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Exogenous Melatonin and Sleep Quality: A Scoping Review of Systematic Reviews

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Abstract

Melatonin is increasingly used to treat sleep disturbances, yet its overall efficacy remains unclear due to variability in existing evidence. This scoping review aimed to synthesize systematic reviews with meta-analyses assessing the effects of exogenously administered melatonin on sleep quality in humans. Seven databases were searched from inception to July 9, 2025. Eligible studies were systematic reviews containing at least one meta-analysis evaluating melatonin's effects on any domain of sleep quality compared to any comparator. Fifty-seven systematic reviews were included, comprising 227 meta-analyses. Overlap in primary studies was low (corrected covered area = 2.5%), suggesting that reviews drew on largely distinct evidence bases. Methodological quality was variable: only 8.8% of reviews met all seven predefined criteria for rigor, including protocol pre-registration, dual screening, and bias assessments. Vote counting based on the direction of effect was used to summarize efficacy. Of the 215 meta-analyses comparing melatonin to an inactive comparator, 80.9% favored melatonin, 7.9% favored the comparator, and 11.2% reported unclear results. Sleep quality was assessed using heterogeneous definitions and tools, with few reviews evaluating overall sleep quality directly. Adverse events were commonly reported and generally mild, with headaches, gastrointestinal problems, and dizziness most frequently observed. However, inconsistent terminology and reporting limited synthesis. Despite heterogeneity in review methods and outcome definitions, the direction of evidence consistently favored melatonin over placebo. These findings support the feasibility of a future quantitative umbrella review to estimate pooled effects and guide clinical practice.

Keywords

autism spectrum disorder, circadian rhythm, dementia, melatonin, sleep hygiene, sleep quality

Introduction

Sleep is essential for both physical and mental well-being. Good sleep quality supports cognition, memory consolidation, immunity, reproductive health, and hormone regulation.[1] Conversely, inadequate sleep has been linked to cardiovascular disease, stroke, and hypertension,[2] obesity and type 2 diabetes,[3] and an increased risk of infectious and inflammatory diseases, contributing to all-cause mortality.[4] Sleep abnormalities are common across various medical conditions,[5] affecting individuals throughout the lifespan, from children[6] and adolescents[7] to adults[8] and older adults.[9]

Treatments for insomnia include both non-pharmacological and pharmacological approaches. Non-pharmacological interventions focus on behavioral and environmental modifications, including sleep hygiene, sleep–wake scheduling, timed physical activity, light therapy, somatic interventions, and cognitive-behavioral therapy.[10,11] These interventions are recommended as first-line treatments in guidelines from the British Association for Psychopharmacology, the European guidelines for the diagnosis and treatment of insomnia, the American College of Physicians, and the American Academy of Sleep Medicine.[12]

Pharmacological treatments include antihistamines (e.g., promethazine) and benzodiazepine receptor agonists, which encompass both benzodiazepines (e.g., temazepam) and non-benzodiazepines or z-drugs (e.g., zopiclone). However, these medications present risks such as an increased likelihood of falls, headaches, nausea, drug interactions, and dependence.[13]

Melatonin is an endogenous hormone secreted by the pineal gland that regulates sleep cycles. Exogenous melatonin is used to treat insomnia and is licensed as either a dietary supplement (e.g., by the US FDA) or a medicine (e.g., by the EMA), depending on the country. As an agonist of melatonin MT1 and MT2 receptors, exogenous melatonin is believed to regulate sleep through receptor activation in the hypothalamic suprachiasmatic nucleus.[14] Several trials and reviews

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have investigated melatonin's efficacy in treating insomnia, with a recent synthesis of 14 reviews reporting statistically significant improvements in sleep latency and mixed findings for total sleep time.[15]

Melatonin is generally considered safe, with no serious adverse effects reported.[13] Mild side effects, such as dizziness, headache, nausea, and drowsiness, have been noted for both short- and long-term use.[16] Unlike benzodiazepines, melatonin does not appear to cause drug dependence.[13,15,16] Consequently, melatonin is becoming an increasingly popular pharmacological adjunct to non-pharmacological insomnia treatments, particularly among individuals who experience adverse effects with other hypnotics.

Umbrella reviews (also referred to as overviews, reviews of reviews, or meta-reviews) synthesize findings from systematic reviews rather than primary research studies.[17] They provide broad summaries of research areas, making them particularly useful in fields with a rapid expansion of literature.[18] The body of research on exogenous melatonin's efficacy in improving sleep quality exemplifies such an expanding field, as interest in both sleep quality and melatonin has surged in recent years. The COVID-19 pandemic led to a marked increase in sleep disturbances due to stress and anxiety,[19] giving rise to terms such as "coronasomnia"[20] and "COVID-somnia."[21] Additionally, melatonin has been investigated for its potential broader health benefits beyond sleep,[22] including its role in mitigating the effects of COVID-19.[23] Consequently, the volume of literature on melatonin and sleep has grown substantially in the past 5 years, necessitating a comprehensive up-to-date review of systematic reviews on melatonin and sleep quality.

A recent umbrella review specifically examining melatonin's effects on insomnia across various populations and conditions was published in 2020 and synthesized literature up to 2018.[15] This umbrella review included 14 systematic reviews on melatonin and one on Circadin. The findings suggested statistically significant improvements in sleep latency, with less consistent evidence for total sleep time. While this earlier review provided a valuable synthesis of existing evidence, it focused specifically on insomnia as a formal diagnosis and synthesized findings primarily on sleep latency and total sleep time. In contrast, our review is broader in scope: we examine the role of melatonin in improving sleep quality more generally, including sleep initiation, maintenance, duration, and refreshment upon awakening. To our knowledge, this is the first scoping review of systematic reviews to map how sleep quality has been conceptualized and measured across the melatonin literature.

