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Reviews in sleep disorders

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Reviews in: Sleep disorders

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Acupuncture and moxibustion in patients with cancer-related insomnia: A systematic review and network meta-analysis

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Objectives: Cancer-related insomnia (CRI) is one of the most common and serious symptoms in patients with cancer. Acupuncture and moxibustion have been widely applied in the treatment of CRI. Nevertheless, the comparative efficacy and safety of different acupuncture and moxibustion techniques remain unclear. This study aimed to evaluate and compare the efficacy and safety of different acupuncture and moxibustion techniques in the treatment of CRI.

Methods: Eight medical databases were comprehensively searched for relevant randomized controlled trials (RCTs) as of June 2022. Two independent reviewers assessed the risk of bias and conducted the research selection, data extraction, and quality assessment of the included RCTs. A network meta-analysis (NMA) was performed using frequency models, combining all available direct and indirect evidence from RCTs. The Pittsburgh Sleep Quality Index (PSQI) was set as the primary outcome, and adverse events and effective rates were set as the secondary outcomes. The efficacy rate was calculated as the ratio of patients with insomnia symptom relief to the total number of patients.

Results: Thirty-one RCTs with 3,046 participants were included, including 16 acupuncture- and moxibustion-related therapies. Transcutaneous electrical acupoint stimulation [surface under the cumulative ranking curve (SUCRA) 85.7%] and acupuncture and moxibustion (SUCRA 79.1%) were more effective than Western medicine, routine care, and placebo-sham acupuncture. Furthermore, Western medicine showed significantly better effects than placebo-sham acupuncture. In the NMA, the acupuncture and moxibustion treatments with the best therapeutic effects for CRI were transcutaneous electrical acupoint stimulation (SUCRA 85.7%), acupuncture and moxibustion (SUCRA 79.1%), auricular acupuncture (SUCRA 62.9%), routine care combined with intradermal needling (SUCRA 55.0%), and intradermal needling alone (SUCRA 53.3%). No serious acupuncture- or moxibustion-related adverse events were reported in the included studies.

Conclusion: Acupuncture and moxibustion are effective and relatively safe in treating CRI. The relatively conservative recommended order of acupuncture- and moxibustion-related therapies for CRI is as follows: transcutaneous electrical acupoint stimulation, acupuncture and moxibustion, and auricular acupuncture. However, the methodological quality of the included studies was generally poor, and further high-quality RCTs are needed to strengthen the evidence base.

KEYWORDS

cancer-related insomnia, network meta-analysis, systematic review, acupuncture and moxibustion, PSQI

1. Introduction

Cancer is a leading cause of mortality worldwide and its incidence (1). Insomnia is among the most prominent symptoms of cancer, with a prevalence rate of 25–59% (2). Cancer-related insomnia (CRI) is a sleep disorder caused by cancer or its treatment (drugs, surgery, radiotherapy, and chemotherapy), which exposes patients to high risks for physical (e.g., pain, fatigue) and psychological comorbidities (e.g., anxiety and depression), in addition to reduced quality of life (3–5). These challenges reduce compliance with conventional anti-cancer treatments, increase financial burden, and threaten long-term survival (6).

CRI is conventionally treated with pharmacotherapy, including antidepressants, benzodiazepine receptor agonists (BZRAs), melatonin receptor agonists, and antihistamines (7). However, conventional Western medicine (WM) treatment is associated with resistance and side effects, such as drug dependence and residual daytime sedation. In addition, cognitive behavioral therapy (CBT) for CRI is the gold standard, but due to the complexity of treatment steps and relatively high cost, patient compliance and acceptance are relatively low. Therefore, complementary and alternative medicine, including acupuncture- and moxibustion-related therapies, have been increasingly introduced into the management of CRI.

Acupuncture and moxibustion are expected to play a non-pharmacological role in managing CRI with acupoint stimulation as an essential modality, considering their potential to alleviate cancer symptoms and their feasibility without adding burden to patients' physical and financial situations (8).

In recent years, various acupuncture- and moxibustion-related therapies have been widely applied to the treatment of cancer-related symptoms, including CRI, cancer-related pain, fatigue, and hot flushes (8). Previous studies have shown that auricular acupuncture (AA) (9), scalp acupuncture (SA) (10), electro-acupuncture (EA) (11), and intradermal needling (IN) (12) might be more advantageous in treating CRI than WM, placebo-sham acupuncture (PSA), or routine care (RC). A systematic review (13) published in 2022 found that acupuncture and/or moxibustion have an affirmative effect on the treatment of CRI. Such treatment could be considered an adjuvant alternative to current CRI management. Additionally, another systematic review (14) published in 2022 showed that acupuncture has great potential to manage CRI in cancer patients, while the evidence of true acupuncture, PSA, and WM in treating CRI has not been entirely conclusive. Clinicians have encountered difficulties in selecting the most favorable acupuncture treatment for CRI. Thus, a comprehensive analysis and evaluation of relevant evidence are required.

In this study, a network meta-analysis (NMA) based on the frequency model was adopted to compare the effects of various acupuncture- and moxibustion-related therapies on CRI and to classify these intervention methods according to the results. From the perspective of evidence-based medicine, it is hoped that this study will provide evidence for the clinical selection of the best acupuncture- and moxibustion-related therapy for CRI.

2. Methods

2.1. Registration

The study protocol was registered (registration number: CRD42022329537) with the International Prospective Register of Systematic Reviews (PROSPERO).

2.2. Search strategy

The following databases were searched, starting from inception to June 7, 2022: PubMed, Embase, Web of Science, The Cochrane Library, Wan Fang database, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), and the China Science and Technology Journal Database (VIP). The inclusion criteria and search strategy were established according to the PRISMA protocol guidelines (15). The following three sets of search terms were adopted in English: (neoplasms OR cancer OR tutor OR malignancy) AND (sleep initiation and maintenance disorders OR insomnia OR early awakening OR disorders of initiating and maintaining sleep) AND (acupuncture therapy OR acupuncture OR moxibustion). All searches were limited to human randomized controlled trials (RCTs) and conducted independently by two authors in an electronic database. Relevant Chinese search terms were also searched. To obtain possible related experiments, the references of the original articles and review articles were searched manually. Meanwhile, a combination of subject and free words were used as the search words. The PubMed search strategy is presented in Supplementary Table S1, and appropriate adjustments to this strategy were made for other databases.

Abbreviations: CRI, cancer-related insomnia; RCTs, randomized controlled trials; PSQI, Pittsburgh Sleeps Quality Index; AEs, adverse events; CBM, Chinese Biomedical Literature Database; CNKI, China National Knowledge Infrastructure; VIP, the China Science and Technology Journal Database; MD, mean difference; OR, odds ratio; CI, confidence intervals; NMA, network meta-analysis; SUCRA, surface under the cumulative ranking curve; TCM, traditional Chinese medicine; WM, western medicine; RC, routine care; AA, auricular acupuncture; CBT, cognitive behavioral therapy; ACU+MOX, acupuncture and moxibustion; AA+ACU, auricular acupuncture combined with acupuncture; RC+AA, routine care combined with auricular acupuncture; RC+MOX, routine care combined with moxibustion; RC+IN, routine care combined with intradermal needling; RC+AA+MOX, routine care combined with auricular acupuncture and moxibustion; WM+AA+MOX, western medicine combined with auricular acupuncture and moxibustion; WM+ACU+MOX, western medicine combined with acupuncture and moxibustion; WM+AA, western medicine combined with auricular acupuncture; SA, scalp-acupuncture; ACU, acupuncture; EA, electro-acupuncture; IN, intradermal needling; IN+OT, intradermal needling combined with other therapies; TEAS, transcutaneous electrical acupoint stimulation; AA+OT, acupuncture combined with other therapies; PSA, placebo-sham acupuncture.

2.3. Eligibility criteria

(1) Adults clinically diagnosed with CRI (>18 years old)
(2) Intervention(s): All modalities of acupuncture [AA, EA, SA, transcutaneous electrical acupoint stimulation (TEAS), IN, etc.] and/or moxibustion (direct, indirect, or combined with a needle) or combined with conventional medicine (conventional medicine includes WM and RC. RC refers to comprehensive therapy such as psychotherapy, basic treatment, and emotional care).
(3) Comparator(s)/control: sham group (sham acupuncture or sham moxibustion), conventional medicine or other therapies (OT).
(4) Primary outcome: Pittsburgh Sleep Quality Index (PSQI) (16).
(5) Secondary outcome: Effective rate, adverse events.
(6) RCTs only.

2.4. Exclusion criteria

(1) Studies with repeated data or secondary analysis.
(2) Studies from non-RCTs (including animal studies, master and doctoral dissertations, books, conference abstracts, protocols, correspondence, case reports, overviews, and systematic reviews).
(3) Non-cancer-related insomnia.
(4) The therapy of the intervention group was non-acupuncture or non-moxibustion.
(5) The experimental or control group involved traditional Chinese medicine (TCM) or ready-for-use TCM.
(6) Outcome indicators do not match.

2.5. Study selection and data extraction

Two researchers (LY and SL) performed independent screening of the literature that met the inclusion criteria and conducted cross-checking. Literature screening was carried out according to research type, research objects, intervention/control measures, and outcome indicators. The steps included duplicate checking, primary screening of titles and abstracts, and rescreening of full texts. Two researchers (KW and JL) independently extracted relevant data, including author, title, publication year, journal, country, cancer type, course of the disease, age, sex ratio, randomization method, distribution concealment, blindness, sample size, course of treatment, intervention measures, outcome indicators, and follow-up. After data extraction, two investigators conducted cross-checks. Discussion with a third researcher was done to resolve differences in the literature screening or data extraction process until a consensus was reached. If inadequate or ambiguous data were encountered, we contacted the corresponding author or the first author of the study *via* email to ask for further information.

2.6. Risk-of-bias assessment

Two reviewers (DL and YO) referred to the built-in risk bias assessment tool in RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) to evaluate the risk of bias in the included literature (17). The following seven aspects were assessed: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) performance bias: blinded implementation (including subjects, investigators, and outcome assessors), (4) detection bias: blinded evaluation of study results, (5) attrition bias: outcome data integrity, (6) reporting bias: selective reporting of results, and (7) other bias. All the above biases were assessed and classified as low, unclear, or high risk. A third researcher was consulted if there was any disagreement in the evaluation process.

2.7. Data analysis

After combining direct and indirect evidence from all available RCTs, continuous variables (e.g., PSQI) were reported as mean differences (MDs) with 95% confidence intervals (CIs), while binary categorical variables (e.g., effective rate) were reported as odds ratios (ORs) and 95% CIs. The lower the PSQI score, the better the sleep status, whereas the greater the effective rate, the better the effect. Considering the potential differences within the studies, a random effects model was selected for analysis instead of a fixed effects model (18).

STATA 15.1 (StataCorp, College Station, TX) was used for data analysis and graph drawing. The nodal method was used for the quantification and demonstration of the agreement between direct and indirect comparisons using STATA 15.1. The consistency test was met at $p > 0.05$ (19).

STATA 15.1 was applied to depict network diagrams of different acupuncture- and moxibustion-related therapeutic interventions. As illustrated in the generated network diagrams, each intervention and control condition is represented by a node, and the lines that connect the nodes embody direct head-to-head comparisons between the interventions. The width of the connecting lines and the size of each node are proportional to the number of studies (20).

The intervention hierarchy was summed and reported as a P score, which is regarded as a frequentist analog of the surface under the cumulative ranking curve (SUCRA) values and is used to measure the extent of certainty that one treatment is superior to another, averaged over all competing treatments. The P score ranges from 0 to 1, where 1 indicates that a treatment is the best with the highest degree of certainty and 0 indicates that it is the worst with the lowest degree of certainty. Although the SUCRA or P score can be usefully re-interpreted as the effective percentage of acupuncture interventions, we should still interpret such scores with caution unless there are valid differences between interventions that are clinically meaningful.

2.8. Publication bias

In NMA, there are no valid statistical tests other than funnel plots for visual confirmation to detect publication bias. In addition, the traditional funnel plots used for paired meta-analyses are not capable of assessing publication bias in NMA. Consequently, in this review, we attempted to determine the asymmetry of the network funnel plot for the primary outcomes to determine the probability of publication bias.

2.9. Quality of evidence

The GRADE approach was adopted to evaluate the confidence of the estimates derived from and NMA of efficacy outcomes (21). In this

approach, direct evidence from RCTs starts at high confidence and can be downgraded to levels of moderate, low, and very low confidence based on indirectness, risk of bias, inconsistency (or heterogeneity), imprecision, and/or publication bias. The rating of indirect estimates starts at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate but can be downgraded further for intransitivity or imprecision (dissimilarity between studies in terms of clinical or methodological characteristics). Higher ratings, directly or indirectly assessed, apply to the quality of evidence in the NMA and are classified as high, moderate, low, or very low.

3. Results

3.1. Study identification and selection

A total of 902 studies were retrieved from electronic databases, and no studies were available from other sources. After eliminating duplicates, we searched the titles and abstracts of the remaining 674 studies and re-excluded 248 studies. The remaining 426 studies were read, and 395 were re-excluded (for non-RCTs, unavailable full-text, research object, intervention method, outcome indicators, research type, and repeated data or secondary analysis). Ultimately, 31 studies were included in this meta-analysis. The detailed process is illustrated in Supplementary Figure S1.

3.2. Description of study inclusion

We identified 31 RCTs with 3,046 independent participants through a literature search. A PRISMA flowchart is presented in Supplementary Figure S1. Among the 31 studies, the main therapies used in the intervention group were as follows: TEAS, acupuncture and moxibustion (ACU+MOX), AA, IN, RC+IN, AA combined with acupuncture (AA+ACU), SA, RC combined with moxibustion (RC+MOX), and WM combined with acupuncture and moxibustion (WM+ACU+MOX). In addition, the control group mainly involved WM, RC, PSA, AA, ACU, CBT, and RC+AA. Among all studies, only four articles involved acupuncture or moxibustion or direct comparison of different acupuncture therapies (22–25): RC+AA+MOX vs. RC+AA, SA vs. ACU, IN+ OT vs. IN, and RC+AA vs. AA. Moreover, there were 11 cases of acupuncture, moxibustion, or different acupuncture compared with WM, nine cases with RC, and four with PSA, one of them is EA vs. PSA, and EA with a 4-Hz frequency and continuous wave. Diazepam (four trials) was involved in most comparisons, followed by estazolam (three trials), shulediazepam (two trials), and fluoxetine hydrochloride (two trials). The remaining seven RCTs experimented with the efficacy of other interventions: AA, ACU, IN, CBT, RC+AA, and WM+AA. The major acupoints were GV20 (Baihui), SP6 (Sanyinjiao), GV29 (Yintang), PC6 (Neiguan), HT7 (Shenmen), GV24 (Shenting), ST36 (Zusanli), KI1 (Yongquan); moreover, the main auricular points were CO15 (Xin) and TF4 (Shenmen) (Supplementary Table S2). The network plots for the primary outcomes (PSQI) of eligible comparisons are presented in Supplementary Figure S2, whereas the secondary outcomes (effective rate) are presented in Supplementary Figure S3. Although each outcome was included in the systematic review, some interventions were eliminated from the NMA because they were either unrelated or had no available data.

Among the included studies, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the second and third editions of the Chinese Classification of Mental Disorders (CCMD-2 and -3, respectively), the Standard for Diagnosis and Efficacy of Chinese Medicine Syndrome (SDECMS) criteria, and the tenth edition of the International Classification of Diseases (ICD-10) were most often used for diagnosing insomnia. Four studies used the DSM-5 criteria to diagnose insomnia (9, 11, 26, 27); six studies used the CCMD-3 (10, 25, 28–31); one study used the CCMD-2 (23); two studies used the SDECMS criteria (32, 33), and one study used ICD-10 (34). In addition, some studies combined various diagnostic criteria for a more comprehensive diagnosis (35–37).

Of the 2,380 patients whose sex was listed, 1,255 (55.7%) were female. For the included RCTs, the mean sample size was 98.0 (range, 22–220), with the ages of the participants ranging from 31 to 80 years. Three studies (9.67%) were conducted in the United Kingdom (26), Germany (9) and Korea (11), and the remaining 28 (90.33%) were conducted in China (10, 12, 22–25, 27–48). The basic features of the included RCTs are presented in Supplementary Table S2.

3.3. Assessment of risk of bias

The assessment of the risk of bias is illustrated in Supplementary Figure S4. Most studies adopted stochastic sequence generation methods with low bias risks (9–12, 22–25, 27, 28, 32, 33, 37, 39–42, 44, 45, 47, 48). Among them, 17 used a random number table (9, 10, 24, 25, 27, 28, 32, 33, 36, 37, 39–42, 44, 45, 48), one used a random sequence (23), two used random sampling (11, 47), and one used computer randomization (22); studies that did not provide a description of the randomization method were given an unclear risk of bias in this domain (30, 35, 38, 43, 46). Five studies were randomized according to the order of visits and were rated as high risk (26, 29, 31, 33, 34). In terms of allocation concealment, two studies used sealed opaque envelopes (11, 26), another study used central randomization (9), and the allocation concealment of the remaining studies was not mentioned. Only Höxtermann et al. (9) conducted blinding of personnel, outcome assessors, and participants. Twenty-nine studies did not provide a description of the blinding strategy of personnel or participants, and some studies were assessed as a high risk given the nature of the intervention (26, 28, 30, 32, 35, 37, 41). The rest were estimated as unclear risks (10–12, 22–24, 27, 29–31, 33, 34, 36, 38, 39, 42–48).

In terms of blinding of outcome assessment, Höxtermann et al. (9), Lee et al. (11), and Garland et al. (26) described the application of blindness to the assessors of the results and were assessed as low-risk, and the remaining ones were not specified and evaluated as unclear. In terms of outcome data, one study, with a loss rate of 8%, was rated as unclear (32), and another study that did not set the primitive PSQI data preliminarily was rated as high-risk (22). The other 29 studies with complete outcome indicators were rated as low-risk. In the domain of selective reporting, 16 studies were evaluated as having a low risk of bias, of which nine had ethical approval (9, 11, 12, 22, 26–28, 40, 45) and 15 were rated as unclear (23, 24, 30–32, 34–38, 42–44, 46, 47). Regarding other biases, according to our protocol, one study without specific inclusion and exclusion criteria was assessed as high-risk (22). Another study was evaluated as low-risk because it included statistical methods, baseline data, and exclusion criteria (26), and the remaining studies were rated as unclear risk (9–12, 23–25, 27–48).

There were no dropouts in 28 studies (9–12, 22, 24–31, 33–46, 48). Dropout cases were mentioned in the remaining studies (23, 32, 47); two studies (23, 47) had a loss rate of less than 5%, and the other was less than 8% (32). However, dropout cases were not considered to have an effect on the study results.

3.4. Network meta-analysis

3.4.1. Results of network meta-analysis of Pittsburgh sleep quality index

The network map for the total PSQI score formed two closed loops: RC-AA-RC+AA and WM-SA-ACU (Supplementary Figure S2). All *p*-values for indirect and direct comparisons between all studies were tested for consistency and inconsistency, and the consistency model was acceptable ($p = 0.8197$).

Through the NMA for the total PSQI score, 20 interventions were estimated for the relative effect, including 28 trials. Based on the SUCRA and mean rank (Supplementary Figure S5), the priorities in relation to effectiveness measured by PSQI total score were as follows: TEAS (SUCRA 85.7%), ACU+MOX (79.1%), RC (77.9%), WM (76.5%), PSA (68.1%), AA (62.9%), RC+IN (55.0%), IN (53.3%), SA (50.3%), RC+AA (45.9%), RC+MOX (43.7%), CBT (43.0%), AA+ACU (40.7%), IN+OT (36.8%), EA (35.4%), WM+AA (32.4%), AA+OT (32.2%), ACU (31.1%), RC+AA+MOX (26.6%), WM+ACU+MOX (32.2%).

Based on the comparative efficacy of the treatment (bolding marks supported) presented in Supplementary Table S3, IN (MD −4.08, 95%CI −7.88 to −0.28), SA (MD −3.99, 95%CI −7.94 to −0.04), and WM+AA (MD −4.92, 95%CI −8.75 to −1.09) were all significantly different from WM. Compared with the control group (RC), RC+AA (MD −2.69, 95%CI −4.59 to −0.79), RC+MOX (MD −2.84, 95%CI −5.13 to −0.56), and RC+AA+MOX (MD −4.66, 95%CI −8.95 to −0.36) showed significant differences. Moreover, TEAS was significantly superior to PSA (MD −2.19, 95%CI −4.34 to −0.03) and EA (MD −5.58, 95%CI −10.79 to −0.36).

3.4.2. Results of network meta-analysis of effective rate

The network plot for the NMA which included 16 trials and 12 interventions is shown in Supplementary Figure S3. Based on the SUCRA and mean rank (Supplementary Figure S6), the priorities in relation to effectiveness measured by effective rate were as follows: RC+AA+MOX (SUCRA 95.1%), WM+AA+ACU (94.6%), RC+AA (71.7%), RC+MOX (67.0%), RC+IN (56.3%), AA+ACU (52.6%), WM+AA (48.0%), SA (41.9%), WM+ACU+MOX (39.9%), RC (21.5%), WM (11.0%), ACU+MOX (0.5%).

Based on the comparative efficacy of the treatment presented in Supplementary Table S4, RC+AA (OR 8.11, 95%CI 1.61–40.77), RC+MOX (OR 10.46, 95%CI 1.39–78.88), RC+IN (OR 14.37, 95%CI 1.90–108.76), and WM+AA (OR 20.76, 95%CI 1.63–264.35) showed significant differences compared to RC+AA+MOX. Furthermore, WM+ACU+MOX differed significantly from WM (OR 4.00, 95%CI 1.02–15.68).

3.4.3. Publication bias

Funnel plots for publication bias are shown in Supplementary Figures S7, S8; no significant publication bias was revealed by visually inspecting the funnel plots.

3.5. Safety

3.5.1. Adverse events

Seven of the included RCTs assessed AEs (9, 23, 25–27, 37, 45). Two studies reported that the AEs of WM were drowsiness, addiction, drug resistance, and insomnia rebound (27, 37). Five studies involving AA+RC, IN, SA, RC+MOX, and AA+ACU reported that the main AEs were pain, somnolence, tiredness, and small hemorrhages (9, 23, 25–27). One study on TEAS reported serious AEs (45), including seven cases of respiratory depression, eight cases of ventricular tachycardia, and 11 cases of sinus tachycardia. However, this is more likely to be related to preoperative anesthesia than acupuncture. Another study reported that eight patients had cognitive decline during acupuncture treatment (37), which was more likely to be related to the poor mental state of patients after receiving chemotherapy, but not related to acupuncture operations. One study reported no adverse reactions in the RC group (9).

4. Quality of evidence

The GRADE levels of the NMA for the total PSQI score were generally medium, low, and very low (Supplementary Table S5). However, the GRADE levels of the NMA for effective rate were generally low to very low (Supplementary Table S6). The main reasons for the degradation were imprecise meta-analysis results and the risk of bias.

5. Discussion

5.1. Summary of the main results

This is the first study to evaluate the efficacy and safety of different acupuncture- and moxibustion-related treatments for CRI, including 31 RCTs with a large population of patients ($n = 3{,}046$).

Compared to WM and PSA, acupuncture-related interventions such as TEAS and ACU+MOX were more effective in the PSQI results. In this NMA, according to the therapeutic effect of acupuncture- and moxibustion-related therapies of CRI, the rankings were as follows: TEAS, ACU+MOX, AA, RC+IN, IN, SA, RC+AA, RC+MOX, AA+ACU, IN+OT, EA, WM+AA, AA+OT, ACU, RC+AA+MOX, and WM+ACU+MOX. In terms of comparative effectiveness for the effective rate, we found that RC+AA+MOX had the highest probability of ranking first in treating CRI. Since the secondary outcome (effective rate) involved limited intervention types, it is difficult to make more comprehensive comparisons of the efficacy of different acupuncture- and moxibustion-related treatments. Although few cases of AEs were reported, the incidence of AEs associated with medication treatment, such as drowsiness, addiction, drug resistance, and insomnia rebound, was higher than that of acupuncture treatment. Except for the local pain and hematoma caused by acupuncture- and moxibustion-related treatment, no serious relevant AEs were reported.

5.2. Possible explanations for the present findings

Acupuncture and moxibustion are effective and relatively safe treatments for CRI. Among the above measures, AA is one of the recommended treatments. AA is a characteristic acupuncture therapy; in

the results of the NMA, the effect was significant, which was consistent with previously reported results (9, 49). Previous studies or reviews focusing on insomnia in breast cancer survivors have evaluated the effects of AA on sleep quality. Furthermore, they have concluded that AA may exert a safe and effective impact in the treatment of breast cancer survivors with insomnia in the short term (22, 50). The sleep-promoting and sleep/wake rhythm-regulating effects of melatonin are attributed to its action on MT1 and MT2 melatonin receptors present in the suprachiasmatic nucleus (SCN) of the hypothalamus (51). Some studies have shown that insomnia is closely related to the decline of central melatonin function (52, 53). The positive feedback loop between parasympathetic vagal nerve excitation and melatonin secretion constitutes the basis for the use of melatonin treatment in insomnia (54, 55). The auricular nail is the only vagus nerve distribution area on the body surface. AA stimulation of the auricular nail area directly stimulates vagal afferent fibers, and the afferent fibers of the auricular branches of the vagus nerve directly project to the nucleus of solitary tract, which then projects directly or indirectly to several nuclei such as the locus coeruleus, parabrachial nucleus, median raphe nuclei, hypothalamus, and other nuclei (56, 57), activating the SCN-pineal gland-melatonin (SCN-PG-MT) axis and promoting the secretion of melatonin to regulate insomnia (58, 59). In addition, the cancer types in this study mainly included breast (9, 11, 12, 22, 24, 26–28, 31, 41, 42, 48), lymph (28, 29, 46), thyroid (11, 34, 40), gastric (31, 37, 41), colorectal (11, 26, 28, 41, 46), and ovarian (27, 28, 31, 41), with breast cancer being the most common type. Whether patients with breast cancer benefit more from acupuncture and whether acupuncture has different curative effects on different cancer types are still unknown.

In addition, acupuncture and moxibustion have remarkable effects in the treatment of CRI. Previous studies have shown that acupuncture and moxibustion can benefit sleep quality and efficiency to a certain extent (27, 32, 60). Several studies have demonstrated effects on various potential neurotransmitters, including melatonin, norepinephrine, endorphin, and gamma-aminobutyric acid (61, 62). Moxibustion is a traditional therapy for insomnia. Previous studies have found that moxibustion has a positive effect on treating insomnia by adjusting the brain's sleep function, improving sleep quality, and promoting periodicity from light to deep sleep (60, 63). According to TCM theory, the key to the treatment of insomnia by acupuncture and moxibustion is to regulate the excess and deficiency of yin and yang according to the attributes of syndromes to balance the yin and yang of the body and restore its normal physiological function. However, there are few reports on the underlying mechanisms of acupuncture and moxibustion of CRI. Therefore, the mechanism of acupuncture and moxibustion combination therapy for treating CRI requires further exploration and confirmation.

Surprisingly, TEAS has a positive effect in treating CRI and is superior to PSA. TEAS combines traditional acupuncture therapy with modern transcutaneous electrical stimulation technology, which is an important supplement and alternative medical method to acupuncture therapy (64). The effect of TEAS is similar to that of EA, with similar peripheral and central mechanisms. Through the sensory transmission of the meridians, qi and blood can be dredged, and the yin and yang of the zang-fu viscera can be adjusted (65). In previous reports, Dong et al. (66) and Ding et al. (67) demonstrated that TEAS could effectively improve sleep quality in insomnia patients. However, the choice of stimulation acupoints, treatment frequency, current intensity, and duration may cause certain heterogeneity (68).

RC is a comprehensive therapy, including psychotherapy, basic treatment, and emotional care, which play an essential role in treating CRI. For example, emotional care in TCM can help patients with insomnia relieve tension, anxiety, depression, and other negative emotions to help them sleep in a relaxed and natural state (69). Low-resistance thought induction psychology in modern TCM psychotherapy allows patients to enter a specific state from waking to sleeping through the induction of language and behavior, which is increasingly widely used in insomnia treatment (70, 71). In our results, the ranking of RC was relatively high, whether alone or in combination with drugs or acupuncture- and moxibustion-related therapies, showing a positive effect.

Based on the results of our review, we found that the most used acupoints for treating CRI are GV20, SP6, and HT7. GV20-SP6-HT7 is also the most used combination of main acupoints for treating insomnia (72). Studies have shown that acupuncture at GV20 can significantly improve the expression levels of clock genes and amino acid neurotransmitters in the brain tissue of rats with insomnia, thus improving sleep (73). Acupuncture at SP6 stimulates cognitive-emotional brain areas such as the anterior cingulate cortex and thalamus after sleep deprivation and promotes sleep (74). In addition, acupuncture at SP6-HT7 can downregulate serum adrenocorticotropic hormone (ACTH) and cortisol levels in patients with insomnia, inhibit the hyperactive hypothalamic–pituitary–adrenal axis, increase serum melatonin levels, and improve the function of the SCN-PG-MT system, thus regulating sleep (58, 75). Therefore, acupuncture at GV20, SP6, and HT7 may exert a calming effect and adjust the sleep state by regulating the activity of the sleep–wake center and related factors.

Acupuncture and moxibustion are two of the most commonly used non-pharmaceutical traditional Chinese medicine therapies in clinical practice. Acupuncture uses different needles or instruments to stimulate acupoints for therapeutic purposes, mainly by mechanical stimulation. Moxibustion uses artemisia argyi or other medicines to stimulate the acupoints by cauterizing them to regulate the body's functions, mainly including thermal effects, light radiation effects, and pharmacological actions of artemisia argyi (76). Based on the characteristics of the moxibustion spectrum, the selection of different wavelength light stimulation sources to simulate the light radiation effect of moxibustion stimulation has also gradually attracted attention. It was found that 10.6 μm wavelength laser acupuncture is close to the peak of the infrared radiation spectrum of moxibustion and human acupuncture points. Its efficacy is similar to traditional moxibustion, producing a moxibustion-like thermal effect without smoke and smell (77–79).

5.3. Limitations of included studies

5.3.1. Evidence and methodological quality

The GRADE profile for the PSQI and the effective rate showed that the evidence quality of all results was mostly low, which was mainly due to methodological limitations such as randomness, risk of bias, blindness, and allocation concealment in reporting results. Therefore, the overall quality was low. Among the 31 enrolled RCTs, five did not provide a detailed description of the randomization process (30, 35, 38, 43, 46). In addition, only three RCTs listed information on allocation concealment (9, 11, 26). Only one RCT met the blinding requirement of treatment allocation (9) and two RCTs met the blinding requirement of outcome assessment (11, 26). Additionally, no description was available to identify the existence of selective reporting bias in the included studies. These various types of bias may have contributed to the false-positive results. Moreover, only one RCT fully mentioned statistical methods, baseline data, and exclusion criteria. In addition, the heterogeneity in diagnostic criteria should be considered when interpreting the results between studies. Therefore, the statistical analysis power of the included RCTs might be extremely low.

5.3.2. Inconsistent interventions

Compared with the interventions involved in this review, the number of the included RCTs is small, which leads to limitations of most outcomes, especially in some interventions involving only one or two RCTs. Moreover, the included RCTs also varied in terms of the number of sessions, frequency, selection of acupoints, number of acupoints, duration of acupuncture, time for needle retention, and needling depth, all of which might have contributed to bias. CBT is the first-line treatment for insomnia. However, due to the lack of inclusion in this review and the incomplete coverage of acupuncture or moxibustion, we cannot comprehensively compare CBT with other acupuncture or moxibustion treatments, and the final ranking results should be treated with caution.

5.3.3. Limited outcomes

Due to the limited outcomes included in the study, it was impossible to comprehensively evaluate the difference in the therapeutic effect of acupuncture on CRI. Moreover, only seven studies reported AEs (9, 23, 25–27, 37, 45), and only six studies mentioned follow-up (11, 25–27, 30, 32). Thus, the safety and long-term effects of acupuncture- and moxibustion-related therapies for CRI require further exploration.

5.3.4. Lack of health economic data

The included studies have no health economic data or related health economic analysis reports.

5.4. Strengths and limitations of this review

Network meta-analysis is a precious method that enables the selection of the most efficient ones among multiple treatment options. Complementary and alternative therapies are important and effective for individuals with CRI. To the best of our knowledge, few studies have attempted to estimate the comparative effectiveness of various acupuncture- and moxibustion-related treatments. Based on the current evidence, the advantage of this review lies in applying the NMA method to compare the effectiveness and safety of different acupuncture treatments for CRI. The results are of great benefit to patients, clinicians, and policymakers in making decisions regarding ideal acupuncture- and moxibustion-related therapies for treating CRI.

