healthcare utilization observed in big data–driven NRS are strongly shaped by reimbursement rules that define what care is eligible for coverage. Because access to treatments, diagnostic tests, and procedures is closely tied to insurance criteria, the care captured in administrative datasets often reflects institutional constraints rather than purely clinical decision-making [11,37]. As a result, exposures identified in observational analyses may represent reimbursable care pathways rather than the full spectrum of clinically considered options.

Reimbursement criteria can directly influence exposure definition in observational studies. Treatments that may be clinically appropriate are often initiated only after specific coverage requirements are met, while diagnostic codes or laboratory findings may be preferentially recorded to justify reimbursement [11]. Stepwise reimbursement structures can further delay treatment initiation or channel patients into predefined therapeutic sequences. In such settings, exposure timing and treatment selection are partially determined by institutional design, complicating causal interpretation in big data–based NRS [38].

These reimbursement-driven patterns also shape the intensity of healthcare utilization. Patients who meet coverage criteria typically undergo more frequent follow-up visits, laboratory testing, and monitoring. Such differences in utilization are closely linked to factors such as healthcare access, socioeconomic status, and health-seeking behavior—variables that are incompletely captured in administrative data [18,36]. Consequently, healthcare utilization itself may act as an unmeasured confounder, generating apparent associations that are not directly attributable to the exposure of interest.

Beyond reimbursement rules, national health policies introduce an additional layer of complexity in the interpretation of observational evidence. Policy changes—such as revisions to coverage thresholds, approval of new therapies, modifications in copayment structures, or expansion of national screening programs—can lead to abrupt shifts in diagnosis rates, treatment uptake, and observed outcomes [27,39]. When such transitions are not explicitly modeled, policy-driven effects may be misattributed to treatment effects in observational analyses.

Taken together, reimbursement rules establish the baseline structure of observable care, while health policies dynamically reshape that structure over time. Failure to distinguish between these institutional mechanisms risks conflating system-level design, rapid shifts in the treatment landscape, and biological or therapeutic causality. In the context of Korea's government-driven single-payer system and its extensive use of claims-based big data, explicit consideration of reimbursement structures, nationally standardized policy incentives, and utilization-driven data capture is therefore essential for responsible interpretation of NRS findings (Table 1).

Rapid Demographic and Societal Change as a Source of Time-Dependent Confounding

Another defining feature of big data–driven NRS conducted in Korea is the exceptionally rapid pace of demographic, societal, and healthcare system change [40]. Within relatively short time frames, population structure, disease burden, diagnostic practices, and standards of care have evolved sub-

Table 1. Institutional Characteristics of Korea's Government-Driven Single-Payer System That Shape Observed Healthcare Utilization in Big Data–Driven Observational Studies

Domain	Key institutional feature	How distortion arises in claims-based big data	Implications for Interpretation
Coverage eligibility and reimbursement rules	Nationally standardized coverage criteria determined by a single public payer	Treatments are initiated only after predefined reimbursement thresholds are met; diagnostic codes and tests may be preferentially recorded to justify coverage	Observed exposures reflect reimbursable care pathways rather than the full range of clinically considered options
Stepwise reimbursement and access control	Sequential approval and escalation requirements enforced at the national level	Delayed treatment initiation and forced stepwise treatment pathways	Exposure timing and sequencing are partially institution-driven rather than clinician-driven
Uniform provider incentives	Homogeneous reimbursement incentives across providers nationwide	Limited variation in practice patterns unrelated to patient characteristics	Reduced heterogeneity may mask clinically meaningful differences
Utilization-driven data capture	Claims data generated primarily for reimbursement purposes	Healthcare utilization intensity influences the probability of diagnosis and outcome detection	Utilization itself may function as an unmeasured confounder

stantially. In such an environment, long-term observational analyses are exposed to layers of time-dependent confounding that are more complex and more densely intertwined than in many other settings [41].

Korea has experienced one of the fastest rates of population aging worldwide, accompanied by a rapid increase in multimorbidity and polypharmacy [42,43]. Consequently, individuals observed at different calendar periods within the same long-term dataset may differ fundamentally in baseline risk profiles, functional status, and life expectancy—even when classified under identical disease codes [17]. These qualitative shifts are only partially captured by variables available in administrative data, leaving substantial residual confounding that cannot be fully addressed through statistical adjustment [18,36].

At the same time, clinical practice has undergone accelerated transformation, driven in part by rapid shifts in the treatment landscape following the introduction of new therapies and evolving clinical guidelines. Diagnostic criteria have been revised, screening programs expanded, and therapeutic options diversified within short intervals. Apparent changes in disease incidence, treatment patterns, or outcomes may therefore reflect altered detection thresholds or evolving clinical definitions rather than true changes in underlying risk [44]. When calendar time is treated merely as an adjustment variable, these structural shifts are easily obscured. This issue is particularly salient in long-term time-series and before–after analyses based on national claims data [45,46]. In Korea, multiple institutional and clinical transitions—including guideline revisions, reimbursement policy changes, and public health initiatives—often occur within the same analytic window [37,38]. As a result, calendar time functions not as a neutral dimension but as a composite proxy for numerous unmeasured and interacting structural factors [17]. Without explicit recognition of Korea's compressed demographic transition, rapid evolution of clinical practice, and overlapping institutional shifts, temporal trends embedded within calendar time may be misinterpreted as treatment effects or causal associations.

Rapid demographic and societal change further complicates cross-national comparisons. Even when similar study designs and follow-up durations are employed, the density of transitions embedded within a given time frame may differ markedly across countries. A ten-year observational period in Korea may encompass far more demographic, clinical, and institutional transformation than an equivalent period in settings with slower socioeconomic and policy evolution. Failure to account for this asymmetry risks misleading conclusions when interpreting or extrapolating findings from Korean big data–driven NRS (Table 2).

Practical Principles for Interpreting Big Data–Driven NRS in Rapidly Evolving Healthcare Systems

Implications for researchers

For researchers conducting big data–driven NRS in Korea, the primary responsibility lies in making the institutional and clinical context of the study explicit. This begins with transparent definition of the study population, including how eligibility and inclusion are shaped by reimbursement rules, healthcare access, and prior utilization patterns. Simply reporting inclusion criteria is insufficient; investigators should clarify why the observed population emerges within

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Table 2. Korea-Specific Sources of Time-Dependent Confounding in Long-Term Big Data–Driven Observational Studies

Category	Korea-specific temporal change	How time-dependent confounding arises	Implications for interpretation
Compressed demographic transition	Rapid population aging within a short historical period	Patient populations with the same diagnosis differ substantially across calendar time	Comparability across time periods is compromised even within identical disease categories
Accelerated epidemiologic and societal change	Rapid shifts in disease burden, lifestyle, and socioeconomic structure	Background risk profiles change faster than analytic models can fully capture	Residual confounding persists despite statistical adjustment
Rapid evolution of clinical practice	Abrupt adoption of new therapies, technologies, and guidelines	Treatment strategies change sharply after specific time points	Calendar time embeds shifts in the treatment landscape
Overlapping institutional and policy changes	Concurrent guideline updates, reimbursement revisions, and public health initiatives	Multiple structural changes are densely layered within short analytic windows	Calendar time functions as a composite proxy rather than a neutral adjustment variable

the healthcare system and how it may differ from the broader clinical population of interest. Exposure definition requires particular care in claims-based analyses. Treatments and interventions recorded in administrative data often reflect what is reimbursable rather than what is clinically preferred. Researchers should explicitly acknowledge institutional constraints that may influence treatment initiation, sequencing, or discontinuation. When stepwise reimbursement structures or policy thresholds affect exposure timing, analytic strategies should be selected accordingly, and their interpretative implications clearly discussed. Finally, restraint in causal language is essential. Even when advanced statistical techniques yield precise estimates, conclusions should reflect the inherent uncertainty of observational evidence and clearly distinguish association from causation.

Implications for reviewers and editors

Reviewers and editors play a critical gatekeeping role in preventing interpretative drift as big data–based NRS become increasingly prominent. Evaluation should extend beyond statistical methodology to include scrutiny of clinical plausibility and institutional context. Reviewers should assess whether population definitions, exposure timing, and comparison groups are meaningful within the reimbursement and policy environment in which the data were generated. Particular attention should be paid to whether observed associations could plausibly reflect policy changes, reimbursement criteria, or time-related structural shifts rather than true treatment effects. Methodological sophistication should not be equated with causal validity. Editors, in turn, should encourage proportional conclusions: large sample size and narrow confidence intervals should not justify strong causal claims in the absence of robust design features. Explicit discussion of contextual limitations should be viewed as a marker of rigor rather than weakness.