Given the uncertainty regarding the scope of systematic review literature on melatonin's efficacy in improving sleep quality, this study aims to clarify: (i) the range of populations reviewed, (ii) the range of conditions reviewed, (iii) the heterogeneity in the concept and assessment of sleep quality, (iv) the degree of review overlap, and (v) evidence for efficacy beyond sleep latency and total sleep time that does not rely on vote counting based on statistical significance (i.e., counting the number of statistically significant results).[24]

To address these points, we conducted a scoping review of systematic reviews. We include only systematic reviews that contain at least one meta-analysis, which allows us to assess the feasibility of a future quantitative synthesis via meta-analysis.

Methods

Research Question

We aimed to identify and summarize all systematic reviews with meta-analyses of evidence of exogenously administered melatonin's efficacy in improving sleep quality in humans. Our research question, structured using the PICOS (Population, Intervention, Comparator, Outcome, Study design) framework, was (i) humans as population, (ii) exogenously administered melatonin as intervention, (iii) any comparator, (iv) measures of sleep quality as outcome, and (v) systematic reviews with meta-analyses as study design. This study did not involve human subjects or individual patient data and, therefore, did not require ethical approval.

Protocol Development

The protocol for this review was written according to PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses—Protocol extension) guidelines[25] and was pre-registered on the Open Science Framework (OSF) on January 28, 2025.[26]

Eligibility Criteria

We provide a full list of our eligibility criteria in Table S1. We included systematic reviews with meta-analyses of primary empirical studies with any study design and without any restriction related to publication date or language. We excluded primary research, narrative reviews, umbrella reviews (i.e., reviews of systematic reviews), systematic reviews that do not include a meta-analysis exploring the effect of exogenously administered melatonin on a measure of sleep quality, and gray literature.

Literature Searches

We searched seven bibliographic databases: MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), CINAHL (EBSCO Industries), Scopus (Elsevier), Cochrane Database of Systematic Reviews (Cochrane Library), and Epistemonikos (Epistemonikos). Databases were searched from inception to July 9, 2025.

For electronic searches, the search strategy was initially developed in MEDLINE, and then translated for other databases. The search focused on the combination of three core topics: melatonin, sleep, and systematic reviews. The search strategies were independently peer-reviewed using the PRESS Checklist by an Outreach Librarian at the Bodleian Health Care Libraries, University of Oxford.[27] All search strategies are presented in full in Supplemental Information.

We used EPPI-Reviewer (Evidence for Policy and Practice Information and Co-ordinating Reviewer) for de-duplication and screening.[28] Study selection was a two-stage process: screening on title and abstract, followed by screening on full text. Screening was carried out in duplicate by two independent reviewers, with any unresolved disagreements between the reviewers being settled by a third reviewer.

Data Extraction and Synthesis

Data extraction was performed by one reviewer and then verified by a second reviewer, with any unresolved disagreements between both reviewers settled by a third reviewer.

We pre-defined an idealized systematic review as meeting seven methodological criteria, which are in line with most guidelines:[29–32] (i) having a pre-registered protocol, (ii) searching more than one database, (iii) providing a search strategy in full for at least one database, (iv) screening of literature to involve more than one reviewer, (v) data extraction to involve more than one reviewer, (vi) an assessment of risk of bias of included studies, and (vii) an assessment of publication bias (see Supplemental Information). We pre-defined a meta-analysis as a statistical combination of results from two or more separate studies yielding a summary quantification of the intervention effect; the statistical modeling should involve inferential statistics, either conditional or unconditional inferences (e.g., equal-, fixed-, random-, or mixed-effects models are all included).[33]

We assessed the extent of primary study overlap between included systematic reviews using corrected covered area (CCA),[17] with standard interpretative benchmarks.[34]

Sleep quality was defined in accordance with the National Library of Medicine's MeSH term database[35] and other sources:[36] Sleep quality is satisfaction with the sleep experience, and integrates aspects of sleep initiation, sleep maintenance, sleep quantity, and refreshment upon awakening. To improve transparency, we have added a mapping of commonly used terminology in the literature to these four sleep quality domains (see Table S2). For example, terms such as sleep latency and sleep onset latency are categorized under sleep initiation, while total sleep time and related measures are classified under sleep quantity. We categorized age into three groups: children (0–18 years), adults (>18 years), and older adults (>65 years).[37] We categorized comparators as inactive or active, in line with the Cochrane Handbook,[38] where inactive comparators included placebo, no treatment, or standard care, while active comparators included a different drug, sleep-aiding intervention, or therapy. We classified melatonin dose into low (up to 3 mg), medium (3–5 mg), and high (5 mg and higher).

To identify similar groupings of systematic reviews, we used the citation matrix developed for CCA analysis to perform a hierarchical cluster analysis using the Ward method, where clustering is based on Pearson correlation coefficients.

We assessed the efficacy of melatonin in treating sleep disturbances using vote counting based on the direction of effect, which answers the question "*is there any evidence of an effect?*"[24] While this approach does not quantify effect size, it provides a high-level summary of the balance of evidence, which is appropriate for a scoping review. To focus on the absolute efficacy of melatonin (rather than its relative efficacy compared to other interventions), we restricted our analysis to meta-analyses that compared melatonin to inactive comparators.

We first summarized the overall direction of effect across these meta-analyses and tested whether the observed proportion favoring melatonin differed from chance using a two-sided sign test (binomial test under the null hypothesis of $P = .5$).[24]

To explore whether the direction of effect varied systematically across subgroups, we compared the proportions of positive versus negative directions across three levels of three variables: (i) aspect of sleep quality (sleep quantity, sleep initiation, and sleep maintenance), (ii) melatonin dose (low, medium, high), and (iii) age (children, adults, older adults). These subgroup comparisons were also limited to studies with inactive comparators and were tested using Fisher's exact test ($\alpha = .05$).

All statistical analyses were post hoc and should be interpreted with caution due to the potential for both Type I (false positives) and Type II (false negatives) errors.