There are also limitations of our study. First, the search languages of literature were limited to English and Chinese articles, excluding studies published in other languages. Biased outcomes may have been attributed to this language limitation. Second, due to the unclear follow-up description in the included literature, it was impossible to further explore the long-term effects of acupuncture on CRI. Third, the quality of the evidence was not ideal because of the imperfect study design and the limited number of included trials.

Analyzing the included studies, we found that many studies lacked attention to the course and follow-up of CRI. We hope that there will be more high-quality RCTs involving more acupuncture and moxibustion treatments to further explore the effects of acupuncture and moxibustion in treating CRI, including safety, effectiveness, stability, and durability.

6. Conclusion

Acupuncture and moxibustion are effective and relatively safe treatments for CRI. The relatively conservative recommended order of acupuncture and moxibustion-related therapies for CRI is as follows: TEAS, acupuncture and moxibustion, and AA. Among these, TEAS had the highest probability of ranking first in treating CRI. Nevertheless, the methodological quality of the included studies was generally poor, and further well-designed, large-scale, high-quality RCTs are required to verify our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YO, DL, and LZ conceived and designed the study. YO, DL, and XN searched the databases. SL and LY participated in the study selection. SL, LY, KW, and JL extracted the data. YO, DL, XN, CF, YY, XW, LW, ZT, and JR interpreted and assessed the data. YO and DL depicted tables and figures. YO, DL, XN, and JR drafted the manuscript. LZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1108686/full#supplementary-material

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A literature review of sleep problems and neurodevelopment disorders

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Introduction: Sleep is an incredibly complex process that goes beyond relaxing and body resting. Disturbance in sleep leads to several short-term and long-term consequences. Neurodevelopmental diseases such as "autism spectrum disorder" (ASDs), Attention-deficit hyperactivity disorder (ADHD), and intellectual disability commonly experience sleep disorders that affect their clinical presentation, daily function, and quality of life.

Discussion: The incidence of sleep problems in ASD patients ranges from 32 to 71.5%, especially insomnia, while an estimated 25–50% of people with ADHD report having sleep issues in clinical settings. The incidence of sleep issues is widespread in persons with intellectual disabilities, reaching up to 86%. This article is a literature review covering the neurodevelopmental disorder interaction with sleep disorder and different management.

Conclusion: Disorders of sleep are key concerns in children with neurodevelopmental disorders. In this group of patients, sleep disorders are common and tend to be chronic. Recognizing and diagnosis of sleep disorders will enhance their function, response to treatment, and quality of life.

KEYWORDS

attention-deficit hyperactivity disorder, intellectual disabilities, electroencephalography, autism spectrum disorders, sleep disorder

Sleep disorder

Sleeping is an incredibly complex process that goes beyond relaxing and body resting. It is a state of involuntary activity in which the brain is relatively still and responds to internal stimuli during NREM, and 20% is approximately active during REM. The exact purpose of sleep is not fully understood. Sleep has many functions, including neuronal plasticity, memory consolidation, immune function, growth, and mental health. Sympathetic overtone, an increase in the activity of hypothalamic–pituitary–adrenal axis, metabolic disorders, and inflammatory responses are factors that may cause disturbance in the sleep rhythm. Disturbance in sleep leads to several short-term consequences such as emotional disturbance, increase in stress response, mood disorder, cognitive and performance deficits, somatic pain, and reduced quality of life. Sleep disturbance influences teenagers' mental health, academic performance, and risk-taking behaviors. Sleep disturbance in children is linked to behavioral issues and impaired cognitive performance. In those who are otherwise healthy, sleep disturbance can have long-term

effects such as dyslipidemia, hypertension, cardiovascular disease, problems with weight, type 2 diabetes, metabolic syndrome, and colorectal cancer (1–3). The basic form of normal sleep organization is called sleep architecture. The sleep cycle is composed of two phases: non-rapid eye movement (NREM) sleep and rapid eye movement (REM). Phases 1, 2, 3, and 4 of NREM sleep form a continuum of relative depth. Every individual has distinctive characteristics of sleep, such as variations in eye movements, muscle tone, and brain wave patterns. Electroencephalogram (EEG) recordings, which monitor electrical patterns of brain activity, have been used to show sleep cycles and phases (4). The aging process has continuous and considerable effects on sleep architecture. There are noticeable differences between childhood and adulthood in sleep initiation and maintenance, the duration spent in each phase, and overall sleep efficiency. Studying age-related decreases in sleep efficiency is a general trend. Though the effects of insufficient sleep are generally well established, the causes are complicated and poorly understood. Therefore, when examining sleep stages in children of different ages, it is critical to take their unique characteristics into account. However, examining sleep characteristics according to age enables a more in-depth comprehension of how sleep contributes to effective aging and human development. Sleep disorders according to DSM-5 are insomnia, parasomnia, breath-related disorders, hypersomnolence, narcolepsy, circadian rhythm sleep–wake disorder and substance, and medication-related disorder (5).

Analysis of phenotypes for sleep disorder

There are several types of sleep assessment methods that should be customized for each child. Subjective methods including parent-reported surveys and sleep diaries are among the most frequently employed methods in the analysis of sleep disorders in human studies. They offer various advantages, including non-invasive acquisition and low costs. Children's Sleep Habits Questionnaire (CSHQ) is considered one of the most popular parent-completed surveys. It is a tool for assessment of sleep in school-aged children based on parental reports (6). Another method is the Electroencephalography (EEG). It involves two electrodes that are attached to the patient's scalp. It provides a recording of the brain's electrical activity throughout sleep and weakness (7). A method known as a polysomnogram (PSG) is regarded as the benchmark for the objective assessment of sleep compared to a single-channel EEG (8). It incorporates physiological indications of normal and abnormal brain electrical activity, sleep architecture, sleep stages, and sleep quality, as well as eye movements and physical activities during sleep. Actigraphy provides a non-invasive evaluation of limb activity using an accelerometer to identify episodes of sleep and wakefulness. It enables the collection of data over several days in unstructured settings. The reliability of actigraphy with PSG was examined and revealed a strong relationship between PSG and actigraphy measures (>0.80) for sleep latency, length, and efficiency (9). Similar to actigraphy, videosomnography's benefits come from its objective documentation over a long period (10). It can also be used to record unusual occurrences like nighttime parasomnias. However, using videosomnography in child sleep research comes with several difficulties.

Sleep problems and autism spectrum disorders

Autism spectrum disorders (ASDs) have a wide range of clinical symptoms that are connected to social communication and interaction. Restrictive, repetitive, and stereotyped behaviors and interests are common in ASD. They have persistent difficulties in reciprocal social interaction and communication across a variety of circumstances. High levels of co-occurring behavioral difficulties are frequently present in children with ASD. According to the most recent report from the United States, the incidence was 1/54 in 2020. One of the most common features of ASD is the sleep disorder that results from the interaction of several factors such as psychological, biological, family factors, environmental, and child practice methods that might not be sleep-friendly (11).

Incidence of sleep disorders in patients with ASD

The incidence of sleep problems in ASD patients ranges from 32 to 71.5%. Children and adolescents with ASD are more likely to experience sleep difficulties, especially insomnia, with incidence rates ranging from 40 to 80%. This wide range of incidence may be due to the different sleep problems assessment methods and different criteria such as different cut-off scores (12). After adjusting for family variables including poor child-rearing practices (for example, little parental supervision at bedtime), and noisy, or stressful environments, children with ASD are also more prone to experience sleep disturbances compared with their normal relatives; 47 and 16%, respectively, (13).

The causes of sleep difficulties in children with ASD

ASD is a multifactorial disease that is affected by multiple factors including neurological, genetic, immunological, and environmental factors. Several neurotransmitters like melatonin, GABA, and serotonin are required to create a regular cycle of sleep and wakefulness. Sleep may be affected by any problems with these neurotransmitters' synthesis (14). The hormone melatonin aids in synchronizing and preserving the circadian cycle. Autism may have improper melatonin regulation. The integrity of synaptic transmissions and the control of melatonin in ASD may both be influenced by clock genes (15). Melatonin exogenous therapy has been demonstrated to improve sleep schedule in ASD kids. Children with ASD showed decreased activity of the final enzyme in the production of melatonin, indicating lower levels of melatonin. This enzyme is encoded by the N-acetylserotonin O-methyltransferase gene (16). GABA is the neurotransmitter that induces sleep by inhibiting cells that are involved in arousal functions. It is produced from the preoptic area which is the sleep area in the hypothalamus. The Bidirectional Theoretical Framework of Sleep Disturbance provides an overview of

the various risk factors that can affect the development of sleep issues in people with ASD (12).

Effect of sleep disturbances in ASD patients on caregivers

Increased parental sleep problems and maternal stress have been associated with sleep abnormalities in children with ASD. Sleep issues can significantly affect a child's quality of life, daily functioning, and family dynamics, adding stress to everyone involved. This has also been linked to more challenging behaviors in ASD children during the day, as well as an influence on the ability to control mood. Sleep quality has been linked to common medical disorders such as upper respiratory problems and vision problems. Poor appetite and a decrease in the rate of growth have been linked to increased nighttime awakening and a reduced desire to go to sleep. Sleep disturbance in ASD children has been linked to increased aggression, hyperactivity, and social issues that may be markers of poor mental health outcomes.

Sleep disorders management

It is crucial to conduct early and frequent screenings for sleep impairment and its related conditions.

Non-pharmacological management

Sleep disturbances in children and adolescents with ASD must be managed on both environmental and behavioral levels. Parents must set bedtime routines and provide a relaxing bedroom atmosphere for their children. These environmental and behavioral strategies can improve their sleep, despite the fact that they are challenging to apply (17). The Sleep Committee of the Autism Treatment Network developed the sleep tool kit (STK), which is a customized behavioral modification tool for children and adolescents with insomnia. STK advocates three approaches: visual scheduling of good evening behaviors, a supplemental relaxing module to reduce arousal levels, and a faded bedtime regimen to sleep when tired. Breathing techniques, muscular relaxation exercises, yoga, massage, mindfulness training, and warm baths are additional soothing modules that aid those patients controlling arousal and anxiety. Taking the developmental characteristics of ASD children into consideration, it is reported that positive routines, unmodified and progressive extinction, and overnight fading are more beneficial in children under 5 years, but older children and adolescents benefit more from cognitive-behavioral therapy (CBT) (17).

Pharmacological management

Medical treatment is considered if the children do not respond to behavioral therapy.

Role of melatonin

It has been suggested that a lack of sociability may be related to sleep difficulties and circadian rhythm disruptions in ASD patients. Indeed, zeitgebers (also known as timeivers) like the natural light–dark cycle, music, and social cues are necessary for the entrainment and synchronization of the circadian clock. Therefore, in ASD patients, poor social cue perception or interpretation may impair the effectiveness of systems that synchronize sleep and wakefulness (18). As an alternative, ASD patients could find it difficult to synchronize with their internal and external settings, leading to eventual rhythm and time problems which affect a variety of fields, including social interaction and circadian cycles. In other words, persons with ASD would experience circadian abnormalities due to their failure to reflect their internal clock on environmental and social rhythms (19).

Melatonin is offered in a variety of over-the-counter preparations ranging from 1 to 10 mg. Most frequently, it is advised to take a dose of 1–3 mg 30–60 min before planned bedtime (46). However, a lower dose (0.5–1 mg) given earlier (3–4 h before night) is advised if a circadian rhythm problem is found. Age or weight has no bearing on the effectiveness of a dose. Melatonin is a pineal hormone that controls the body's circadian cycle. Melatonin appears to help shorten the time it takes to fall asleep, but its effectiveness at reducing overnight awakenings and other elements of sleep disruptions varies (20). A study included 24 ASD children aged 1–3 years who exhibited improvement in sleep latency as determined by actigraphy when given 1 mg or 3 mg. This treatment improved not just the children's sleep patterns, but also their conduct and parental stress (21).

Antipsychotic medication

This drug class has minimal tolerability and efficacy data for the treatment of insomnia in children. Few trials on the influence on sleep architecture have found that ziprasidone, olanzapine, and risperidone increase slow-wave, although ziprasidone and risperidone reduce REM sleep. Risperidone and olanzapine are two atypical antipsychotic that have been recommended for sleep disorders in children (22). These medications are used for the treatment of insomnia off-label, and it is not advised that they be regularly prescribed for this use, particularly as a first-line pharmacotherapeutic medication. In particular, the Canadian Academy of Child and Adolescent Psychiatry has advised against using them as a first-line line treatment for insomnia in children, adults, or the elderly (23). Other countries have likewise attempted to limit the number of prescriptions that government-subsidized programs may allow.

Antidepressant

There is limited evidence on the use and effectiveness of sedative antidepressants, selective serotonin reuptake inhibitors (SSRI), and tricyclic antidepressants (TCA) for the management of sleep disturbances in ASD children. Such medications might be effective if the sleeplessness is accompanied by concomitant psychiatric disorders. Children with comorbid depression may benefit from sedative antidepressants like trazodone and mirtazapine. These antidepressants enhance sleep by reducing the effects of neurotransmitters that promote wakefulness, including acetylcholine, histamine, noradrenaline, and serotonin. As a side effect, the majority of such medications reduce REM sleep and prolong daytime sleepiness. In psychiatric practice, trazodone is widely chosen and employed. Its effectiveness has primarily been shown in people with psychiatric illnesses. Trazodone has a noticeable morning hangover effect due to the antagonism of the 5-HT2A/C and being powerful sedating antidepressant. In contrast, fluoxetine is frequently connected to insomnia. Comparatively

speaking to doses used to treat mood disorders, doses used to treat insomnia are typically lower.

Alpha-adrenergic agonist

The two main alpha agonists that are frequently used off-label to treat autism-related sleep disorders are clonidine and guanfacine. Clonidine (dosing range: 0.05–0.225 mg/day) significantly reduced sleep initiation and maintenance insomnia in children and adolescents (aged 4–16 years) with autism and neurodevelopmental problems, with good tolerability and few side effects (24). Hypotension, irritability, bradycardia, dry mouth, and REM suppression are some of the side effects of clonidine that may occur, and its rapid withdrawal may result in rebound hypertension and rebound REM (25).

Sedative and hypnotics drugs

Hypnotics and sedatives benzodiazepines (BZDs) are routinely given to adults with insomnia. However, because of their side effects, which include drowsiness, headaches, cognitive impairment, dizziness and rebound sleeplessness, and physical and behavioral dependence, they are recommended less frequently to children. Clonazepam was the only benzodiazepine tested for sleep issues in autistic children. Children with developmental disabilities were found to benefit from the treatment of partial arousals, parasomnias, periodic limb movement disorder, and nocturnal biting with clonazepam, an intermediate-acting BZD (26, 27).

Other medication

Several medications which are used in the treatment of the Alzheimer's disease are also found to be effective in the management of ASD symptoms (28). Drugs such as donepezil and rivastigmine are cholinesterase inhibitors that increase the acetylcholine by preventing its destruction. ASD is associated with anomalies in the cholinergic system, according to previously published evidence (29). First, research looking at post-mortem brain samples from people with ASD has discovered cholinergic system anomalies (30, 31).

According to several studies, a large percentage of children with ASD condition experience seizures. It is reported that the incidence of ASD cases that suffered from epilepsy may range from 5 to 38% which is much higher than the incidence of the epilepsy in the normal children population which is 1–2% (32, 33). There is very limited evidence about the use of anti-epileptic drugs in ASD patients. A randomized controlled trial has been valproate in ASD cases (34). They found that valproate monotherapy reduced the irritability and repetitive behaviors in ASD cases (35).

Sleep disorder and ADHD

One of the most frequently identified illnesses in both children and adults is attention-deficit/hyperactivity disorder (ADHD). It affects 2.9% of adults and 3 to 5% of children. It continues into adolescence and adulthood. The diagnostic criteria of ADHD include symptoms of inattention or/and impulsivity that appear prior to 12 years old, and hyperactivity. Untreated ADHD patients suffer from a decrease in several critical functional domains, including the academic, social, and occupational realms (36).

Types of sleep disorders

An estimated 25–50% of people with ADHD report having sleep issues in clinical settings (37). Besides, adults who do not have enough time of sleep are more prone to have symptoms of ADHD (38). Such individuals' sleep disruptions have been linked to concomitant primary sleep problems and/or changes brought on by ADHD drugs (6). Researchers have looked into the connections between ADHD and narcolepsy, insomnia, circadian rhythm sleep disorders (CRSDs), restless leg syndrome, and sleep-disordered breathing (SDB) (39, 40).

Obstructive sleep apnea and ADHD

Obstructive sleep apnea (OSA) is characterized by partial or total obstruction of the upper airway, which results in interrupted sleep, while SDB is associated with unpredictable breathing rhythm during sleep (41, 42). People with ADHD have a higher incidence of SDB, and those with a history of snoring or possible OSA throughout childhood are associated with a two-fold higher susceptibility of diagnoses with ADHD (43). Through several processes, involving negative effects of hypoxic outcomes, the inflammation that leads to brain, and/or recurrent arousal-based sleep disturbances, SDB influences psychological outcomes. These pathways may change the prefrontal cortex's neurochemical substrates, resulting in the neurobehavioral abnormalities that underlie the symptoms of ADHD (44).

Restless leg syndrome and ADHD

Restless leg syndrome (RLS) is a common sensorimotor condition characterized by an intense need to move the legs, which is frequently accompanied by unpleasant leg or (less frequently) body-part feelings. These feelings are particularly uncomfortable in the evening or at night and get better with activity. Due to their need to walk about and the stiffness in their legs, patients frequently have sleeplessness. This comorbidity is thought to be caused by iron deficiency and dopaminergic disorders (45, 46). Even though the incidence of RLS in children is unknown, the disorder affects 10% of adults in the United States. According to the data, up to 44% of people with ADHD have RLS or symptoms similar to it, while up to 26% of those with RLS have symptoms similar to it (47, 48).

Circadian rhythm sleep disorder and ADHD

The timing of when a person sleeps and is awake is a concern in CRSDs. They result from changes to the circadian clock, its entrainment processes, or a misalignment of the internal circadian rhythm with the external environment. When a person routinely falls asleep and awakens more than 2 h later than is deemed normal, this condition is known as delayed sleep phase syndrome (DSPS). Changes in these processes, reductions in pineal gland volume, and/or anomalies in clock genes have all been discovered in people with

ADHD. In adolescents and adults with ADHD, late chronotype and DSPS are typically co-occurring disorders. CRSD and ADHD may share a biological and behavioral etiology (49, 50). Impulsivity control issues might impair a person's capacity to calm down, causing resistance to going to bed and a delayed start to sleep. It is also suggested that those with ADHD might have a greater circadian preference for the evening and a potential endogenous melatonin rise delay (50).

Narcolepsy and ADHD

A persistent neurological condition called narcolepsy causes problems with sustaining constant wakefulness and sleep. A diagnosis of narcolepsy needs symptoms of rapid eye movement (REM), sleep dissociation (such as sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy), and disturbed nighttime sleep, regardless of how the clinical presentation manifests itself. In the past, it was discovered that adults with narcolepsy had a twice as high probability of receiving an ADHD diagnosis as children as compared to controls (51). Additionally, data points to children with ADHD experiencing hypo arousal and hypo arousal-related hyperactivity/impulsivity as possible signs of exhaustion (52). Although the relationship between the two disorders is unclear, it has been postulated that EDS in narcoleptics may cause inattention, deficient executive function, and issues with impulse control that are similar to ADHD and react well to psychiatric drugs (53–55). Finally, the overlap of ADHD and narcolepsy symptoms may result in diagnostic ambiguity or incorrect diagnosis of the diseases. Another theory is that the connection could be due to a common pathology in the brain (56).

ADHD medication

Stimulants

The effects of stimulants on sleep vary from patient to patient in those with ADHD, reflecting the intricacy of the relationships between sleep disturbance and ADHD (57). Clinical experience suggests that stimulants generate paradoxical effects, whereby symptom relief can relax patients and encourage sleep, although there is evidence linking stimulants to disturbed sleep in ADHD cases (58, 59). Furthermore, increasing the dosage of a short-acting inducer or using a formula with prolonged action may minimize sleep disruptions caused by an increase in hyperactivity or behavioral disorders at bedtime due to the risk of symptom rebound when the concentrations of the drug in the blood is decreased (60, 61).

Non-stimulants

The most frequent side effect associated with atomoxetine that is connected to sleep, in contrast to stimulants, is somnolence (a noradrenaline reuptake inhibitor permitted for the management of ADHD). In atomoxetine placebo-controlled trials, somnolence was observed to present in 15–17% of patients as reported by a 2009 comprehensive review (62). Atomoxetine was found to have less of an impact on subjective sleep measures than methylphenidate and was taken three times per day in a randomized, double-blind trial.

Management

After evaluation and diagnosis, the first stage of treatment will be psychoeducation. In addition to learning about the prognosis, course, therapy, and probable functional implications of the sleep disorder, the affected individuals and their social entourage will require proper psychoeducation on ADHD symptoms and sleep problems. Additionally, educating people about healthy sleep habits and sleeping patterns will enable non-pharmacological sleep enhancement. It is common practice to use medicine to address sleep disturbances. The choice of medication can be directed to address related issues such as daytime malfunction and should be combined with behavioral techniques. Surgery to remove the tonsils or adenoids is the first line of treatment for children with ADHD and SDB, whereas oral appliances, positive airway pressure devices, or surgery are suggested treatments for adults with OSA and ADHD (63). The sleep environment may need to be changed for people with RLS and ADHD, and behavioral therapies such as iron supplements (64) (for example, ferrous sulfate) or gabapentin (65) may also be investigated, especially for a younger population. In an adults, using dopaminergic substances such as L-DOPA, ropinirole, and pramipexole, in addition to, a recently developed drug called rotigotine may also be a possibility (66).

Treatment options for people with DSPS and ADHD include scheduled melatonin therapy, light therapy (67), and chronotherapy (68, 69). Furthermore, because treatment for DSPS differs from that for insomnia, a clear distinction between the two must be made. Treatment for ADHD and insomnia can differ depending on the age group.

People with intellectual disabilities and sleep disorders

The incidence of sleep issues in children ranges from 24 to 86%, and they are widespread in persons with intellectual disabilities (70). Adults with mental disabilities are reported to have an incidence of sleep disorders ranging from 8.5 to 34.1%, with a serious sleep problem rate of 9.2%. In one study, it was discovered that 551 older persons with intellectual disabilities had sleep issues in 72% of the cases (47). The treatment of physical and mental health issues in people with intellectual disabilities is an area that needs more study. Studies conducted on people without intellectual disabilities were often the basis for the development of diagnostic and management techniques. The same pattern is observed in persons with intellectual impairments who have sleep difficulties. There is a lack of information specifically on the causes, effects, and treatments of sleep problems in people with developmental disabilities. Assessment and treatment of sleep issues in persons with intellectual impairments can be informed by knowledge of the several types of sleep issues that these people encounter and the numerous factors that affect their sleep (71).

Adults with intellectual disabilities have a higher risk to have sleep issues, which could be due to several factors. In individuals with intellectual impairments, a systematic review of the published literature on sleep problems found links between sleep and several characteristics, such as respiratory diseases, psychoactive drugs, mental health illnesses, and challenging behavior (47). Understanding and taking into account the social, psychological, and biological aspects influencing the higher occurrence of sleep issues in persons with intellectual impairments is crucial for providing person-centered and individualized care. We have looked at several significant contributing elements that must be taken into account when evaluating sleep issues in persons with intellectual disabilities. The association between sleep disturbances and neurodevelopmental diseases like ADHD and ASD has been thoroughly studied above (47).

Genetic conditions

Our comprehension of the underlying genetic causes of intellectual impairments has recently improved (72). For example, Down's syndrome is characterized by obesity, hypotonia, and craniofacial anomalies, all of which raise the likelihood of sleep disorders including obstructive sleep apnea (OSA). Similarly to this, those who have cri du chat syndrome have a higher risk of getting OSA (73).

Environmental and psychological factors

People with mental disorders frequently experience sleep disturbance as the first sign of a decline in their mental health, and low-quality sleep represents a common feature of many psychotic and affective diseases (11). When compared to individuals without cognitive disabilities, those with cognitive disabilities have a higher incidence of mental problems, which helps explain why sleep disturbances are so common in this population (12). When determining the etiology of sleep issues in a person with cognitive disabilities, it is crucial to take the environment's role in the development of sleep disorders into account. According to Kerr and Wilkinson (13), staffed residential homes may not be the best places to sleep because people may check on residents at odd hours, which would result in more noise and lights that would be disruptive to sleep (13).

Diagnosis of sleep disorders

Adults with intellectual impairments are frequently given subjective sleep information by their caregivers, who may disagree with the severity of the problem or may even accept sleep disturbance as a symptom of the person's underlying condition (74).

Because of this, sleep problems are more likely to be noticed by a physician when they induce nocturnal or daytime malfunction, including behavioral disorders, impairing a person's subjective impression of their quality of life (75). When evaluating sleep disturbances, general population guidelines stress the significance of checking for coexisting medical diseases. This is may be even more crucial for people with intellectual impairments since they are more prone to experience physical health illness that impacts their sleep, such as OSA or epilepsy (76). For example, it is advised that everyone with Down's syndrome be evaluated for OSA due to the condition's high incidence in people with Down's syndrome. When sleep–wake duration (including naps) is irregular or unpredictable, caregiver-completed sleep diaries and/or actigraphy, ideally conducted for at least 2 weeks, can be used. Individuals with intellectual impairments can be evaluated for physical sleep disorders such as OSA and nocturnal epilepsy using home or in-patient sleep examinations (such as pulse oximetry or the gold standard, polysomnography) (77). Even though these tests should always be provided when clinically indicated, if a patient is unable to endure the sleep tests, a practical therapy trial may be necessary. The variety of underlying causes of intellectual disability and the characteristics of related comorbidities make managing sleep disturbances challenging. While intellectual disability psychiatrists can easily address some problems, others will need the assistance of sleep physician and/or primary care givers. According to a study, continuous positive airway pressure therapy can significantly enhance behavior, cognitive function, and subjective drowsiness in individuals with Down's syndrome and OSA (78). But as this study correctly notes, access to care may be difficult, and as was already said, some individuals with intellectual disabilities might find it difficult to tolerate these tests and treatments. Working together, sleep specialists and psychiatrists may be able to address these issues. For instance, sleep clinics assist the training of mental health nurses for people with intellectual disabilities in exposure treatment to aid those individuals become used to positive airway pressure masks. The initial management for persistent insomnia in the general population is multicomponent cognitive-behavioral therapy (CBT-I), and there are elements of this that can be helpful for individuals with intellectual impairments (74). Understanding the impacts of environment and lifestyle on sleep, such as caffeine use, exercise, and regular sleep schedules, along with lighting, noise, and temperature, can be achieved through education on sleep hygiene (75).

Adults with cognitive disabilities are more prone than the general population to lack appropriate daily activity and regular exposure to natural light, thus even small changes to everyday routine and the sleeping environment can be beneficial (75). The needs of the person should be taken into consideration when making such recommendations, such as lowering external noise for autistic people sensitive to sounds. The evidence is not strong enough to support the use of pharmaceuticals to treat sleep disturbances in adults with intellectual impairments. Melatonin is the drug that has drawn the most attention, maybe due to its favorable side-effect profile and the fact that several trials have demonstrated its efficacy (75). According to a meta-analysis, melatonin consumption enhances total sleep time and reduces the number of wake-ups per night in people with intellectual disabilities. Currently, the pharmacological management of illnesses other than insomnia tends to use the same routes as those for the general public (75).

Conclusion

Disorders of sleep are key concerns in children with neurodevelopmental disorders. In this group of patients, sleep disorders are common and tend to chronicity. Various solutions are required based on the neurodevelopmental problem, but all patients should get behavioral intervention. Understanding the distinctive characteristics of sleep disturbances in patients with neurodevelopmental disorders is critical for effective therapy.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Progress of autonomic disturbances in narcolepsy type 1

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Narcolepsy type 1 is a kind of sleep disorder characterized by a specific loss of hypocretin neurons in the lateral hypothalamus and reduced levels of hypocretin-1 in the cerebrospinal fluid. Hypocretin deficiency is associated with autonomic disorders. This article summarizes the autonomic disorders and possible mechanisms associated with narcolepsy type 1. Patients with narcolepsy type 1 often have various systemic autonomic symptoms, including non-dipping blood pressure, reduced heart rate variability, dynamic cerebral autoregulation impairment, reduced gastric motility and emptying, sleep-related erectile dysfunction, skin temperature abnormalities, and blunted pupillary light reflex. Similar findings should strengthen the recognition and intervention of these disturbances in clinical practice. In addition to hypocretin deficiency, current evidence also indicates that pharmacological therapy (including psychostimulants and anti-cataplectic drugs) and comorbidities may contribute to the alterations of autonomic system observed in narcolepsy type 1.

KEYWORDS

narcolepsy type 1, hypocretin, autonomic nervous system, sympathetic, parasympathetic

1. Introduction

Narcolepsy type 1 (NT1) is a chronic sleep disorder with major clinical manifestations including excessive daytime sleepiness, cataplexy (a sudden loss of muscle tone triggered by strong, mainly positive, emotions), sleep paralysis, hypnagogic hallucinations, and nocturnal sleep disorder (1). Patients can also present with multiple chronic comorbidities including obesity, depressive disorder, migraine, precocious puberty and other sleep disorders (such as rapid eye movement sleep behavior disorder and obstructive sleep apnea) (2). The most significant neuropathological change is the selective and irreversible loss of hypocretin-producing neurons in the lateral hypothalamus (3). Hypocretin neuropeptides consisted of hypocretin-1 (hcrt-1) and hypocretin-2 (hcrt-2), and they modulate their actions *via* hcrt-1 and hcrt-2 receptors. Patients with NT1 often have low levels of hcrt-1 in the cerebrospinal fluid.

Hypocretin neurons have widespread projections to different areas involved in regulating the sleep-wake cycle, energy metabolism, neuroendocrine, body temperature, and cardiovascular functions, which are associated with changes in the autonomic nervous system (4). Clinically, autonomic dysfunction often affects visceral organs, vascular smooth muscle, myocardium, and glands activities (5). However, autonomic symptoms are easily ignored compared with the typical symptoms in NT1. Here, we review the autonomic disorders and their possible mechanisms in patients with NT1 (Figure 1).

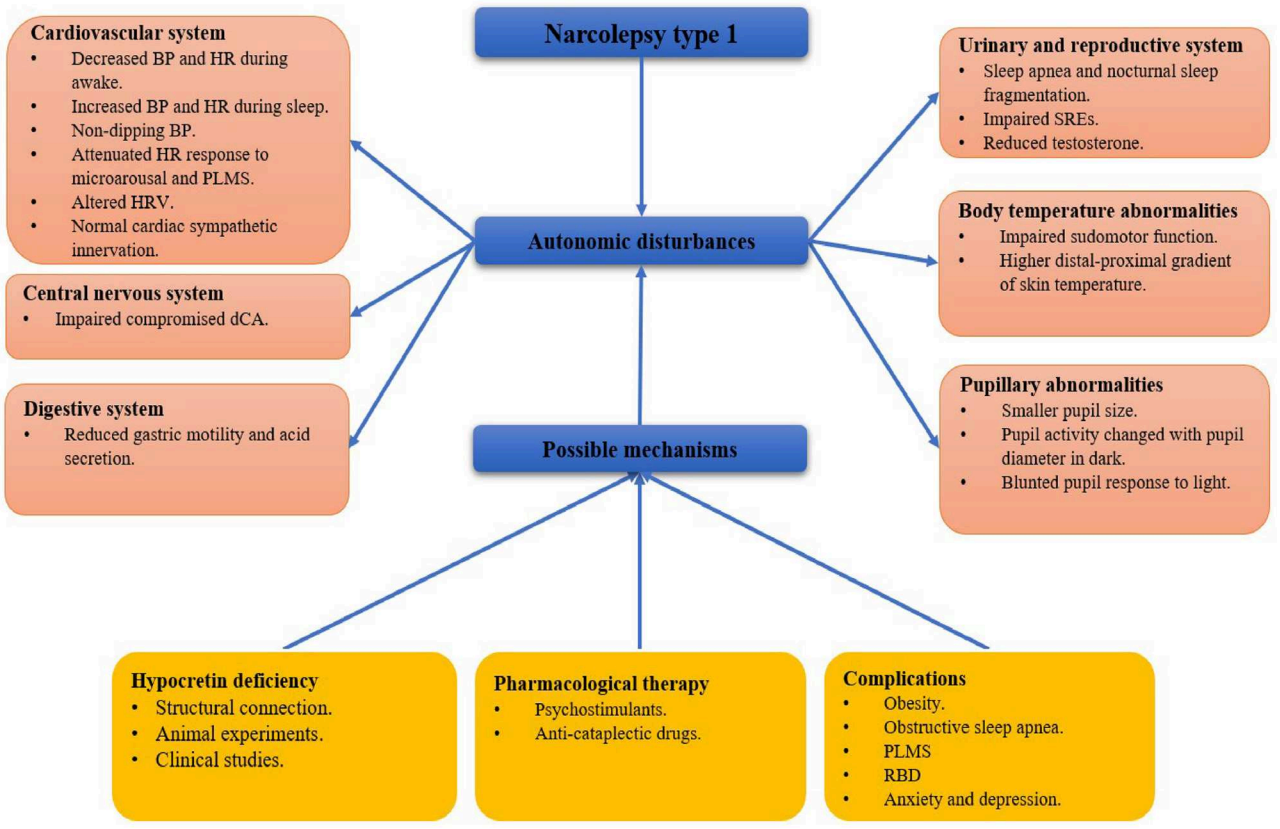

FIGURE 1
A framework of autonomic disturbances and possible mechanisms in narcolepsy type 1. BP, blood pressure; HR, heart rate; PLMS, period limb movements during sleep; HRV, heart rate variability; dCA, dynamic cerebral autoregulation; SRE, sleep-related erection; RBD: rapid eye movement sleep behavior disorder.