Implications for guideline developers and policymakers

For guideline developers and policymakers, big data–driven NRS often represent an indispensable source of evidence, particularly when randomized data are unavailable or insufficiently generalizable. However, incorporation of observational findings into recommendations requires careful calibration of evidentiary weight [47,48]. Panels should consider whether reported effects reflect clinical mechanisms or institutional artifacts arising from reimbursement rules, policy incentives, or healthcare utilization patterns [11,26]. Evidence derived from a single national healthcare system should also be evaluated with attention to transferability, especially when recommendations are intended for broader application [5,24]. Rather than seeking definitive causal answers, guideline developers should use observational evidence to inform direction, plausibility, and hypothesis generation, while maintaining flexibility in recommendation strength [26,49]. Transparent articulation of uncertainty and contextual dependence is essential to avoid overconfidence in conclusions drawn from big data–based NRS [33,50].

Concluding Remarks

Big data–driven NRS have become an increasingly influential component of evidence-based medicine, particularly in healthcare systems where randomized evidence is limited or insufficiently generalizable. In Korea, comprehensive population coverage and longitudinal administrative data have enabled large-scale observational analyses that inform clinical practice, guidelines, and policy, while simultaneously introducing distinctive interpretative challenges. Reimbursement structures, policy-driven healthcare utilization, rapid demographic aging, and compressed transitions in clinical practice collectively shape observed associations, which may reflect institutional and temporal dynamics as much as true

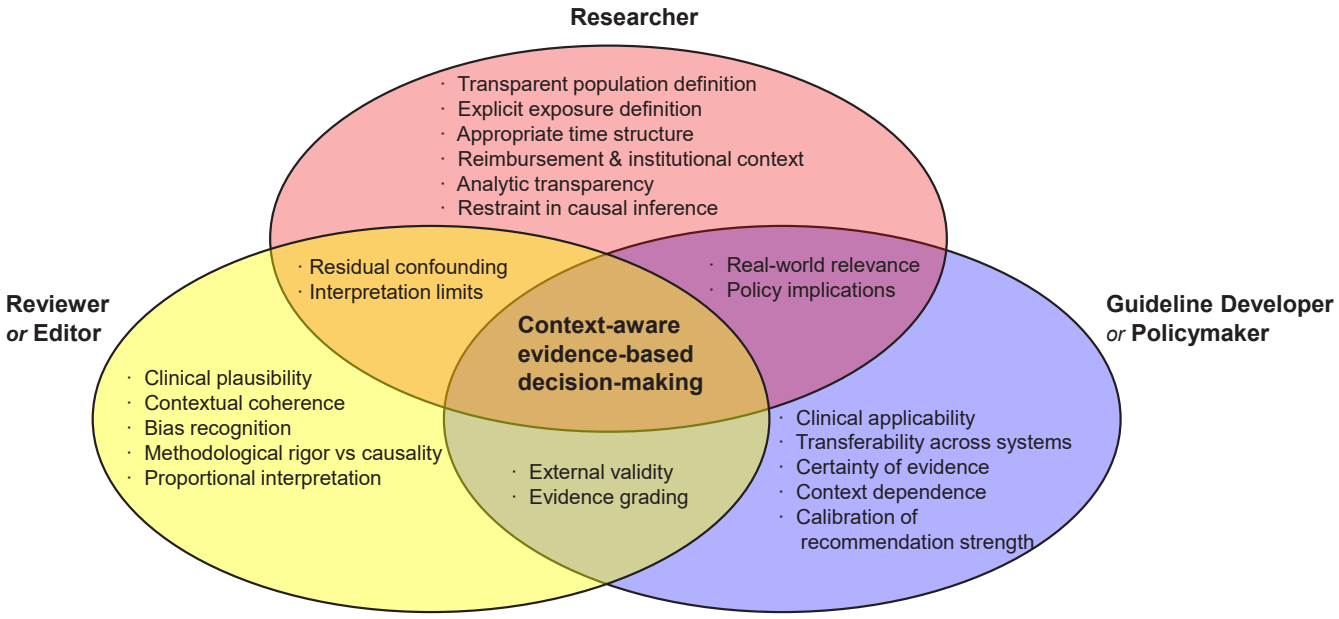

Fig. 1. Shared and Role-Specific Responsibilities in Interpreting Big Data–Driven Non-Randomized Studies. This figure illustrates the complementary and overlapping responsibilities of researchers, reviewers/editors, and guideline developers in interpreting big data–driven non-randomized studies within rapidly evolving healthcare systems. Researchers are responsible for transparent study design and explicit acknowledgment of institutional constraints; reviewers and editors for evaluating contextual and clinical plausibility beyond statistical rigor; and guideline developers for calibrating evidentiary weight and transferability. The overlapping domains highlight shared accountability for recognizing residual confounding, contextual dependence, and limitations of causal inference. Responsible interpretation of observational evidence emerges at the intersection of these roles.

clinical effects. Although advanced analytic methods can reduce certain biases, they cannot fully resolve ambiguities related to population definition, exposure timing, or unmeasured context. As illustrated in Fig. 1, responsible interpretation of big data–driven NRS requires shared accountability among researchers, reviewers and editors, and guideline developers, grounded in contextual awareness and proportional inference. When approached with such rigor and restraint, observational evidence can strengthen—rather than distort—evidence-based clinical and policy decision-making in rapidly evolving healthcare systems.

Conflict of Interest

The author declares no competing financial or non-financial interests related to this work.

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Data Availability Statement

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

Ethics Approval and Consent to Participate

Not applicable.

Authors Contributions

Jong Han Choi conceived the study concept and design, performed the literature review, synthesized the evidence, and drafted the manuscript. The author critically reviewed the manuscript for important intellectual content and approved the final version for publication.

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Methodological bias and study design influence the reported link between Vitamin-D deficiency and postoperative hypocalcemia

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ABSTRACT

Background: Post-thyroidectomy hypocalcemia is the most frequent complication after total thyroidectomy. Preoperative vitamin D deficiency has been suggested as a potential risk factor, but inconsistencies exist in the literature, possibly related to methodological differences. To evaluate whether study design and risk of bias influence the association between preoperative vitamin D deficiency and postoperative hypocalcemia in patients undergoing total thyroidectomy.

Methods: This is a secondary analysis of a previously conducted systematic review. We included observational studies evaluating the association between preoperative vitamin D levels and postoperative hypocalcemia. Methodological quality was assessed using the QUIPS tool. Subgroup analyses were performed based on study design (prospective vs. retrospective) and overall risk of bias (high vs. low/moderate).

Results: Twenty-eight studies comprising 4994 patients were included. Nineteen studies had a prospective design. Both prospective and retrospective studies showed an association between vitamin D deficiency and hypocalcemia; however, the effect size was lower in prospective studies (OR 1.95; 95% CI 1.28-2.97) compared to retrospective ones (OR 2.18; 95% CI 1.02-4.7). Studies with high risk of bias showed a significant association (OR 2.55; 95% CI 1.4-3.6), while those with low/moderate risk did not (OR 1.71; 95% CI 0.96-3.06).

Conclusion: Study design and methodological quality influence the reported association between vitamin D deficiency and postoperative hypocalcemia. These findings suggest caution when recommending preoperative vitamin D supplementation based solely on observational data.

Keywords: thyroidectomy; vitamin d deficiency; hypocalcemia; risk of bias; systematic review

Introduction

Thyroidectomy is the most frequently performed endocrine surgical procedure in the world [1]. Almost all of total thyroidectomy complications occur as a result of postoperative hypocalcemia [2]. Symptomatic temporary hypocalcemia is usually mild and transient, however permanent hypocalcemia could occur in almost 16% of patients [3], and is associated with prolonged hospital stay, reduced quality of life, and an increased use of resources. Advanced age, female sex, hyperthyroidism, inadvertent resection of the parathyroid glands, and low preoperative vitamin D levels have been sug-

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gested as risk factors for the development of postoperative hypoparathyroidism [4].

Vitamin D deficiency is frequent and asymptomatic because of a mix of poor dietary intake of Vitamin D-rich foods, malabsorption and inadequate exposure to natural sunshine. Individuals with vitamin D deficiency are more likely to develop hypocalcemia following thyroidectomy and several researchers have suggested preventive calcitriol and calcium treatment before surgery [5]. In a recent systematic review [6], we demonstrated that there is a threshold effect in the classification of vitamin D deficiency, which influences its association with postoperative hypocalcemia. Other factors to explore are differences in study design and methodological quality. There is considerable evidence in the literature that retrospective and observational studies inform a greater association between causal variables and outcomes than prospective and experimental studies [7]. Besides, studies having a high risk of bias are more likely to provide statistically significant results than those with a low risk of bias [8]. This support investigating this aspect as a possible moderator of the relationship between vitamin D deficiency and postoperative hypocalcemia.