To assess adverse events, we quantified the number of reviews in which particular adverse events were reported. To improve transparency, we have added a mapping of commonly used adverse events terminology in the literature to the terms used in the current review (Table S3). For example, terms such as gastrointestinal upset and tummy aches are categorized under gastrointestinal problems, while nightmares, bad dreams, and related measures are classified under nightmares. Due to the heterogeneity of reporting, it was not possible to

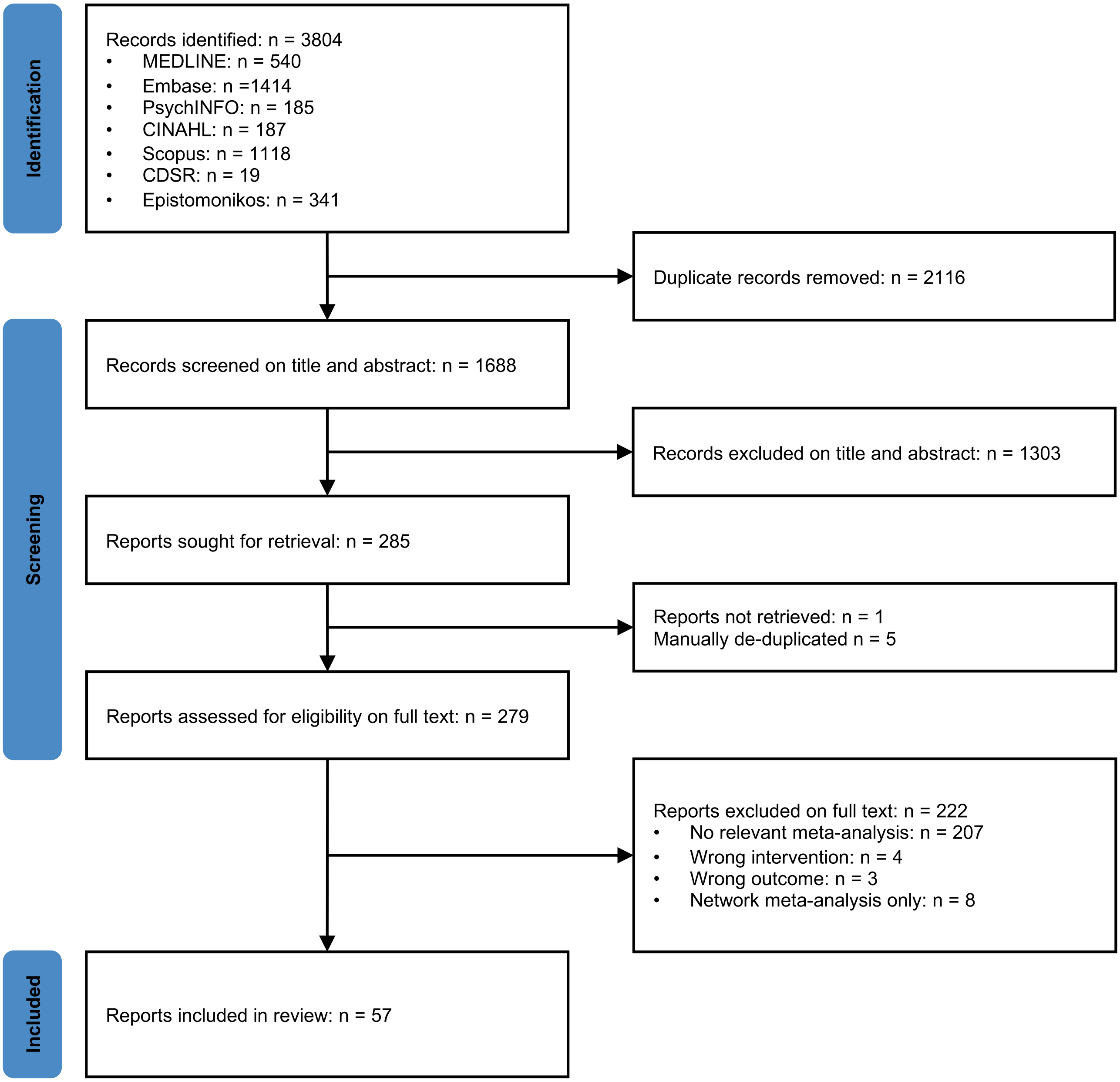

Figure 1. PRISMA flow diagram. CDSR, Cochrane Database of Systematic Reviews; CINAHL, Cumulative Index to Nursing and Allied Health Literature; MEDLINE, Medical Literature Analysis and Retrieval System Online; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

assess the duration or severity of adverse events or to assess the causality.

Results

Systematic Review Characteristics

Of the 1688 records screened, we identified 57 systematic reviews relevant to this scoping overview, encompassing 227 meta-analyses (Figure 1).[13,39–94]

The systematic reviews were published over a 21-year period (2004–2025), with an average publication rate of fewer than three reviews per year (Figure 2a). However, there was a notable surge in publications between 2022 and 2023, with an average of 11 systematic reviews per year during this period.

The degree of review overlap, estimated using CCA, was 2.5% (N = 513 total citations, r = 212 unique primary studies, c = 57 systematic reviews). A CCA value between 0% and 5% indicates slight overlap, suggesting that the included reviews largely drew from distinct sets of primary studies (Figure 2b).

Only 5 out of 57 (8.8%) systematic reviews met all seven predefined methodological criteria, while 8 out