1.1. Autonomic disorders

1.1.1. Cardiovascular system

1.1.1.1. Changes in blood pressure and heart rate

Previous studies suggested that 52% of adults with NT1 and 37% of children with NT1 and other hypersomnia disorders had the symptoms of orthostatic intolerance, indicating impairment of cardiovascular autonomic regulation (5, 6). Autonomic disorders in the cardiovascular system may increase the risk of cardiovascular events and reduce the quality of life of patients with NT1.

Several studies on cardiovascular changes have focused on daytime wakefulness, different sleep stages, and wake-sleep transitions. Donadio et al. (7) demonstrated lower heart rate (HR), blood pressure (BP), and resting muscle sympathetic nerve activity using direct microneurographic recordings in patients with NT1 during wakefulness. In contrast, other studies found a significant increase in HR in patients with NT1 vs. controls during wakefulness, and the non-rapid eye movement (NREM) and rapid eye movement (REM) stages (8–10). In addition, it is generally believed that patients with NT1 are prone to have non-dipping blood pressure, defined as a nocturnal BP decrease <10% of the daytime BP (8, 11, 12). Dauvilliers et al. (13) reported a higher percentage of non-dipping BP in NT1 compared to healthy controls (31 vs. 3%). Grimaldi et al. (8) observed a significantly increased systolic BP in 10 untreated patients with NT1 vs. controls during nighttime REM sleep.

In summary, BP and HR were lower during resting wakefulness but higher during nighttime sleep in patients with NT1. Impaired cardiovascular regulation ability is not beneficial for the maintenance of normal physiological functions. Furthermore, microarousal and periodic leg movement events during sleep (PLMS) may affect BP and HR. Two previous studies found that the amplitude of microarousal and PLMS-related HR responses was significantly reduced in patients with NT1 compared to controls, suggesting poor cardiac autonomic nervous regulation (14, 15).

1.1.1.2. Measurement of cardiovascular autonomic disorders

Heart rate variability is widely used to evaluate autonomic changes, including frequency-domain, time-domain, and non-linear correction analysis. In the frequency domain, low frequency (LF) is modulated by both the sympathetic (SNS) and parasympathetic (PNS) nervous systems, while high frequency (HF) is only affected by PNS activity.

The LF/HF ratio provides a measure of sympathovagal balance, which generally increases with high SNS activity and decreases with high PNS activity (16). Grimaldi et al. (17) studied heart rate variability in NT1 in the resting supine position and found an

increased LF/HF ratio favoring enhanced SNS activity. However, after removing the effect of respiratory frequency on the HF component, there were no significant differences in the LF/HF ratio between NT1 and controls during any sleep stage or wakefulness (9). Silvani et al. (10) observed a significant reduction of cardiac baroreflex sensitivity and time-frequency index [—square root of the mean of the sum of the squares of differences between adjacent normal-to-normal interval (RMSSD)] in NT1 vs. controls during wakefulness before sleep, which reflect the function of cardiac PNS modulation.

^{123}I-metaiodobenzylguanidine cardiac scintigraphy is a reliable method for the objective evaluation of cardiac adrenergic nerve activity. Barateau et al. found normal cardiac sympathetic innervation in NT1 by comparing the delayed heart/mediastinum ratio of patients with NT1 to that in control subjects. However, the study did not calculate the early heart/mediastinum ratio and washout rate, with the latter being the most reliable biomarker to reflect cardiac sympathetic nerve activity (18).

Generally, non-dipping BP and decreased heart rate variability indicate that the ability of cardiovascular autonomic regulation is decreased in patients with NT1, making it impossible to better adapt to the changing environment. As for the increase or decrease in SNS and PNS during the wake and sleep stages, there are contradictions between studies, for which possible reasons are the small sample size, insufficient adjustment of confounding factors, and lack of standard measurement methods.

1.1.2. Possible mechanisms of cardiovascular autonomic disorders

1.1.2.1. Hypocretin deficiency

Hypocretin neurons have widespread connectivity with neurons involved in autonomic control, including the paraventricular nucleus of the hypothalamus, homonymous noradrenergic cell groups of the pons, medullary raphe nuclei, rostral ventrolateral medulla, rostral ventromedial medulla, nucleus ambiguus, nucleus of the tractus solitarius, and dorsal motor nucleus of the vagus nerve, which set the foundation for the involvement of hypocretin in autonomic regulation and autonomic disturbances in NT1 (4).

Several animal studies have confirmed the involvement of hypocretin in the regulation of cardiovascular autonomic nervous activity. Machado et al. (19) observed an increase in BP and HR by injecting hcrt-1 into the rostral ventromedial medulla of conscious rats, but no cardiovascular changes were observed following the injection of saline. Shirasaka et al. (20) also found an increase in BP, HR, renal sympathetic nerve activity, and plasma catecholamine levels following intracerebroventricular injection of hcrt-1 in conscious rats. Two animal studies showed that hcrt-1 has an activating effect on the cardiovascular sympathetic nerve, but it is worth noting that hcrt-1 concentration was much higher under experimental conditions than under physiological conditions. Iigaya et al. (21) observed a decrease in BP, HR, and renal sympathetic nerve activity by blocking the hcrt receptor. Three previous studies also showed decreased BP and HR in hypocretin gene-deficient or gene-silent animals by gene knockout, small interfering RNA, and transgenic techniques (22–24).

A clinical study showed that all patients with narcolepsy had a significantly attenuated HR response to arousals and PLMS, particularly patients with NT1, and hcrt-1 deficiency could be an independent predictor of reduced HR response in multivariate linear regression analysis (15). Donadio et al. (7) demonstrated a correlation between cerebrospinal fluid hcrt-1 concentration and HR or muscle sympathetic nerve activity. There is a negative correlation between the pulse transit time and arterial BP, with pulse transit time lengthensing if vessels become less stiff due to a decrease in arterial BP. Vandi studied 27 pediatric patients with NT1 and found a reduced lengthening of pulse transit time during total sleep and REM sleep compared with nocturnal wakefulness, which was more severe in subjects with lower cerebrospinal fluid levels of hcrt-1 (12).

These results support the direct effect of hcrt-1 on autonomic regulation. However, other studies have not supported this conclusion. Barateau et al. (5) reported that a higher "scales for outcomes in Parkinson's disease-autonomic" (SCOPA-AUT) score was not associated with cerebrospinal fluid hcrt-1 levels. In the same year, another study found that a delayed heart/mediastinum value was independent of hcrt-1 (18).

1.1.2.2. Pharmacological therapy

Life-long treatment with psychostimulants and anti-cataplectic drugs can affect the autonomic nervous system of patients with NT1. Bosco et al. found that patients with NT1 treated with psychostimulants had higher 24-h diastolic BP and HR than untreated patients. The prevalence of hypertension was also significantly higher than that in untreated patients. They also found that the combination of anti-cataplectic drugs and psychostimulants showed a synergistic effect on BP (25). The effects of psychostimulants (such as methylphenidate) and anti-cataplectic drugs (such as venlafaxine and fluoxetine) on the autonomic nervous system are related to their sympathomimetic mechanisms of action, including the promotion of presynaptic membrane release of monoaminergic transmitters and inhibition of monoaminergic transmitters reuptake.

1.1.2.3. Comorbidities

Patients with NT1 have a variety of comorbidities such as obesity, obstructive sleep apnea, PLMS, sleep behavior disorder during REM, anxiety, and depression, which are all closely associated with autonomic dysfunction (26–29). Rocchi et al. (30) demonstrated a significant and positive correlation between body mass index and systolic BP in the supine resting position at 3 and 10 min head-up tilt test; therefore, it is speculated that body weight plays an important role in cardiovascular sympathetic tone. Nocturnal sleep fragmentation has been frequently reported in patients with obstructive sleep apnea, PLMS and REM sleep behavior disorder, which affects the autonomic nervous system in NT1 (14, 15, 31, 32). Symptoms of anxiety and depression have been demonstrated to be common among patients with NT1 (33). Barateau et al. (34) suggested that the severity of depressive symptoms was associated with autonomic impairment. Research showed that the component formula of Suanzaoren Tang had anti-anxiety function by reducing hippocamps 5-hydroxytryptamine level in rats (35, 36). These results indicate the link between psychiatric symptoms and autonomic disorders in NT1.

1.1.3. Central nervous system

Cerebral autoregulation is the ability of the brain to maintain adequate cerebral blood flow in the presence of changes to blood or cerebral perfusion pressure. Dynamic cerebral autoregulation (dCA) is used to study transient changes in cerebral blood flow (37). dCA is regulated by the autonomic nervous system; therefore, sympathovagal balance is important to maintain relative stabilization of cerebral blood flow (38–40). Our previous study found that dCA was impaired in patients with NT1, possibly indicating dysfunction of autonomic nerves innervating cerebral vessels. The hypocretin neurons send projections to monoaminergic neurons, including dopamine, norepinephrine, and 5-hydroxytryptamine. A previous study found that hcrt neurons play critical roles in the sleep/wakefulness pathway by regulating monoaminergic transmitter levels (41). Norepinephrine is a sleep autonomic neuromodulating transmitter and 5-hydroxytryptamine is a vasoactive substance that may have potential effects on dCA (42–44). Hypocretin and monoaminergic transmitter reduction or deficiency can lead to impairment of dCA and autonomic dysfunction in patients with NT1 (45).

1.1.4. Digestive system

It has been reported that 88% of untreated adult patients with NT1 have gastrointestinal disturbances, including drooling, early abdominal fullness, constipation, and straining for defecation. These symptoms may be related to vagal nerve dysfunction regulated by hcrt-1 (5).

Previous studies mainly focused on animal models. Jin et al. found that gastric motility and emptying were enhanced by injecting hcrt-1 into the central nucleus of the amygdala of rats, which expresses the hcrt-1 receptor. This effect was abolished by subdiaphragmatic vagotomy. These results show that the amygdala-vagus-stomach pathway may be involved in regulating gastric motility through hcrt-1 (46). In addition, many other nuclei are directly or indirectly involved in the regulation of gastric acid secretion and gastric motility mediated by hypocretin neurons, including the paraventricular nucleus of the hypothalamus, raphe nucleus of the medulla oblongata, ventral tegmental area and nucleus accumbens (46–48).

1.1.5. Urinary and reproductive system

Barateau et al. found that most patients with NT1 (92%) had urinary symptoms, especially nocturia and incomplete bladder emptying (5). Nocturia symptoms may be related to sleep apnea and nocturnal sleep fragmentation, which improve after continuous positive pressure ventilation (49).

Sexual dysfunction has been reported in 48% of men (erection problems) and 81% of women (vaginal lubrication problems) (5). Sleep-related erection (SRE) often occurs during REM sleep. The results from a study in rats suggested that SRE is regulated by the hypothalamus (49). Karacan et al. conducted SRE tests on 28 patients with NT1 and found that 23 of them who were receiving methylphenidate and imipramine therapy had 20% shorter SREs and incomplete erection, and only two of the other five untreated patients had impaired SRE. These results suggest that sexual dysfunction may be related to the use of stimulants and antidepressants (50). In addition, insufficient testosterone and abnormal hypothalamic-pituitary-gonadal axis activity may be related to male sexual dysfunction. Joshi et al. (51) reduced the level of testosterone in the serum by injecting an hcrt-1 receptor antagonist into adult mice to prove its involvement in sex hormone synthesis. In a study comparing serum gonadotropin levels in males with NT1, pulsatile luteinizing hormone release was diminished compared to controls, indicating that hcrt-1 is involved in the regulation of hypothalamic-pituitary-gonadal axis activity (52).

1.2. Other autonomic disorders

1.2.1. Body temperature abnormalities

Up to 87% of patients with NT1 have symptoms related to abnormal thermoregulation, including daytime hyperhidrosis during the day and heat intolerance (5). Abnormal sweat gland function can be assessed using the sudomotor function test. Rocchi et al. (30) found lower hand sudomotor activity significantly in patients with NT1, suggesting an impairment in cholinergic sympathetic activity. However, the results conflict with the clinical symptoms of hyperhidrosis. Other techniques, such as sympathetic skin response and quantitative sudomotor axon reflex tests, are needed to verify this discrepancy.

Previous studies have focused on altered distal and proximal skin temperatures and their relationship with clinical symptoms and sleep architecture. Fronczek et al. measured the skin temperature in 15 untreated patients with NT1 throughout the day and found an increased distal skin temperature and a decreased proximal skin temperature, resulting in a higher gradient. This change is indicative of decreased distal sympathetic vasoconstrictor tone and increased distal skin blood flow in NT1, which may ultimately be attributed to hypocretin deficiency (53).

Skin temperature dysfunction in patients with NT1 is associated with their two core symptoms: excessive daytime sleepiness and nocturnal sleep disorder. Influencing distal skin temperature increased daytime alertness and time of wakefulness (53, 54). An elevated distal-proximal gradient of skin temperature to some extent lead to an increase in slow wave and REM sleep and a decrease in wakefulness, which is helpful in improving the quality of nighttime sleep (55). Vander Heide and colleagues reported that the greater the distal and distal-proximal gradient of skin temperature before daytime sleep episodes, the more likely patients with NT1 were to fall asleep, indicating a strong predictive value of increased distal and distal-proximal gradients of skin temperature for daytime sleep episodes in patients with NT1 (56).

1.2.2. Pupillary abnormalities

Pupillomotor symptoms with increased sensitivity to bright light were observed in 64.2% of patients with NT1 (5). The pupil size is influenced by the degree of arousal, and hcrt-1 is an important neurotransmitter that maintains alertness. Pressman et al. observed that the mean pupillary diameter was significantly smaller in patients with NT1 compared to controls. Pupil activity was correlated with pupil diameter in dark conditions, with maximum pupil size at the highest ratings of alertness and minimum at the lowest alert level (57). Zhou et al. (58) blunted

the pupillary response to light by intravitreal injection of an hcrt-1 receptor antagonist in mice, while enhancing the pupil response to light by injection of hcrt-1. It is evident that hcrt-1 plays a role in regulating pupil size and changes, and the clinical symptoms of pupillary abnormalities may be related to reduced pupil diameter and a blunted light response.

2. Conclusion

Patients with NT1 often have various clinical autonomic symptoms, but relevant epidemiological studies are still lacking. The SCOPA-AUT questionnaire has been validated for Parkinson's disease, and the feasibility of the subjective tool to assess the severity of autonomic symptoms in NT1 needs further investigation. With more clinical attention being paid to autonomic symptoms, standard objective measurement methods need to be developed. In addition, hypocretin reduction or deficiency alone cannot explain the extent of autonomic disorders in patients with NT1. Finally, it is generally accepted that prolonged autonomic disorders could increase the risk of cardiovascular disease in patients with NT1, and long-term follow-up is necessary in the future.

Author contributions

QT and YZ were involved in the retrieval of literature and collected the data. YW wrote the initial manuscript. QS, MT, and DW drafted the Figure 1. QS redesigned and revised the manuscript. ZW designed and approved the final version of the manuscript. All authors have read the final manuscript and approved it for submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Polysomnography findings in sleep-related eating disorder: a systematic review and case report

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Background: Sleep-related eating disorder (SRED) consists of recurrent episodes of uncontrolled, involuntary eating and drinking 1–3 h after falling asleep with partial or full unconsciousness. This condition is diagnosed based on interviews with the patients affected and the diagnostic criteria of the International Classification of Sleep Disorders. However, polysomnography (PSG) is not necessary to confirm this disease. This systematic review aims to evaluate the findings of PSG in SRED patients.

Methods: For this systematic review, PubMed, Embase, and Scopus databases were searched in February 2023, which resulted in 219 records. After removing duplicates, the articles that included the presentation of PSG results of SRED patients in English were selected. In addition, only original studies were considered. The risk of bias by using case reports and descriptive studies was assessed using the Joanna Briggs Institute critical appraisal tools and the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. Furthermore, a case report of a 66-year-old woman with SRED was included.

Results: A total of 15 papers were selected for further analysis, of which 7 were descriptive studies, 6 were case reports, and 2 were observational studies. The risk of bias in the majority of the studies was moderate or high. Unexpectedly, if the eating episode occurred during PSG, in most cases it was not observed during deep sleep (the N3 sleep stage). Moreover, studies did not report significant deviations in the sleep parameters measured using PSG. Among SRED patients, the prevalence of sleepwalking was much higher than the general population. Our case report presented a potentially life-threatening episode of holding an apple in the mouth that might result in choking, which was captured using PSG.

Conclusion: Polysomnography is not necessary for the diagnosis of SRED. However, it could facilitate the diagnosis and differentiation of SRED from other eating disorders. PSG also has limitations in capturing eating episodes and in addition, its cost effectiveness should be considered during the diagnostic process. More studies into the pathophysiology of SRED are needed because classifying SRED as non-rapid eye movement parasomnias can be inappropriate as it does not always occur during deep sleep.

KEYWORDS

sleep-related eating disorder, SRED, polysomnography, PSG, nocturnal eating, parasomnia

1. Introduction

Sleep-related eating disorder (SRED) consists of recurrent episodes of uncontrolled, involuntary eating and drinking 1–3 h after falling asleep with partial or full unconsciousness (1). After arousal from non-rapid eye movement sleep (NREM), patients often consume high-calorie food products but also inedible and toxic food (2). In addition, cases of life-threatening or dangerous situations of eating food have been described in the literature (3). SRED is an example of NREM parasomnias, which also includes sleepwalking, confusional arousals, and sleep terrors (4). The presence of disease is estimated in about 5% of the general population (5), especially occurring in women in their mid-20 s (6). Other sleep diseases are often associated with SRED: sleepwalking called formerly somnambulism, obstructive sleep apnea (OSA), narcolepsy, periodic limb movements syndrome (PLMS) or restless leg syndrome (RLS) (2). The pathophysiology of SRED is not completely understood, but it is probably associated with the disability of the brain's reward system activation (7). Predisposing factors for SRED include female gender, mental stress, depression, and genetic factors (2), but the most common is drug-induced SRED by drugs such as zolpidem, serotonin norepinephrine reuptake inhibitors, and quetiapine (8), which is called secondary SRED. According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), the condition under concern should meet all the following criteria from Table 1 to be diagnosed as SRED (9).

Importantly, a polysomnography (PSG) examination is not required for the diagnosis of SRED although it is a "gold standard" procedure nowadays to detect sleep disorders. PSG includes electroencephalography, electromyography, electrocardiography, recording of body and limb movements, airflow measurement, oxygen saturation recording, recording of chest and abdomen wall movements, and video monitoring; therefore, it provides qualitative and quantitative parameters for abnormalities during sleep (10). In addition, the level of awareness of SRED episodes can be measured (2). Full consciousness during eating episodes and eating at least >25% of the total daily calories at night are characterized by a similar condition to SRED called Nocturnal Eating Syndrome (NES) (11). Despite obvious mentioned differences between these 2 conditions and other features of NES from Table 1 (12), sometimes their symptoms may overlap (13). Additionally, previously mentioned sleep disorders may coexist with SRED (14); thus, PSG should be performed to exclude any aforementioned disturbances. Many previous studies have reported only suspected side effects of drugs or patients' symptoms, such as suspicious behavior of uncontrolled nocturnal eating, without confirming any additional sleep disturbances. However, PSG findings, especially with video recording, have revealed the characteristic behavior of parasomnia in difficult cases and helped distinguish these conditions from SRED to treat the patients appropriately (4).

Given these circumstances, the primary objective of this review was to evaluate the existing results of PSG performed in patients with SRED. This review also included a case report of a patient admitted to the Sleep Laboratory at the Wroclaw Medical University due to fatigue, daytime drowsiness, snoring, obesity, and several nocturnal eating episodes per month, which were observed using PSG and not commonly found in the literature of eating during sleep.

2. Methods

2.1. Search strategy and data sources

This systematic review, which was not a registered review, was designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) Checklist (15, 16). Three databases, namely Embase, PubMed, and Scopus, were searched with appropriate filters on February 8, 2023. All studies without limited time frame were included. The search term used was "sleep related eating disorder" OR "sleep-related eating disorders" OR "SRED" AND "polysomnography" OR "PSG" OR "polysomnographic" OR "examination results". Two authors (BB and HM) separately performed the search, and the results were compared. After removing duplications, the remaining records were screened based on their title and abstract. Then, according to the exclusion criteria presented in Section 2.2 and PRISMA 2020 guidelines, studies that did not meet the criteria were excluded. To confirm eligibility, appropriate full-text papers were read by two authors (BB and HM). In case of disagreements, the third researcher (MM-Z) resolved them via discussion.

2.2. Inclusion and exclusion criteria

The inclusion criteria of the studies were as follows: full-text papers, published in English and presentation of SRED patients with video-PSG (v-PSG) results. All patients' age, gender, and comorbidity disorders were considered. The difference between primary SRED and drug-induced SRED was not considered. PSG results could be presented as analytical or descriptive outcomes. The following were the exclusion criteria: non-English papers, lack of access to the records and type of studies as review, systematic review, book chapters, letters to the editor, commentaries, conference abstracts and articles where PSG results of SRED were combined with the nocturnal eating syndrome (NES). Furthermore, if an article had insufficient data to assess eligibility, they were excluded.

2.3. Data extraction and assessment of bias risk

After selecting the studies that fulfilled the above criteria, the data from the selected studies were extracted. Two reviewers (BB and HM) created a table containing the primary characteristics of the articles, such as author, type, number of participants, age and gender of patients, and their actual concomitant sleep disorders. In addition, episodes of nocturnal eating during PSG and polysomnographic parameters were also obtained from the selected studies.

Finally, the risk of bias in the included studies was assessed. Due to the diverse variety of article types, the Joanna Briggs Institute (JBI) critical appraisal tools for case reports and qualitative

TABLE 1 The diagnostic criteria for sleep-related eating disorder (SRED) and for nocturnal eating syndrome (NES).

Diagnostic criteria for sleep-related eating disorder (SRED) according to the international classification of sleep disorders, third edition	Diagnostic criteria for nocturnal eating syndrome (NES) according to the international symposiums on night eating
1. Recurrent episodes of eating following arousal from sleep or during the main sleep stages	1. Evening or nocturnal hyperphagia, characterized by eating at least >25% of the total daily calories or at least two episodes of nocturnal food ingestion per week
2. Coexisting with at least one of the following condition in association with the recurrent episodes of involuntary eating: - eating of toxic/inedible food or substances; - adverse effects of nocturnal eating on health; - sleep-related injurious behaviors related to capturing/cooking the food	2. Coexisting to nocturnal eating at least three of five below features: - lack of desire to eat in the morning (morning anorexia); - strong urge to eat between dinner and sleep initiation or in night; - problems with sleep initiation or sleep insomnia at least four times per week; - persistent belief that eating allow to initiate or return to sleep; - decreased mood or depression during the night
3. There is partial or complete loss of consciousness, inability to regain awareness on eating episodes	3. Full awareness during nocturnal eating episodes, complete ability to remind about ingestion circumstances
4. Exclusion of other causes/disorders	4. Exclusion of other causes/disorders
	5. Significant distress or daily impairment in functioning
	6. Episodes maintain at least 3 months

(descriptive) studies were used (17). For the remaining findings, the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tools for non-randomized studies were used (18).

To evaluate the methodological quality, in accordance with the JBI checklist, 8 questions were answered for case reports, and 10 questions for qualitative studies. The possible answers were "yes", "no", "unclear", or "not applicable". A low risk of bias was assumed when the answer "yes" was observed at least 7 times for case reports and 8 times from 10 categories for descriptive studies. A high risk of bias was assumed when the answer "yes" was observed less than 5 times for case presentations and less than 6 times for qualitative records. A moderate grade was observed between the two mentioned ranges.

The 7 domains of each study were checked using ROBINS-I to assess the quality of the studies. The risk of bias was graded as "low", "moderate", "serious", "critical", or "no information". The risk of bias was considered "serious" or "critical" if the article obtained "serious" or "critical" ratings at least in one domain. Studies that achieved "low" in all categories were considered having a low risk of bias, and studies without any "serious" and "critical" ratings were considered having a moderate risk of bias. Assessments of the risk of bias were always conducted separately by two researchers (BB and HM), who reached the final result via discussion.

3. Results

3.1. Study selection

The search resulted in 219 studies, 102 in Embase, 31 in PubMed, and 86 in Scopus, of which 108 were duplicates and hence removed. Among the remaining 111 studies, 17 did not belong to the subject of interest, 6 were not published in English, and 5 could not be retrieved. Among 83 full-text papers, 36 studies were reviews of literature, 3 were letters to the editor, 4 were book chapters, 14 were conference abstract and 1 was commentary. In addition, the PSG examination was not performed in 9 articles and in 1 article authors combined the PSG result of SRED with NES. Hence, only 15 manuscripts were selected for further analysis and evaluation (7, 13, 14, 19–30). A detailed description of the studies selection process is presented in Figure 1. The primary characteristics of studies with PSG examination in patients with SRED are summarized in Table 2.

3.2. Risk of bias in studies

The risk of bias was evaluated for the 6 case reports included in this review. Five studies (7, 14, 19–21) was evaluated on 5 to 6 answers of "yes" using the JBI checklist; therefore, their overall risk of bias was considered moderate. One of them showed a high risk of bias as it achieved "yes" less than 5 times (22). The steps of the assessment for case reports are presented in detail in Supplementary Table 3. Among descriptive articles, a moderate risk of bias was observed in 6 studies as 3 study achieved "yes" 6 times and 3 achieved the same 7 times (23–28). 1 study was estimated as having a low risk of bias as it achieved "yes" 8 times (13). The detailed steps of the assessment for descriptive studies are presented in Supplementary Table 4. The ROBINS-I tool was used to evaluate 2 studies. Komada et al. (29) had missing data; therefore, it was considered having a serious risk of bias. Brion et al. (30) achieved low or moderate scores in each domain, and according to the relevant criteria, the overall quality was moderate. This evaluation is presented in Supplementary Table 5.

3.3. Study characteristics

3.3.1. The general information

All the included studies presented PSG results of patients with SRED who were examined for the reported symptoms (7, 14, 19–22) for the following reasons: detecting the polysomnographic features of this syndrome (13, 23, 24, 29, 30), differentiating SRED from other diseases characterized by nocturnal eating (25–27), and explaining the pathophysiology of SRED (28). The majority of the included records were descriptive studies (13, 23–28), as well as case reports (14, 19–22), the rest of them were 1 case series (7), 1 cohort

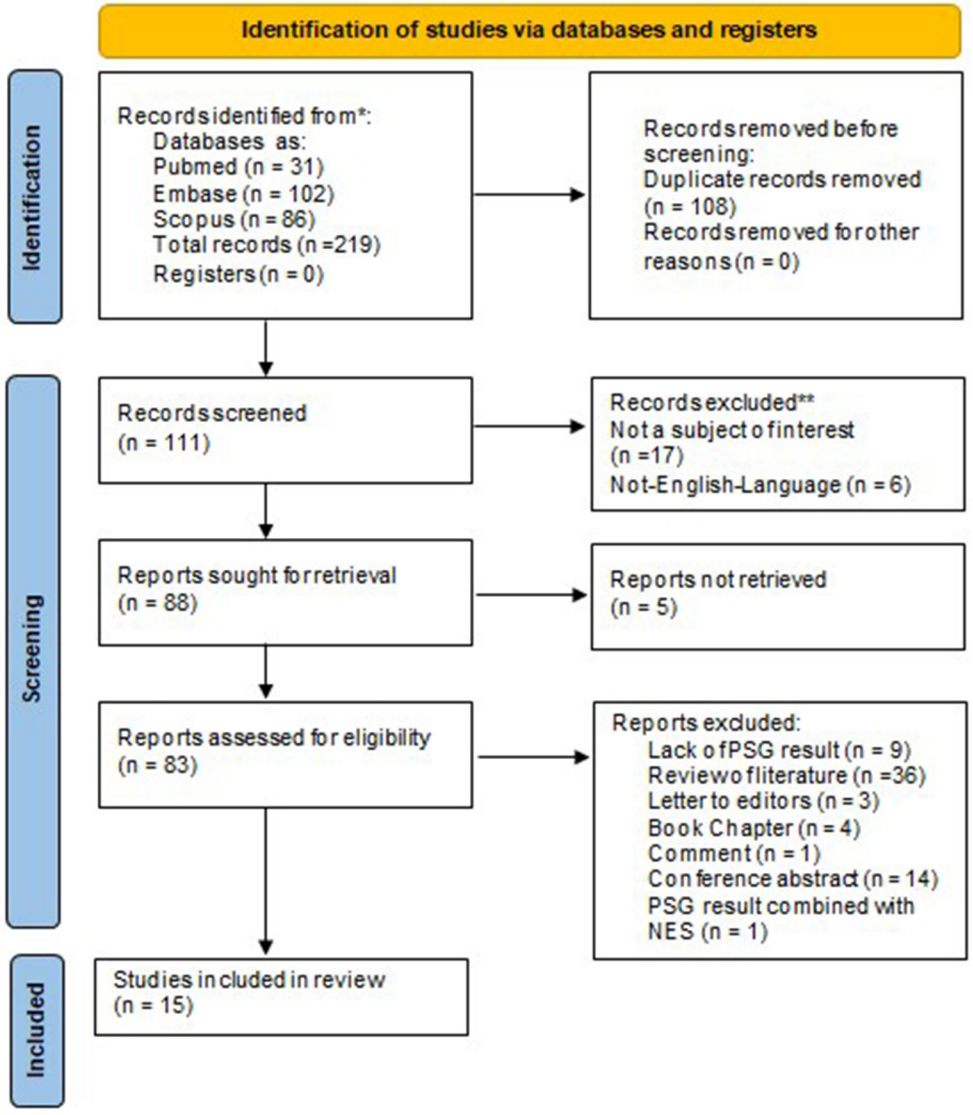

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram. PSG, polysomnography.

study (29) and 1 case control study (30). In the studies presenting individual cases, i.e., in case reports and case series, the exact age and polysomnographic parameters were provided. However, if a study included a large number of patients, the average values were presented with appropriate standard deviations (13, 23–30). In eight studies, the majority of the participants were female (20, 24–30). The total number of presented patients in included studies were 206 people. The youngest patient in this review was 9 years old (19), whereas the oldest one aged 70 years (30).

3.3.2. Concomitant sleep disorders

Coexisting sleep disorders such as NREM parasomnias and those predisposing to SRED were also considered (14). Single disorders were diagnosed, mainly sleepwalking in Perogamvros et al. (7) and Winkelman (24). It is worth mentioning that a single patient may have several sleep pathologies (22), e.g., narcolepsy–catalepsy and obstructive sleep apnea. In studies with a large sample size, only the number of disorders in the group was reported, without specifying whether these disorders affected **one** or more patients. For example, OSA was observed 18 times (22, 23, 27, 28), RLS 31 times (25, 27, 28, 30), PLMS 12 times (23, 25–27), sleepwalking 49 times (7, 24–28, 30), and sleep terrors 1 time (28). Only in 6 studies, no current sleep disturbances were reported (13, 14, 19–21, 29). Therefore, the prevalence of mentioned sleep disorders among presented patients were: 8.73% of OSA, 15.0% of RLS, 5.83% of PLMS, 23.9% of sleepwalking and 0.5% was sleep terrors.

3.3.3. Polysomnography findings

Due to the use of v-PSG, which is a good diagnostic software, and the consumption of food during the study, nine studies observed sleep arousals for food intake, which occurred once or

TABLE 2 The major characteristics of studies containing polysomnography examination in patients with sleep-related eating disorder.