Aims

The purpose of this study is to identify that study design characteristics are moderators in the causal association between preoperative vitamin D deficiency and the incidence of biochemical hypocalcemia in patients having total thyroidectomy. The present analysis builds upon a previously published systematic review but addresses specific methodological dimensions, such as study design, risk of bias, and the distribution of statistically significant outcomes, that were not prespecified or explored in the original protocol.

Methods and Material

This is a study that does not use patient data, and no evaluation by the research ethics committee was necessary. The methodology for this study was detailed in a previous publication, which examined the threshold effect in identifying vitamin D deficiency and its impact on the occurrence of hypocalcemia [6]. A systematic review of the literature was conducted following the Cochrane Collaboration and PRISMA methodology guidelines. Studies that described the preoperative measurement of vitamin D in adult patients undergoing total thyroidectomy and investigated its association with the development of postoperative hypocalcemia were included. There were no limitations on the publishing date, language, design, number of patients studied, or type of publication. Vitamin D levels were measured before surgery, as well as biochemical post-operative hypocalcemia using the study-specific method. The literature search included Medline, EMBASE, Google Scholar and LILACS databases, Finally, the selected studies were evaluated, and those that met the inclusion criteria were included. Data about methodological characteristics of the studies and the clinical characteristics of the patients were collected. The Quality In Prognosis Studies (QUIPS) instrument was used to assess the methodological quality of the studies. The RevMan 5.3 software was used (Review Manager (RevMan) [Computer program]. The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). For dichotomous outcomes, results were expressed as odds ratio (OR) with 95% confidence intervals using a random effects model. A subgroup analysis based on study design (prospective or retrospective), global methodological quality and domains from the QUIPS instrument was made to investigate the effect.

Statistical heterogeneity was estimated using the Higgins I^2 statistic. The results of the intervention effects are illustrated with a forest plot graph.

Results

After literature review 28 studies published between 2007 and 2022 were included [9-11,2,12-18,3,19-34]. The overall analysis included 4994 patients, categorized into two groups: 2256 with sufficient vitamin D levels and 2738 with vitamin D deficiency.

Study design

Nineteen studies (67%) had a prospective design [9,2,12-18,3,20-22,25-27,31-33], whereas the remainder were retrospective. Both types of designs found an association between vitamin D deficiency and postoperative hypocalcemia, but the magnitude of the effect was smaller in prospective studies (OR = 1.95 (1.28-2.97) vs. retrospective studies (OR = 2.18 (1.02-4.7)), though this was not statistically significant (p for subgroup differences = 0.8). (Fig. 1).

Risk of bias

The overall risk of bias of the studies included was suboptimal, with 17 (60%) falling into the high risk of bias group [9-11,2,13,18,3,23,27-30,32-34,14,21]. Studies with a high risk of bias found an association between vitamin D deficiency and postoperative hypocalcemia (OR 2.55 (95% CI 1.40-3.63), but those with a moderate or low risk showed no such association (OR 1.71 (95% CI 0.96-3.06), although this difference was not statistically significant (p for group comparison =0.48)

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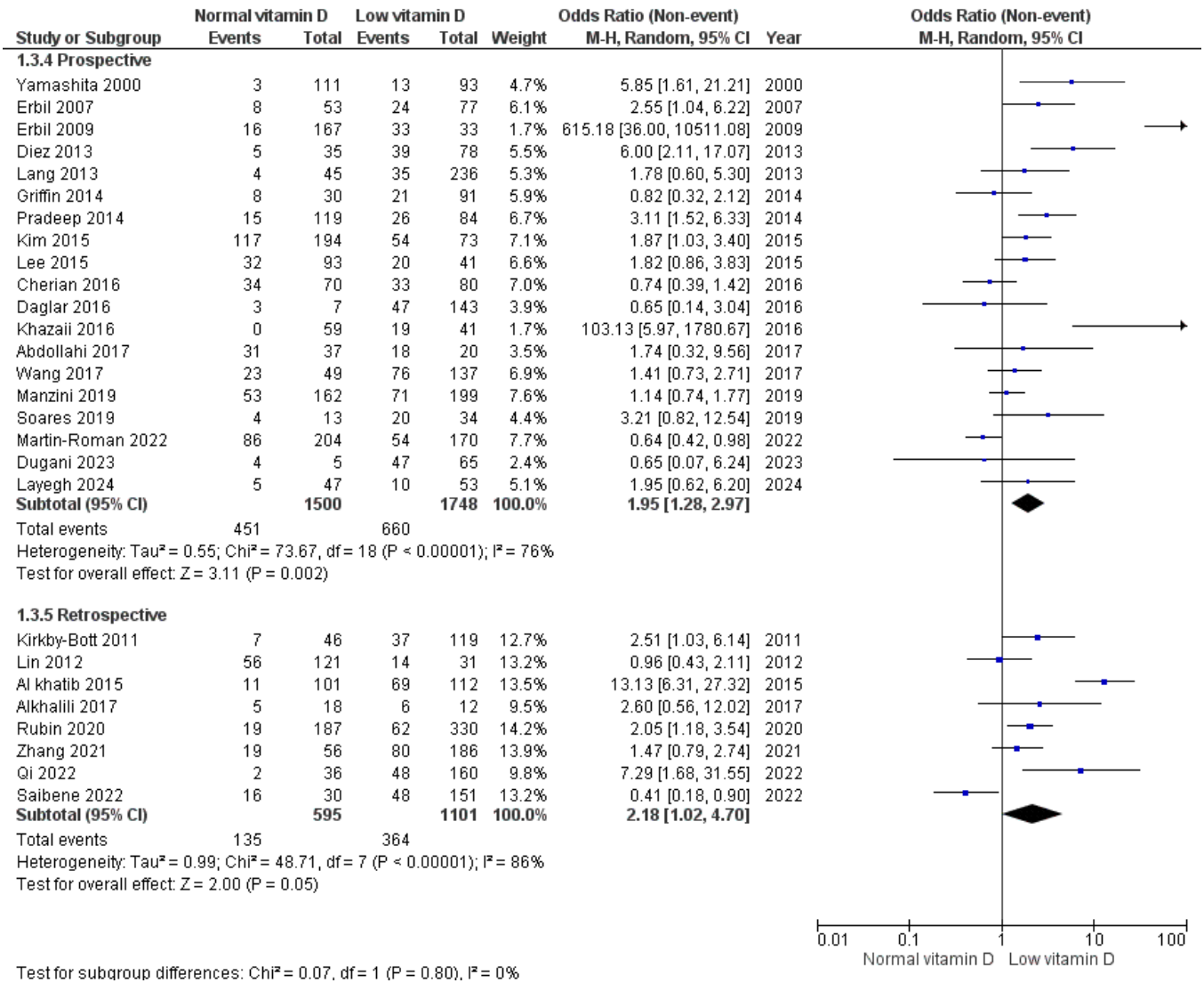

Fig. 1. Forrest plot comparing biochemical hypocalcemia and Vitamin D deficiency according to study design.

(Fig. 2).

Twenty-five percent of the studies were judged to have a high risk of bias in the study participation domain, 36% in the study attrition, 46% in the study confounding and 29% in the statistical analysis domain (Table 1).

The confounding domain revealed the most frequent flaws. There were significant shortcomings in the identification, definition, and measurement of potential clinical confounders (need for neck dissection) and co-interventions (use of autologous parathyroid transplantation, routine postoperative calcium administration), as well as the methods employed to adjust for the association. This is also relevant to statistical analysis and reporting, as the statistical studies did not apply adjustment models to test the causal association's independence. Studies with a confounding domain assessed as low/moderate risk of bias reported no link between vitamin D deficiency and hypocalcemia (OR 1.50 (95% CI 0.99-2.28) versus 2.92 (95% CI 1.55-5.51) (Fig. 3).

The attrition study domain major flaws were an inadequate description of the response rate, the lack of attempts to acquire information from patients who dropped out of the trial, and the description of the causes and characteristics of these patients. Studies with a low/moderate risk of bias in the study attrition domain demonstrated an association between hypocalcemia and vitamin D deficiency (OR 2.17 [95% CI 1.37–3.42] vs 1.84 [95% CI 0.94–3.60]) (Fig. 4).