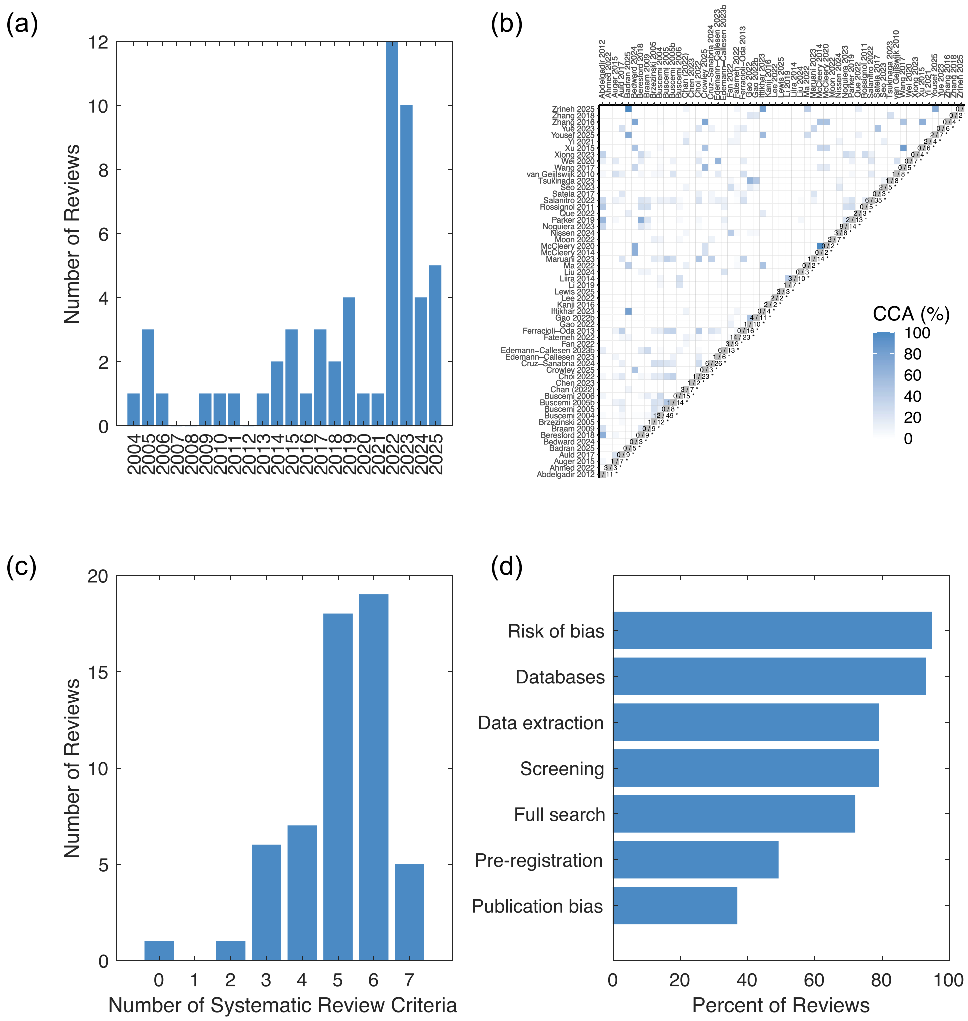

Figure 2. Systematic review characteristics. (a) The number of systematic reviews (y-axis) published per year (x-axis). (b) The citation matrix visualizes the degree of similarity in primary literature for all 57 systematic reviews. Each cell in the matrix indicates the corrected covered area (CCA), which provides a numerical measure of the extent of primary study overlap between the systematic reviews. The numbers on the diagonal indicate the number of single primary studies for that review in the numerator and the total number of primary studies for that review in the denominator. For example, 3/7 indicates that a review included seven primary studies in total, but only three were unique to that review. The CCA value for the overall citation matrix was 2.5%, indicating only slight overlap among reviews in this overview. (c) The number of systematic reviews (y-axis) that met systematic review criteria. Only five of 57 systematic reviews met all seven systematic review criteria. (d) The percent of reviews (x-axis) that met each individual systematic review criterion.

of 57 (14.0%) met fewer than half of these criteria (Figure 2c). Among the seven criteria, the most met were risk of bias assessment and searching multiple databases, while the least commonly met were pre-registration of review protocols and publication bias assessment (Figure 2d).

Sleep Quality

Overall sleep quality was assessed in 15.0% of reported meta-analyses (Figure 3a). However, most meta-analyses focused on individual components of sleep quality: sleep quantity (37.0%), sleep initiation (26.4%), sleep maintenance (13.7%), and refreshment upon awakening (4.4%). Other less frequently analyzed measures included circadian entrainment, light-off time, time in bed, and wake-up time, collectively accounting for 3.5% of reported meta-analyses.

The most common methods used to assess sleep quality were: actigraphy, sleep diaries, polysomnography, and questionnaires. These four methods constituted 86.1% of reported assessment approaches (Figure 3b).

Populations and Conditions

Approximately one-third of reported meta-analyses grouped adults and children in the pooled analysis. A total of 40.1% of pooled studies were on adults