Study	Type of study	Patient group	Age	Actual concomitant sleep disorders	Episodes of nocturnal eating during PSG	Polysomnographic parameters
Yeh & Schenck (21)	Case report	1 male	29 years old	Not reported	4 episodes in the N2 stage	TST: 240 min (N1: 2.4%, N2: 50.6%, N3: 13.1%, REM: 8.7%), SE: Not reported, AI: Not report, AHI: Not reported, PLMSI: Not reported, WASO: Not reported, REM latency: Not reported
Wallace et al. (22)	Case report	1 male	42 years old	Narcolepsy–cataplexy, OSA	Not reported	TST: 513.0 min (N1: 4%, N2: 41.4%, N3: 49.3%, REM: 5.4%), SE: 95.2%, AI: Not reported, AHI: Not reported, PLMSI: Not reported, WASO: 1.0 min, REM latency: 418.5 min
Perogamvros et al. (7)	Case series	2 males	45 years old	Sleepwalking	Not reported	TST: 438 min (N1: 11%, N2: 66%, N3: 9%, REM: 14%), SE: 79%, AI: Not reported, AHI: 13.4/h, PLMSI: 0/h, WASO: Not reported, REM latency: 273 min
			29 years old	Sleepwalking	Not reported	TST: 440 min (N1: 8%, N2: 46%, N3: 25%, REM: 21.5%), SE: 94.6%, AI: Not reported, AHI: 13.4/h, PLMSI: 1/h, WASO: Not reported, REM latency: 108 min
Nzwalo et al. (20)	Case report	1 female	53 years old	Not reported	1 episode in the N1 stage	TST: 424 min (N1: Not reported, N2: Not reported, N3: Not reported, REM: Not reported), SE: 81.9%, AI: Not reported, AHI: Not reported, PLMSI: 0/h, WASO: Not reported, REM latency: Not reported
Varghese et al. (14)	Case report	2 males	35 years old	Not reported	Not reported	TST: 416 min (N1: 9%, N2: 54%, N3: 14.5%, REM: 22.5%), SE: 85%, AI: 11/h, AHI: 2.8/h, PLMSI: 0/h, WASO: 52 min, REM latency: Not reported
			37 years old	Not reported	Not reported	TST: 414 min (N1: 3%, N2: 49%, N3: 20%, REM: 28%), SE: 92%, AI: 20/h, AHI: 1/h, PLMSI: 0/h, WASO: 52 min, REM latency: Not reported
Ghosh et al. (19)	Case report	1 male	9 years old	Not reported	Not reported	TST: 210.5 min (N1: 2.6%, N2: 37.2%, N3: 44.2%, REM: 15.9%), SE: 47%, AI: 4/h, AHI: 0/h, PLMSI: 0/h, WASO: 191.0 min, REM latency: 341.5 min
Schenck et al. (26)	Descriptive	14 females and 5 samales	37.4 ± 9.1 years old	16 Sleepwalking, 2 PLMS, 2 Narcolepsy	Not reported	TST: 447.2 ± 91.5 min (N1: 6.2 ± 4.4%, N2: 48.6 ± 7.6%, N3: 23.4 ± 5.5%, REM: 21.8 ± 5.9%), SE: 85.6 ± 17.7 %, AI: Not reported, AHI: Not reported, PLMSI: 0/h, WASO: Not reported, REM latency: 76.2 ± 28.3 min
Schenck et al. (27)	Descriptive	11 females and 8 males	40.1 ± 10.6 years old	8 Sleepwalking, 3 RLS/PLMS, 4 OSA,	4 episodes in the N1 and N2 stages, 2 in the N3 stage, 1 in REM	TST: Not reported (N1: Not reported, N2: Not reported, N3: Not reported, REM: Not reported), SE: Not reported, AI: 16/h in 1 case, AHI: Not reported, PLMSI: 49/h in 1 case, WASO: Not reported, REM latency: Not reported
Winkelman et al. (24)	Descriptive	19 females and 4 males	21.6 ± 10.9 years	11 Sleepwalking,	3 episodes in N3 stage, 1 in N2 stage, 1 in REM	TST: 392.5 ± 51.9 min (N1: 11.0 ± 4.0%, N2: 48.9 ± 6.1%, N3: 21.6 ± 10.0%, REM: 20.4 ± 6.6%), SE: 88.3 ± 8.8 %, AI: 18.3 ± 5.8/h, AHI: 4.6 ± 8.3/h, PLMSI: 2.4 ± 4.7/h, WASO: Not reported, REM latency: 115.1 ± 60.1 min
						TST: 352.4 ± 52.7 min (N1: 16.5 ± 10.1%, N2: 55.0 ± 15.6%, N3: 12.5 ± 10.0%, REM: 12.4 ± 9.9%), SE: 80.2 ± 8.6 %, AI: 22.0 ± 12.6/h, AHI: 10.8 ± 25.5/h, PLMSI: 9.2 ± 12.1/h, WASO: Not reported, REM latency: 142.7 ± 91.5 min

(Continued)

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TABLE 2 (Continued)

Study	Type of study	Patient group	Age	Actual concomitant sleep disorders	Episodes of nocturnal eating during PSG	Polysomnographic parameters
Vetrugno et al. (25)	Descriptive	21 females and 14 males	44 ± 12.7 years old	1 Sleepwalking, 8 RLS, 4 PLMS	19 episodes in the N2 stage, 13 in the N3 stage, 1 in REM, 2 in wakefulness	TST: 426.9 ± 96.7 min (N1/N2: 60.5 ± 8.2%, N3: 17.9 ± 8.1%, REM: 21.6 ± 5.8%), SE: 76.2 ± 18.5%, AI: 19 ± 11.3/h, AHI: Not reported, PLMSI: 26.7 ± 18.7, WASO: Not reported, REM latency: 108.5 ± 72 min
Santin et al. (28)	Descriptive	23 females and 11 males	39.0 ± 13.8 years old	9 OSA, 16 RLS, 4 Sleepwalking, 1 sleep terror	4 episodes in the N2 and N3 stages	TST: Not reported (N1: Not reported, N2: Not reported, N3: Not reported, REM: Not reported), SE: Not reported, AHI: Not reported, AI: average 48.4/h, PLMSI: Not reported, WASO: Not reported, REM latency: Not reported
Vinai et al. (13)	Descriptive	2 females and 4 males	44.6 ± 12.93 years old	Not reported	2.2 ± 1.9 episodes	TST: 354.0 ± 80.1 min (N1/N2: 56.0 ± 6.0%, N3: 23.0 ± 6.2%, REM: 19.2 ± 3.8%), SE: 82.1 ± 16.9%, AI: 14.4 ± 7.5/h, AHI: Not reported, PLMSI: Not reported, WASO: Not reported, REM latency: 135.8 ± 77.0 min
Drakatos et al. (23)	Descriptive	2 females and 5 males	43.8 ± 18.2 years old	2 OSA, 1 PLMS, 2 OSA and/or PLMS	Not reported	TST: 391.3 ± 63.4 min (N1:8.4 ± 3.5%, N2: 52.7 ± 12.4%, N3: 25.8 ± 7.1%, REM: 17.0 ± 5.4%), SE: 82.3 ± 10.4%, AI: 20.3 ± 7.2/h, AHI: 6.5 ± 10.9/h, PLMSI: 12.7 ± 24.4/h, WASO: 58.3 ± 37.3 min, REM latency: Not reported
Komada et al. (29)	Cohort study	20 females and 10 males	32.2 ± 0.5 years old	Not reported	3 episodes in wakefulness, 12 in the N2 stage, 1 in the N3 stage	TST: 449.0 ± 68.2 min (N1: 10.2 ± 4.6%, N2: 52.9 ± 11.8%, N3: 6.8 ± 5.4%, REM: 18.9 ± 5.0%), SE: 86.7 ± 10.8%, AI: 14.1 ± 5.0 /h, AHI: 2.4 ± 3.5/h, PLMSI: 0/h, WASO: Not reported, REM latency: 90.9 ± 72.7 min
		5 females and 5 males	45.3 ± 15.0 years old	Not reported		TST: 460.4 ± 113.5 min (N1: 7.4 ± 3.0%, N2: 62.5 ± 5.7%, N3: 1.4 ± 1.3%, REM: 15.2 ± 6.5%), SE: 82.2 ± 12.7%, AI: 10.9 ± 2.9/h, AHI: 1.3 ± 0.7/h, PLMSI: 1.2 ± 2.8/h, WASO: Not reported, REM latency: 162.3 ± 155.1 min
Brion et al. (30)	Case–control study	12 females and 3 males	47.5 ± 15.1 years old	4 RLS, 7 Sleepwalking	9 episodes in the N2 stage, 6 in the N3 stage	TST: 426.9 ± 96.7 min (N1: 6.7 ± 4.6%,N2: 49.2 ± 9.7%, N3: 25.9 ± 10.7%, REM: 18.5 ± 7.9%), SE: 85.2 ± 12.9%, AI: 18.4 ± 13.9/h, AHI: 7.6 ± 13.7, PLMSI: 9.9 ± 19.6/h, WASO: Not reported, REM latency: 135.8 ± 77.0 min

RLS, restless legs syndrome; OSA, obstructive sleep apnea; PLMSI, Periodic Limb Movement in Sleep Index; TST, total sleep time; N1 stage sleep; N2 stage sleep; N3 stage sleep; REM, rapid eye movement; SE, sleep efficiency; AI, Arousal Index; AHI, Apnea–Hypopnea Index; WASO, wake after onset sleep; min, minutes.

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multiple times (13, 20, 21, 24, 25, 27–30). Episodes of eating were observed 5 times from N1 sleep stage (5.26% of total episode eating) (20, 27), 53 times from N2 sleep stage (55.81%) (21, 24, 25, 27–30), 29 times from deep sleep – N3 sleep stage (30.51%) (24, 25, 27–30), 3 times in rapid eye movement (REM) (3.16%) (24, 25, 27) and 5 times during wakefulness (5.26%) (25, 29). The last characteristic considered in this systematic review was PSG results, which consisted of the following parameters: total sleep time (TST) presented in minutes and in percentages (%); stage of sleep, N1, N2, N3, REM; sleep efficiency (SE) in percentages (%); Arousal Index (AI) in events per hours (e/h); Apnea–Hypopnea Index (AHI) in e/h; Periodic Limb Movements During Sleep Index (PLMSI) in e/h; wake after sleep onset (WASO) in minutes; and REM latency in minutes. When a study did not include these parameters, it was indicated as "Not reported" in the table. The results can be divided according to the approach of presentation. In 1 study, only 1 selected parameter was presented (27, 28), and in 7 studies that were not case studies/series, the 1 were presented as means with standard deviations (13, 23–26, 29, 30). The remaining studies had complete PSG results. These results are presented in Table 2.

4. Case presentation

A 66-year-old Caucasian woman with multiple disease conditions, namely hypertension, type 2 diabetes, overweight, atherosclerosis, osteoporosis, hypercholesterolemia, post-stroke conditions, insomnia, benzodiazepine drug dependence, visual impairment, and major depressive disorder (MDD), was admitted to the Sleep Laboratory in the Department of Internal Medicine, Occupational Diseases, Hypertension and Clinical Oncology, Wroclaw Medical University, Poland. She had a long history of various diseases sleep disorders, including problems with sleep, daytime sleepiness, and snoring. Informed consent was obtained from the patient for the publication of her case.

4.1. Description of sleep problems

During the detailed medical interview, she reported eating episodes at night, usually several times a month. These episodes had been occurring for the past 2 years, and the patient did not report any parasomnia episodes in the earlier years. She remembered some of these events, whereas some were covered by partial or complete amnesia. She often used products with a high glycemic index, i.e., fruit and sweets. She had never eaten an inedible product. Her husband, who witnessed her eating at night, informed her about some of the episodes. In the morning, she often found a mess in her kitchen, such as open cabinets, torn food packages, etc.

4.2. Laboratory tests upon admission and patient's pharmacotherapy

Physical examination was within normal limits, apart from an increased BMI of 29.05 kg/m2; the patient was diagnosed as being overweight (weight 82 kg, height 168 cm). Laboratory tests were performed in accordance with the relevant standards, which showed the following findings: complete blood count (CBC), basic metabolic panel (BMP), liver function test (LFT), renal function panel (RFT), fasting lipid panel (FLP) were within norm, urinalysis (UA) showed iatrogenic glucosuria related to dapagliflozin pharmacotherapy; total iron binding capacity (TIBC), total iron (Fe), vitamin B12 (Vit B12), vitamin D3 (Vit D3), and folate tests were also within normal limit. Her current medication therapy was as follows: acetylsalicylic acid 75 mg, valsartan 80 mg, torasemide 5 mg, metoprolol 100 mg, nitrendipine 10 mg, chlortalidone 50 mg, doxazosine 8 mg, eplerenone 50 mg, dapagliflozin 10 mg, metformin 1,000 mg, atorvastatin 20 mg, pantoprazole 20 mg, clonazepam 1 mg, paroxetine 20 mg, fluoxetine 10 mg, mianserin 30 mg, estazolam 2 mg, and vitamin D 2,000 IU daily. Based on her interview and the previous treatment for MDD, the decision to perform PSG and psychiatric examination was made.

4.3. The polysomnography findings

The PSG equipment used to examine the patient was Nox-A1 (Nox Medical, Reykjavík, Iceland). The v-PSG evaluation was performed without adaptive night. The results of v-PSG were evaluated by sleep specialists according to the AASM (American Academy of Sleep Medicine). Full-night PSG recordings were divided into 30-s epochs and scored. PSG findings included the following: sleep latency; REM latency; TST; SE; and the duration of N1 (sleep stage 1), N2 (sleep stage 2), N3 (sleep stage 3), and REM. Polysomnograms were supplemented with all-night video and audio recordings in high resolution. Respiratory events were scored according to the AASM: the reduction of more than 90% of airflow for ≥10 s was scored as apnea, and a reduction of ≥30% for ≥10 s, with a ≥3% decline in blood oxygen saturation or followed by arousal, was scored as hypopnea.

4.3.1. The PSG examination

During the PSG examination, the patient was diagnosed with mild obstructive sleep apnea (AHI=6.7/h), but in the video recording, an episode of nocturnal eating was observed. At the beginning, there was a transition from REM sleep to wakefulness, and the patient got up from the bed, reached for an apple from the table, and began to eat it. Then, she put the apple on the bedside table and went to the toilet. With the lights off, she walked from the toilet to her bed with her eyes closed and began searching for the apple by palpating the things on the table in the dark. After a few seconds, she found the apple, laid down in her bed, and began to eat it greedily. 5 min later, she stopped eating and just kept the apple in her mouth where the EEG showed theta waves and microsleep episodes. After a short break, she began to eat the apple again and in N1 sleep cycle, the patient holding the apple in her mouth the whole time. An image of the patient during this situation is presented in Figure 2. At the end, the core of the apple fell out of her mouth. The eating episode was covered by partial amnesia. The patient remembered the eating episode but did not remember the details. It is worth noting that the patient had food in her mouth in the N1 stage, which could be potentially dangerous

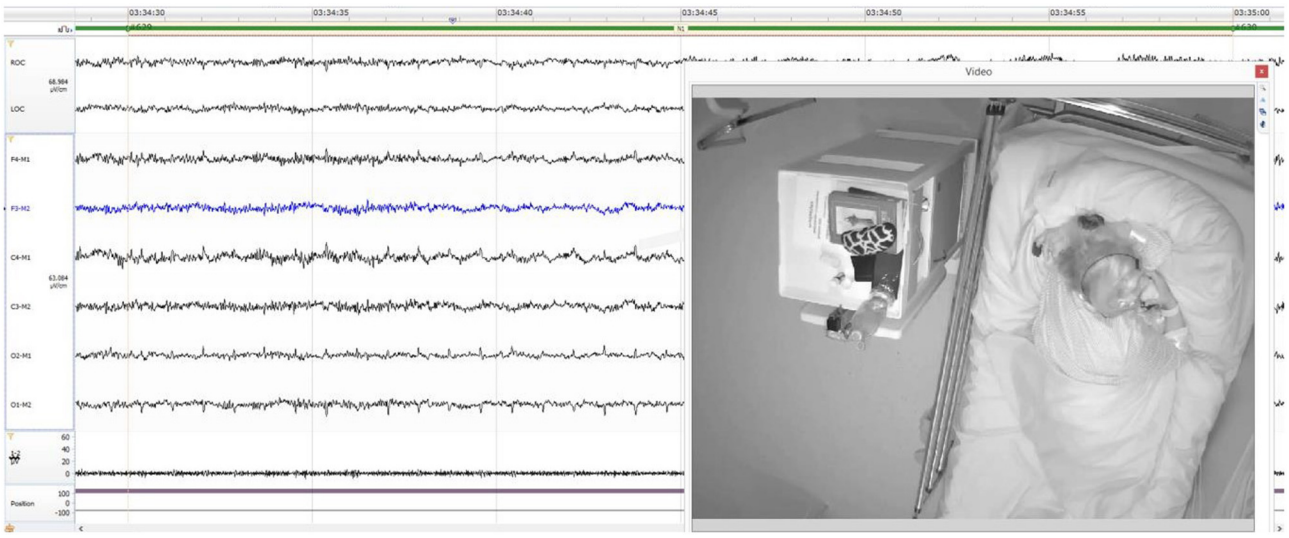

FIGURE 2
The patient during the N1 sleep stage holding an apple in her mouth.

due to the possibility of choking. Based on these findings, SRED was suspected. The other parameters measured by PSG are presented in Table 3. The patient was discharged from the ward in good condition, with recommendations of reducing her body weight and avoiding sleeping on her back.

4.4. Psychiatric consultation

A 66-years-old married female were invited to psychiatric evaluation. Her past medical history also consisted of psychiatric disorder—major depressive disorder (MDD). She was diagnosed with MDD and insomnia at the age of 49 years. For the most of the time, she was being treated with pharmacotherapy and was hospitalized thrice in an inpatient ward (last stay in 2009). She reported many suicidal attempts, the first one at the age of 22 and the most recent one 5 years ago.

In the past, the patient was treated with several antidepressive and anxiolytic agents. At the time of the enrollment to the study and v-PSG examination, she was being treated with paroxetine 20 mg daily, fluoxetine 10 mg daily, mianserin 30 mg daily, and clonazepam 1 mg in the morning and estazolam 2 mg at night (before sleep). This medication was followed for the past 4 years except for clonazepam, which was introduced 1 year ago, and fluoxetine, which was reduced from 20 mg down to 10 mg daily in mid-2022. She was reporting increased appetite and problems with the maintenance of her body weight to her psychiatrist, but the changes in pharmacotherapy did not address these problems. According to the patient, SRED episodes started around 2 years prior, but they happened rarely. Their frequency and intensity increased dramatically around 1 year ago, when clonazepam was introduced. At the time of the examination, she was in the remission of depressive symptoms. However, she reported that she cannot withdraw clonazepam in the morning because without it she became extremely anxious, angry, and irritable, and she could not fall asleep without estazolam in the evening. The interview and examination revealed that she has developed a dependence on benzodiazepine agents.

As the present pharmacological treatment could have led to drug-drug interaction with probably presentation e.g., a significant increase in appetite and the number of SRED episodes, to reduce the symptoms and avoid the interactions, changes were introduced. Firstly, paroxetine was withdrawn, and instead, fluoxetine dosage was increased up to 30 mg. Secondly, a slow reduction in clonazepam and estazolam was recommended, and low-dose (150 mg) pregabalin was introduced to reduce anxiety. The dose of mianserin dose was reduced with a plan of total withdrawal.

5. Discussion

In this systematic review, the available literature on SRED patients was assessed, in particular their PSG findings and video-recorded sleep behavior. Moreover, this review aimed to investigate whether there was any relationship between deviations in PSG findings and the presence of SRED. Although the majority of the studies reported a moderate or high risk of bias, this review may allow us to draw several conclusions.

Firstly, the prevalence of SRED is higher in women. This is also the case in our review, in which the female gender predominated among included studies, where there were 130 women of 206 patients (63.01%). Furthermore, SRED was found in young people in their mid-20 s, whereas most studies reported on 30-year-olds (6). This syndrome can develop at any age, e.g., in a 9-year-old boy (19) or, as in the present case, a 66-year-old woman. While examining comorbidities with NREM parasomnia or those predisposing to SRED, 9 studies indicated the presence of these, as suggested in the available literature (6), sleepwalking was the most common comorbidity disease to SRED among included papers. In comparison to the general population, the prevalence of

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TABLE 3 Polysomnography results of the case report presented.

Polysomnography parameters	The polysomnography examination
Episode of nocturnal eating	Present
Total sleep time (TST)	405.0 min
N1 sleep stage	5.3% of TST
N2 sleep stage	57.2% of TST
N3 sleep stage	6.90% of TST
Rapid eye movement (REM)	30.60% of TST
Sleep latency	19.8 min
REM latency	133.5 min
Sleep efficiency	86.2%
Snoring	36.2% of TST
Arousal index	1.80 events/h
Apnea–Hypopnea index	6.7 events/h
Oxygen desaturation index	5.9 events/h
Respiratory disturbances index	6.7 events/h
Mean saturation O2	91.90%
Minimal saturation O2	74.00%
O_2 saturation <90%	23.10%
Mean desaturation drop	4.50%
Wake after sleep onset	44.5 min
Periodic limb movement in sleep index	0 events/h
Movement	7.60% of TST
Mean heart rate	70.90 beats/min
Minimal heart rate	66.00 beats/min
Maximal heart rate	80.00 beats/min

sleepwalking among SRED patients is higher (23.9%) than healthy people (1.5%) (31). However, obstructive sleep apnea and periodic legs movement syndrome were less common in contrast to the general population (8.73% vs. 28.6%) and (5.83% vs. 7.6%) (32, 33). Restless leg syndrome and sleep terrors were presented within the normal range (3.0% to 15% for RLS, 1.0% to 2.6% for sleep terrors) (34, 35). In the present case, it was obstructive sleep apnea (OSA).

In accordance with the NREM definition, parasomnia presents with awakening from sleep or the behavior typical of the presented syndrome in the deep sleep stage, i.e., most often in the N3 stage (4). This review revealed quite large differences in this area. The literature rarely describes an episode of nocturnal eating during PSG, which may be due to several causes. Firstly, nocturnal eating in SRED may not occur every night depending on the duration of the disease and the patient. The literature describes from 1 episode per week to as many as 10 episodes per night (36). Furthermore, changing the environment can be stressful for the patient, and a night spent in an unfamiliar hospital environment can result in enough sleep to prevent SRED behavior (7). Finally, the lack of food in the patient's room should also be considered. Following the recording of the episode, 95 episodes of eating occurred in 57 patients among gathered 206 people, therefore prevalence of episodes is 27.77%. But they should occur in the N3 sleep stage, as mentioned earlier. However, in 9 articles reporting these episodes, only 30% (29 from 95 episodes) were in the N3 stage. Vertrugno et al. (25) reported only the average number of eating episodes; however, it is not known at which point in the sleep they occurred, therefore it was not included in these calculations. As shown, the N3 stage was in the minority. In the present case report, the patient awoke from REM sleep and experienced an episode of eating while awake. The partial or complete loss of awareness of eating is one of the criteria for the diagnosis of SRED, and the majority included studies that met this criteria. However, in one study (25), all participants diagnosed with SRED were fully aware of what was happening at night and in Winkelman (24) 2 from 23 patients also had consciousness during the episode of eating, which is a rather unusual and typical characteristic of NES.

In Table 2, the PSG parameters measured during sleep studies as part of individual studies are presented. Unfortunately, this review has some limitations. Due to the large discrepancy in the years of studies and the lack of appropriate equipment and standardization of the results, not all records include the selected values, and in some studies, the authors provide only abnormal results. According to Hertenstein et al. (37), PSG parameters may vary depending on age, sex, and habituation to a particular environment as PSG findings varied based on the number of nights spent in the sleep laboratory. The mean reference ranges for PSG results came from Hertenstein et al. study (37) and based on the analysis of these data and values shown in Table 2, it seems that most of the measurements of the characteristics are within this norm. But some of them are reduced, such as the N3 sleep stage in the group of 10 participants in Komada et al. (29), or increased, such as the AHI in Vetrugno et al. (24) or PLMSI in Schenck et al. (27); however, these differences may be attributable to comorbid sleep disorders or medications. Patients diagnosed with SRED using PSG do not show altered parameters specific to this syndrome; in fact, when an eating episode was observed during the examination, the parameters were still normal or the given values were different in each study. Not surprisingly, some authors have not distinguished between SRED and NES and described these disorders in one category (38, 39). In order to eliminate the effect of "first night" during hospital stay on PSG results, portable PSG e.g., headbands should be considered to use (40). These devices have similar accuracy in monitoring sleep parameters like PSG, however, also have some limitations in detecting state of wakefulness (41).

A sleep disorder similar to SRED characterized by nocturnal eating and sometimes causing problems in making diagnose is NES. NES involves episodes of consuming at least 25% of daily calorie intake during night with remaining consciousness, which is the complete opposite to SRED. As a consequence of NES, the patient experiences morning anorexia, daily dysfunction, decreased mood and other features from Table 1. The disorder has not been included in ISCD-3 and has recently been classified in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (11). In spite of the obvious differences in symptoms between SRED and NES, sometimes are resulting in diagnostic problems if a thorough anamnesis, nutritional questionnaires, and PSG are not applied. PSG allows

us to check the level of awareness during an eating episode, which can be conclusive for the diagnosis (13). Additionally, Schenck et al. (27) indicated, that SRED itself is already a heterogeneous disease with many causes and polysomnography is crucial to made correct diagnosis and select appropriate treatment, similar results were received in Winkelman study (24). These conclusions were drawn before diagnostic criteria for sleep-related eating disorder were established in ISCD, however, nowadays in ISCD-3 PSG was considered as not necessary to confirm this disease.

In light of the presented case and systematic report, it is clear that this woman with coexisting MDD and benzodiazepine drug dependence has iatrogenic SRED induced by clonazepam. As mentioned in World Health Organization (WHO) databases, clonazepam is estimated as a cause of SRED in about 1.3% of cases (8). Unfortunately, reports of this condition in WHO databases are based on patient history, reported by anyone to this register. In the literature, one confirmed case of SRED induced by clonazepam with full medical examination is present, enriched by PSG records (19). Based on the findings of the present case report, the observed metabolic disturbances and sleep-related eating could be linked to pharmacotherapy. The patient presented changes in the parameters during PSG, during the PSG examination; however, this could be a result of OSA.

The present review focused on evaluating the PSG findings of SRED patients. Unfortunately, this review has limitations and drawbacks. First of all, most of the studies included in our review contained data obtained from studies with a large sample size, which contained inaccurate conclusions and from the description of single cases, thus receiving high imprecision according to the risk of bias assessment tools. Based on this review, it can be emphasized that there is a need for further intensive research into the pathophysiology of SRED and a better understanding of it, as well as developing objective methods that will reliably and independently contribute to the appropriate diagnosis and initiation of effective treatment. Future studies using v-PSG on a large group of patients may improve the diagnostic evaluation and uncover new characteristics associated with SRED. In the future to made a correct diagnosis may help modern technology consist of e.g., portable cameras. At the time these devices could be used in patient houses to reduce the influence of hospital stay on PSG results. Currently, however, the diagnosis is based on a thorough clinical interview, but PSG can be a valuable additional tool for clinicians.

6. Conclusion

Polysomnography is not necessary for the diagnosis of SRED. However, it could facilitate the diagnosis and differentiation of SRED from other eating disorders. PSG also has limitations in capturing eating episodes and additionally, its cost effectiveness should be considered in the diagnostic process. More original studies into the causes and pathophysiology of SRED are needed with a potential low risk of bias because classifying SRED as NREM parasomnias can be inappropriate as it does not always occur during deep sleep. In the present case report, the patient took drugs to treat multiple diseases, and they could have side effects. SRED may lead to choking and obesity, which contributes to the occurrence and difficulty in the treatment of primary diseases such as diabetes, atherosclerosis, hypertension, and cardiovascular diseases.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HM was involved in the conception, visualization, and supervision of the study. BB, TW, and MM-Z collected the data and wrote the manuscript. MM-Z and HM examined the patient. TW conducted the psychiatric consultation. MW and GM were involved in the revision of final version of the manuscript. All authors have agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Delayed sleep–wake phase disorder and its related sleep behaviors in the young generation

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Delayed sleep–wake phase disorder (DSWPD) is a sleep disorder in which the habitual sleep–wake timing is delayed, resulting in difficulty in falling asleep and waking up at the desired time. Patients with DSWPD frequently experience fatigue, impaired concentration, sleep deprivation during weekdays, and problems of absenteeism, which may be further complicated by depressive symptoms. DSWPD is typically prevalent during adolescence and young adulthood. Although there are no studies comparing internationally, the prevalence of DSWPD is estimated to be approximately 3% with little racial differences between Caucasians and Asians. The presence of this disorder is associated with various physiological, genetic and psychological as well as behavioral factors. Furthermore, social factors are also involved in the mechanism of DSWPD. Recently, delayed sleep phase and prolonged sleep duration in the young generation have been reported during the period of COVID-19 pandemic-related behavioral restrictions. This phenomenon raises a concern about the risk of a mismatch between their sleep–wake phase and social life that may lead to the development of DSWPD after the removal of these restrictions. Although the typical feature of DSWPD is a delay in circadian rhythms, individuals with DSWPD without having misalignment of objectively measured circadian rhythm markers account for approximately 40% of the cases, wherein the psychological and behavioral characteristics of young people, such as truancy and academic or social troubles, are largely involved in the mechanism of this disorder. Recent studies have shown that DSWPD is frequently comorbid with psychiatric disorders, particularly mood and neurodevelopmental disorders, both of which have a bidirectional association with the pathophysiology of DSWPD. Additionally, patients with DSWPD have a strong tendency toward neuroticism and anxiety, which may result in the aggravation of insomnia symptoms. Therefore, future studies should address the effectiveness of cognitive-behavioral approaches in addition to chronobiological approaches in the treatment of DSWPD.

KEYWORDS

delayed sleep–wake phase disorder, DSWPD, circadian rhythm sleep–wake disorder, adolescent and young adult, circadian-entrained DSWPD

1. Introduction

Circadian rhythm, which runs for approximately 24 h, is present in all animate beings and acts as a regulatory mechanism that promotes optimal adaptation to various biological activities, including not only sleep and wakefulness but also various biological activities such as feeding, reproduction, and social activities (1). Normally, when circadian rhythms are synchronized with the light–dark cycle of the external world, melatonin is secreted as light exposure diminishes during the night and sleep is initiated during the downward phase of the core body temperature (CBT). Among the circadian rhythm markers, dim light melatonin onset (DLMO) and CBT rhythms show a phase relationship with the 24-h cycle. The relationship between the circadian rhythm markers (i.e., DLMO or CBT rhythm) and sleep timing (i.e., sleep onset or offset) is called the "phase angle" of circadian entrainment. Both Earth's rotation and social activity rhythms run on the 24-h cycle, but the endogenous circadian rhythm in humans may be typically a little longer than 24 h. The length of the intrinsic circadian period is called "tau." Although the length of tau varies from individual to individual, the mean period of tau is reported to be 24.15 h (standard deviation 0.2 h) (2–4), with the length of tau of women being approximately 6 min shorter than that of men (5). Endogenous circadian rhythms are entrained to follow a 24-h cycle of the external world by various zeitgebers, which are the external factors that serve as cues for entrainment. Among these, light stimulation at a certain time of the day alters the firing rate of neurons in the brain's suprachiasmatic nucleus (SCN; the command center of the circadian clock), activates the molecular signaling pathway, and alters the transcription of clock genes that determine the phase of the circadian cycle by regulating the rhythm of endogenous melatonin secretion (6). The effect of circadian phase resetting through melatonin and photic stimulation in the SCN follows the phase-response curve (PRC). In the PRC, if light is applied before the minimal point of CBT (CBTmin) appears, the melatonin secretion phase is likely to be delayed, whereas if light is applied after CBTmin, the phase is likely to advance (7). In a normal lifestyle, evening light delays the circadian clock by delaying the sleep onset timing, whereas morning light advances the circadian clock. Light exposure is the most important entrainment factor, but other zeitgebers, such as exercise, mealtime, and social activities also contribute to circadian rhythm entrainment. However, the entrainment ability of these factors is weaker than that of light (8, 9).