Finally, in terms of selection bias, the most significant weaknesses were an inadequate description of the method used to identify the population, a lack of definition of specific inclusion and exclusion criteria, and a lack of information

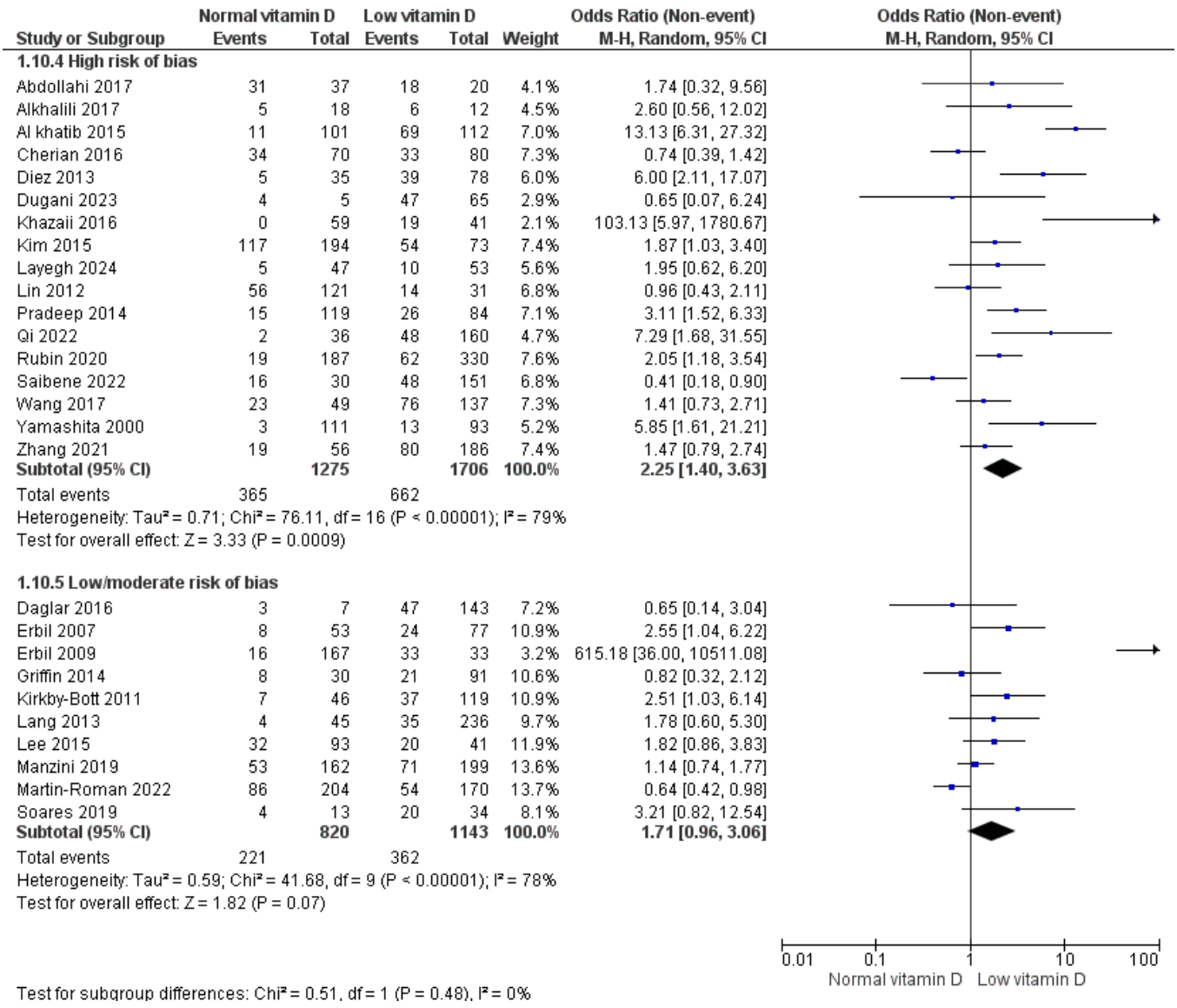

Fig. 2. Forrest plot comparing biochemical hypocalcemia and Vitamin D deficiency according to study risk of bias global evaluation.

about eligible individuals' participation. Studies categorized into a low/moderate risk of bias participation domain showed an association between vitamin D deficiency and hypocalcemia (OR 2.06 [95% CI 1.41–3.01] compared to 1.81 [95% CI 0.62–5.28]) (Fig. 5).

Discussion

We previously demonstrated the existence and impact of the threshold effect in defining vitamin D deficiency on its association with postoperative hypocalcemia [6], where a lower threshold corresponds to an increased incidence of hypocalcemia. Nonetheless, there are other aspects in the original studies, which have not been well assessed and may influence the strength of this association [5,11,17,35].

The literature provides information about the overestimation of association estimates in observational research compared to randomized clinical trials. Nonetheless, in causality research, employing a randomized approach is unfeasible due to clinical or ethical considerations. Consequently, other components of observational research design are pertinent, including direction (cohort or case-control studies), temporality (prospective vs retrospective), and risk of bias assessment. Cohort studies are superior to case-control studies due to the potential for improved data quality and lower susceptibility to biases, such as recall bias. This systematic review

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Table 1. Evaluation of Risk of Bias Using the Domains of QUIPS Tool

Study	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement	5. Study Confounding	6. Statistical Analysis and Reporting
Abdollahi	High	Low	High	Low	High	High
Alkhalili	High	High	Low	Low	High	High
Alkhatib	High	High	Low	Low	High	Moderate
Cherian	High	High	Low	Low	High	Moderate
Daglar	Low	Low	Low	Low	Moderate	Low
Diez	Moderate	Low	Low	Low	High	Low
Dugani	Low	Low	Low	Low	High	High
Erbil 2007	Low	Low	Low	Low	Moderate	Low
Erbil 2009	Low	Low	Low	Low	Moderate	Low
Griffin	Low	Low	Low	Low	Moderate	Low
Khazaii	Moderate	Moderate	Moderate	Low	High	High
Kim	Low	High	Low	Low	Moderate	Low
Kirbi	Moderate	Moderate	Low	Low	Moderate	Moderate
Lang	Low	Low	Low	Low	Low	Low
Layegh	Low	Low	Low	Low	High	High
Lee	Low	Low	Low	Low	Moderate	Low
Lin	Moderate	High	Low	Low	Moderate	Low
Malikarjuna	High	High	Low	Low	High	High
Manzini	Low	Low	Low	Low	Low	Low
Martin	Low	Low	Low	Low	Low	Low
Pradeep	Low	Low	Low	Low	High	High
Qi	Moderate	High	Low	Low	High	Moderate
Rubin	High	High	Low	Low	Moderate	Low
Saibene	High	High	Low	Low	Moderate	Low
Soares	Low	Low	Low	Low	Low	Low
Wang	Moderate	High	Low	Low	Moderate	Low
Yamashita	Low	Low	Low	Low	High	High
Zhang	Low	Low	Low	Low	High	Moderate
Number of high risk of bias studies	7	10	1	0	13	8
%	25%	36%	4%	0%	46%	29%

predominantly includes cohort studies, which improves the reliability of the results relative to other observational designs.

The relationship between the prospective or retrospective design of cohort studies and the risk of bias is among the most extensively examined methodological issues [36]. Prospective cohort studies are thought to be of greater quality than retrospective studies because they provide more exact control over the collection of causal variables, co-interventions, and outcomes while also ensuring the temporal link between exposure and outcome. However, this comes at the expense of a longer research time and the inability to collect an adequate number of subjects when outcomes are extremely infrequent [36]. Nonetheless, elements such as variability in the definitions of prospective versus retrospective studies and adequate compliance with additional factors, including the thorough collection of primary data, pertinent confounding variables, and appropriate statistical adjustments, indicate that the study design alone does not ensure high methodological quality [37]. Although this study included 67% of retrospective cohorts, it found that the design was not a statistically significant methodological factor in the relationship between vitamin D insufficiency and postoperative hypocalcemia. However, prospective studies had a lower effect size (OR 1.95 vs 2.18). This data suggests that while there is an association between vitamin D deficiency and hypocalcemia, its extent may be influenced by design considerations, indicating that future research should account for this condition to mitigate the possibility of overestimation.