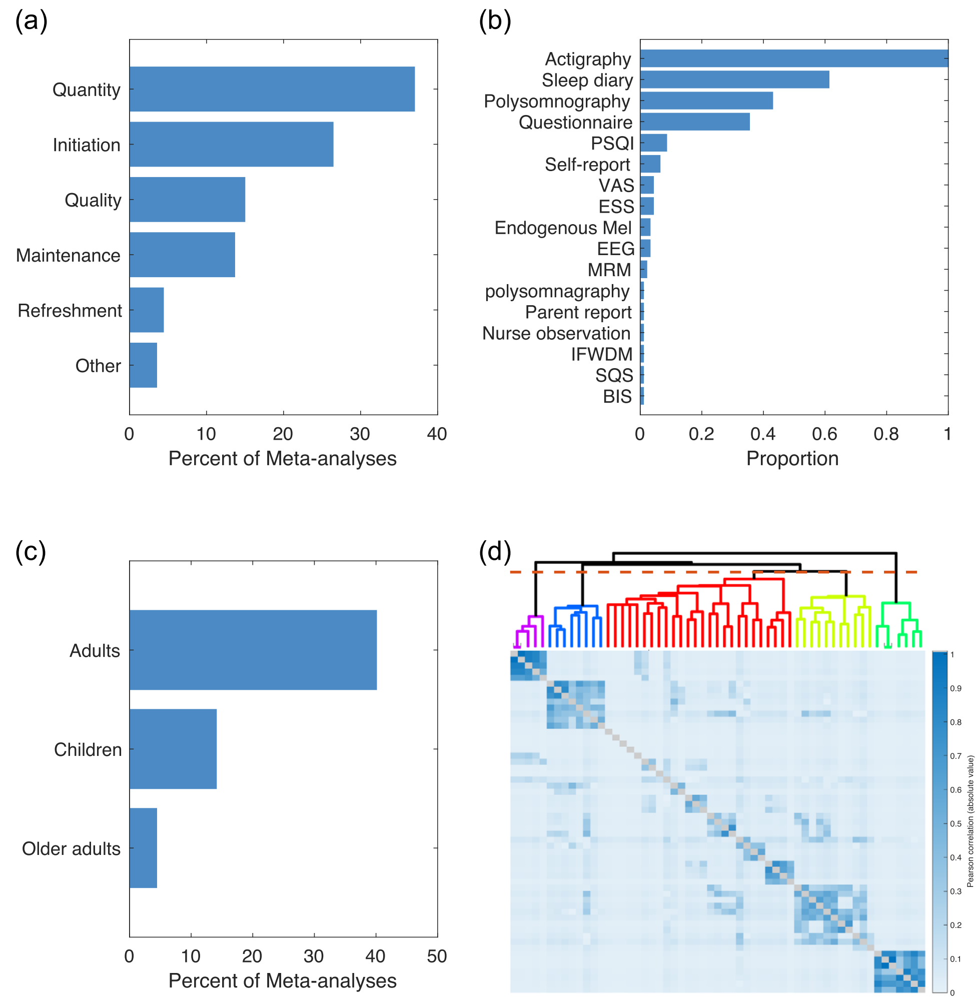

Figure 3. Sleep quality, study population ages, and sleep disorder conditions. (a) Sleep quality can be defined as satisfaction with the sleep experience, and integrates aspects of sleep initiation, sleep maintenance, sleep quantity, and refreshment upon awakening. Of the meta-analyses assessed in this overview (x-axis), sleep quantity was assessed most often, followed by sleep initiation, then sleep maintenance, and then refreshment upon awakening. Other measures of sleep quality that did not fit easily into these sleep quality aspects included circadian entrainment, light-off time, time in bed, and wake-up time. (b) The most reported method for assessing sleep quality or aspects of sleep quality was actigraphy. The proportions (x-axis) are plotted relative to actigraphy. EEG, electroencephalography; endogenous Mel, endogenous melatonin; VAS, visual analogue scale; MRM, muscle relaxation monitoring; IFWDM, index finger switch depression method; SQS, sleep quality scale; PSQI, Pittsburgh sleep quality index; BIS, bispectral index. (c) The percent of meta-analyses (x-axis) that pooled primary studies on adults only (>18 years), children only (<18 years), or older adults only (>65 years). (d) The systematic review citation matrix was used to generate a correlation matrix based on primary studies, and the correlation matrix was reorganized using hierarchical cluster analysis to identify clusters of systematic reviews of similar primary studies. Five clusters were identified, which are visible in the dendrogram above the correlation matrix (branches of the dendrogram with variable shades of color). The dashed horizontal line running through the dendrogram indicates the cluster-forming threshold. The values of the correlation matrix are the absolute values of Pearson correlation coefficients.

only, 14.1% of pooled studies were on children only, and 4.4% of pooled studies were on older adults only (Figure 3c).

We used a hierarchical cluster analysis to explore similarities between the 57 included systematic reviews, based on the primary studies they included. The analysis grouped reviews into five distinct clusters, each representing sets of reviews that drew on overlapping evidence bases (Figure 3d, clusters numbered from left to right):

- Cluster 1 (5/57 reviews) focused on Parkinson's disease.
- Cluster 2 (8/57 reviews) covered neurodevelopmental disorders such as autism spectrum disorder, ADHD, epilepsy, and intellectual disabilities.
- Cluster 3 (25/57 reviews) brought together reviews addressing a wide range of clinical populations and indications, including insomnia in the context of comorbid conditions (e.g., hypertension, cancer, neurological disorders, and psychiatric disorders).

- Cluster 4 (11/57 reviews) focused primarily on insomnia, particularly in populations without major comorbidities.
- Cluster 5 (8/57 reviews) included reviews of dementia, Alzheimer's disease, and mild cognitive impairment.

While there was some overlap between conditions across clusters, the analysis identified broad thematic coherence within each group, suggesting that reviews were generally organized around shared clinical topics and populations, with the degree of primary study overlap reflected in the clustering.

Efficacy

Across the 227 meta-analyses identified, 94.7% (215/227) assessed melatonin's efficacy relative to an inactive comparator (placebo), 0.9% (2/227) assessed it relative to an active comparator (sleep deprivation, clonazepam), and 3.1% (7/227) used a combination of both by pooling across studies that used both active and inactive comparators. The comparator type could not be determined in 1.3% (3/227) of meta-analyses. Using vote counting based on direction of effect, the two meta-analyses assessing active comparators and the seven meta-analyses using combined comparators all favored melatonin. Among the 215 meta-analyses comparing melatonin to an inactive comparator, 80.9% (174/215) favored melatonin, 7.9% (17/215) favored the comparator, and 11.2% (24/215) reported unclear direction of effect.

To test whether this overall distribution of effect directions differed from what would be expected by chance, we conducted a two-sided sign test restricted to comparisons with inactive comparators. This yielded strong evidence that melatonin was more likely than not to be favored ($P < .0001$).

To further explore efficacy, we analyzed the meta-analyses according to aspects of sleep quality, dose, age, and age-related condition. In each sub-analysis, we split the variable into three subgroups. For aspects of sleep quality, we selected the three most analyzed aspects: sleep quantity, sleep initiation, and sleep maintenance (Figure 3a). For dose, we selected meta-analyses that only pooled over low dose studies (0.1–3 mg), medium dose (3–5 mg), and high dose (5 mg and higher). Given that many of the meta-analyses included dose ranges that crossed these boundaries, they were excluded from this analysis, which resulted in the inclusion of a relatively low number of meta-analyses. For age, we grouped by children, adults, and older adults. The results are presented in Figure 4.

We found no evidence of significant variation in the direction of effect across these subgroups, with Fisher's exact test yielding non-significant results for sleep quality domain ($P = .2668$), dose ($P = .4055$), and age ($P = .1181$). These exploratory findings suggest that the overall direction of effect favoring melatonin was consistent across subgroups, although statistical power was limited.

In summary, the large majority of meta-analyses comparing melatonin to placebo favored melatonin. Our exploratory subgroup analysis found no significant differences in direction of effect across dose, age, sleep quality domain, or clinical condition.