Many adolescents and young adults worldwide exhibit a delayed sleep pattern, which can be considered a disorder when it significantly affects important areas of an individual's functioning. Delayed Sleep–Wake Phase Disorder (DSWPD) (10) is a circadian rhythm disorder in which the delay of sleep phase causes difficulty in falling asleep and waking up at a desired time, resulting in daytime dysfunction. This disorder is associated with multiple factors including specific biological traits, socio-psychological backgrounds, sleep hygiene problems, and comorbid psychiatric diseases. DSWPD is prevalent during adolescence and young adulthood. The establishment of treatment strategies against this disorder is therefore important because the incidence of DSWPD during these critical developmental stages can damage an individual's future prospects. However, the pathological mechanism of DSWPD as well as many aspects such as the adequate classification, assessment, and treatment strategy of subgroups based on patients' backgrounds, psychosocial characteristics, and physiological findings remain unclear. Furthermore, recent changes in the light environment surrounding adolescents have increased the likelihood of eveningness chronotype possibly leading to the development of DSWPD (11). A significant number of young people do not meet the diagnostic criteria of DSWPD but have delayed sleep phases (DSP) (12). Social jetlag (SJL) is a new concept that refers to the difference in sleep timing between weekdays and rest days has also been proposed as a concern regarding circadian rhythm related sleep hygiene in young people (13).

The development of DSWPD reflects the multifaceted interaction between social schedules, timing of exposure to light and dark, genetic factors, homeostatic pressure on sleep, and the circadian system. The extent to which a combination of any of these factors is impaired is difficult to identify in a clinical setting. Moreover, approximately 40% (14) of patients with DSWPD have normal timing of melatonin secretion profile (the most important marker of circadian rhythm) even though their sleep–wake schedule is clearly delayed. This subgroup of DSWPD without circadian misalignment is termed circadian-entrained DSWPD and occurs based on the psychological and behavioral backgrounds in addition to biological factors in the young generation (15). Recent studies have also shown that DSWPD is frequently comorbid with some psychiatric disorders, particularly neurodevelopmental and mood disorders, both of which have a bidirectional association with the pathophysiology of DSWPD. In 2015, the American Academy of Sleep Medicine (AASM) published revised guidelines for the treatment of circadian rhythm sleep–wake disorders (CRSWDs), including DSWPD. However, additional treatment methods for circadian-entrained DSWPD and DSWPD complicated by psychiatric disorders should be established.

In this review, we describe the physiological and psycho-behavioral backgrounds of circadian-entrained and non-entrained DSWPD in young people, as well as the relationship between psychiatric disorders and DSWPD. Furthermore, we discuss the current problems and future development of the treatment of this disorder based on the results of psychological and psychiatric assessments.

2. Features of delayed sleep–wake phase disorder

2.1. Diagnosis of delayed sleep–wake phase disorder

In 1981, Weitzman et al. (16) first proposed the concept of delayed sleep phase syndrome (DSPS) as a chronobiological disorder in a group of patients with chronic difficulty falling asleep and waking, distinguishing it from insomnia and hypersomnia. The concept of DSPS, along with sleep disorders in shift workers, jet lag, and other chronobiological disorders, was included in the first edition of the International Classification of Sleep Disorders (ICSD) (17) as a group of circadian rhythm sleep disorders (CRSD). In the second edition (ICSD-2) (18), DSPS was conceptualized from a syndrome to a single disorder and was referred to as CRSD, delayed sleep phase type (DSPT), or delayed sleep phase disorder (DSPD). However, it is now referred to as DSWPD in ICSD-3 (10). In ICSD-3, the category of CRSD was also renamed circadian rhythm sleep–wake disorder (CRSWD). The ICSD-3 criteria of CRSWD consist of the following three items. First, chronic or recurrent pattern of sleep–wake rhythm

disruption primarily because of alteration in the endogenous circadian timing system or misalignment between the endogenous circadian rhythm and the sleep–wake schedule that is desired or required by an individual's physical environment or social/work schedules. Second, circadian rhythm disruption that leads to insomnia symptoms, excessive sleepiness, or both. Third, sleep and wake disturbances that cause clinically significant distress or impairment in mental, physical, social, occupational, educational, or other important areas of functioning.

The ICSD-3 (10) classifies CRSWD into the following seven categories: (a) DSWPD, (b) advanced sleep–wake phase disorder (ASWPD), (c) irregular sleep–wake rhythm disorder (ISWRD), (d) non-24-h sleep–wake rhythm disorder (N24SWD), (e) shift work disorder (SWD), (f) jet lag disorder (JLD), and (g) circadian sleep–wake disorder not otherwise specified (NOS). DSWPD is the most common sleep–wake disorder, accounting for 83% of CRSWDs in clinical settings (19). In addition to the above three common criteria items for CRSWD, the diagnostic criteria for DSWPD in ICSD-3 requires the fulfillment of the following five criteria. First, a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or caregiver of the inability to fall asleep and difficulty awakening at a desired or required clock time. Second, symptoms are present for at least 3 months. Third, patients exhibit improved sleep quality and duration for their age and maintain a delayed phase of the 24-h sleep–wake pattern when they are allowed to choose their *ad libitum* schedule. Fourth, sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrates a delay in the timing of the habitual sleep period. Fifth, sleep disturbance is neither satisfactorily explained by another current sleep disorder nor by any medical, neurological, or mental disorder; medication use; or substance use disorder.

2.2. Symptomatic characteristics of DSWPD

The sleep duration of patients with DSWPD is mostly well maintained during their free days, although the sleep phases are apparently delayed. However, on weekdays, they experience difficulty falling asleep and waking up at socially desirable times, such as school or work timings, which interferes with their daily lives. Patients with DSWPD frequently experience daytime sleepiness, fatigue, headache, anorexia, and depression. DSWPD with a regressed rhythm of melatonin secretion, as well as other hormones such as cortisol, may also present with decreased blood pressure during the daytime. This is particularly observed in the morning hours and is often manifested as orthostatic dysregulation (20). Patients with DSWPD with severely delayed circadian rhythms may also exhibit serious sleep inertia when attempting to wake them up at socially desirable times.

Many studies have reported a certain relationship between DSWPD and psychological problems or decreased social functioning, although some negative observations have also been reported (21). Cross-sectional studies have shown higher depression and anxiety scores in patients with DSWPD (14, 22–25), as well as lower health-related quality of life (25) and more frequent self-harm and suicidal ideation (26). Individuals with DSWPD may be unable to adjust to school life or employment (12, 27) when their symptoms are severe. In contrast, the removal of the constraints of attendance at school or work, the most important social zeitgebers, may worsen the symptom severity of the disorder (28). DSWPD has been suggested to be associated with lower grades in students (23, 29) and frequent absenteeism, as well as lower productivity and presenteeism in the working generation (25, 30). Socially, patients with DSWPD tend not to enjoy leisure time and are unable to fulfill their household responsibilities (30). Substance use issues, such as smoking, alcohol, caffeine, and cannabis, may also arise (12, 21, 23, 31). The above associations observed in patients with DSWPD are sometimes observed in individuals with the evening chronotype (32), which suggests that DSWPD is possibly an extreme phenotype of the eveningness chronotype.

2.3. Assessment of DSWPD

The diagnosis of DSWPD requires a thorough investigation of the medical, mental, or sleep disorders that may cause sleep–wake cycle alterations, insomnia, or excessive daytime sleepiness. Social maladjustment, family dysfunction, school avoidance, and comorbid mood disorders should also be investigated in adolescents and young adults.

A sleep diary (sleep log) monitored for at least 7 days (ideally longer) is mandatory as an indicator for the diagnosis of DSWPD in ICSD-3. Actigraphy, which uses a non-invasive wrist-worn accelerometer, can capture rest-activity rhythms from which the timing and regularity of sleep can be estimated. In the ICSD-3 diagnostic criteria, an actigraphic recording is not necessary for diagnosis (listed as "whenever possible"). However, because sleep diaries may cause misunderstanding and recall bias, supportive actigraphic recording is desirable for objectively measuring an individual's sleep–wake schedule. In ICSD-3, actigraphic recording is set as a mandatory item only for the diagnosis of N24SWD. Nevertheless, we believe that actigraphic recordings along with a sleep diary for a minimum evaluation period of 14 days are necessary for the accurate diagnosis of DSWPD. Although the information provided by actigraphy is inherently limited with respect to the assessment of the underlying chronobiological complexity associated with CRSWDs (11), previous studies (as shown below) showed that actigraphy can reflect the status of the melatonin secretion profile of patients with DSWPD (33). Alternatively, low burden and relatively inexpensive consumer-grade wearable and mobile technologies are now attracting interest as devices for measuring the conventional biomarkers of sleep (34). However, further studies are necessary to validate whether these devices can serve as a useful assessment tool for an individual's sleep–wake schedule.

The CBT and melatonin secretory rhythms, which are generated by the SCN in parallel with the circadian sleep propensity rhythm, are well-established indicators of circadian rhythms and often used in clinical studies of DSWPD (35, 36). However, they are difficult to measure in general clinical practice. Previously, CBT assessment was a highly invasive approach that used a rectal probe. In recent years, a simple non-invasive tool that can be attached to the surface of the chest or other body parts has been developed to assess CBT (37, 38). Melatonin secretion can be measured through serial salivary assays, serum assays, or the measurement of urinary 6-sulphatoxymelatonin. Among these, DLMO, which is measured in light less than 10 lx,

enables the estimation of the circadian phase of melatonin secretion (35, 39). However, since CBT and melatonin secretion can be obscured by masking effects (e.g., light suppresses melatonin secretion and activity and sleep modifies the CBT rhythm), these measurements are highly recommended to be performed in highly controlled conditions to minimize contamination by the masking effects.

Self-administered chronotype questionnaires have also been commonly used to assess patients highly suspected of having DSWPD. Among these, the morningness-eveningness questionnaire (MEQ) (40) and Munich chronotype questionnaire (MCTQ) (41) have been accepted as reliable chronotype measures. The MEQ can evaluate an individual's circadian preference, whereas the MCTQ is advantageous in that it can evaluate an individuals' sleep-midpoint and SJL, both of which are important indicators of circadian rhythm (42). As described later, DSWPD is commonly observed inpsychiatric disorders, particularly bipolar disorder, suggesting the close relation of pathophysiology between bipolar disorder and CRSWDs (43, 44). The Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) was first developed to measure circadian rhythm dysfunction in patients with bipolar disorder (45). However, our recent studies have shown that BRIAN can be effectively used also for the screening and severity assessment of DSWPD without comorbid psychiatric disorders (25, 46).

Although nocturnal polysomnography is not necessary to establish the diagnosis of DSWPD, it should be performed when the existence of other sleep disorders that may be responsible for subjective insomnia and sleep inertia in the morning is suspected. When performed during conventional sleep laboratory hours, the polysomnographic findings of individuals with DSWPD tend to show prolonged latency for sleep onset and normal or relatively long total sleep time, which are consistent with their sleep logs or actigraphic findings (47, 48).

2.4. Epidemiology of DSWPD

DSWPD has a prevalence of 0.17–1.51% in the general population (49, 50), which is reported lower than that of DSP (12). In comparison, a survey of 10,220 adolescents aged 16–18 years in Norway found a relatively higher rate of 3.3% (27), while a more recent Norwegian survey of 50,054 students aged 18–35 years also showed a prevalence of 3.3% (26). These results suggest that DSWPD is possibly more prevalent in the younger generation than in the older generations. Similarly, a recent large Japanese survey estimated that 4.3% of the youth (15–30 years) is at risk for DSWPD (25). The higher prevalence of DSWPD in adolescents and young adults may reflect a preference for a "night owl" lifestyle and biological change in this generation (3, 51).

As aforementioned, studies on the sex differences in the prevalence of DSWPD have been inconclusive. The results of previous epidemiological studies demonstrated a higher prevalence in males (12, 26), females (25, 27), or no sex differences (49, 50, 52). Although the effect of a delayed sleep–wake schedule on the development of depression may be greater in women because of their intrinsically earlier circadian rhythm (53), sex differences in the effect of the disorder on daytime functioning has not been clarified.

No international comparative studies on racial or regional differences in the prevalence of DSWPD have been conducted to date. However, in Germany, people living in the western region of the country have later chronotypes than those living in the eastern region (42). The relatively later sunrise in the western part of the country (although both regions share the same time zone) was speculated to contribute to this difference (54). Table 1 shows a list of the major epidemiological studies on DSWPD over the last decade.

3. Pathophysiology of DSWPD

3.1. Biological factors of DSWPD

Although the pathogenesis of DSWPD is heterogeneous and complicated by various factors, one of the most important features of typical DSWPD is the delayed circadian rhythm, which is assessed using DLMO or CBT measurements. Many studies have shown a circadian rhythm delay in DLMO in patients with DSWPD (55, 56).

As mentioned in the introduction, light stimulation is the most important zeitgeber; however, individual sensitivity to light varies 50-fold on a logarithmic scale (57). Studies have also shown that light exposure at the same timing and intensity may have different effects on the entrainment phase between individuals (58, 59). In DSWPD, photosensitivity seems to be weak (or the time width of the phase advance is narrow) during the phase advance portion of the circadian PRC to light stimuli (60). Additionally, photosensitivity at night is higher in patients with DSWPD than in normal sleepers, which may contribute to the delay in circadian rhythm (61).

Individual differences in the intrinsic circadian cycle are another cause of DSWPD. The length of tau varies among individuals, and individuals with longer tau are entrained at a later phase than those with shorter tau (62, 63). Furthermore, the circadian cycle of both melatonin secretion and CBT rhythms is longer in patients with DSWPD than in controls, with tau length being associated with the likelihood of developing DSWPD (63, 64). The PERIOD2 (*PER2*) gene encodes a core molecule in the circadian clock and plays an important role in the generation and maintenance of diurnal rhythms. Minor allele carriers of the *PER2* variant have significantly longer circadian cycles than non-carriers, as demonstrated by CBT or plasma melatonin profile (65).

Problems with sleep inertia and sleep architecture may also be related to the pathophysiology of DSWPD. Previously, sleep architecture and sleep duration in patients with DSWPD were considered normal (66). However, several studies have reported prolonged sleep duration in patients with DSWPD (36, 67–69). Moreover, patients with DSWPD have a low amount of slow-wave sleep during the first half of sleep, corresponding to a delay in the timing of CBTmin (69). Patients with DSWPD also have a higher arousal threshold during REM sleep (47) and a prolonged interval between CBTmin and arousal (36, 67, 70). These factors may be related to the difficulty in waking up at a desirable time in the morning, possibly resulting in the decreased light exposure during the phase-advance portion of the PRC.

Chronotype change with age may also be involved in the development of DSWPD. In this regard, some researchers have suggested the role of age and sex differences in the development of DSWPD based on sex hormone changes (71, 72). Gonadal steroid receptors are expressed at most sites that receive direct inputs from

TABLE 1 Prevalence of DSWPD-related disorders by region/country as reported over the past decade.

Region/country (author, year)	Prevalence/sex difference	Study design (*n*/age in years)	Findings
Europe			
Norway (Sivertsen, 2021)	3.3% (DSWPD)/male, 4.7% > female, 2.7%**	Cross-sectional study (50,054/18–35)	Single status, financial difficulties, parental divorce, obesity, and physical inactivity were associated with DSWPD.
Norway (Hysing, 2018)	3.9% (DSP)/n.s.	Longitudinal study (2,200/16–19)	Sleep duration of < 9 h/night at the age of 11–13 years was associated with DSP at 16–19 years.
Sweden (Danielsson, 2016)	4.0% (DSPD)/n.s. 4.6% (DSP)/ male, 7.3% > female, 2.4%*	Cross-sectional study (10,000/16–26)	DSPD was associated with non-attendance of educational activities or work and elevated levels of anxiety.
Norway (Sivertsen, 2013)	3.3% (DSPS)/female, 3.7% > male, 2.7%*	Cross-sectional study (9,338/16–18)	DSPS was associated with non-attendance at school, with half of the adolescents with DSPS also meeting the criteria for insomnia.
Norway (Saxvig, 2012)	8.4% (DSP)/n.s.	Cross-sectional study (1,285/16–19 years)	DSP was associated with lower average school grades, smoking, alcohol usage, and elevated anxiety and depression scores.
Asia			
Japan (Tomishima, 2022)	4.3% (at risk of DSWPD)/ female, 4.9% > male, 2.5%**	Cross-sectional study (7,810/15–30)	Long-term LCD viewing at night and relatively loose social constraints were associated with the presence of DSWPD.
Oceania			
New Zealand (Paine, 2014)	1.51% (DSPD)/n.s.	Cross-sectional study (4,386/20–59)	DSPD prevalence was higher in deprived areas and decreased with age. This disorder was associated with the presence of night work.
Australia (Lovato, 2013)	1.1% (DSPD)/n.s.	Cross-sectional study (374/13–18)	Patients with DSPD showed relatively greater alcohol and caffeine consumption, lesser sports participation, and more time spent on extracurricular activities.

DSP, delayed sleep phase; DSPS, delayed sleep phase syndrome; DSPD, delayed sleep phase disorder; DSWPD, delayed sleep–wake phase disorder; LCD, liquid crystal display; n.s., not significant. *$p < 0.05$, **$p < 0.001$.

the SCN. At each stage of the circadian system, brain nuclei bear estrogen receptors, androgen receptors, or both. From adolescence to young adulthood, the activational effects of sex hormones on the circadian timing system are associated with the phase delay of the circadian rhythm (71). Although the prevalence of DSWPD declines after middle age, a large survey of chronotypes in Brazil ($n = 14,650$) (73) showed that women were on an average more morning-oriented than men up to the age of 30 years. However, from age 30 to 45 years, the sex difference in the chronotype disappeared, and women tended to be more evening-oriented than men aged 45 years and older. The age-related plastic changes associated with sex differences in chronotypes remain largely unknown, however, changes in the sex hormone status may be partially related to the differences in the circadian phases among the respective generations.

Patients with DSWPD have been demonstrated to have a larger phase angle between sleep timing and circadian rhythm markers (67, 69, 74). Polymorphisms or mutations in clock genes may contribute to this expansion of the phase angle (75). Furthermore, DSWPD is frequently associated with difficulty in initiating sleep (27), which may be related to the expansion of the phase angle in DSWPD. Additionally, a sleep homeostatic problem leading to difficulty in increasing sleep pressure has been reported (74).

DSWPD and N24SWD often occur alternately in the same patient, suggesting pathological continuity between the two disorders. A large proportion of individuals with DSWPD as well as those with N24SWD exhibit longer periods of melatonin and temperature rhythms, with longer circadian tau appearing to be the common basis for these disorders (63). N24SWD can occur even in patients without visual impairment and could be an extreme form of DSWPD. On the other hand, DSWPD has also been suggested as the prodromal manifestation of N24SWD without visual impairment (76). In addition to longer intrinsic tau, other potential etiologies shared by DSWPD and N24SWD include altered light sensitivity (77) and homeostatic issues (difficulty in increasing sleep pressure) (63).

3.2. Behavioral and social factors in DSWPD

DSWPD appears to be strongly related to youth-specific behavioral factors. Our previous epidemiological study showed that behavioral patterns particular to youth, such as long-term liquid crystal display (LCD) viewing at night, were associated with the presence of DSWPD (25). Considering this, prolonged exposure to LCD screen-based devices, such as TVs, PCs, and smartphones, from evening to bedtime may be associated with the development or worsening of DSWPD. Similarly, the duration of monitor viewing time was also demonstrated to be adversely associated with sleep

health, primarily via delayed bedtime and reduced sleep duration among school-aged youth (78). The scarcity of physical exercise habits (21, 25, 26) and the presence of night work (50) and extracurricular activities (21) were also associated with the risk of developing DSWPD. Another longitudinal study (52) showed that sleeping less than 9 h/night at the age of 11–13 years was associated with DSP at 16–19 years. In addition, one study reported smoking and drinking habits as factors associated with the presence of DSWPD (23).

DSWPD is a disorder that can develop on a psychosocial basis. In support of this, our recent study showed that being at risk for DSWPD had a greater association in students than in young adult workers of the same age group (25), suggesting that less social constraints could be associated with the presence of DSWPD in this generation. Several studies have also shown that absenteeism at school or work was associated with DSWPD (12, 27). Thus, the teenagers' sleep–wake rhythm may be delayed because of their non-attendance at school, which was related to their maladjustment to school or relationship problems. Furthermore, DSWPD in students has been suggested to be associated with financial deprivation, parental divorce (26), and depression (31). However, many of these reports were cross-sectional studies, making the causal relationship unclear. Nevertheless, DSWPD and psychosocial issues may have a bidirectional relationship.

3.3. Psychological characteristics of DSWPD

Many researchers have suggested that chronotypes and DSWPD occurrence are associated with specific personality traits. To date, the "Big Five" model, which proposes that personality can be grouped across five broad personality traits that include neuroticism (i.e., emotional instability and moodiness), extroversion (i.e., excitability and sociability), conscientiousness (i.e., thoughtfulness and goal-directed behaviors), agreeableness (i.e., altruism and kindness), and openness (i.e., imagination and insight), has been widely used as the personality trait model in studies on sleep hygiene and chronotypes (79). A meta-analysis of the studies published before the end of January 2009 found that conscientiousness was mostly related to morningness. Moreover, agreeableness was also related to morningness, albeit to a lesser degree (80). In contrast, studies conducted on college students after 2010 reported that high extroversion was associated with eveningness and high conscientiousness, openness, and low neuroticism was related to morningness tendency (81, 82). However, these were cross-sectional studies, and a longitudinal study showed that only low neuroticism predicted morningness 1 year later (83). Another study found that patients with DSWPD had higher neuroticism, lower extroversion, and lower conscientiousness than a healthy control group (84, 85). Taking these findings into consideration, levels of conscientiousness and neuroticism could be associated with the variation in the morningness-eveningness chronotype. Apart from these two personality traits, low extroversion could contribute to DSWPD development. Although few studies have directly examined the relationship between personality traits and sleep-related behavior, low conscientiousness and high neuroticism may become strong predictors of poor sleep hygiene (81) Taking these findings together, certain personality traits may contribute to the development and maintenance of sleep problems including DSWPD through indirect influences on behavioral aspects.

Individuals with DSWPD commonly report difficulty initiating sleep, and 89% of adolescents with DSWPD experience "racing thoughts" in bed (86). Moreover, it has been suggested that individuals with DSWPD may exhibit cognitive pre-sleep arousal (e.g., worry and rehearsal today and planning tomorrow), dysfunctional beliefs about sleep (e.g., "I know that it will not work and then, I sort of just give up"), and safety behaviors (e.g., use of music, television, and computer games as a sleep aid), similar to patients with chronic insomnia (87). Furthermore, an overlap between DSWPD and insomnia has been reported, wherein more than half of the adolescents with DSWPD also met the criteria for insomnia (27). However, whether these cognitive-behavioral characteristics are specific to patients with DSWPD remains unclear.

3.4. Neuropsychiatric disorders in DSWPD

3.4.1. Neuropsychiatric disorders and DSWPD

DSWPD is frequently observed in neuropsychiatric disorders, such as major depressive (88); bipolar (89); obsessive–compulsive (90); neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) (91); and schizophrenia (92). Previous studies have suggested that the presence of DSWPD could result in an increased risk of the occurrence of neuropsychiatric disorders, worsened depressive symptoms, increased relapse risk of mood episodes, and deterioration in social and occupational functioning in the affected individuals. Therefore, accurate diagnosis of DSWPD, definitive biomarkers that can identify the association between DSWPD and psychiatric disorders, and the establishment of a treatment strategy for DSWPD in patients with neuropsychiatric diseases are required. Table 2 shows a list of the major studies investigating the relationship between DSWPD and neuropsychiatric disorders.

3.4.2. Mood disorders and DSWPD

Many studies have reported a relationship between mood disorders and circadian rhythm dysfunction, including DSWPD. Although the causal relationship between depressive symptoms and delayed sleep–wake phase is unclear, depressive symptoms in individuals with DSWPD have been frequently reported. Abe et al. (22) reported that 46% of patients with DSWPD had moderate-to-severe depressive symptoms, as evaluated using the Zung Self-Rating Depression Scale. In contrast, DSWPD was reported in 9.6% of patients with major depressive disorder (93). Interestingly, another study suggested that DSWPD with delayed DLMO was associated with more severe depressive symptoms than DSWPD without delayed DLMO (14), which implies a pathophysiological relationship between depressive symptoms and circadian rhythm dysfunction.

Circadian rhythm dysfunction may be more prominent in bipolar disorder than in major depressive disorder (93, 94). Many studies have suggested a strong pathophysiological relationship between bipolar disorder and circadian rhythm dysfunction (95, 96), and this dysfunction has been suggested to act both as a trait marker of bipolar disorder and a risk factor for the relapse of mood episodes (43). Based on these results, chronobiological treatment focusing on circadian

TABLE 2 Relationship between psychiatric disorders and circadian rhythm dysfunctions, particularly delayed sleep phase.

Psychiatric disorders (author, year)	Study design participants	Findings
Mood disorders		
BD (Takaesu, 2016)	Cross-sectional study 104 euthymic outpatients with BD	Thirty-five participants with BD (32.4%) met the criteria for CRSWD. The presence of CRSWD was associated with a younger onset age of BD and a family history of suicide.
BD (Takaesu, 2018)	Prospective 48-week study 104 euthymic outpatients with BD	Circadian rhythm dysfunction might be a trait marker of BD and risk factor for the relapse of mood episodes.
BD (Steinan, 2016)	Cross-sectional study 404 adults with BD	Younger age, higher BMI, and impairment of energy as well as activity were associated with DSP in adults with BD.
BD (Harvey, 2008)	Review article	Sleep disturbance and circadian dysregulation were critical pathophysiological elements in BD.
BD (Gottlieb, 2019)	Systematic review	Chronobiological treatment focusing on circadian rhythm dysfunction was recommended in the treatment guidelines for BD.
MDD (Robillard, 2018)	Case–control study 34 young adults with MDD and 15 controls	Delayed and disorganized circadian rhythms might be linked to worse psychiatric profiles in young people with depressive disorders.
MDD and BD (Takaesu, 2017)	Case–control study 104 patients with BD and 73 with MDD	The rate of CRSWD in patients with BD was significantly higher than in those with MDD (33.7% vs. 9.6%; $p < 0.001$).
Neurodevelopmental disorders		
ADHD (Spera, 2020)	Cross-sectional study 102 adults with ADHD	Thirty-four participants met the criteria for DSWPD, which was associated with young age, cannabis use, cyclothymic temperament traits, and severe global impairment in ADHD.
ADHD (Lunsford-Avery, 2018)	Editorial perspective	Delayed sleep–wake phase could play an important role in the development of late-onset ADHD.
ASD (Carmassi, 2019)	Systematic review	A bidirectional relationship was suggested between circadian sleep dysfunction and ASD.
ASD (Baker, 2017)	Case–control study 36 adults with ASD and normal controls	DSWPD was common in adults with ASD. Employment status, comorbid anxiety, and depression appeared to influence the sleep patterns of the participants with ASD.
Other psychiatric disorders		
Schizophrenia (Matsui, 2021)	Cross-sectional study 105 patients with schizophrenia	A total of 18.1% of the patients with schizophrenia had CRSWD. The CRSWD group showed more severe psychiatric symptoms (anxiety) than the non-CRSWD group.
OCD (Nota, 2015)	Review article	Individuals with OCD had shorter sleep duration and higher prevalence of DSPD than controls.

BD, bipolar disorder; MDD, major depressive disorder; CRSWD, circadian rhythm sleep–wake phase disorder; DSP, delayed sleep phase; DSWPD, delayed sleep–wake phase disorder; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; OCD, obsessive–compulsive disorder.

rhythm dysfunction in bipolar disorder has been recommended in the treatment guidelines for bipolar disorder (97). In particular, bright light therapy has been indicated for depressive symptoms, whereas dark therapy has been suggested for manic symptoms in patients with bipolar disorder (97).

3.4.3. Neurodevelopmental disorders and DSWPD

Recent studies have suggested a significant relationship between circadian rhythm dysfunction and neurodevelopmental disorders, such as ADHD (98) and ASD (99). A study on ASD indicated that a higher proportion of adult patients with ASD met the criteria for CRSWD than adult controls. Moreover, DSWPD was found to be particularly common in individuals with ASD (100). Similarly, a cross-sectional study reported that 34 of 102 adult patients with ADHD met the criteria for DSWPD (91). Considering these findings, delayed sleep–wake phase has been hypothesized to play an important role in the development of ADHD symptoms in late adolescence and young adulthood (101), although no clear evidence supporting this hypothesis has been reported. Therefore, longitudinal studies evaluating the causal relationship between neurodevelopmental disorders and DSWPD are required to understand the pathophysiological relationship between these disorders.

3.5. Phenotypes of DSWPD

DSWPD is diverse in not only its pathogenesis but also in its phenotypes. DSWPD phenotypes differ depending on a combination of various background factors. Delayed circadian rhythm is the most prominent feature of DSWPD; however, a recent study identified a group of patients with DSWPD having normal circadian entrainment (48, 102). As previously mentioned, 43% of DSWPD cases are

circadian-entrained DSWPD (14). Circadian-entrained DSWPD often develops primarily based on problems of behavioral factors (103). "Conditioned insomnia" and "aversion to trying to sleep early" are considered as causes of delayed bedtime in circadian-entrained DSWPD (15). Patients with circadian-entrained DSWPD may be associated with negative experiences with going to bed early or have personality traits (e.g., perfectionism) that interfere with bedtime (e.g., staying up late to complete tasks) (104). In contrast, DSWPD with longer tau and an enlarged phase angle shows the most severe delay of sleep–wake phase, and this phenotype is suggested to have pathological continuity with N24SWD (36). The background factors and phenotypes of DSWPD are shown in Figure 1.

4. Recent changes in lifestyle and new concerns of DSWPD in the young generation

4.1. Social and environmental changes that may exacerbate eveningness chronotype in the young generation

Compared to the natural light/dark cycle during outdoor camping, the nocturnal light exposure of modern lifestyles are associated with sleep phase delay (105). With this regard, a Finnish study found a decline in sleep duration and an increase in eveningness among the adult population even in the first decade (2007–2017) of the 21st century (106). The effect of light exposure on circadian rhythm differs depending on an individual's age. Because the lenses in adolescents are relatively more transparent than those of older adults (107), melatonin secretion in adolescents is suppressed even with a relatively small amount of nighttime light exposure that would not affect adults (108). Therefore, nighttime light exposure may become an important risk factor for the development of the eveningness chronotype in this generation (109). Recent changes in the light environment surrounding adolescents have increased the risk of them developing the eveningness chronotype (110). In particular, one study found that the long-term use of smartphones in bed could be a significant risk factor for the eveningness chronotype because using it while lying down and observing the screen at very close range exposes one's eyes to bright light that exceeds 100 lx (111).

A recent cohort study has shown that the number of individuals who meet the diagnostic criteria of DSWPD and the number of people who only have DSP without any sleep complaints for at least 3 months is roughly equal among those who have a sleep–wake schedule delay (12). Undoubtedly, the pathological significance is higher for individuals with DSWPD; however, DSP in the young generation reportedly possesses identifiable psychological risk indicators (52). In the case of DSWPD, no sex difference exists in its prevalence, whereas elevated anxiety levels and the presence of absenteeism (absence from school or work) have been demonstrated (12). In contrast, DSP is more common in men and is associated with a lack of educational activity or work, the presence of shift work, the use of nicotine and alcohol, and less rumination score. Therefore, individuals with DSP could possibly include a substantial number of those in whom the sleep–wake phase is intentionally delayed by personal preference or lifestyle rather than by biological reasons. The ICSD-3 has subtyped DSWPD with poor motivation for treatment as motivated delayed sleep–wake phase disorder (MDSWPD), which is considered more common in adolescents and young adults with comorbid psychiatric disorders, such as developmental and anxiety disorders (10). Considering that MDSWPD is a state of poor internal motivation to regain a normal social life, many MDSWPD cases could be included in the DSP category. As described later, the chronobiological approach is the mainstay treatment for patients with DSWPD; however, behavioral approach would be a better choice for correcting DSP.

In the youth with eveningness chronotype, SJL is commonly observed along with DSP (13). SJL can be easily measured with the result of the aforementioned MCTQ (42). Individuals with larger SJL are more likely to report excessive daytime sleepiness (112, 113) and daytime dysfunction because of the internal desynchronization caused by circadian phase delay (13, 114), including low cognitive function (115), poor academic performance (116), depression (117), and substance use (118). In order to test the hypothesis that SJL can easily develop during adolescence and young adulthood (119), we previously conducted a cross-sectional survey in a large Japanese population. The result showed that the younger the age, the greater the SJL, with 61% of those in their 20s versus 53% of those in their 30s showing a SJL of >1 h (120). SJL is associated with the delay in circadian rhythms (13), and sometimes exacerbates the problem of falling asleep when resuming weekdays during the following week (121). However, whether SJL is a precursor of DSWPD remains unclear. Moreover, SJL is a relatively new concept and literature on its physiological characteristics and natural course is scarce. Therefore, further research from multiple perspectives is required to delineate the relationship between SJL and DSWPD.