The overall assessment of the risk of bias is an important

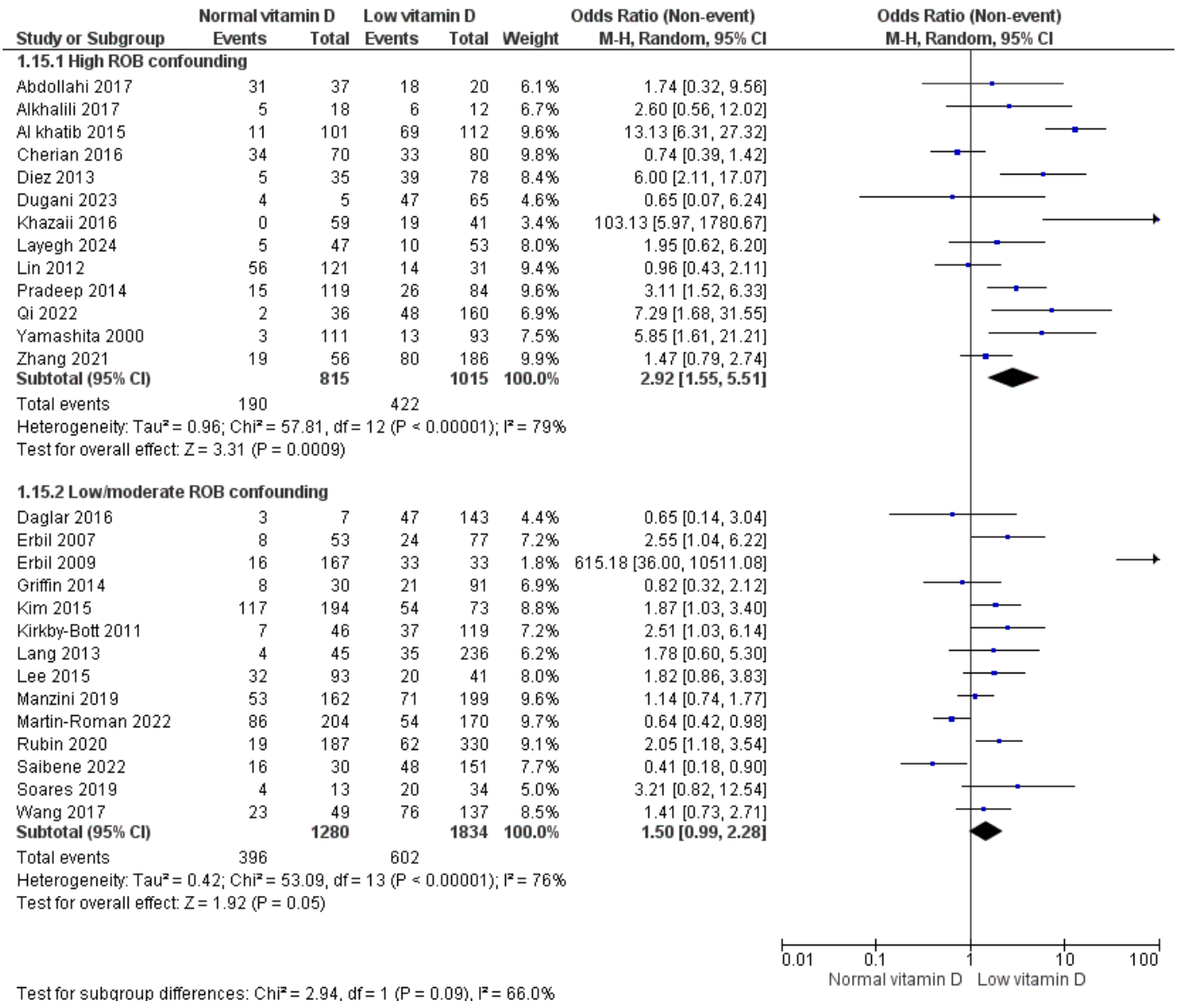

Fig. 3. Forrest plot comparing biochemical hypocalcemia and Vitamin D deficiency according to study risk of bias domain confusion.

component in the critical interpretation of observational study results [8]. A high risk of bias compromises the study's internal validity by adding distortions that might change the magnitude, direction, or even the presence of an association between exposure and result, establish false associations, or mask true effects. Even when the results are statistically significant, the study's ability to establish accurate causal conclusions is limited by the significant risk of bias.

Nineteen studies included in this systematic review were identified as having a high risk of bias, and it was possible to show that the association between vitamin D deficiency and postoperative hypocalcemia varies between studies with different methodological quality. This finding jeopardizes the established association between these two factors.

A more comprehensive review of the QUIPS domains that assessed the risk of bias provided some reasons. First, the most common weakness in primary research was adjustment for confounding factors. This bias happens when a variable has an association to both the exposure and the outcome without being part of the causal pathway, resulting in inaccurate estimations of the real effect. These deficiencies threaten the validity of impact estimates [38]. Gao et al. [39], examined 162 observational studies published between 2018 and 2023 and discovered that only 6.2% adopted the suggested approach of confounder correction for each exposure-outcome association. In this review, studies that did not adequately

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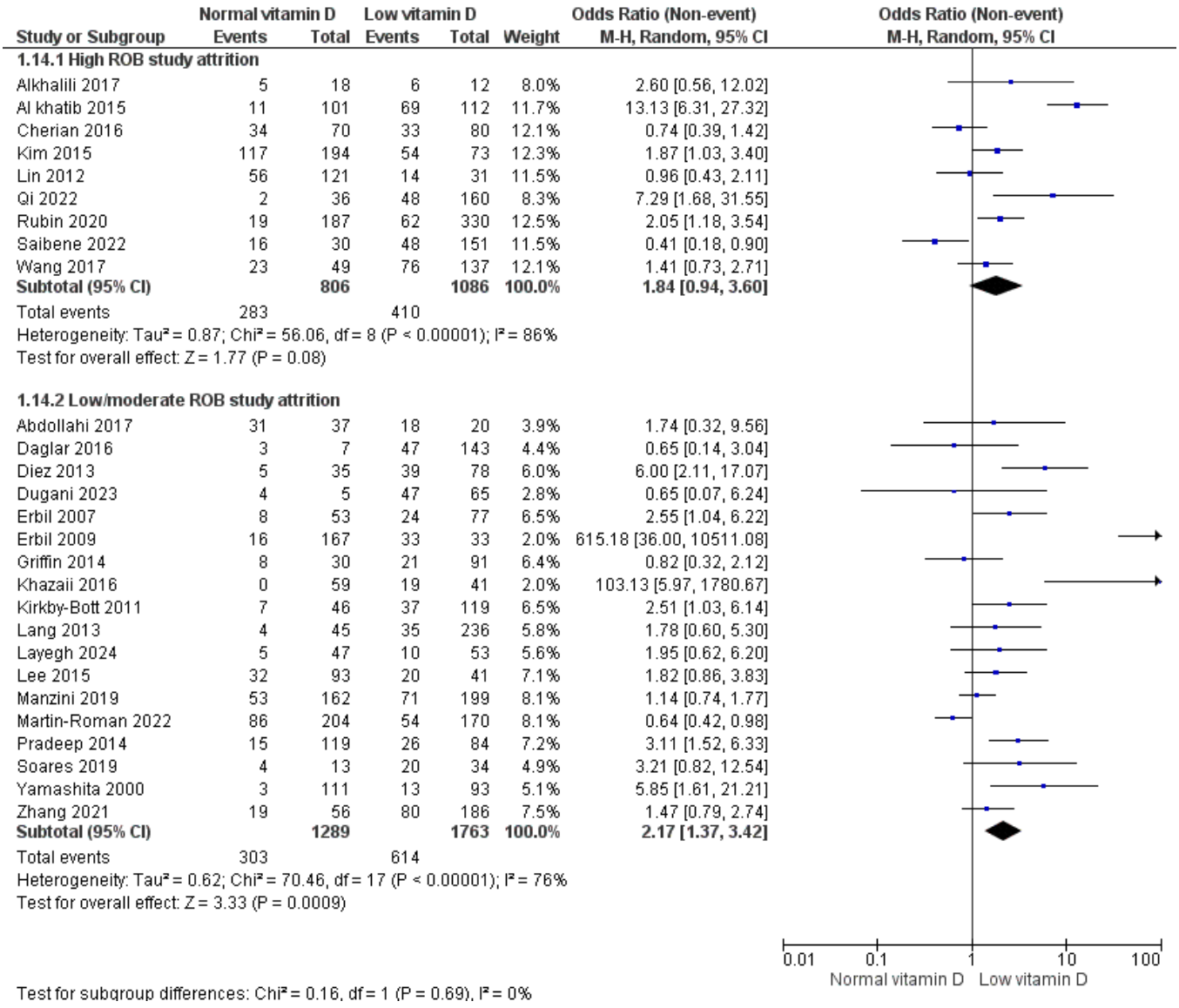

Fig. 4. Forrest plot comparing biochemical hypocalcemia and Vitamin D deficiency according to study risk of bias domain attrition.

adjust for clinical factors reported significantly stronger associations between vitamin D deficiency and hypocalcemia (OR 2.92; 95% CI: 1.55–5.51) than those with a low or moderate risk of bias in the confounding domain, where the association was inconclusive (OR 1.50; 95% CI: 0.99–2.28).