We attempted to assess the timing and duration of melatonin administration to investigate optimal administration timing. However, across the included systematic reviews, there was substantial heterogeneity in both the timing and duration of melatonin administration, reflecting the wide range of therapeutic applications. For sleep-related interventions, administration typically occurred in the evening, ranging from 15 min to 2 h before bedtime or sleep onset. Specific time windows such as 7 p.m. to 9 p.m. were commonly cited. In some cases, timing was tailored to chronobiological markers, such as administration 5 hours before dim light melatonin onset, or adapted to situational contexts, such as after night shifts or around surgery.

The duration of melatonin use also varied considerably. Acute regimens ranged from a few days to several weeks (e.g., 1–6 days, 3–9 weeks), often for transient sleep disturbances or perioperative care. Medium-term regimens extended from several weeks to several months (e.g., 4–12 weeks, up to 6 months), while some studies documented long-term administration (e.g., up to 1 year during cancer treatment,[55] or 3.5 years in patients with dementia).[84] This variability suggests that melatonin protocols are highly individualized, depending on the clinical indication and intended physiological effect.

Adverse Events

The most commonly reported adverse event was headache or migraine (22/57 reviews, 38.6%). There were eight categories of adverse events reported in 10% or more of the systematic reviews (≥6/57 reviews) assessed in this overview: headaches/migraines (38.6%), gastrointestinal problems (26.3%), dizziness (22.8%), fatigue (21.1%), drowsiness (19.3%), nausea (17.5%), mood changes (12.3%), and agitation (12.3%). A full list of adverse events reported across all systematic reviews is presented in Figure 5. Due to the heterogeneity in how adverse events were reported, we also provide a table that maps the terminology used in the reviewed literature to the terminology used here—see Table S3.

Discussion

This scoping review synthesizes evidence from 57 systematic reviews encompassing 227 meta-analyses on the

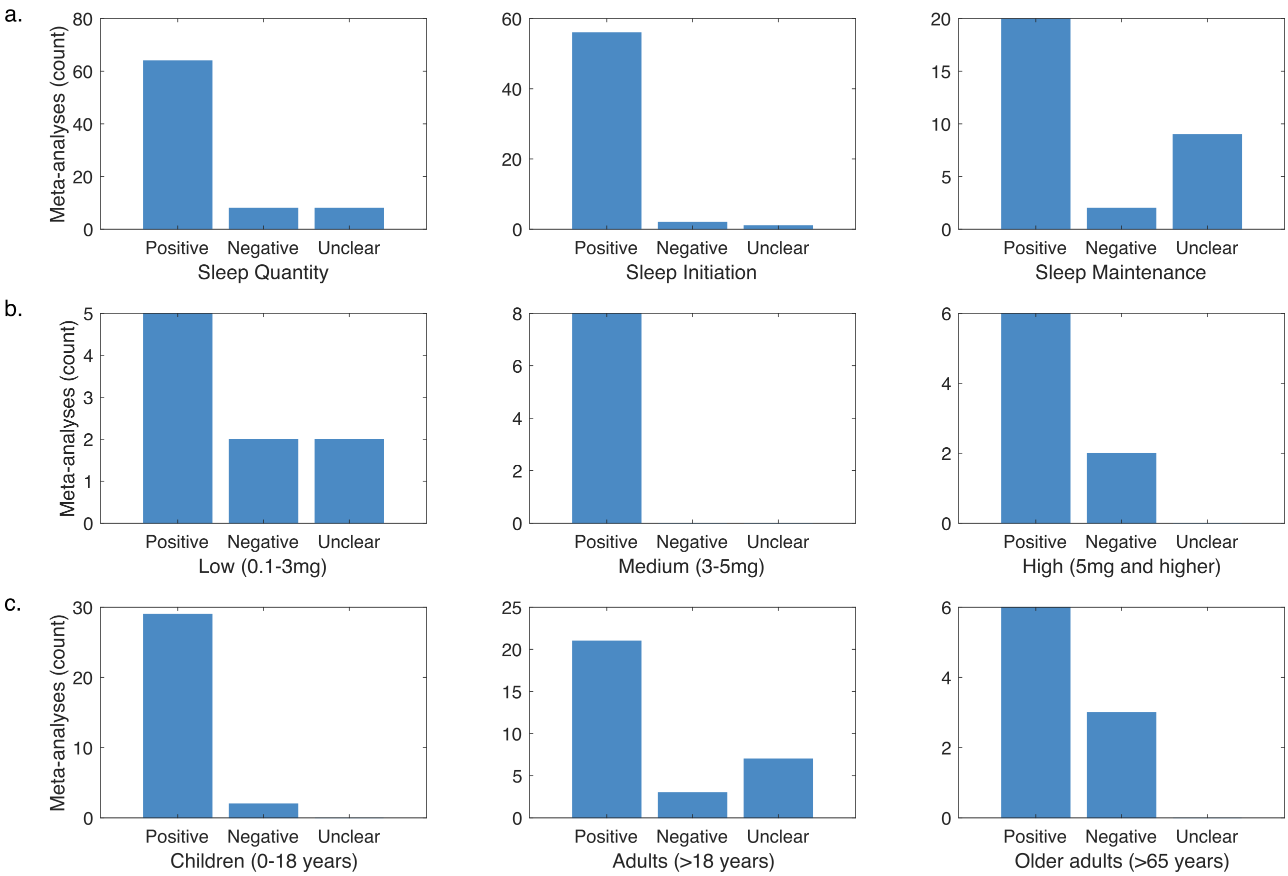

Figure 4. The efficacy of melatonin in improving sleep quality. For all nine bar plots, the y-axis is the number of meta-analyses, and the x-axis is the effect direction comparing melatonin to an inactive comparator (e.g., placebo). Effect direction can be positive (favors melatonin over inactive comparator), negative (favors inactive comparator over melatonin), or unclear (the reported effect direction is unclear whether melatonin or inactive comparator is favored). (a) Aspects of sleep quality. The proportions of positive, negative, and unclear effect directions across the three most studied sleep quality aspects: sleep quantity (left), sleep initiation (middle), and sleep maintenance (right). (b) Dose. The proportions of effect directions across three dose ranges: low dose range (left), medium dose range (middle), and high dose range (right). (c) Age. The proportions of effect directions across three age groups: children (left), adults (middle), and older adults (right).

efficacy of exogenous melatonin for improving sleep quality. Over the past 5 years, we observed a marked increase in the number of systematic reviews, reflecting growing clinical and public interest in melatonin's therapeutic role. The reviews covered a broad range of populations and sleep-related conditions and used diverse definitions and metrics of sleep quality. Despite methodological variation, the majority of meta-analyses reported a direction of effect favoring melatonin over inactive comparators. Together, these findings offer a high-level overview of the current evidence base—its strengths, limitations, and implications for future synthesis efforts.