4.2. COVID-19 pandemic and sleep behavior in adolescents and young adults

From 2020 to 2022, the novel coronavirus disease (COVID-19) has spread globally. During this period, sleep disturbances were observed in up to two-fifths of the general population and up to three-fourths of the patients with COVID-19 globally (122, 123). Older age, presence of a partner, and residence in a high-income country were thought to reduce the risk of sleep disturbances during the pandemic, whereas younger age, female sex, financial problems, and coexisting stress, anxiety, and depression enhanced the risk of sleep disturbances (124). To prevent further spread of the infection, governments of many countries, particularly Western countries, imposed social restrictions on the general population. The resultant changes in lifestyle associated with home confinement, such as the lack of morning sunlight exposure, lack of physical exercise, and excessive use of blue light devices at night, contributed to the changes in sleep behaviors of the general population (125). Of note, the effect of sleep hygiene-related behavior during the pandemic was larger in the young population than in the middle-aged or elderly population (126). Consistent with the studies by Wright et al. (127) and Marelliet et al. (128), we recently reported a significant delay in sleep phase, prolongation of total sleep time, and decrease in SJL from before to during the pandemic in 2222 Japanese participants from a young population cohort of 15–30 years of age (129). However, the worsening of insomnia and depression, as well as deterioration in health-related quality of life that was observed in Western countries was unexpectedly not observed in our study population. This could possibly be because

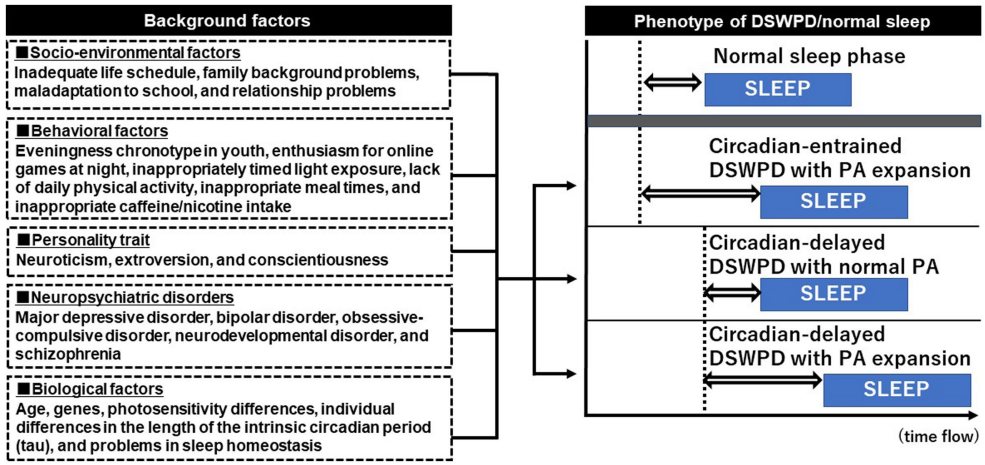

FIGURE 1
Phenotype of delayed sleep–wake phase disorder and its background factors. The dotted vertical line (---) indicates dim light melatonin onset (DLMO) and the blue box shows the sleep phase. The double-headed arrow (⇔) shows the phase angle (PA) between the DLMO and sleep period onset. The PA between the DLMO and sleep period onset is approximately 2h in a normal sleeper. Delayed sleep–wake phase disorder (DSWPD) exhibits multiple phenotypes owing to the various combinations of background factors. Approximately 40% of DSWPD cases are reported as circadian-entrained DSWPD, in which the timing of DLMO is normal but the PA is enlarged because of night-oriented behavioral or psychological characteristics. Circadian-delayed DSWPD with PA expansion shows the most severely delayed sleep phase, and this phenotype may have pathological continuity with non-24-h sleep–wake rhythm disorder.

of the smaller infection intensity and milder social restrictions in Japan than in Western countries at the survey point. However, considering that chronic sleep phase delay may result in subjective sleep problems and psychological distress (130) and that Japanese outpatients with DSWPD tended to show symptom aggravation because of a decrease in social zeitgeber during the pandemic (28), prolonged sleep phase delay along with extended social restrictions possibly impairs psychological distress and health-related quality of life. Fortunately, social restrictions owing to the COVID-19 pandemic have already ended in most countries. Nevertheless, we should carefully monitor sleep behaviors and their impact on the daytime function of the youth during the post-social restriction period. This is because the social advancement of the sleep phase and shortened nocturnal sleep time after the resumption of their work or school life may cause a significant psychological dysfunction (131).

4.3. Gaming disorder and DSWPD

Gaming is one of the most popular leisure activities. The COVID-19 pandemic greatly expanded the market of video game industry because people spent more time playing games worldwide (132, 133). Healthy gaming benefits education and training (134), however, some minority gamers experience negative consequences from excessive gaming (135). Gaming disorder (GD) is a relatively new mental disorder that shows the persistence of gaming behavior (online as well as offline) with a loss of control for gaming despite harm to individuals, and conflicts stemming from gaming and functional impairment (136).

In particular, online games allow players to select opponents and cooperating partners from all over the world, making it much easier for players to continue playing and enjoying games than offline games. In 2013, "internet gaming disorder (IGD)" was included in the "diagnostic and statistical manual of mental disorders, fifth edition (DSM-5)" (137) published by the American Psychiatric Association. In 2019, with strong encouragement from Japan, the World Health Organization (WHO) decided to adopt "Gaming Disorder (GD)" in the "international classification of diseases 11th Revision (ICD-11)" (136), and its use started in 2022. Although the content of the criteria differed, the concordance between GD and IGD diagnoses was reported to be fairly high (138).

As expected from elevated enthusiasm and prolonged exposure to blue light emitted from game devices at night, patients with GD have been reported to be frequently complicated with DSWPD (139). Adolescent patients with DSWPD need to be carefully checked to identify if there is a GD in their background. Interestingly, DSWPD and GD may have the following commonalities. First, both GD and DSWPD tend to appear in younger generations, including adolescents (140, 141). Second, not only patients with DSWPD but also those with GD are often complicated by neurodevelopmental disorders. Several studies have indicated that patients with GD are frequently complicated by either ADHD (142) or ASD (143). In such cases, treatment approach focusing on neurodevelopmental disorders should be included.

5. Current status and future challenges of DSWPD treatment

5.1. Chronobiological approaches

The 2007 CRSWD treatment guidelines of the AASM recommended light therapy as the first-line treatment for DSWPD (66). As mentioned earlier, exposure to morning light after achieving CBTmin advances the phase of the circadian rhythm. Generally, light therapy for patients with DSWPD is administered for 30 min to 2 h at 2500–10,000 lx during the

time for phase advancement (or at 1–3 h before spontaneous awakening) (66). Expectedly, higher light intensity and longer duration of light exposure lead to a greater phase-shifting effect; however, this effect is nonlinear in humans (144, 145). Human circadian rhythms are most sensitive to short-wavelength blue light (~480 nm) (146, 147). Short-wavelength blue light is a more potent melatonin suppressor than long-wavelength light (148), and its application in light therapy has the potential to reduce light intensity and exposure time (149). However, effectiveness may also be lost if the light exposure timing is extremely late and out of the phase-advancing zone.

The side effects of light therapy on the skin and retina should also be noted. Although commercial light therapy products do not emit ultraviolet light, patients with eye diseases or those using photosensitizing drugs should be monitored regularly by ophthalmologists and dermatologists for underlying conditions during the administration of light therapy (150–152). Mania induction as a side effect of light therapy should also be considered (153). Melatonin release appears to decrease during depression and increase during mania (96, 154). Careful monitoring of psychiatric symptoms is crucial to maintain the safety of light therapy in patients with DSWPD and bipolar disorder (155). The AASM guidelines updated in 2015 noted that little evidence exists for the efficacy of light therapy in adults and recommended that light therapy should be administered only for DSWPD in children and adolescents after spontaneous awakening in combination with behavioral approaches provided by caregivers or others (156). As for the case of circadian-entrained DSWPD, no studies have investigated the effectiveness of light therapy in this phenotype.

The DSWPD treatment guidelines of AASM, which were revised in 2015 (156), recommend the use of melatonin and melatonin receptor agonists for the treatment of DSWPD in children, adolescents, and adults. Exogenous melatonin and its agonists have hypnotic effects along with decrease in CBT via the MT1 receptor and circadian phase resetting effect via the MT2 receptor. As for the role of the MT2 receptor, the PRC of melatonin administration on circadian rhythm is approximately 180° out of phase with that of light. Similar to CBTmin serving as an "inflection point" for the phase-delay and -advance effects of light, DLMO serves as an approximate inflection point for the phase-delay and -advance effects of melatonin (157). In patients with DSWPD, melatonin (0.3 mg) administration for a 4-week period between 1.5 and 6.5 h prior to DLMO showed phase advance of the circadian rhythm, wherein the magnitude of phase advance was strongly correlated with the time of melatonin administration and earlier administration times were more effective (158). Another study also showed that the administration of melatonin (5 mg) for 4 weeks between 19:00 and 21:00 h reduced sleep onset latency in patients with DSWPD (159). Evidence for the efficacy of melatonin in DSWPD, including the result of a meta-analysis (160) is being accumulated. Melatonin administration has been shown to improve comorbid depression and advance the melatonin secretory rhythm in patients with DSWPD (161). A small dose of melatonin administered 6–7 h before natural sleep onset (158, 162) or 5 h before DLMO (157) has been reported to be effective for the treatment of DSWPD. However, a consensus regarding the optimal timing, dose, and duration of melatonin administration has not yet been achieved.

Concerning the side effects of melatonin, the use of <10 mg/day in adults has been reported to be safe (163, 164). However, side effects, such as headache, somnolence, hypotension, hypertension, gastrointestinal upset, and worsening of alopecia areata, have been reported with high-dose usage (165). Cases of side effects, such as increased depressive symptoms (166) and decreased glucose tolerance (167) have also been reported. In the case of children, several studies have not found any adverse events with melatonin treatment in pediatric patients with DSWPD complicated by neurodevelopmental disorders (168–170). However, concerns exist about the effects of melatonin treatment on growth hormones during this developmental stage (171, 172) and the resulting potential adverse effects on reproductive function (173). One study (Meldos Trial) has reported no adverse events with reproductive development of the children when using melatonin at 0.3–10 mg doses (mean dose 2.69 mg) (174). In 2018, follow-up study of this trial also reported that adverse events were scarce but the study showed a tendency towards delayed puberty in the former and current users of melatonin (175). Another longitudinal study of melatonin treatment in 44 children with neurodevelopmental disorders showed that pubertal timing was considered within normal limits except in five children with severe neurodevelopmental disability, most of whom experienced precocious puberty prior to the start of melatonin treatment (170). A recent review of this area concluded that no consensus could be reached yet, as only a few studies with small samples have investigated the pubertal timing of melatonin users (176).

Ramelteon is the first melatonin receptor agonist developed as a hypnotic in Japan. Ramelteon has a high affinity for the MT1 receptor, which is considered to be involved in human sleep, and the MT2 receptor, which seems to regulate circadian rhythms (177, 178). Therefore, similar to melatonin, ramelteon is expected to exhibit therapeutic effects in DSWPD (179). Administration of 1–4 mg of ramelteon at 30 min before bedtime produces a phase advance. However, no difference in the effect was found between a dose of 8 mg and a placebo (180), suggesting that a small drug dose would be preferable for the treatment of DSWPD (181, 182). However, clinical evidence regarding the optimal timing of ramelteon administration for the treatment of DSWPD remains scarce. In addition to ramelteon, other melatonin receptor agonists are available. Tasimelteon is a melatonin receptor agonist that was approved as an orphan drug by the US FDA in 2010 for treating N24SWD in blind individuals. This drug exhibits high affinity for MT1 and MT2 melatonergic receptors in humans, which is similar to the action of melatonin or ramelteon (183, 184). Agomelatine (185) acts as both a melatonin receptor agonist and serotonergic receptor antagonist and was approved by the European Union for the treatment of depression in 2009. Agomelatine may promote sleep at night through its melatonergic effect and help maintain alertness during the day via its 5-HT_{2C} antagonistic effect (184). However, little evidence exists on agomelatonine's ability to improve circadian rhythms when compared to other melatonergic drugs.

Among other DSWPD treatment methods, chronotherapy (60), in which sleep is intentionally delayed for 3 h each day to fix the sleep–wake rhythm to the desired time, has been formerly advocated. Although the literature on chronotherapy is scarce, few studies have reported cases that were effectively treated with chronotherapy. One case report showed that chronotherapy improved nighttime sleep and daytime psychiatric symptoms in children with attention deficit disorder complicated by DSWPD (186), while another case report found that the combination of chronotherapy and light therapy was effective in the treatment of DSWPD (187). However, chronotherapy is labor-intensive and carries the risk of developing N24SWD (188). Therefore, this therapy is not currently recommended in the AASM guidelines.

5.2. Newer candidates for DSWPD treatment

Aripiprazole is an antipsychotic drug that acts as a partial agonist of D2 receptors (189), but it appears to have no direct chronobiological action. However, a low dose of aripiprazole (3 mg or less) was reported to be effective in enabling patients with DSWPD to wake up in the morning (190). Although the detailed mechanism of its action is unknown, this drug appears to help in waking up at the desired time in the morning, which leads to a decrease in sleep time and consequent advancement of the sleep phase (191). Furthermore, aripiprazole is an effective adjunctive therapy for major depressive disorders (192). As previously mentioned, patients with DSWPD often have complications, such as depressive symptoms or prolonged sleep duration. Therefore, aripiprazole may be a new potential treatment option for DSWPD. Aripiprazole has fewer side effects than other antipsychotics and is increasingly prescribed to children, but drowsiness, extrapyramidal effects, metabolic effects, and weight gain should be noted (193). Although this drug is only used at low doses in DSWPD, it is an off-label prescription and requires careful monitoring of side effects in children and adolescents.

To date, the treatment of DSWPD has mainly focused on the chronobiological background. However, DSWPD is often recurrent and likely to follow a chronic course (19, 66), and either environmental or psychosocial factors may also contribute to the development and perpetuation of the disorder. Particularly in adolescent DSWPD, late work schedule, involvement in extracurricular activities, exposure to indoor lighting during evening hours (194), and/or delay in weekend wake-up time (195) may affect treatment responses (196). In these situations, a carefully individualized approach to change problematic situations is necessary. Furthermore, repeated exposure to frustration about sleep initiation can lead to psychological hyperarousal at night, which may contribute to the perpetuation of the disorder. Considering this process and that patients with DSWPD are likely to have elevated neuroticism (83), a cognitive-behavioral approach consisting of stimulus control, sleep hygiene education, cognitive restructuring, and mindfulness-based stress reduction to address sleep latency, in conjunction with the chronobiological approach, may become a treatment option for DSWPD. However, evidence for the effectiveness of combination treatment confirmed through randomized controlled trials on a large number of cases remains scarce. Of note, cognitive and behavioral approaches are also possible candidates for the treatment of circadian entrained-DSWPD. Given that, the likelihood of a favorable response to chronobiological treatment is quite low in patients with a lack of social zeitgebers, such as school attendance and employment or those without motivation for treatment; thus, less complex interventions should be considered for patients with these characteristics (156). In addition, ensuring diversity in social institutions so as to provide accommodation for the circadian preference of patients with DSWPD may be an important choice for some refractory cases (197).

6. Conclusion

From a psychiatric perspective, we reviewed the sleep behavior of adolescents and young adults, the psycho-behavioral characteristics of DSWPD in this young generation, and the association of DSWPD with psychiatric disorders. The pathogenesis of DSWPD is heterogeneous, with many mechanisms yet to be elucidated. The phenotype of DSWPD (including the presence or absence of circadian entrainment and phase angle expansion) varies depending on the interrelationship among various factors, including biological, social, and environmental factors, psycho-behavioral characteristics, and psychiatric disorders. DSWPD is a recurrent disorder, and its treatment is labor-intensive and time-consuming. Conventional DSWPD treatment has focused on biological factors; however, individually optimized treatment that considers not only the chronobiological factors but also psychological factors as well as the lifestyle and environment of young people should be developed.

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KF reported personal fees from Eisai., Ltd. and MSD outside the submitted work. YT reported lecture fees from Takeda Pharmaceutical, Sumitomo Pharma, Otsuka Pharmaceutical, Meiji Seika Pharma, Kyowa Pharmaceutical, Eisai, MSD, and Yoshitomi Pharmaceutical outside the submitted work. KM reported personal fees from Eisai, Meiji Seika Pharma, MSD, Otsuka Pharmaceutical, Takeda Pharmaceutical, and Yoshitomi Pharmaceutical outside the submitted work. AS reported personal fees from Eisai and Sumitomo Pharma outside the submitted work. IO reported grants from NEC Solution Innovators Co., Ltd. and Infocom Co.; personal fees from Otsuka Pharmaceutical MSD, and Eisai.; and consultation fees from NEC Solution Innovators Co., Ltd. and Suntory Wellness Ltd. outside the submitted work. YK reported lecture fees from Eisai outside the submitted work. YI reported personal fees from Eisai, Otsuka Pharmaceutical, Takeda Pharmaceutical, Astellas Pharma Inc., and MED K.K. and grants from Philips Japan Co., Ltd., Koike Medical Co., Ltd., and Teijin Pharma Ltd. outside the submitted work.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect of light therapy on sleep quality in cancer patients: a systematic review and meta-analysis of randomized controlled trials

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Background: Sleep problem is one of the major issues of cancer patients and may have detrimental effects on the ongoing treatment and recovery of patients. However, the evidence for the effect of light therapy on sleep problems in this population remained scarce. This study aimed to examine the effect of light therapy on self-reported and physiological measures of sleep quality of cancer patients. It also aimed to quantify the magnitude of the effect using a meta-analytical approach.

Methods: Six databases were searched for randomized control trials (RCTs). The primary outcome was the sleep quality using the Pittsburgh sleep quality index (PSQI) measurement of self-reported scores, and the secondary outcomes included total sleep time and sleep efficiency measured by actigraphy. Meta-analyses were performed with the random effects model using the RevMan software. The standardized mean difference (SMD) of the PSQI scores and other measures with their 95% confidence intervals (CIs) were used for assessing the treatment effect (CRD42023370947).

Results: Nine RCTs were identified and included in the study. Light therapy significantly improved the self-reported sleep quality with a reduction of the pooled PSQI score (SMD=−0.72; 95% CI: −1.24 to −0.21; p=0.006). Regarding total sleep time (p=0.72) and sleep efficiency (p=0.47), no significant effects of light therapy were found.

Conclusion: Light therapy could improve self-reported sleep quality in cancer patients. However, due to the heterogeneity and small sample size of the included trials, the results should be interpreted cautiously. Trials with better designs and larger sample sizes are suggested to be conducted for a more definitive conclusion.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=370947.

KEYWORDS

light therapy, sleep quality, sleep problems, cancer, systematic review, meta-analysis

1. Introduction

Cancer is one of the main causes of death, with mortality of nearly 10 million accounting for one in six deaths in 2020 worldwide (1). During the progression and the treatments of cancer, patients may have experienced other co-morbidities, such as emotional disorders (including anxiety and depression), fatigue, and sleep disorders (2–4). It has been shown that nearly 60% of cancer patients have suffered from sleep problems, such as somnolence, short duration of nighttime sleep, poor sleep quality, and difficulty falling asleep (5). Previous reports have also indicated that many patients may suffer from sleep problems for at least 6 months or longer (6). Sleep problems among patients with different advanced cancers have been reported to be more severe with a prevalence of 72% (7). Sleep disorders, if undiagnosed and untreated, could be conducive to severe mental and physical problems in cancer patients (8). For example, a previous study showed that sleep problems were bidirectionally associated with depression, and sleep problems could also cause serious cardiovascular problems and reduced immunity (9). These adverse effects of sleep problems on the overall health of cancer patients could be exacerbated due to their compromised health condition. This, in turn, adds a burden to the treatment, management, and recovery of patients.

Sleep disturbances and different sleep disorders (e.g., insomnia, sleep-related breathing disorder, and obstructive sleep apnea syndrome) are common and considerable complaints of cancer patients. Pharmacological therapies (e.g., melatonin, mirtazapine, and valerian herbal extracts) (10–12) and nonpharmacological therapies [e.g., psychoeducational intervention and cognitive behavior therapy (CBT)] are conducted to deal with sleep problems (13). Pharmacological therapies for sleep disorders are available and effective, however, the side effects of these medications may be generated. These include psychomotor and cognitive problems, drowsiness, poor judgment, drug dependence, and tolerance (14, 15). Due to the side effects of pharmacological therapies, non-pharmacological treatment options have been advocated with the benefits of having fewer side effects and being more cost-effective (4, 16–18).

Compared with other non-pharmacological therapies, light therapy has been gaining attention because it is critical to all forms of life, and the circadian rhythms of human beings and other species are strongly affected by light (19). Biologically, the suprachiasmatic nucleus of (SCN) hypothalamic system generates circadian rhythms through sensing the light and other stimuli in animals including humans (20). Based on this biological fact, light therapy has been developed as a treatment option for sleep disorders. It was proposed that light therapy other than natural light could retrain the circadian rhythms by triggering the SCN in sleep disorder patients (20–23). A previous study also showed that light therapy influenced the sleep/wake cycle by its action on the inhibition of melatonin and its alerting effects on the ascending arousal system (24). Normal secretion of melatonin is the key factor in maintaining the regular sleep/wake cycle. Moreover, the secretion of melatonin is regulated by the SCN in response to light signals received directly through the retinohypothalamic tract (20). Therefore, the circadian rhythm of melatonin secretion is considered the best peripheral estimator of the timing of the internal circadian pacemaker, which plays an essential role in human sleep (20, 25). Previous studies also showed that light therapy had clinical effects on depression (26–28), which can indirectly improve the sleep quality of cancer patients. Hence, the biological and psychological mechanisms provide the basis for light therapy to be considered a possible option for the treatment of sleep problems. In terms of the application of light therapy, some devices have been designed and used in clinical treatment. These include light boxes and light glasses which can emit varied types and different intensities of light (21). The advantages of light therapy, including its safety, low cost, and easy to handle, are the reasons for it to be advocated (21, 29).

In terms of the effectiveness of light therapy as a treatment option, there have been an increasing number of clinical trials investigating the effect of light therapy on sleep problems in patients with cancers (18, 24, 30). Several studies have shown that bright light therapy relieved fatigue, improved self-reported sleep quality, and reduced insomnia symptoms of post-treatment in cancer survivors (18, 31, 32). However, the strength of evidence provided by these studies is still inadequate and further research is required to further confirm the clinical effectiveness of light therapy for sleep problems in cancer patients (18, 31, 32). Currently, there are very few studies examining the magnitude of the treatment effect to provide an accurate estimation as evidence for the application of light therapy for sleep problems. Hence, this systematic review and meta-analysis aimed to examine the treatment effect of light therapy on the self-reported and physiological measures of sleep quality of cancer patients.

2. Materials and methods

2.1. Studies search and selection based on inclusion and exclusion criteria

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (33). The study protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, registration number: CRD42023370947).

According to the PRISMA guidelines, the flow diagram of the study selection process, including the literature search, the reasons for exclusions, and the number of included studies was depicted (see Figure 1). Two authors (LQY and ZYZ) conducted the database search. The systematic search yielded 597 studies (70 from PubMed, 237 from Embase, 73 from Cochrane, 82 from Web of Science, 126 from Scopus, and 9 from PsycINFO) between January 1970 and November 2022. Medical Subject Headings (MeSH) and free terms were combined in the process of the systematic search, using the following MeSH terms: phototherapy, neoplasms, and sleep quality. More detailed search strategies were presented in Supplementary Table S1 as supporting materials.

The same two authors (LQY and ZYZ) independently screened all selected titles and abstracts, and read the full texts of relevant articles for eligibility. The eligibility criteria for inclusion were: (1) The studies are randomized controlled trials (RCTs) being published in English; (2) The participants were cancer patients or survivors; (3) Intervention measures were specifically bright light therapies, while the control measures were dim light therapies, placebo or usual care; (4) The primary outcomes were measured by the Pittsburgh Sleep Quality Index (PSQI); the secondary outcomes, namely the total sleep time and sleep efficiency at the end of the intervention, were assessed using

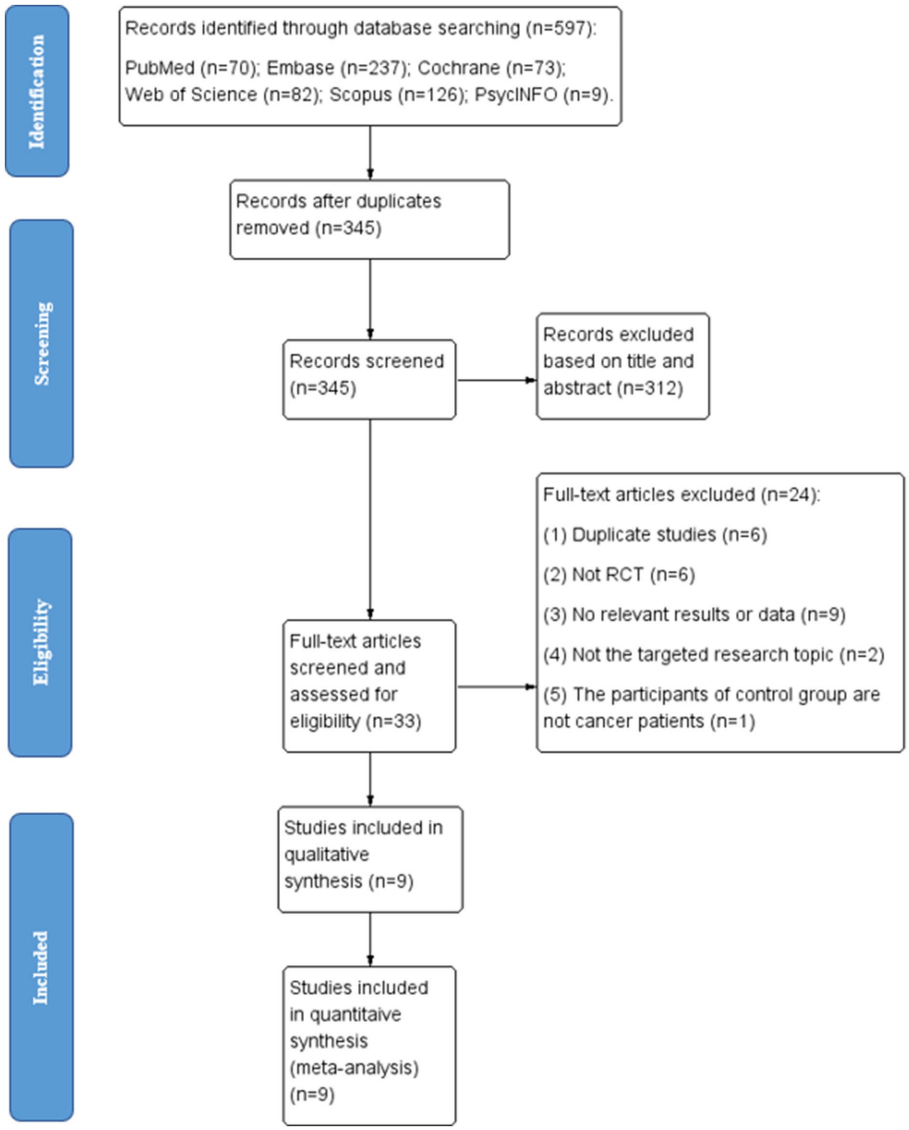

FIGURE 1
Study flow diagram based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

physiological sleep measurement devices (e.g., sleep wrist actigraphy). Studies were excluded if they were: (1) not RCTs; (2) duplicated studies; (3) missing data on the primary and secondary outcomes; (4) not published in English; (5) the controls were not cancer patients; (6) the intervention measures included a combination of light therapy with another treatment (e.g., cognitive behavior therapy), while the control group did not receive the same extra treatment. For duplicated studies, data were only extracted from the one with the most complete and updated information.

2.2. Data extraction and assessment for risk of bias

Data were individually extracted and checked by authors YLQ and ZYZ independently using a predesigned data extraction form designed with Microsoft Excel. The following data of study characteristics were extracted: author, year of publication, country, sample size, age, gender, type of cancer, stage of cancer, the timeframe of diagnosis or therapy, previous treatment, intervention, and control descriptions, intervention duration, primary and secondary outcomes. The risk of bias was independently evaluated according to the Cochrane risk-of-bias assessment tool (34). Selection bias, performance bias, detection bias, attrition bias, and reporting bias were included as assessment items. The risk of bias was classified as low, high, or unclear. Any discrepancies were resolved by consensus or discussions with the third author (LTL).

2.3. Data synthesis and statistical analysis

Review Manager software (RevMan version 5.3) was used to perform the meta-analysis. The mean and standard deviations (SDs) of the outcomes at the trial were extracted and estimated. If the studies did

not report mean and SDs, the authors of the trials were contacted via email to request the information. According to Cochrane Handbook Version 6.3 and the previous study (35, 36), if it was possible to calculate mean and SDs from other data provided in the included studies (e.g., standard error (SE), p values, or t values), it would be performed. If the information was unavailable to assess the mean and SDs, the studies were excluded from the meta-analysis, although they had been included in the systematic review. The effect sizes were presented as the standardized mean differences (SMDs) between the intervention group with the light therapy and control groups with the corresponding 95% confidence intervals (CIs). Cohen's classifications were used to categorize the effect sizes (SMD 0.2–0.5 = small effect, SMD 0.6–0.8 = moderate effect, and SMD > 0.8 = large effect) (37). In this study, a negative SMD indicated an improvement in sleep quality outcomes. Heterogeneity was assessed by using the Cochran's Q test and I^2 statistic. In general, $p < 0.10$ in the Cochran's Q test or $I^2 > 50\%$ indicated a substantially significant heterogeneity. More specifically, 0–25% suggested that the heterogeneity issue is insignificant, 26–50% represented a low heterogeneity issue, 51–75% moderate, and 76–100% high heterogeneity (38). The random effects model was used in the meta-analysis for effect estimations, based on the assumption that the sample used is one of the many selected from the population. To explore the source of any heterogeneity issues, subgroup analyses were conducted, based on different characteristics of the studies, to examine for any differences in the effect estimates. Furthermore, sensitivity analyses involving deleting each study one by one were also carried out to investigate the source of heterogeneity and assess the robustness of the pooled estimates.

3. Results

3.1. Characteristics of included studies

Nine studies in total met all eligibility criteria and were included in the meta-analysis. These studies included a total of 451 participants, with 234 in the intervention group and 217 in the control group. Of these, five were conducted in the US (24, 30, 31, 39, 40), two in Turkey (41, 42), one in Canada (43), and another one in the Netherlands (44). The average age of the participants in these studies was 55.32 years. Participants in five RCTs were patients with specific types of cancers including breast cancer, lung cancer, ovarian, endometrial cancer, Hodgkin lymphoma (HL), and diffuse large B-cell lymphoma (DLBCL) (31, 39–41, 44). The rest included patients with nonspecific cancers (24, 30, 42, 43). These participants had previously received basic treatment such as radiotherapy and chemotherapy. In terms of the color of the lights, white, green, green-blue, or white-blue were used in the intervention groups, while the dim red/white lights or usual care were performed in the control groups. The light intensities ranged from 417.9 lux to 10,000 lux, and the intervention duration was 1, 2, 3.5, 4, and 8–12 weeks with the exposure time ranging between 30 and 60 min in the morning or afternoon. Characteristics of the included literatures of this study are presented in Table 1.

3.2. The effect of light therapy on sleep quality in different sleep indexes

Nine studies were included in the meta-analysis reporting PSQI as the primary outcome (24, 30, 31, 39–44). The results revealed that the average PSQI scores of the light therapy group were significantly lower than that of the control group (SMD = −0.72; 95% CI: −1.24 to −0.21; $p = 0.006$), suggesting light therapy might improve the overall sleep quality in cancer patients. However, the level of heterogeneity in the overall analysis was high ($p < 0.00001$; $I^2 = 80\%$), suggesting a considerable amount of variabilities in these studies.

Six studies were included in the meta-analysis reporting total sleep time (30, 31, 40, 42–44). The pooled results showed that there were no significant differences between groups (SMD = 0.04; 95% CI: −0.20 to 0.29; $p = 0.72$), with insignificant heterogeneity issues ($p = 0.32$; $I^2 = 14\%$).

Five studies were included in the meta-analysis reporting sleep efficiency (30, 31, 40, 43, 44). The pooled results showed that light therapy had no significant effect on sleep efficiency (SMD = 0.11; 95% CI: −0.19 to 0.41; $p = 0.47$). The results indicated that the heterogeneity was low ($p = 0.24$; $I^2 = 27\%$).

The forest plots of light therapy on PSQI and physiological sleep quality indexes were presented in Figure 2.