This study also found flaws in both selection and attrition bias [40]. In terms of selection bias, typical issues included a lack of a clear description of the population identification process, poorly defined inclusion and exclusion criteria, and insufficient information on eligible persons' participation. These methodological flaws could threaten the study's representativeness and provide erroneous associations if the inclusion probabilities are related to exposure or outcome. Studies with a low or moderate risk of bias in this area found a stronger link between vitamin D insufficiency and hypocalcemia (OR 2.06; 95% CI: 1.41-3.01) than those with a high risk (OR 1.81; 95% CI: 0.62-5.28). On the other hand, attrition bias was characterized by an inadequate description of the response rate, the absence of attempts to reach patients who fell out of follow-up, and a lack of information on the causes and characteristics of these losses. This omission may generate bias if patients who do not finish the research differ significantly from those who do. In fact, studies with a lower risk of attrition bias found a stronger association between hypocalcemia and vitamin D deficiency (OR 2.17; 95% CI: 1.37-3.42) than those with higher risk (OR 1.84; 95% CI: 0.94-3.60)

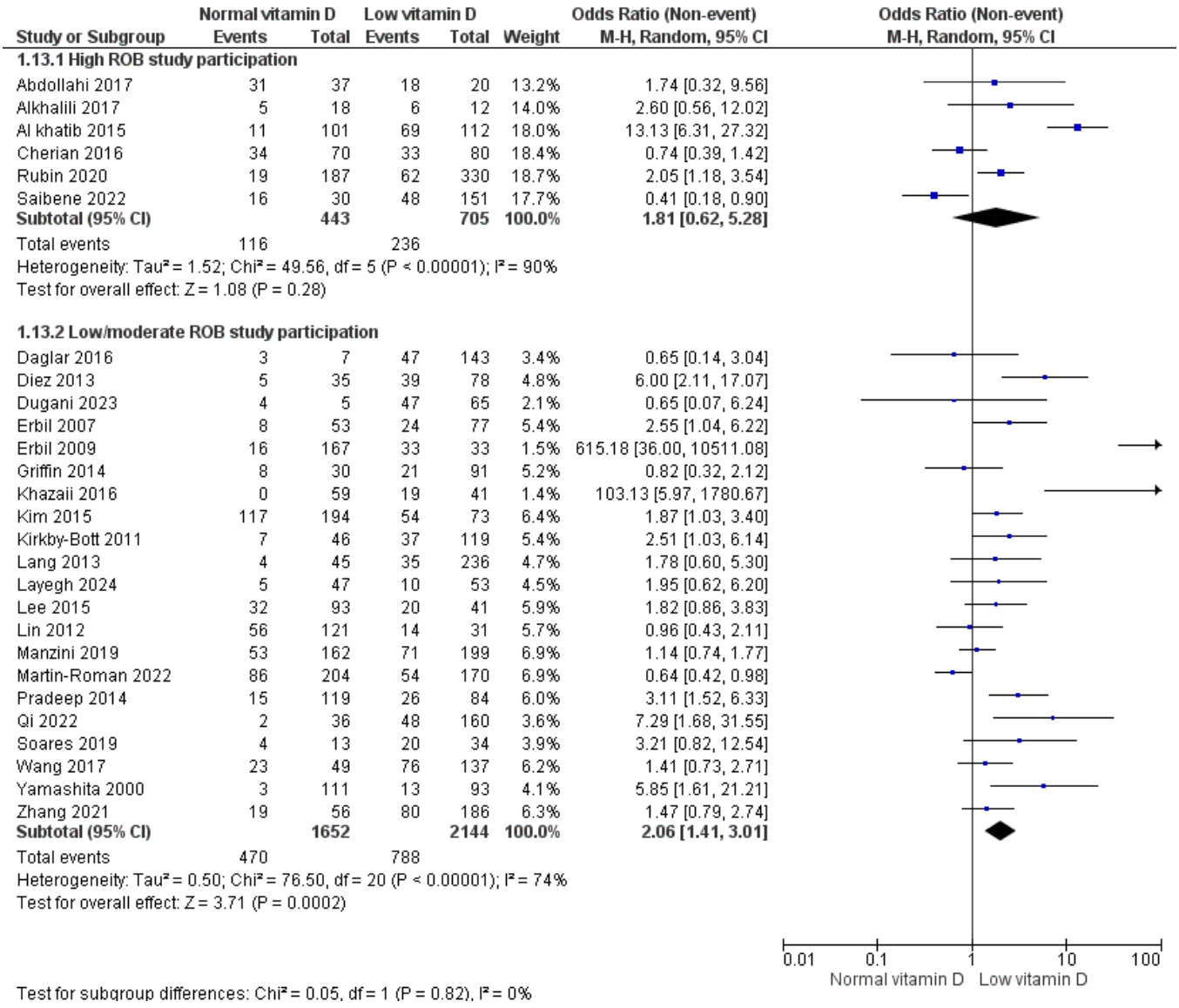

Fig. 5. Forrest plot comparing biochemical hypocalcemia and Vitamin D deficiency according to study risk of bias domain participation.

[41]. The findings of this study [6] indicate flaws in fulfilling some of requirements as size of the effect, specificity and experimental proof [5] and call into question the causal hypothesis between vitamin D deficiency with post-thyroidectomy hypocalcemia. They may also explain why trials evaluating preoperative prophylactic administration of vitamin D to prevent postoperative hypocalcemia have reached divergent conclusions [42]. Finally, it is a source of information that can be utilized to develop new research that addresses the flaws of existing ones.

The current study has various limitations due to its design as a secondary analysis of a systematic review, as it was not originally designed with the current research issue in mind. However, the primary review followed current recommendations for this type of study. Potential interactions between the domains used to assess risk of bias were also not investigated, making it impossible to determine which of these domains is more prominent.

Conclusion

This analysis demonstrates that the methodological quality and design of observational studies have an important influence on the magnitude of the established association between vitamin D insufficiency and postoperative hypocalcemia. Although a tendency toward a positive association

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is evident, it is more prominent in studies with a high risk of bias and retrospective designs. These findings stress the importance of caution when interpreting existing results in conjunction with development of new research with prospective designs, confounding control, and a comprehensive assessment of bias risk. Clinical decisions for vitamin D supplementation in the surgical setting should be based on individual clinical judgment rather than a presumption of causality.

Conflict of Interest

The author declares no conflict of interest.

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Data Availability Statement

Not applicable.

Ethics Approval and Consent to Participate

Not applicable.

Authors Contributions

Conceptualization: KL, AS. Data curation: KL, AS. Formal analysis: KL, AS. Methodology: KL, AS. Project administration: KL, AS. Visualization: KL, AS. Writing – original draft: KL, AS. Writing – review & editing: KL, AS.

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- Duration for the first decision: The result of the first peer review is usually finished within two months. If there is no correspondence from the editorial office on the fate of the submitted manuscript two months after the submission, please get in touch with the editorial office via ksebm.office@gmail.com
- Revision process: The Editorial Board may request authors to revise the manuscripts according to the reviewer's opinion. After revising the manuscript, the author should send the revised files with a reply to each item of the reviewer's opinion. Additions and amendments to the revised manu-

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- The publication date is published with all published papers, including dates of submission, revision, and acceptance.
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IV. Research and Publication Ethics Guidelines

For the policies on research and publication ethics, the "Good Publication Practice Guidelines for Medical Journals" (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13) or the "Ethical Guidelines on Good Publication" (http://publicationethics.org/resources/guidelines) or "Ethical Considerations in the International Committee of Medical Journal Editors" (http://www.icmje.org/recommendations) are applied.

1. Conflict-of-interest statement

The corresponding author is required to summarize all authors' conflict of interest disclosures. The disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (www.icmje.org/conflicts-of-interest). A conflict of interest may exist when an author (or the author's institution or employer) has financial or personal relationships or affiliations that could influence (or bias) the author's decisions, work, or manuscript. All authors should disclose their conflicts of interest, i.e., (1) financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony), (2) personal relationships, (3) academic competition, and (4) intellectual passion. These conflicts of interest must be included as a footnote on the title page or in the Acknowledgements section.

All funding sources should be declared on the title page or in the Acknowledgements section at the end of the text. If an author's disclosure of potential conflicts of interest is determined to be inaccurate or incomplete after publication, a correction will be published to rectify the originally published disclosure statement, and additional action may be taken as necessary.

If one or more editors are involved as authors, the authors should declare conflict of interest.

Ex) AAA has been an editor of the Journal of Evidence-Based Practice since 2017; however, he was not involved in the

peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

2. Statement of informed consent

Copies of written informed consents and Institutional Review Board (IRB) approval for clinical research are recommended to be kept. The editor or reviewers may request copies of these documents to clarify potential ethical issues.

3. Protection of privacy, confidentiality, and written informed consent

Identifying details should not be published in written descriptions, photographs, or pedigrees unless it is essential for scientific purposes and the patient (or his/her parents or guardian) provides written informed consent for publication. Additionally, informed consent should be obtained in the event that the anonymity of the patient is not assured. For example, masking the eye region of patients in photographs is not adequate to ensure anonymity. If identifying characteristics are changed to protect anonymity, authors should assure that alterations do not distort scientific meaning. When informed consent has been obtained, this should be indicated in the published article.