A key observation from our review was the wide variability in the methodological quality of existing systematic reviews. While most reviews searched multiple databases and conducted a risk of bias assessment, fewer than half had a pre-registered protocol or reported on publication bias. These omissions limit transparency and may introduce bias, particularly in an area where clinical recommendations can be shaped by perceived consensus.[31,32] Only a small proportion of reviews (8.8%) met all seven predefined methodological quality criteria, raising concerns about the reliability and replicability of some conclusions.

We found a low degree of review overlap, suggesting that the included systematic reviews drew from a broad and relatively distinct set of primary studies.[34] This breadth of evidence may help mitigate the influence of limitations within any single review. However, the uneven quality across reviews underscores the need for greater adherence to rigorous standards in future synthesis efforts, particularly given melatonin's widespread use and its status as both a prescription drug and an over-the-counter supplement in different regulatory contexts.

Our synthesis found that most meta-analyses reported a direction of effect favoring melatonin over inactive comparators, indicating a generally positive signal for efficacy across diverse populations and

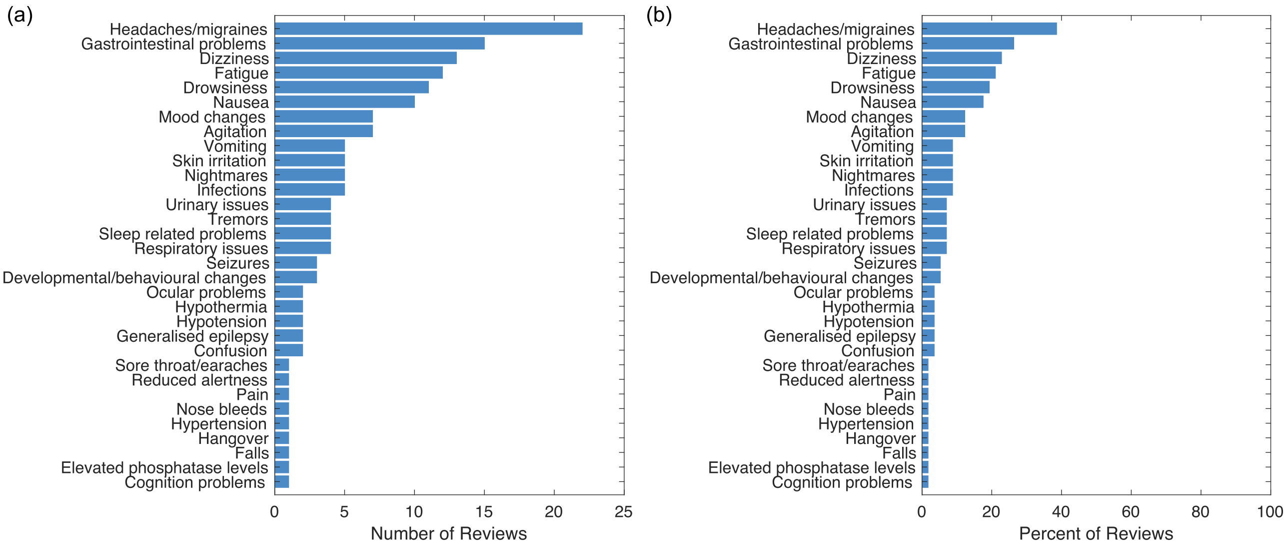

Figure 5. Adverse events. (a) The number of reviews in which each adverse event was reported. (b) The percent of reviews (out of 57 reviews in total) in which each adverse event was reported.

sleep outcomes. Post hoc subgroup analyses examined whether this signal varied by sleep quality domain, dose level, age group, or clinical condition. These analyses did not reveal any statistically significant differences, suggesting no clear evidence that efficacy systematically varies by subgroup.

These findings may reflect a broadly consistent benefit of melatonin across diverse settings, or they may stem from limitations in the underlying data. Several subgroup comparisons included relatively few eligible meta-analyses, and differences in how studies defined dose levels, populations, or sleep outcomes introduced additional heterogeneity. As a result, the absence of significant variation should be interpreted cautiously.

We identified several sources of notable heterogeneity in the melatonin and sleep quality literature, which may hinder the ability to investigate several important topics. Variation in how sleep quality is defined and measured across reviews complicates comparisons. Although we proposed a mapping framework to clarify terminology, the lack of standardization across studies limits the precision with which specific sleep outcomes can be evaluated. There was substantial variability in tools used to assess sleep quality, from objective measures such as actigraphy to subjective tools such as sleep journals, and from approaches that focused on a single aspect of sleep (e.g., sleep latency) to questionnaires that assess sleep quality more comprehensively (e.g., the Pittsburgh Sleep Quality Index). Another potential source of heterogeneity relates to geographical differences in melatonin regulation, which may affect dosage accuracy, formulation, and purity. In regions where melatonin is classified as a dietary supplement and not subject to strict regulatory oversight, products may vary in composition, potentially influencing outcomes in the primary studies included in the systematic reviews we assessed. Finally, we were unable to comprehensively explore how comorbidities, concurrent medications, or subtypes of sleep disturbance might moderate melatonin's efficacy, as such stratified data were rarely reported. Most systematic reviews did not report or stratify findings by participant ethnicity, race, or genetic background, limiting the ability to assess variation in efficacy across populations and reducing the generalizability of findings.