3.3. Risk of bias in the included studies

The results of the risk of bias assessment were summarized in Figures 3, 4. As shown, performance bias was the most common type of bias in these studies. Of the nine studies included in the systematic review, five had issues with blinding with four having definite and one possible risk (24, 30, 31, 39, 41). Given the design of these studies, it was likely that the blinding issue was more related to research personnel than the participants. The second most common bias noted was the detection bias which related to the blinding of the outcome assessment. Nearly half of these studies (four of the nine) had been identified with an issue of blinded outcome assessment (30, 39, 41, 42). Three studies were found to have a problem of attrition with incomplete outcome assessments (30, 41, 43). There were also other biases involved in these studies. For example, three failed to report the details of random sequence generation (30, 40, 41); four did not mention the process of allocation concealment (30, 39–41); one was high-risk of bias because this study was a factorial design which used two of eight arms (24). Of the nine studies, one had a considerable risk of bias with four on high and two on moderate of the seven risk item (30).

3.4. Subgroup analyses

The study's authors further conducted subgroup analyses for PSQI, total sleep time, and sleep efficiency based on the following variables: country, gender, the number of participants, and light duration. Regarding the country, the effect size for PSQI showed a significant difference between the intervention group with the light therapy and control groups in the US (SMD = −1.05; 95% CI: −1.89 to −0.21; $p = 0.01$; $n = 5$) (24, 30, 31, 39, 40), while there was no significant difference among the studies conducted in other countries (SMD = −0.45; 95% CI: −1.11 to 0.22; $p = 0.19$; $n = 4$) (41–44). As for the number of participants (< 50 versus ≥50), the results showed that the studies involving less than 50 participants had a significant reduction in the PSQI scores (SMD = −0.93; 95% CI: −1.60 to −0.25; $p < 0.01$; $n = 6$) (24, 30, 31, 39–41), while there was no significant

TABLE 1 Characteristics of included studies.

Author (Year)	Country	Participants		Type of cancer	Timeframe of diagnosis or therapy	Treatment	Duration	Outcome	
		Intervention	Control					Primary outcome	Secondary outcome
Ozkaraman et al. (2018)	Turkey	Number: 11 Age: 53.36 ± 2.35 Gender: *F* = 11	Number: 12 Age: 49.25 ± 3.33 Gender: *F* = 12	Breast cancer	Undergoing radiotherapy	I: 2000–3000 lux bright white light; C: Daily radiotherapy session.	30 min/d before radiotherapy sessions in the afternoon, 1 week	PSQI	NA
Weiss et al. (2018)	United States	Number: 7 Age: 68.8 ± 7.2 Gender: *F* = 5/M = 2	Number: 5 Age: 66.0 ± 10.1 Gender: *F* = 1/M = 4	Lung cancer	Completed treatment at least 6 weeks and no longer than 3 years	I: 417.9 lux green-blue light (500 nm), light glasses; C: 152.3 lux red-yellow light.	60 min/d in the morning for 60 min within 1 h upon awakening, 1 week	PSQI	NA
Wu L. M. et al. (2018)	United States	Number:25 Age: 53.0 ± 12.1 Gender: *F* = 20/M = 5	Number: 19 Age: 54.1 ± 9.4 Gender: F = 13/M = 6	Hematological malignancy, breast cancer, gynecological cancer	Time since primary treatment: 1.04 ± 0.72 years (intervention), 1.60 ± 0.82 years (control)	I: 1,350 lux full spectrum white light, Litebook; C: <50 lux dim red light	30 min/d every morning, 4 weeks	PSQI	Actigraphy: total sleep time/min, sleep efficiency/%
Yennurajalingam et al. (2020)	United States	Number:8 Age: NA Gender: NA	Number: 8 Age: NA Gender: NA	Advanced cancer	Undergoing treatment	I: 1350 lux white light, the Litebook; C: 50 lux dim red light.	30 min each morning within 2 h of arising before noon, 2 weeks	PSQI	NA
Garland et al. (2020)	Canada	Number: 42 Age: 56.57 ± 10.49 Gender: *F* = 38/M = 4	Number: 39 Age: 59.97 ± 9.26 Gender: *F* = 32/M = 7	Cancer	Completed treatment at least 3 months	I: 1250 lx white-blue light (~465 nm), light-emitting diodes (LEDs); C: <400 lx red light (~633 nm)	30 min/d every morning, 4 weeks	PSQI	Actigraphy: total sleep time/min, sleep efficiency/%
Fox et al. (2020)	United States	Number: 9 Age: 53.89 ± 11.20 Gender: *F* = 9	Number: 9 Age: 60.33 ± 7.94 Gender: *F* = 9	Ovarian and endometrial cancer	Had no history of chemotherapy or had completed primary chemotherapy at least 30 days	I: 506 lx lm/m2 bright light, LEDs; C: Dim red light or green light.	45 min/d or at least 30 min/d every morning, 4 weeks	PSQI	Wrist actigraphy: total sleep time/min, sleep efficiency/%
Starreveld et al. (2021)	The Netherlands	Number: 83 Age: 46.7 ± 11.9 Gender: *F* = 50/M = 33	Number: 83 Age: 44.8 ± 12.5 Gender: *F* = 49/M = 34	Hodgkin lymphoma (HL) and diffuse large B-cell lymphoma (DLBCL)	The time since diagnosis of all survivors was 12.9 ± 9.9 years	I: 1500 lux bright white light (468 and 570 nm), Luminette glasses; C: 8 lux dim white light (468 and 570 nm).	30 min/d after waking, 25 days	PSQI	Sleep wrist actigraphy: total bedtime (total sleep time)/min, sleep efficiency/%

(Continued)

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TABLE 1 (Continued)

Author (Year)	Country	Participants		Type of cancer	Timeframe of diagnosis or therapy	Treatment	Duration	Outcome	
		Intervention	Control					Primary outcome	Secondary outcome
Celik et al. (2022)	Turkey	Number: 26 Age: NA Gender: $F = 13$/M = 13	Number: 26 Age: NA Gender: $F = 13$/M = 13	Breast cancer, gynecological cancer, gastrointestinal cancer, lung cancer, head and neck cancer and urological cancer	The total diagnosis time: <23 months ($n = 26$), >23 months ($n = 26$)	I: 10,000 lux bright white light, a specially designed lightbox; C: <50 lux dim red light.	30 min every morning, 2 weeks	PSQI	Smart wristbands: total sleep time/min
Rissling et al. (2022)	United States	Number: 23 Age: 54.26 ± 9.31 Gender: $F = 23$	Number: 16 Age: 53.50 ± 8.96 Gender: $F = 16$	Breast cancer	Undergoing chemotherapy	I: 1500 lux white light, Litebook; C: <50 lux dim red light.	30 min upon awakening every day, 8–12 weeks	PSQI	Actigraphy: nighttime total sleep time/min and sleep percentage (sleep efficiency)/%

I, Intervention group; C, Control group; F, Female; M, Male; NA, Not available; PSQI, Pittsburgh Sleep Quality Index.

difference among the studies involving more than 50 participants (SMD = −0.44; 95% CI: −1.25 to 0.38; $p = 0.29$; $n = 3$) (42–44). Regarding the light duration of the light intervention (< 4 weeks versus ≥4 weeks), as for the pooled effect size of PSQI scores, the studies of <4 weeks and the studies of ≥4 weeks both showed no significant differences between light therapy groups and control groups (all $p > 0.05$). As for total sleep time and sleep efficiency, the pooled effect size for the subgroups of all variables showed no significant differences between light therapy groups and control groups (all $p > 0.05$), and no significant subgroup differences of enhancing effects were found in total sleep time and sleep efficiency (all $p > 0.05$). The results of subgroup analyses were presented in Table 2.

3.5. Sensitivity analysis and publication bias

Due to the high heterogeneity in PSQI outcomes, sensitivity analysis was conducted by deleting each study to estimate the effect of the individual study on the final results. Consistent results were yielded in most of the outcomes. However, when the study conducted by Starreveld was excluded, the I^2 value of heterogeneity decreased slightly from 80 to 68%, however, the p-value was significant (44). As the number of included studies in our meta-analysis was less than 10, funnel plots and the Egger's test were not performed to measure publication bias. The results of the sensitivity analysis were presented in Table 3.

4. Discussion

To our knowledge, this is the first systematic review and meta-analytical study on the effect of light therapy in improving sleep quality including both self-reported and physiological measures of the sleep quality outcomes in cancer patients. The findings of this systematic review and meta-analysis are in line with the results obtained from other reviews that light therapy had a beneficial effect on the self-perceived sleep quality in cancer patients (29, 45). On the other hand, there were no significant differences between the intervention group with the light therapy and control groups in terms of total sleep time and sleep efficiency. Recent systematic review studies on light therapy as an interventional therapeutic approach had also been conducted in cancer patients (29, 45). While the main outcome measures of one of these two studies were patient fatigue and depression, it also included meta-analytical results on sleep disturbance as assessed by PSQI (29). The results obtained in the Xiao et al. (29) study suggested a significant reduction in the overall PSQI score in favor of the light therapy group. The results obtained from the current study are consistent with that reported in the literature. Moreover, the current review and meta-analyses have covered, not only the self-reported measure of sleep quality but also actigraphy information collected from the wearable devices. This could be considered an extension of the existing literature in contributing to the pool of knowledge.

It is worth noting that there were a considerable amount of variabilities in the included studies as reflected in the test of heterogeneity with an I^2 value of about 80% for the meta-analysis of the primary outcome PSQI. These variabilities could have been related to the included studies with a range of sample sizes, particularly with

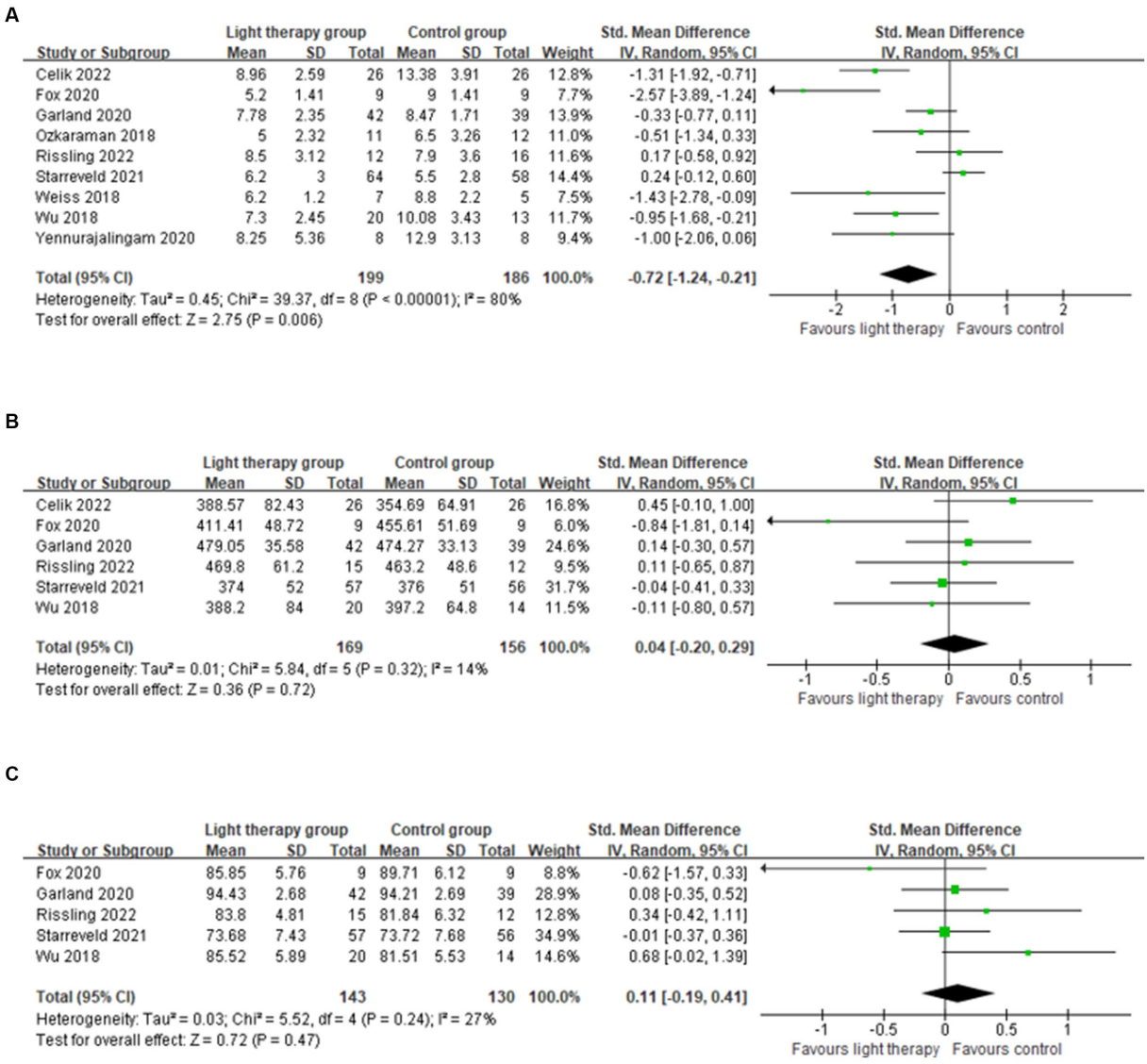

FIGURE 2
Forest plot of light therapy on self-reported instrument and physiological sleep quality indexes. **(A)** Forest plot of light therapy on PSQI. **(B)** Forest plot of light therapy on total sleep time (min). **(C)** Forest plot of light therapy on sleep efficiency (%).

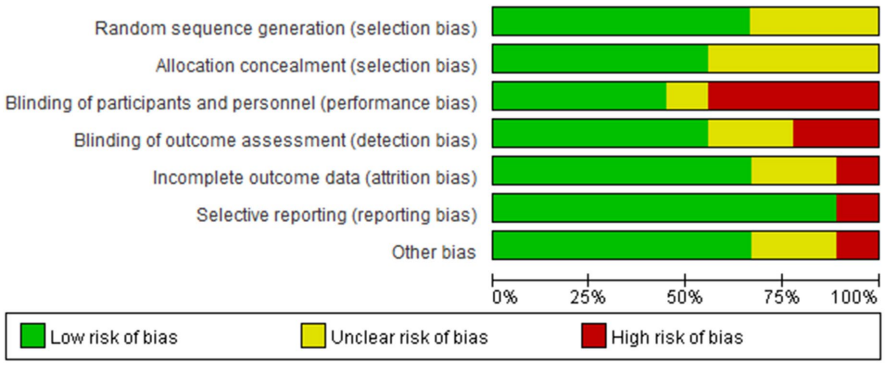

FIGURE 3
Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

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TABLE 2 Subgroup analyses of all sleep indexes.

Sleep indexs	Variable	No. of studies	Sample size	SMD (95%CI)	Test for overall effect		Heterogeneity		*p* value for subgroup difference
					Z	*p* value	I^2	*p* value	
PSQI	Country								0.27
	US	5	107	−1.05 (−1.89, −0.21)	2.44	0.01	72%	<0.01	
	Other countries	4	278	−0.45 (−1.11, 0.22)	1.32	0.19	85%	<0.01	
	The number of participants								0.37
	<50	6	130	−0.93 (−1.60, −0.25)	2.69	<0.01	66%	0.01	
	≥50	3	255	−0.44 (−1.25, 0.38)	1.05	0.29	90%	<0.01	
	Duration								0.97
	<4 weeks	5	225	−0.73 (−1.53, 0.07)	1.79	0.07	84%	<0.01	
	≥4 weeks	4	160	−0.76 (−1.57, 0.06)	1.82	0.07	79%	<0.01	
Total sleep time	Country								0.26
	US	3	79	−0.20 (−0.69, 0.29)	0.79	0.43	15%	0.31	
	Other countries	3	246	0.12 (−0.13, 0.38)	0.94	0.35	4%	0.35	
	The number of participants								0.26
	<50	3	79	−0.20 (−0.69, 0.29)	0.79	0.43	15%	0.31	
	≥50	3	246	0.12 (−0.13, 0.38)	0.94	0.35	4%	0.35	
	Duration								0.5
	<4 weeks	2	165	0.16 (−0.31, 0.63)	0.67	0.50	52%	0.15	
	≥4 weeks	4	160	−0.04 (−0.38, 0.31)	0.22	0.83	12%	0.33	
Sleep efficiency	Country								0.67
	US	3	79	0.20 (−0.51, 0.90)	0.54	0.59	57%	0.10	
	Other countries	2	194	0.03 (−0.25, 0.31)	0.21	0.83	0%	0.77	
	The number of participants								0.67
	<50	3	79	0.20 (−0.51, 0.90)	0.54	0.59	57%	0.10	
	≥50	2	194	0.03 (−0.25, 0.31)	0.21	0.83	0%	0.77	
	Duration								0.55

(Continued)

TABLE 2 (Continued)

Sleep indexs	Variable	No. of studies	Sample size	SMD (95%CI)	Test for overall effect		Heterogeneity		*p* value for subgroup difference
					Z	*p* value	I^2	*p* value	
	<4 weeks	1	113	−0.01 (−0.37, 0.36)	0.03	0.98	NA	NA	
	≥4 weeks	4	160	0.17 (−0.27, 0.61)	0.76	0.45	40%	0.17	

NA, Not available.

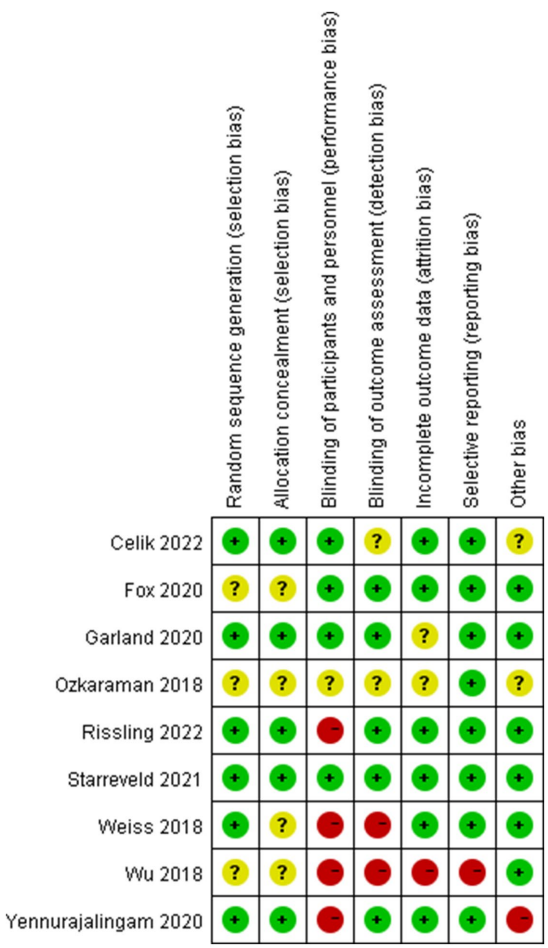

FIGURE 4
Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

three very small studies with less than 10 in each arm. However, such an argument might not be supported by the results obtained from the subgroup analyses with sample sizes <50 and ≥50 as shown in Table 2. As shown, studies with smaller sizes provided a significant result and a smaller I^2 value, in comparison to the larger size studies. Moreover, further sensitivity analyses revealed little changes in the overall results and the test of heterogeneity results between the full sample (i.e., nine studies included) and the trimmed sample (with three small-sized studies removed). Hence, the sample size might not be the main reason, and there would be other sources of variabilities, such as the clinical characteristics of different samples. This is worthy of further research in the future. The results obtained on the risk of biases analyses suggested a heterogeneity issue with the outcome of PSQI scores. In addition, only a small number of trials were found on the topic and the sample sizes of most of these trials were small. This might render the meta-analyses lacking the power to demonstrate a true effect. Hence, these results should be interpreted with caution. As aforementioned, as a treatment option, light therapy could be considered complementary to the current pharmacological management of sleep problems in cancer patients (24, 31, 39, 46).

In terms of the possible biological mechanism for light therapy as a treatment option for sleep problems, particularly among cancer patients, had been briefly described above in the previous section. In brief, light therapy performed at specific periods during the day may stimulate the SCN and suppress the release of the sleep hormone melatonin (21). Therefore, light therapy may increase the cancer patient's activity during the day and reduce it at night to regulate individual circadian rhythm, and subsequently improves sleep quality.

There are strengths as well as limitations in the current meta-analysis. First, this study is one of the few to quantitatively evaluate the effect of light therapy on improving sleep quality in cancer patients. It has evaluated multiple dimensions of sleep quality including self-reported and physiological measures of sleep outcomes. Second, this is a study that includes RCTs only aiming to elicit the best evidence from studies of a better design in terms of strength of evidence. Third, the outcome measures, particularly the physiological sleep quality outcomes of total sleep time and sleep efficiency, were measured by using actigraphy in the included studies. Although the use of the actigraphy method for data collection may offer some objective measures of the outcome, however, due to the lack of comparisons among different types and brands of actigraphy equipment for accuracy and sensitivity, there could also be bias introduced. The use of actigraphy for the assessment of sleep quality is considered a better choice for physiological measures in sleep studies (47). Some limitations have also been identified in this study. First, the heterogeneity issue of the meta-analysis suggested a high degree of variability in the included studies. There could be many reasons for such an observation. One may be due to the differences in various intervention characteristics of light therapy. Second, there were only 9 randomized controlled trials included with limited sample sizes, which might have caused an overall underpower of the meta-analysis, and in turn, caused a type II error. Third, subgroup analyses and sensitivity analyses had been conducted to explain this heterogeneity but there remained substantial or high heterogeneity in most of the results. Other underlying variables such as types of cancer, cancer stage, previous

TABLE 3 Sensitivity analysis of PSQI scores.

Deletion	Heterogeneity	SMD; 95%CI; *p*-value
Celik 2022	$p < 0.001$; $I^2 = 76\%$	SMD-0.62; 95%CI (−1.14, −0.10); $p = 0.02$
Fox 2020	$p < 0.001$; $I^2 = 76\%$	SMD-0.56; 95%CI (−1.03, −0.08); $p = 0.02$
Garland 2020	$p < 0.001$; $I^2 = 82\%$	SMD-0.82; 95%CI (−1.45, −0.18); $p = 0.01$
Ozkaraman 2018	$p < 0.001$; $I^2 = 82\%$	SMD-0.76; 95%CI (−1.34, −0.19); $p < 0.01$
Rissling 2022	$p < 0.001$; $I^2 = 81\%$	SMD-0.85; 95%CI (−1.41, −0.28); $p < 0.01$
Starreveld 2021	$p = 0.003$; $I^2 = 68\%$	SMD-0.86; 95%CI (−1.36, −0.37); $p < 0.01$
Weiss 2018	$p < 0.001$; $I^2 = 81\%$	SMD-0.67; 95%CI (−1.20, −0.13); $p = 0.01$
Wu 2018	$p < 0.001$; $I^2 = 81\%$	SMD-0.70; 95%CI (−1.27, −0.14); $p = 0.01$
Yennurajalingam 2020	$p < 0.001$; $I^2 = 82\%$	SMD-0.70; 95%CI (−1.25, −0.15); $p = 0.01$

treatments, phototherapy intensities and devices and therapeutic environment might account for this. However, due to the small number of studies for each variable above, a more detailed classification of these variables for subgroup analyses is not feasible. Last, the study was limited to trials reported in the English language which limits the generalizability of the conclusion drawn from the study.

Light therapy could be useful for cancer patients experiencing sleep problems in clinical practices and it is safe, easy to deliver, and low-cost. However, well-designed large-scale RCT studies are needed to determine more accurately the treatment effects of light therapy on sleep quality in cancer patients. For future studies, there should include more diverse participants regarding race, and ethnic group as well as more specific types and stages of cancer. In addition, future studies could also investigate the effect of different phototherapy intensities (the cut-off points should be based on standard protocols) and different devices, which are shown to be lacking in the current research. Last but not least, future studies could apply cost-effectiveness analyses as part of the outcome measures.

5. Conclusion

Light therapy has the potential to improve sleep quality and support mental health in cancer patients. However, this systematic review and meta-analysis found no evidence regarding the effects of light therapy on some physiological sleep indexes. Additionally, due to the heterogeneity, and small sample size of included RCT studies, future trials need to consider using a larger sample, different characteristics of participants, phototherapy intensities and devices, longer intervention, and follow-up durations, to obtain a more accurate estimation of the benefit of light therapy in sleep quality for cancer patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LY and ZZ conducted the literature review, wrote and revised the manuscript. LY performed the statistical analysis. LL formulated the study objectives, conceptualized the study plan, supervised LY, and reviewed and edited the manuscript. All authors have read and approved the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1211561/full#supplementary-material

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Sex differences in alpha-synucleinopathies: a systematic review

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Background: Past research indicates a higher prevalence, incidence, and severe clinical manifestations of alpha-synucleinopathies in men, leading to a suggestion of neuroprotective properties of female sex hormones (especially estrogen). The potential pathomechanisms of any such effect on alpha-synucleinopathies, however, are far from understood. With that aim, we undertook to systematically review, and to critically assess, contemporary evidence on sex and gender differences in alpha-synucleinopathies using a bench-to-bedside approach.

Methods: In this systematic review, studies investigating sex and gender differences in alpha-synucleinopathies (Rapid Eye Movement (REM) Behavior Disorder (RBD), Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB), Multiple System Atrophy (MSA)) from 2012 to 2022 were identified using electronic database searches of PubMed, Embase and Ovid.

Results: One hundred sixty-two studies were included; 5 RBD, 6 MSA, 20 DLB and 131 PD studies. Overall, there is conclusive evidence to suggest sex-and gender-specific manifestation in demographics, biomarkers, genetics, clinical features, interventions, and quality of life in alpha-synucleinopathies. Only limited data exists on the effects of distinct sex hormones, with majority of studies concentrating on estrogen and its speculated neuroprotective effects.

Conclusion: Future studies disentangling the underlying sex-specific mechanisms of alpha-synucleinopathies are urgently needed in order to enable novel sex-specific therapeutics.

KEYWORDS

alpha-synucleinopathies, sex differences, estrogen, Parkinson's disease, Dementia with Lewy Bodies

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Highlights

Key findings

- There is conclusive evidence to suggest sex- and gender-specific differences in multiple aspects of alpha-synucleinopathies (i.e., genetics, demographics)
- The alpha-synucleinopathy process has a distinct motor and non-motor symptoms phenotype in men, compared to women.
- Gender, societal and lifestyle factors should be always considered when improving the quality of life and clinical management of patients suffering with alpha synucleinopathy.

What is known, and what is new?

- Male sex has been implicated as a predisposing factor toward developing alpha synucleinopathy.
- While there is evidence for the neuroprotective effects of female sex hormones, it is still unclear to what extent estrogen, or any other sex hormones, could be neuroprotective within the broad framework of alpha-synucleinopathies.

What is the implication, and what should change now?

- Addressing sex and gender differences in clinical and research settings has significant implications in improving diagnosis and management, implementing prevention strategies, and developing novel sex-specific health therapeutics.

1. Introduction

It has been more than twenty years ago since the discovery of the essential role of α-synuclein in the pathogenesis of Parkinson's disease (PD) (1, 2). Since then, abnormal aggregates of α-synuclein, such as Lewy bodies and Lewy neurites, and glial cell inclusions, have been similarly linked with several other sporadic neurodegenerative diseases termed alpha-synucleinopathies [also please refer to (3, 4)]. The alpha-synucleinopathies, including idiopathic PD, Dementia with Lewy Bodies (DLB), Multiple systems atrophy (MSA), pure autonomic failure and REM sleep behavior disorder (RBD), have been also associated with synaptopathy and inflammation, as of yet poorly understood α-synuclein-related mechanisms, that likely contribute to the initiation and propagation of the disease (3). A body of work suggests that abnormal forms of α-synuclein may trigger selective and progressive neuronal death and dopaminergic transmission through mitochondrial impairment, lysosomal dysfunction, and alteration of calcium homeostasis not just in PD, but also in RBD, DLB and MSA (3). Alpha-synuclein aggregates perturb dopaminergic transmission and induce presynaptic and postsynaptic dysfunctions (5). Similarly, the presence of early inflammation in experimental models and PD patients, known to occur before deposition and spreading of α-synuclein, further supports a mechanistic link between inflammation and synaptic dysfunction (5).

All alpha-synucleinopathies appear to share synuclein-related neuroinflammation and many clinical, neurochemical and morphological features (3). Nonetheless, multiple clinical phenotypes exist for each of the three main α-synucleinopathies (PD, DLB and MSA), and a diverse dynamic distribution of their underlying neuropathologies has been demonstrated [also see (4, 5)]. For instance, in both PD and DLB α-synuclein inclusions are thought to be predominantly present in neurons and neurites (3, 4). However, while in PD their occurrence is associated with the loss of dopaminergic neurons in the substantia nigra, resulting in the prevalent motor symptoms; in DLB, it predominates in the neocortex with most prevalent symptoms being fluctuating cognition, recurrent visual hallucinations and spontaneous extrapyramidal motor features (5). On the other hand, in MSA the predominant presence of α-synuclein inclusions is thought to occur in the cytoplasm of oligodendrocytes, with selective neurodegeneration of the multiple brain areas resulting in parkinsonism, cerebellar ataxia and autonomic failure (4, 5). The understanding of these mechanisms is of pivotal importance to support the research on reliable biomarkers to identify the disease and possible disease-modifying therapies (3, 5).

In a similar vein, sex and gender differences have been a focus of interest in alpha-synucleinopathies in recent years, due to their potential to disentangle sex-specific disease phenotypes, and translate them to develop novel sex-specific therapeutics – known as a 'bench-to-bedside' approach (6–8). According to the Institute of Medicine's Committee on Sex and Gender Differences, sex and gender differences are biological, physiological, and clinical differences between males and females that arise due to environmental factors and biological effects due to sex chromosomes and gonadal hormones (9).

Cumulative evidence has reported higher prevalence, incidence, increased disease severity and susceptibility of men compared with women in alpha-synucleinopathies such as PD (10), MSA (11, 12) and DLB (13), and even in the prodromal stage of alpha-synucleinopathies such as REM Behavior Disorder (RBD) (14). To address this, animal and clinical studies have posited the notion of neuroprotective properties of the female sex hormone estrogen against alpha-synucleinopathies (15–18). However, asserting any causality to estrogen as a protective factor in alpha-synucleinopathies remains speculative without a thorough investigation into the observable

sex-and gender-specific differences. Hence, this systematic review aims to critically review the literature on sex differences in alpha-synucleinopathies, broadening our scope to sex-lineated assessments of prevalence, demographics, biomarkers, genetic factors, clinical features, neuroinflammatory and neurochemical responses, interventions, and quality of life themes. A comprehensive assessment of sex and gender differences in alpha-synucleinopathies holds promise for improving clinical diagnosis and developing treatments with optimal efficacy in both men and women.

2. Methods

2.1. Search strategies

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines (19) (see Figure 1). Relevant studies were identified by two reviewers using the electronic databases of PubMed, Embase (Ovid) and Medline (Ovid). The following keywords were used: (sex OR gender differences) AND (alpha-synucleinopathies OR REM Behavior Disorder OR Parkinson's disease OR Dementia with Lewy Bodies (DLB) OR multiple system atrophy (MSA)) (see Table 1). Eligible papers were extracted from 2012 until October 2022. The references of the selected articles were also examined to retrieve documents missed by the literature search.

2.2. Inclusion and exclusion criteria

Each article was first considered by title and abstract. This systematic review included: (1) original research articles; (2) only papers written in English; (3) observational, descriptive, longitudinal, retrospective, cross-sectional, or cohort studies; (4) meta-analyzes and systematic reviews that investigated sex differences in alpha-synucleinopathies; (5) human studies. Two reviewers (KR and GD) independently screened each eligible study, and disagreements were resolved through discussion after retrieving full text to determine whether inclusion and exclusion criteria were met (see Table 2). Please also refer to PICOS statement in Table 3.

2.3. Data extraction

For each article, two reviewers (KR and GD) independently extracted the following data: study name and year, the country, type of study, study aim, the subtype of alpha-synucleinopathy, sample size and age of male and female patients, the methods used, main findings and critical evaluation of the study. Then, the articles were classified and grouped according to the theme of the study (i.e., genetics, demographics, clinical features, interventions, or quality of life) (see Figure 2).