4. Protection of human and animal rights

In the reporting of experiments that involve human subjects, it should be stated that the study was performed according to the Helsinki Declaration of 1975 (revised 2013) (Available from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) and approved by the Institutional Review Board (IRB) of the institution where the experiment was performed. Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. Identifying details should not be published (such as name, initial of name, ID numbers, or date of birth).

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6. Reporting guidelines

The *J Evid-Based Pract* recommends that a submitted manuscript follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the EQUATOR Network (www.equatornetwork.org) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

7. Author and authorship

An author is considered to be an individual who has made substantive intellectual contributions to a published study and whose authorship continues to have important academic, social, and financial implications.

Authorship credit should be based on: (1) substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work; (2) the drafting of the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement on taking accountability for the accuracy or integrity of the work. Authors should meet these four criteria. and these criteria distinguish the authors from other contributors.

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When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship. Journals gener-

ally list other members of the group in the Acknowledgments section.

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Plagiarism is the use of previously published material without attribution. Prior to peer review, all manuscripts are screened for plagiarism by the Editor-in-Chief using iThenticate. When plagiarism is detected at any time before publication, the *J Evid-Based Pract* editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. Text copied from previously published work is interpreted using the following taxonomy:

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Use of verbatim text without identifying it as a direct quotation but citing the source

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Manuscripts are only accepted for publication if they have not been published elsewhere. Manuscripts published in this journal should not be submitted for publication elsewhere. Duplicate submissions identified during peer review will be immediately rejected, and duplicate submissions that are discovered after publication will be retracted. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

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V. Manuscript Preparation

J Evid-Based Pract recommends compliance with some or all of the following guidelines (https://www.equator-network.org).

CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)

STARD for reporting of diagnostic accuracy studies (http://www.stard-statement.org)

STROBE for reporting of observational studies in epidemiology (http://www.strobe-statement.org)

PRISMA for reporting of systematic reviews (http://www.prisma-statement.org)

MOOSE for reporting of Meta-analyses of observational studies (https://jamanetwork.com/journals/jamasurgery/article-abstract/2778476)

CARE for reporting of clinical cases (https://www.care-statement.org)

AGREE for reporting clinical practice guidelines (http://www.agreetrust.org/resource-centre/agree-reporting-checklist/)

ARRIVE for reporting of animal pre-clinical studies (https://arriveguidelines.org/arrive-guidelines)

1. Word processors and format of manuscripts

A manuscript must be written in proper and clear English. Our preferred file format is DOCX or DOC. Manuscripts should be typed double-spaced on A4-sized paper, using 12 point font in English.

2. Abbreviation of terminology

Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviated words should be provided at the first use, with the abbreviation following in parentheses. Common abbreviations may be used, however, such as DNA. Abbreviations can be used if they are listed as a MeSH subject heading (https://www.ncbi.nlm.nih.gov/mesh).

3. Word spacing

1) Leave 1 space on each side when using arithmetic marks such as +,–, ×, etc.
   Ex) 24 ± 2.5
   Leave no space when using a hyphen between words.
   Ex) intra-operative
2) When using parentheses, leave 1 space on each side.
3) When using brackets in parentheses, apply square brackets.

Ex) ([ ])

4. Citations

1) If a citation has 2 authors, write as "Hirota and Lambert". If there are more than 3 authors, apply "et al." at the end of the first author's surname.
   Ex) Kim et al. [1]
2) Citations should be applied after the last word.
   Ex) It is said that hypertension can be induced [1] and the way to injure the brain [2] is…
   Ex) Choi and Kim [1] reported…
3) Apply citations before a comma or period.
   Ex) ….is reported [1],
4) Several or coupled superscripts can be written as [1–5] or [1,3,5].

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The manuscript should be organized in the order of title, abstract, introduction, methods, results, discussion, acknowledgments, references, tables, figures, and figure legends. Figures should be uploaded as separate files. The title of each new section should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page of the manuscript. Page numbers should be placed in the middle of the bottom of the page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be included as a supplement in an appendix.

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1) Original Article

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① Title

Title should be concise and precise. The first word should be capitalized. Drug names in the title should be written with generic names, not brand names. For the title, only the first letter of the first word should be capitalized.

Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia …. [○]

Ex) Effect of Smoking on Bronchial Mucus Transport Velocity under Total Intravenous Anesthesia … [×]

Provide drug names as generic names, not product names.

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A running title should be provided with no more than 40 characters, including letters and spaces in Korean, or 10 words in English. If this title is inappropriate, the Editorial Board may revise it.

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Title of the conference, date of presentation, and the location of the conference may be described.

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All manuscripts should contain a structured abstract that is written only in English. Authors should provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Citation of references is not permitted in the abstract. A list of key words at least 6, with a maximum of 10 items, should be included at the end of the abstract. Key words should be selected from MeSH (https://www.ncbi.nlm.nih.gov/mesh), and these should be written in small letters with the first letter capitalized. Separate each word with a semicolon (;), and include a period (.) at the end of the last word.

Ex) Keywords: Carbon dioxide; Cerebral vessels; Oxygen; Spinal analgesia.

③ Introduction

The introduction should address the article's purpose concisely and include background information relevant to the paper's purpose.

④ Methods

The methods section should include sufficient details regarding the design, subjects, and methods of the research in order, as well as methods used for data analysis and control of bias in the study. Sufficient details must be provided in the methodology section of an experimental study so that others can further replicate it. The study design whether descriptive analysis, randomized controlled study, cohort study, or meta-analysis should be stated.

Materials and/or Participants: The materials used in the research should be clearly detailed to facilitate follow-up studies. Any materials purchased should be listed with the source or manufacturer. Research participants should also be precisely described with parameters such as age, sex, region, school, country, date of intervention period, occupation, etc. Reasons for inclusion or selection of participants should be explained. If a certain group was excluded, this should be explained as well. Questionnaires in non-English languages may also be included in the Appendix. Statistical analysis should be meticulously described. If reviewers want to analyze the data to confirm the results, the raw data may be provided to the editorial office. Computer programs used for the statistical analysis should be stated with the name, manufacturer, and software version used. Along with the statistical results, we encourage the inclusion of measurement error or uncertainty, such as listing confidence intervals in addition to providing P-values.

Institute and author names should be avoided.

When reporting experiments with human or animal subjects, the authors should indicate ethics statement whether they received approval from the Institutional Review Board for the study. If no IRB number is available, this should be discussed with the editor during the review process. When reporting experiments with animal subjects, the authors should indicate whether the Institutional Board supervised the handling of the animals for the Care and Use of Laboratory Animals.

Demographic data should be included in the materials and methods section if applicable. As a rule, subsection titles are not recommended. If several study designs were used, then subtitles can be used without assigning numbers.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer).

Authors should define how they determined race or ethnicity and justify their relevance.

- Units Laboratory information should be reported using the International System of Units [SI], available at: https://www.nist.gov/pml/special-publication-811

<Exceptions>

A. The unit for volume is "L", while others should be written as "dl, ml, μl".
   Ex) 1 L, 5 ml
B. The units for pressure are mmHg or cmH_2O.
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E. When more than 2 items are presented, diagonal slashes are acceptable for simple units.
   Negative exponents should not be used.
   Ex) mg/kg/min [O], mg・kg^{-1}・min^{-1} [×]
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   Ex) 5%, 36oC
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   Ex) hour: 1 h = 60 min = 3,600 s, day: 1 d = 24 h = 86,400 s

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  According to the 11th edition of the American Medical Association, provide the model name and manufacturer's name without the country.
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Results should be presented in a logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data provided in the tables or figures in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. The citation of tables and figures should be provided as Table 1 and Fig. 1.

Type or print each table on a separate page. Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files.

⑥ Statistics

Precisely describe the methods of statistical analysis

and computer programs used. Mean and standard deviation should be described as mean ± SD, and mean and standard error should be written as mean ± SEM. Median and interquartile should be described as median (1Q, 3Q). When displaying P values, use a capital P and do not put a "-" between "P" and "value".

A. Describe the statistical tests employed in the study in enough detail so readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

B. Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.

C. The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met.

For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

D. When analyzing a categorical variable, an exact test or asymptotic method with appropriate adjustments should be used if the number of events and sample is small. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and the number of events are sufficiently large.

E. The *J Evid-Based Pract* strongly encourages authors to show confidence intervals. and it is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.

F. Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (ex. P = 0.160 not as P = 0.16 or P < 0.05). If the value is less than 0.001, it should be described as "P < 0.001" but never as "P = 0.000." For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.

G. A priori sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.

H. When reporting a randomized clinical study, a CONSORT type flow diagram, as well as all the items in the CONSORT checklist, should be included. If limited in terms of the space of the manuscript, this information should be submitted as a separate file along with the manuscript.

I. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean (SD) of cardiac indices in patients measured on a scale that is accurate to 0.1 L/min/m^2 should be expressed as 2.42 (0.31) L/min/m^2.

J. Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.

⑦ Discussion

The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat in detail the results or other information that is provided in the introduction or the results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the discussion section.

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⑨ Authors' contributions

J Evid-Based Pract participates in the CRediT standard for author contributions. As such, the contribu-

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The corresponding author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions before this time.

Examples of authors' contributions:

- Conceptualization: OL.
- Data curation: OL.
- Formal analysis: GJC.
- Funding acquisition: OL.
- Methodology: OL HK GJC.
- Project administration: GJC.
- Visualization: OL HK GJC.
- Writing – original draft: OL GJC.
- Writing – review & editing: OL HK GJC.

⑩ Conflict of Interest

Any conflicts should be disclosed here. This statement must be included regardless of the existence of conflicts of interest. If the authors have nothing to disclose, please state: "No potential conflict of interest relevant to this article was reported."

⑪ Funding

Financial support, including foundations, institutions, pharmaceutical and device manufacturers, private companies, intramural departmental sources, or any other support, should be described.

⑫ Data Availability Statement

J Evid-Based Pract has implemented a mandatory data sharing policy, requiring authors to submit raw data or data files at the time of manuscript submission for editorial review. Manuscripts submitted without the required dataset will not proceed to peer review. These data are essential for verifying the accuracy of the analysis and ensuring the reproducibility of results. Authors must upload data files in csv, xls, xlsx, or txt format. If an alternative file format is necessary, prior approval from the editorial office is required. If data sharing is restricted due to agreements with the data provider or other justified reasons, authors must consult with the editorial office before submission to discuss alternative data-sharing arrangements.

⑬ Acknowledgments

Persons or institutes that contributed to the manuscript but not sufficiently to be co-authors may be recognized.

⑭ Supplementary Materials

If supplementary materials are available, either to aid in reader understanding or because data are too abundant for inclusion in the main text, these may be included as supplementary data. Data files, as well as abstract recording, text, audio, or video files, can be added here.

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A. Regular journal

- Author name. Title of article. Name of journal published year; volume: start page-final page.
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  Ex) Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 1996; 77: 741-4.
  Ex) Kang JG, Lee SM, Lim SW, Chung IS, Hahm TS, Kim JK, et al. Correlation of AEP, BIS, and OAA/S scores under stepwise sedation using propofol TCI in orthopedic patients undergoing total knee replacement arthroplasty under spinal anesthesia. Korean J Anesthesiol 2004; 46: 284-92.
- Journal article volume with supplement
  Ex) Doherty JS, Froom SR, Gildersleve CD. Pediatric laryngoscopes and intubation aids old and new. Paediatr Anaesth 2009; 19 Suppl 1: 30-7.
- Journal article issue with supplement
  Ex) Lee S, Han JW, Kim ES. Butyrylcholinesterase deficiency identified by preoperative patient interview. Korean J Anesthesiol 2013; 65(6 Suppl): S1-3.

B. Monographs

- Author. Book name. Edition. Place, press. Published year, pp (start page)-(End page).
- If reference page is only 1 page, mark 'p.'
- Note if it is beyond the 2nd edition.
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C. Chapter

Any separate author of a chapter should be provided.
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D. Electronic documents

Ex) Grainge MJ, Seth R, Guo L, Neal KR, Coupland C, Vryenhoef P, et al. Cervical human papillomavirus screening among older women. Emerg Infect Dis [serial on the Internet]. 2005 Nov [2005 Nov 25]. Available from wwwnc.cdc.gov/eid/article/11/11/05-0575_article.

E. Online journal article

Ex) Sampson AL, Singer RF, Walters GD. Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. Cochrane Database Syst Rev 2017; 10: CD009460.

F. Advance access article

Ex) Baumbach P, Gotz T, Gunther A, Weiss T, Meissner W. Chronic intensive care-related pain: Exploratory analysis on predictors and influence on health-related quality of life. Eur J Pain 2017. Advance Access published on Nov 5, 2017. doi:10.1002/ejp. 1129.

The reference style for *J Evid-Based Pract* is conveniently available as an out-of-the-box style within both EndNote and RefWorks.

⑯ Tables

Only one table is to be drawn per page in the order cited in the text.

The title of the table is to be in English and written at the top of the table in the form of a phrase.

Words in the table excluding the title should use capital letters for the first word, and the following words are to be written in small letters.

For demographic data, gender is recorded as M/F, age as yr, (if necessary, use days or months in children) without decimal point. The "±" sign within the table is to be aligned with the rows above and below.

Footnotes are to be written in the following order: "Values are mean ± SD (or SEM) or median (1Q, 3Q)", the explanations for the groups and the abbreviations in order of appearance, and statistics. Abbreviations apart from internationally recognized abbreviations are to be explained with their full spellings at the bottom of the table. Full spellings are to be presented even for repeated abbreviations for each table in order of appearance.

Significance marks are to conform to the Vancouver style (Uniform Requirements for Manuscripts Submitted to Biomedical Journals. JAMA 1997; 227: 927-34). In other words, these must be in the order of *, †, ‡, §, ∥, ¶, **, ††, ‡‡ and written as superscripts.

⑰ Legends for figures and photographs

All of the figures and photographs should be described in the text separately.

The description order is the same as in the footnotes in tables and should be in recognizable sentences.

Define all abbreviations every time they are repeated.

(3) Figures and Photographs

① JBEP encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to frame the image clearly. Axis labels should be large enough to be easily readable, and printed in black.
③ Figures should be uploaded as separate tif, jpg, pdf, gif, or ppt files. The width of figure should be 84 mm (one column). The contrast of photos or graphs should be at least 600 dpi. The contrast of line drawings should be at least 1,200 dpi. Number figures as "Fig. (Arabic numeral)" in the order of their citation (ex. Fig. 1).
④ Photographs should be submitted individually. If Fig. 1 is divided into A, B, C, and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.
⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.
⑥ Connections between numbers should be denoted by "–", not "~". Do not space the numbers (ex. 2–4).
⑦ An individual should not be recognizable in photographs or X-ray films unless written consent has been obtained from the subject and is provided at the time of submission.
⑧ Pathological samples should be pictured with a measuring stick.

2) Review

This review article synthesizes previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles are invited only by editorial board. If authors want to submit an unsolicted review article, please contact editorial office (ksebm.office@gmail.com). Review articles should include unstructured abstracts written in English equal to or less than 250 words. The organization should be in order of abstract, introduction, text following each title, conclusion and references. Figures and tables should be provided in English. Body text should not exceed 30 A4-sized pages, and the number of figures and tables should each be less than 6. However, if necessary, the number of pages, the number of figures and tables can be added in accordance with the decision of the editorial committee.

3) Systematic review and meta-analysis

Systematic review and meta-analysis are considered as an original article. Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitle should include the phrase "A systematic review" and/or "A Meta-analysis." Organization of systematic review and meta-analysis: Same as original article, except,

- All systematic reviews and meta-analyses should be registered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission. Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.
- Number of references has no limitation in systematic review and meta-analysis.

4) Case Report

A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible. Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Copies of written informed consents should be kept. If necessary, the editor or reviewers

may request copies of these documents. If these steps are impossible, Institutional Review Board approval should be obtained prior to submission. The rarity of a disease condition is itself not an acceptable justification for a case report. Statement describing compliance with CARE for reporting of clinical cases (https://www.care-statement.org) guideline is recommend.

(1) Cover page: Same as that for clinical and experimental studies.
(2) Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a Minimum of 6, should be included at the end of the abstract.
(3) Introduction: Should not be separately divided. Briefly describe the case and background without a title.
(4) Case report: Describe only the clinical information that is directly related to the diagnosis and anesthetic management.
(5) Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
(6) References: The number of references should be less than 20. However, if necessary, the number of reference can be added in accordance with the decision of the editorial committee.
(7) Tables and figures: Proportional to those for clinical and experimental studies.

5) Letter to the Editor

Letter to the Editor should include brief constructive comments that concern previously published articles and interesting cases. Letters to the Editor should be submitted no more than 3 months after the paper has been published.

(1) Cover pages should be formatted in the same way as those of clinical research papers. The corresponding author should be the first author. A maximum of five authors is allowable.
(2) The body text should not exceed 1,000 words and should have no more than 5 references. A figure or a table may be used.
(3) Letters may be edited by the Editorial Board, and if necessary, responses by the author of the subject paper may be provided.

6) Editorial

Editorial is invited by the editorial committee and should be commentaries on articles recently published in the *J Evid-Based Pract*, and can be described in free style.