Despite these notable sources of heterogeneity, the consistency in direction of effect across meta-analyses suggests that these factors did not obscure the signal of efficacy. This underscores the value of high-level synthesis, even when terminology, assessment methods, melatonin formulations, clinical conditions, and populations vary widely across primary studies and systematic reviews.[17]

While this review identified a clear overall signal of efficacy, an important but underexplored question in the literature is the role of administration timing versus dose in determining melatonin's effectiveness. Timing is likely to influence therapeutic effects, particularly in relation to circadian rhythms,[14] but our ability to synthesize this factor was limited by inconsistent and heterogeneous reporting across systematic reviews. It was often described in vague terms (e.g., "before bedtime") and varied widely across clinical contexts, precluding meaningful analysis of its role in treatment outcomes. Although we conducted a limited post hoc analysis of dose as a potential moderator, most systematic reviews pooled primary studies that used a broad range of doses, limiting the ability to examine dose effects at the overview level. Optimizing the balance between dose and timing to maximize efficacy and minimize adverse effects remains a major gap. Health care practitioners prescribing melatonin (or advising on over-the-counter use, depending on country-specific regulations) would greatly benefit from clearer guidance on this issue.

Several methodological decisions made in this review warrant discussion. First, we did not apply formal methodological quality and risk-of-bias tools for reviews (AMSTAR 2 and ROBIS)[31,32] in this scoping overview. Given the project's scoping aims and scale (57 reviews; 227 meta-analyses), these tools itemized, domain-level judgments, and calibration/consensus requirements were beyond scope. Instead, we used a pre-specified seven-criterion appraisal (Figure 2c) as an indicative screen of review conduct. Accordingly, these indicators should be interpreted as indicative rather than definitive, and residual risk of bias in the included reviews may influence our direction-of-effect summaries. A planned quantitative umbrella review would be the appropriate context to apply AMSTAR 2/ROBIS (and related certainty frameworks) and to perform sensitivity analyses by review quality.

Second, our use of vote counting based on direction of effect enabled us to summarize a broad and heterogeneous body of evidence, but it did not capture effect sizes or variances.[24] This limits interpretability, particularly in areas where effect magnitude or clinical importance is key. Future umbrella reviews incorporating pooled effect sizes could offer a more detailed understanding of melatonin's efficacy.

Third, we restricted inclusion to systematic reviews that contained at least one meta-analysis. This ensured a minimum threshold of quantitative synthesis but may have excluded high-quality narrative reviews addressing relevant populations or questions. Including such reviews in future syntheses could enrich understanding, particularly for under-researched groups.

Fourth, a methodological decision that may have introduced heterogeneity was our definition of inactive comparators. We grouped placebo, no treatment, and usual care under this umbrella, consistent with best practice.[95] However, these represent different points on the explanatory–pragmatic continuum.[96] For example, placebo-controlled trials may yield different effect sizes than those using no treatment or usual care, the latter of which may include concurrent management strategies that reduce apparent efficacy. Although our synthesis treated these comparator types as a single group, potentially introducing variability, all included meta-analyses used placebo as the inactive comparator, mitigating this concern.

This review provides the most comprehensive synthesis to date of systematic reviews and meta-analyses evaluating the effects of melatonin on sleep quality. Compared to the 2020 umbrella review by Low et al,[15] which focused exclusively on insomnia, our review adopted a broader conceptual scope, encompassing multiple domains of sleep quality across both clinical and non-clinical populations.[35,36] Despite narrower methodological inclusion criteria (requiring at least one meta-analysis), the rapid growth of literature in this area enabled us to include over three times as many systematic reviews as the only related umbrella review in this area. While their review reported statistically significant improvements in sleep latency and mixed findings for total sleep time, they concluded that the evidence base was limited by methodological heterogeneity and variable review quality. Our findings help explain why these issues persist, due in part to heterogeneity in outcome definitions and measurement tools, limited subgroup reporting, and pooling across broad ranges of melatonin doses and administration timings. By identifying these persistent limitations and gaps and documenting the diversity of populations and methods used, our review clarifies where the evidence is most consistent and where further investigation is urgently needed.

Persistent uncertainty around clinically important questions, such as the optimal dose and timing of melatonin, does not serve the needs of health care practitioners or patients seeking effective sleep interventions. While industry sponsored research, such as the current review, is associated with a higher likelihood of favorable conclusions in published research,[97] we have sought to minimize this risk of bias through following best practice guidelines at all stages, for example, preregistering our protocol,[26] making our data and code openly available, carefully avoiding interpretive spin,[98] and reporting our findings according to PRISMA guidelines.[99] We hope this review serves as a resource for future efforts to reduce ambiguity in this area and to support evidence-based decision-making by clinicians, researchers, and policy-makers.

Conclusion

While a high proportion of meta-analyses reported favorable outcomes for melatonin compared to inactive comparators, variability in methodological quality and inconsistency in outcome definitions limit the certainty of conclusions. Nevertheless, our review highlights key patterns in the evidence base and identifies critical priorities for future research. Addressing these gaps can improve the quality and applicability of evidence guiding melatonin use in both clinical and real-world contexts. In particular, the large number of systematic reviews focused on specific sleep-disturbance conditions confirms the feasibility of future umbrella reviews incorporating quantitative synthesis via meta-analysis.

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Author Contributions

Samyuktha Iyer: Investigation; data curation; writing—review and editing. **Vaneesha Monk**: Investigation; validation; writing—review and editing. **Rebeccah Slater**: Conceptualization; resources; writing—review and editing; supervision; funding acquisition. **Luke Baxter**: Methodology; software; formal analysis; writing—original draft; visualization; supervision; project administration.

Conflicts of Interest

Luke Baxter and Rebeccah Slater were compensated by Cooper for activities related to the execution of the study. Vaneesha Monk and Samyuktha Iyer declare no competing interests.

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Data Availability Statement

The completed data extraction form, which contains all data underpinning the results, is available along with the code to generate the results on Zenodo: https://doi.org/10.5281/zenodo.17180052.

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