2.4. Quality assessment

Two reviewers (KR and GD) independently evaluated the quality of studies that were included using the two quality assessment scales: (1) Quality Assessment Tool for Quantitative Studies, developed by the Effective Public Health Practice Project (EPHPP)[1] for observational, descriptive, longitudinal, cross-sectional, or cohort studies original research articles (20) and (2) A Measurement Tool to Assess Systematic Reviews-2 (AMSTAR-2) for meta-analyzes and systematic reviews (21). Any disagreements were resolved by discussion or by consulting with a senior reviewer. For the EPHPP scale, the following criteria were rated for each study on a scale of strong, moderate, or weak: selection bias, study design, blinding, data collection methods, confounders, and withdrawals/attrition (if any). Subsequently, these ratings were compiled to form a global rating: studies were rated as strong if they had no weak ratings, moderate if they had one weak rating, and weak if they received two or more weak ratings. As for systematic reviews and meta-analyzes, the AMSTAR-2 is a comprehensive critical appraisal tool focusing on weaknesses in multiple domains. AMSTAR-2 assesses 16 questions, among which 7 are critical domains (21) (Questions 2, 4, 7, 9, 11, 13, and 15; See Supplementary section). Subsequent evaluation is conceptualized into three options, "Yes," "Partial Yes," and "No."

3. Results

3.1. Rapid eye movement behavior disorder

Rapid Eye Movement (REM) behavior disorder (RBD) is a parasomnia characterized by abnormal behaviors during REM sleep, accompanied by the loss of REM sleep muscle atonia and dream enactment (22–24). RBD can be categorized as either idiopathic RBD (iRBD) when not ascribable to other conditions or secondary RBD (sRBD) when associated with other neurological conditions or the use of certain medications (e.g., antidepressants) (25). Importantly, iRBD has been recognized as a prodromal stage in the development of alpha-synucleinopathies such as Parkinson's disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA) (26–28). Sex differences demonstrated in RBD studies from 2012 to 2022 are summarized in Table 4.

RBD has long been considered a male-dominant parasomnia, with more than 80% of patients being male (29–31). Additionally, women with RBD were reported to have a significantly later age onset of iRBD than men with RBD (32, 33). However, when sRBD patients were included, females make up a higher proportion of early-onset RBD patients than males (14). This latter result corroborates findings from previous studies that found a greater proportion of females in early onset RBD, as compared to the late-onset groups, predominantly due to secondary factors such as narcolepsy and antidepressant use (34–37).

Apparent sex differences in clinical presentation and polysomnography (PSG) findings have also been reported (32, 33, 38) (Table 4). In sleep architecture, sex differences in time spent in different sleep stages and electromyography (EMG) activity were found (14, 32, 33, 38). More specifically, sleep stage N1 percentage was significantly higher in males with RBD than in females with RBD (11.96 ± 7.32 vs. 9.60 ± 6.23, $p = 0.047$; 19.9 ± 13.1 vs.

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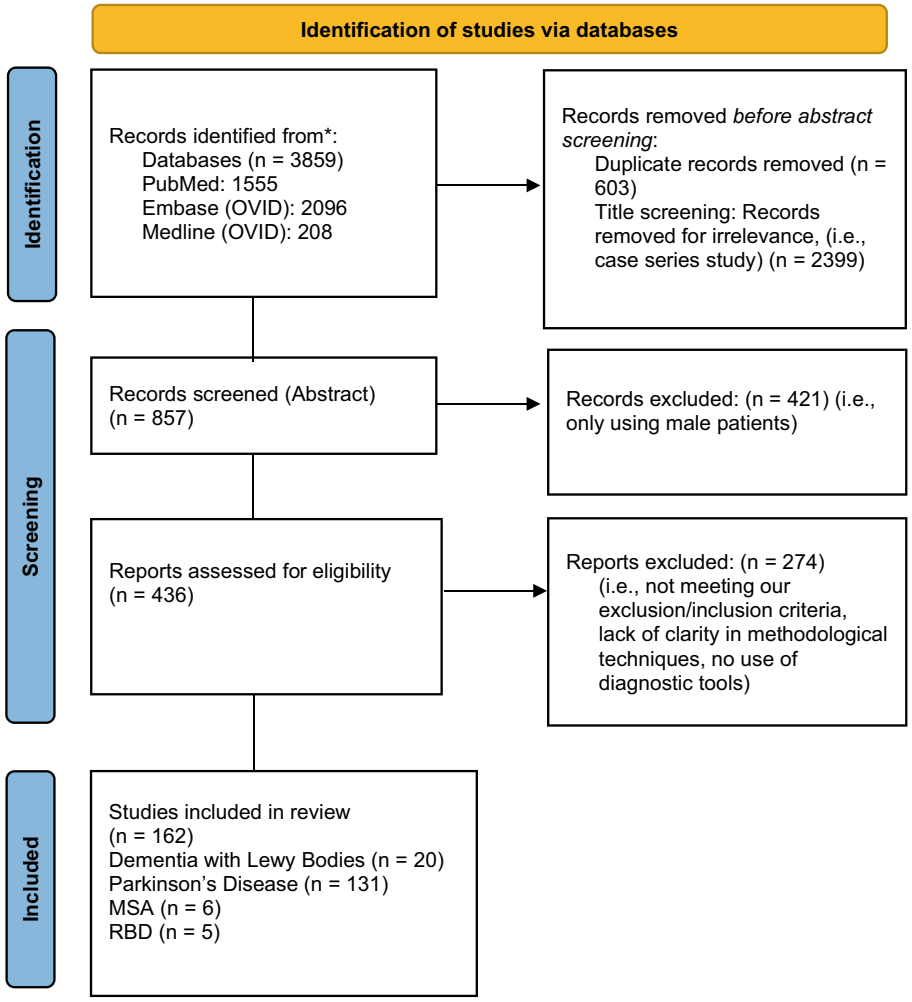

FIGURE 1
PRISMA 2020 Flow Diagram of study selection process.

TABLE 1 The search strategy and exclusion/inclusion criteria.

Database	Search strategy	Limits
PubMed	(Gender differences OR sex differences) AND (alpha synucleinopathies OR Parkinson's disease OR Dementia with Lewy Bodies (DLB) OR Parkinson's disease dementia (PDD) OR multiple system atrophy)	Year: 2012–2022 Species: Human Age: > 18 Only in English
Embase (Ovid)	(Sex differences) AND (Parkinson's disease OR diffuse Lewy body disease OR multiple system atrophy OR Shy Drager syndrome)	Year: 2012–2022 Species: Human
Medline (Ovid)	(Sex characteristics) AND (Parkinson's disease, Multiple System Atrophy or shy Drager syndrome, or alpha synucleinopathies)	Year: 2012–2022 Species: Human

12.1 ± 10.8, $p = 0.028$) [14, 33], while REM latency (132.03 ± 76.37 vs. 108.86 ± 69.99, $p = 0.049$) and slow wave sleep latency (9.3 ± 7.9 vs. 13.1 ± 6.0, $p = 0.032$) were significantly higher in females with RBD (14, 33). This could be due to the effects of female hormones on sleep architecture (39, 40), as female adults tend to engage in more deep sleep than males. It is also worth noting that slow wave sleep decreases with age, and in sRBD, younger age could explain the longer deep sleep in females with RBD (14, 40).

With regards to EMG activity, significantly higher phasic EMG activity was reported in females with RBD compared to males with RBD ($p = 0.009$), although no sex differences were found in the percentage of RBD patients with motor events (simple/complex) and vocalization (32). In contrast, Bugalho and Salavisa demonstrated a significantly higher phasic muscle activity index and relative number of myoclonic and trunk movements in males with RBD compared to females with RBD ($p = 0.005$) (38). This is supported by the fact that

TABLE 2 Search criteria.

	Exclusion criteria	Inclusion criteria
Manuscript characteristics	1. Conference abstracts and proceedings, unpublished data, preprints, government publications and reports, dissertations, and theses 2. Animal studies 3. Studies involving under 18 s, infants, pediatric 4. Guidelines, statements, and comments 5. General review papers	1. Original research articles 2. Observational, descriptive, longitudinal, retrospective, cross-sectional, cohort, meta-analyzes, and systematic review studies that investigate sex differences in alpha-synucleinopathies 3. Sample was well-described (e.g., number of subjects, recruitment criteria, age mean or age range etc)
Patients' diagnosis	1. No use of any diagnostic tools	1. Clinical/probable diagnoses of alpha synucleinopathies 2. Parkinson's Disease (PD): Diagnosis of PD assessed using Unified Parkinson's Disease Rating Scale (UPDRS) III or the United Kingdom Brain Bank criteria (41) or the International Classification of Diseases, 10th revision (ICD-10), or post-mortem, autopsy confirmation of PD pathology. 3. Dementia with Lewy Bodies: Diagnosis made according to the international consensus criteria (42) or post-mortem, autopsy confirmation of DLB pathology. 4. Multiple System Atrophy (MSA): Diagnosis made according to the Unified Multiple System Atrophy Rating Scale (UM-SARS) Part I and II (43) or post-mortem, autopsy confirmation of MSA pathology. 5. REM Behavior Disorder (RBD): Diagnosed according to the International Classification of Sleep Disorders (ICSD) criteria (44) or polysomnography (PSG)
Study design	1. No comparison of male and female cohort	1. Case controlled study and/or with males and females' comparison

TABLE 3 The PICOS statement.

Component of question	Example
Patient population	Alpha-synucleinopathies: Parkinson's Disease, Dementia with Lewy Bodies, Multiple System Atrophy, REM Behavior disorder
Intervention	Medications, Surgical interventions
Control	Male and Female patients and/or healthy controls
Outcomes	Sex differences in PD, RBD, MSA and DLB
Study design	Retrospective, longitudinal, cross-sectional, observational, cohort studies, case–control studies, meta-analyzes, systematic reviews, randomized, controlled trials

the periodic limb movements (PLM) index was significantly higher in males with RBD compared to females ($p < 0.001$) (33). However, Zhou et al. did not find any significant sex differences in phasic ($p = 0.466$) or tonic ($p = 0.988$) EMG quantification (14). These conflicting findings could be due to methodological discrepancies in stratifying for disease severity, stage of RBD and age onset.

Men with RBD were also more likely to exhibit violent and aggressive behavior (otherwise incongruous to their premorbid personality), while women with RBD experienced less dream-enacting behavior (14, 33, 45). Fernández-Arcos et al. reported that men with RBD displayed significantly more aggressive behavior [e.g., punching, assaulting bed partner, vocalizations (swearing)] and increased recall of violent, action-filled dreams, while females with RBD dreamt more about children in life-threatening situations (45). With the inclusion of sRBD patients, women with RBD also displayed significantly less dream-enacting behaviors, especially in movement-related dreams and falling out of bed (14).

Several biological and societal factors could explain the male predominance of RBD. Firstly, sex hormones (i.e., estrogen, androgens) may mediate the distinct phenotypical presentation of RBD (46, 47). Notwithstanding this, in a study conducted on men with RBD and healthy controls, no differences in serum sex hormone levels were found, suggesting that androgenic abnormalities may not account for this male predominance (46). More specifically, in this study, serum levels of total testosterone, calculated free testosterone, calculated bioavailable testosterone, luteinizing hormone, follicle stimulating hormone, estradiol-17 beta, sex-hormone binding globulin, and prolactin were not found different between male idiopathic RBD patients and healthy male controls (46). On the other hand, some evidence seems to point to the neuroprotective effect of estrogen against neurodegeneration in the nigrostriatal regions, although this remains obscure (48). Furthermore, on a more behavioral level, women with RBD tend to experience less disruptive behavior. This might make them less likely to seek medical consultation (49, 50). Additionally, RBD occurrence in females might also be underreported, predominantly due to the inadequacy of questionnaires for detecting female sleep behaviors (37).

3.2. Parkinson's disease

Demographics, epidemiology, and prevalence: Parkinson's Disease (PD) is the second most common neurodegenerative disorder associated with multiple neuropathological hallmarks, including neuronal loss in the substantia nigra (51). Consequently, patients with PD (PwP) typically display a range of motor and non-motor symptoms, including cognitive impairment, dementia, and motor dysfunction (52, 53) (please see Supplementary Table S1 for further details). Across prevalence, incidence, and mortality studies in PD, two trends emerged; (1) Higher incidence, prevalence, and mortality

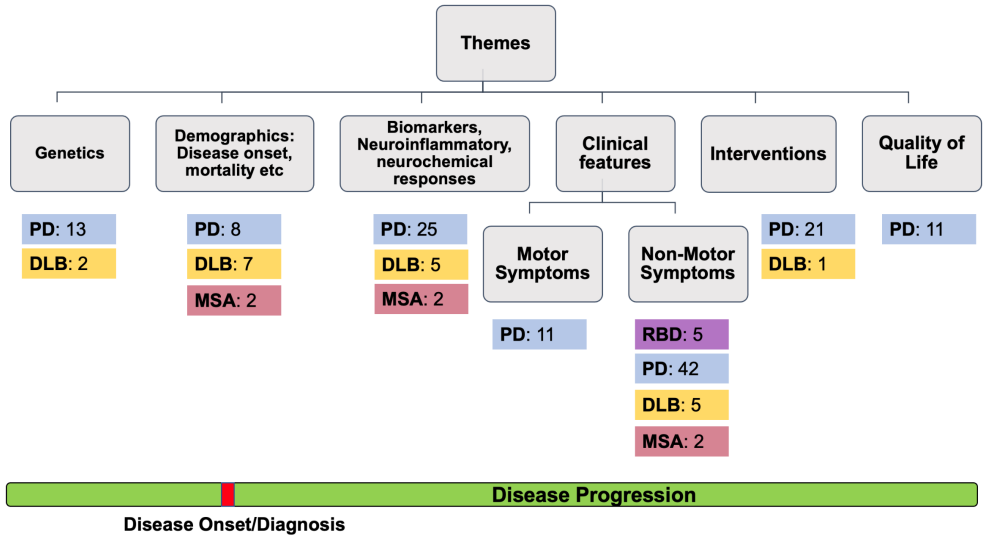

FIGURE 2
The number of studies found for REM Behavior Disorder (RBD), Parkinson's Disease (PD), Dementia with Lewy Bodies (DLB) and Multiple System Atrophy (MSA).

rate were consistently reported in male PwP, and (2) male-to-female incidence ratio across age groups were not constant; instead, it strikingly increases with age, and this was observed across different countries (54–61).

In a French nationwide study and meta-analysis, Moisan et al. reported that the prevalence and incidence of male-to-female ratio increased by 0.05 and 0.14 per decade, respectively, with incidence increasing over 1.6 ($p < 0.001$) times higher in male PwP, in age group over 80 years (59). When geographical locations are considered, Pringsheim et al. also showed a significantly higher prevalence of PD in males, particularly in Western countries and South America (60). However, when parsed by age groups, a significantly higher sex ratio PD prevalence was reported only in the younger age group 50 to 59 (PD prevalence of 41/100000 in females and 134/100000 in males; $p < 0.05$) (60). However, in a Norwegian study, Brakedal et al. did not observe an age-dependent change in male-to-female ratio of PD prevalence, which remained at approximately 1.5 across all age groups (54). Surprisingly, when adjusted for sex-specific mortality of the general population, mortality among female PwP was equal to or higher than mortality in male PwP (54). These findings also did not support previous mortality studies in which a higher mortality rate was consistently reported in male PwP (55, 58).

For example, an Italian mortality study conducted from 1980 to 2015 reported that male PwP have higher mortality, as compared to female PwP (Annual Mortality Rate (AMR)/100,000: 9.0 in males, 5.25 in females) (55). Similarly, PwP with dementia and male PwP had a higher mortality risk of 3.78-fold and 2.05-fold, respectively (58). Indeed, the male sex remains a significant predictor of mortality and survival predominantly due to increased disease severity in multiple domains, including cognition, postural instability, and a higher prevalence of dementia (56–58, 61).

Genetics: Mutations in Leucine-Rich Repeat Kinase 2 (LRRK2) and Glucosidase Beta Acid (GBA) have often been considered the most common genetic cause of monogenic and sporadic forms of PD (62–66). Several studies have posited a higher prevalence of LRRK2 PD mutations in female PwP (67–69). In a meta-analysis that included 66 studies, Shu et al. parsed clinical heterogeneity among four LRRK2 variants in PD (G2019S, G2385R, R1628P and R1441G) and confirmed the association of female sex to G2019S. Interestingly, PwP with G2019S were more likely to have high University of Pennsylvania Smell Identification Test (UPSIT) scores ($p = 0.01$) and good response to levodopa ($p < 0.0001$) (68). Other variants of the LRRK2 mutation, such as G2385R, also displayed sex-related phenotypes differences, with male carriers of G2385R having a lower risk of cognitive impairments ($p = 0.003$) and female G2385R carriers displaying a lower risk of autonomic dysfunction ($p = 0.04$) (70). Crucially, these findings emphasize genetics' key role in driving sex-specific phenotypical differences. Conversely, the GBA gene encodes for the lysosomal enzyme glucocerebrosidase known to maintain glycosphingolipid homeostasis (71). It has been suggested that up to 15% of PD patients may have mutations in the GBA gene, making it one of the most important genetic risk factor for PD (71). Clinically, GBA-associated PD may have an earlier age at onset, common cognitive impairment and more rapid progression (72, 73). Despite its importance, the relationship of sex and GBA mutation remains unclear to date.

Genes related to mitochondrial functions have also been identified to exhibit a sex-specific protective mechanism (74–76). For example, mitochondrial haplogroup U demonstrated a significant protective effect in female PwP of the Cypriot population (74); mutations on mitochondrial DNA (51782A) were lower in male PwP, particularly in younger age groups and provided a protective effect on longevity in Chinese Han, Uygur, and Japanese populations (76–78) while, variants of mitochondrial transcription factor A (TFAM) increase the risk of PD in males (75).

Other genes involved in immunological and inflammatory responses, estrogen regulation, dopamine modulation and chromosome condensation were similarly to affect (either direction) the pathogenesis of PD, especially in male PwP (79–82) (See Figure 3). For example, male PwP carriers of MAO-B G allele had a 2.84-fold increased risk of being

TABLE 4 Sex differences in REM Behavior Disorder (RBD) studies from 2012 to 2022.

Author/year country type of study	Subtype	Sample size (age at time of study unless stated otherwise)	Methods	Main findings	Critical evaluation
Clinical features: non-motor symptoms; cognition					
Takeuchi et al. (32) Tokyo, Japan Retrospective, cross-sectional study	iRBD	$N = 220$ $M = 141$ (66.7 ± 6.7) $F = 43$ (68.7 ± 7.3)	Demographics and Clinical Assessments: 1. Clinical interview with patient or bed partners 2. RBDQ-JP 3. ESS 4. SST 5. MoCA-J PSG: 1. Video-PSG	Clinical/Demographics: 1. Female iRBD patients had significantly later first symptom-witnessed age (e.g., sleep talking) 2. No gender differences were found in the age of diagnosis, clinical severity, or olfactory or cognitive function PSG: 1. No gender differences were found in the percentage of patients with motor events (simple/complex) and vocalization 2. Phasic EMG activity was significantly higher in female patients, although no differences were found in tonic EMG activity 3. Regarding neurodegenerative markers, no significant gender difference was found in the TDI score or proportion of patients with MCI	1. No inclusion of any other neurodegenerative markers, such as DAT scan or test for autonomic nervous symptoms 2. No consideration of patients' disease progression on symptoms manifestation 3. EMG: phasic EMG activity was evaluated only on the chin, not the distal muscle of the arms 4. Limitations of retrospective studies include recall bias
Castelnuovo et al. (33) Milan, Italy Retrospective, cross-sectional, clinical study	iRBD	$N = 329$ $M = 280$ (61.47 ± 6.66) $F = 49$ (64.88 ± 6.46)	1. Phonemic fluency 2. 15 words test by Rey 3. Raven's Progressive Matrix 4. Alternative matrix 5. MMSE PSG	1. Significant gender differences in RBD-onset age 2. No patients showed a cognitive impairment 3. Females scored significantly better in tests that assess phonemic fluency ($p = 0.014$) and long-term verbal memory in learning (p = 0.012) and in false positive components ($p < 0.001$) 4. Males performed significantly better in tests that assess nonverbal reasoning ($p = 0.04$) and visual selective attention ($p = 0.046$)	1. No inclusion of any other neurodegenerative markers, such as DAT scan or test for autonomic nervous symptoms 2. No consideration of patients' disease progression on symptoms manifestation 3. Limitations of retrospective studies include recall bias
Clinical features: non-motor symptoms; sleep					
Bugalho and Salavisa (38) Lisbon, Portugal Retrospective, cross-sectional, study	iRBD sRBD	$M = 40$ (71.13 ± 9.87) $F = 17$ (71.69 ± 10.62) IRBD: M = 18\u00B0F = 4 sRBD: PD = 23 DLB = 11 MSA = 1 M = 22, $F = 13$	1. Clinical history and demographic information were obtained 2. RBD-SQ Video-PSG REM Sleep Motor Event Assessment: 1. Quantification of motor events according to type (myoclonic versus simple etc.)	1. The relation between sex and diagnostic category was nonsignificant, although there was a tendency for a higher frequency of iRBD in the male group	1. Small sample size 2. Certain demographic information is not available (i.e., bedpartner information) 3. EMG of the upper extremities was not available – missed patients with RBD

(Continued)

TABLE 4 (Continued)

Author/year country type of study	Subtype	Sample size (age at time of study unless stated otherwise)	Methods	Main findings	Critical evaluation
Fernández-Arcos et al. (45) Barcelona, Spain Retrospective, cross-sectional, longitudinal study	iRBD	*N* = 203 *M* = 162 (age at diagnosis = 68.6 ± 6.1) *F* = 41 (age at diagnosis = 68.8 ± 6.7)	Demographics and Clinical Assessments: 1. Clinical history and demographics information were obtained (i.e., medication history) 2. Sleep habits, dream recall and its content, self-awareness and characteristics of abnormal motor and vocal behaviors during sleep, resulting in injuries during sleep and overall subjective sleep quality Video-PSG	Clinical/Demographics: 1. No significant differences were found for age of iRBD diagnosis, RBD duration and follow-up duration between males and females Dream Content: 1. Males displayed more frequently aggressive behavior (e.g., punching, assaulting bed partner) and vocalizations (e.g., swearing), recalled more violent and action-filled dreams (E.g., flights, arguments) and were more likely to have a bed partner 2. Females dreamed more commonly about children in life-threatening situations and had depression more commonly	1. Gender differences in PSG findings not mentioned 2. Retrospective study: recall bias and complete information were not available in some instances 3. Dream content was assessed *via* semi-structured interviews and not systematic analyzes
Zhou et al. (14) Sichuan, China Cross-sectional, clinical study	iRBD sRBD	*N* = 90 *M* = 63 (age at onset = 56.2 ± 14.1) *F* = 27 (age at onset = 45.3 ± 19.3)	Demographics and Clinical Assessments: 1. Clinical interview to obtain demographics (i.e., disease duration, associated comorbidities and use of medications) 2. RBDQ-HK Questionnaire Video-PSG: 1. Quantification of EMG activity	Clinical/Demographics: 1. Females were significantly younger than males in the mean age of RBD onset and mean age at diagnosis. 2. Secondary RBD is significantly higher in females 3. Antidepressant use more common in females PSG: 1. No gender differences in the quantification of EMG activity during REM sleep 2. Females spent significantly more time in SWS and less stage 1 time than males 3. Behaviors during sleep in females were fewer than in males, although no gender differences were found in phasic or tonic activities Dream Enactment/ Content: 1. No significant gender differences in dream content, although: 2. Females have less dream-enacting behaviors, especially in movement-related dreams and falling out of bed	1. The first study to quantify EMG activity in males and females with RBD

DLB, Dementia with Lewy Bodies; EMG, Electromyography; ESS, Epworth Sleepiness Scale; F, Female sample; iRBD, idiopathic RBD; M, Male sample; MMSE, Mini-Mental State Exam; MoCA-J, Japanese version of Montreal Cognitive Assessment; MSA, Multiple System Atrophy; N, Total number of sample; PD, Parkinson's Disease; PLM index, Periodic Limb Movement index; PSG, Polysomnography, REM, Rapid Eye Movement; RBD, REM Sleep Behavior Disorder; RBDQ-JP, Japanese version of RBD Questionnaire; RBDQ-HK, Hong Kong version of RBD questionnaire; sRBD, secondary RBD; SST, Sniffin' Sticks Test.

treated with higher doses of levodopa (79); rs1113666 polymorphism of GAPDH gene was found to be a significant risk factor for PD, especially in male PwP (81); and A allele of rs7311174 and T allele of rs2072374 was reported to be protective in males (82). On top of this, male PwP with the APOE4 allele had steeper cognitive decline than female PwP groups, both with and without APOE4 (83), while association of rs12817488 with PD was reported only in females PwP (84), further reiterating the need to consider genes and sex differences in PD.

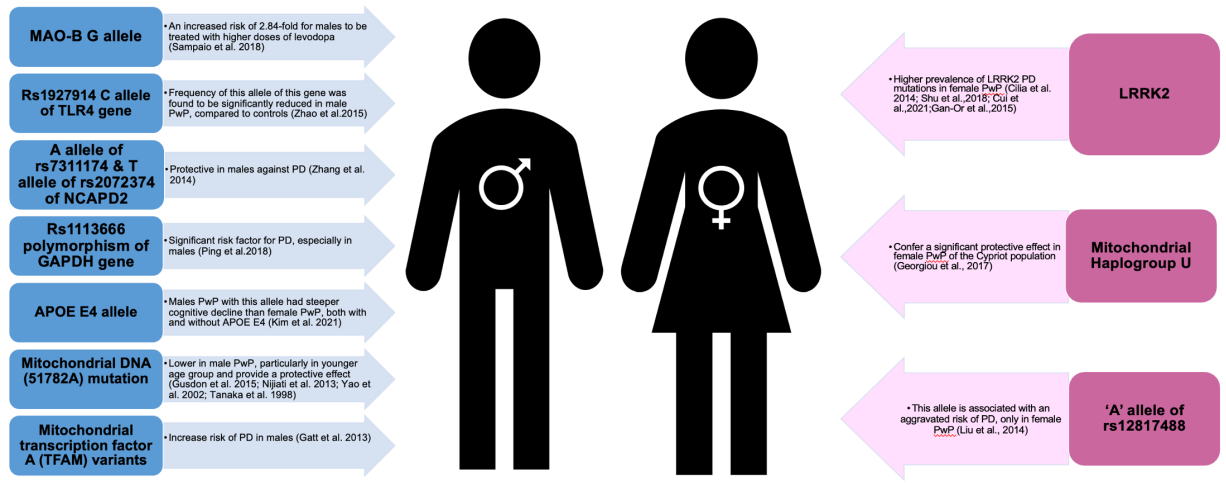

FIGURE 3
Schematic presentation of genes implicated in male and female patients with Parkinson's disease.

Biomarkers: Low uric acid (UA) levels have been consistently linked with an increased risk of PD and increased disease severity, particularly in male PwP (85–91). However, controversial findings were obtained when analyzes were stratified by age and estrogen levels (92). Notably, Cortese et al. showed a significant association between exposure to urate-lowering drugs in reducing PD risk in females in a higher age group (>70 years old) when there were higher UA levels premenopausally, but not in males (92). Based on these findings, there seems to be a sex-dependent predisposition of uric acid on nigrostriatal dopaminergic neurons and estrogen, which may confer beneficial neuroprotective properties in females, although further analyzes are warranted.

Another potential sex-specific biomarker for PD progression is serum homocysteine (93, 94). Elevated homocysteine levels displayed a sex-specific profiling of PD (93, 94). For instance, a positive association of elevated homocysteine with motor impairments (Unified PD Rating Scale (UPDRS)-III) in only male PwP ($p < 0.001$) and a negative association of elevated homocysteine with cognition only in female PwP ($p = 0.021$), further reiterating the distinct phenotypical sex-specific profiles of PD (93).

Metabolites and lipoproteins could also serve as sensitive biomarkers in identifying sex-specific profiles of PD (95–99). In lipid profiling studies, there is a mutual agreement on sex-specific lipid profiling and functioning in cognitive manifestations of PD (96, 97). For example, in female PwP, a positive association between hypertriglyceridemia and cognitive performance on the Frontal Assessment Battery (FAB) task was found ($p = 0.013$) and a negative correlation between triglyceride serum levels and cognitive performance on FAB task ($p = 0.005$) (96). However, in male PwP, a negative association was found between hypercholesterolemia and normal FAB performance and between high low-density lipoprotein cholesterol levels and FAB score ($p = 0.027$) (96), suggesting a differential functional role of lipids in sex-specific phenotype presentation of symptoms.

Biomarkers, such as alpha-synuclein, DJ-1 protein, and serum brain-derived neurotrophic factor (BDNF) levels, have also been expressed differently between sexes (100–102). Immunoenzymatic analyzes revealed lower plasma alpha-synuclein concentration levels in severe PD stages only in male PwP (100). This association is in line with more severe cognitive impairments, hallucinations, and sleep disorders, experienced by male PwP (100). Furthemore, DJ-1 protein levels was reported to be significantly higher by 1.7-fold in male PwP than male controls, suggesting a clear sex-specific biomarker of PD (101). In females, on the other hand, decreased BDNF levels were reported to be associated with females only among depressed PD patients, suggesting a sex-specific expression of biomarker and symptom profiling (102).

Sex differences in the expression of gut microbiome and immunological biomarkers have also been identified (103–105). In the first-ever metabolites profiling study using nuclear magnetic resonance (NMR), Baldini et al. analyzed 129 microbial metabolites through personalized metabolic modeling using microbiome data and genome-scale metabolic reconstructions of human gut microbes (103). The reported PD-associated microbial patterns were statistically dependent on sex, with *Paraprevotella genera* (a genus of bacteria) significantly influenced in female PwP (103). This was the first study to portray sex differences in the microbiome environment in PD, which supports the association of the gut-brain axis in immune response. Other analyzes of immune biomarkers in the stools of PD patients also reported a disease-related increase in numerous immune and angiogenesis mediators, only in stools of female PwP (106). This needs further research as monocyte response and phagocytic markers in PD have been reported to exhibit distinct sex-specific expression (104, 105, 107).

3.2.1. Clinical features

3.2.1.1. Motor symptoms

There is a general trend for severe motor impairment in male PwP than in females (108, 109). This is accompanied by an altered pattern of functional networks (e.g., sensorimotor networks), abnormal motor cortex measurements and lower dopaminergic binding in male PwP (110–112). In a recent study, Boccalini et al. investigated dopaminergic dysfunction according to PD-stratified clinical subtypes of motor

function (i.e., mild, intermediate, or diffuse-malignant) in *de novo* PD patients using the Parkinson's Progression Markers Initiative (PPMI) database (108). In mild motor and intermediate subtypes, they found that male PwP exhibited poorer cognitive performance than females, and those with motor impairments had lower dopamine binding in the putamen with more severe widespread connectivity alterations in the nigrostriatal dopaminergic neurons than female PwP (108). This dysfunction was also observed on a behavioral level (113, 114). For instance, in a 5-year longitudinal study, Picillo et al. reported that male PwP experienced a significantly higher longitudinal decline in self-reported motor symptoms, with a yearly increase in UPDRS-II by 0.57 relative to females (1.27 vs. 0.7, $p < 0.001$) (113).

Nonetheless, the findings of several studies suggest a more complex relationship between female hormones and motor symptoms in PD (115). For instance, in a study on female PwP, younger age of onset and higher Hoehn and Yahr (H&Y) stage were identified as risk factors of wearing off phenomenon, while younger onset age was associated with dyskinesia (115). Moreover, female PwP with wearing-off phenomenon and dyskinesia were shown to have higher levels of prolactin (115). It has been hypothesized that in some patients age onset and disease severity might override the neuroprotective benefits of female hormones.

Furthermore, motor symptoms tend to emerge later in female PwP and display a sex-specific phenotypical motor presentation (116, 117). Female PwP were more likely to experience reduced rigidity (116), tremor (117), and levodopa-induced dyskinesias (115, 118), while male PwP were reported to be more susceptible to later development of freezing of gait (119), and camptocormia (abnormal severe forward flexion of the trunk) (120).

3.2.1.2. Non-motor symptoms

Non-motor symptoms (NMS) consist of a wide range of symptomology spectrum and severity, such as cognitive deficits, sexual and urinary dysfunction, sleep, mood disorders and psychosis and odor discrimination (8, 53, 72, 113, 121–150). Despite methodological differences due to different screening tools being adopted, two trends emerged, (1) male PwP were more likely to experience severe non-motor symptoms, particularly in cognition, olfaction, sleep, speech problems, impulse control disorders (i.e., pathological gambling and hypersexuality), dementia, urinary and sexual dysfunction (113, 121, 125–127, 129, 131, 132, 136, 138–144, 151, 152) (2) female PwP were more likely to experience fatigue, higher pain levels, and psychosis and mood disorders (i.e., depression (153), anxiety) and impulse control disorders (i.e., binge eating and compulsive buying) (131–133, 139, 145–147, 151, 154–156).

The correlates of cognitive sex differences in healthy, neurotypical people remain poorly understood (157). It is thought that many biological and psychosocial factors act to modulate these cognitive abilities leading to mixed results in the scientific literature (157). Nonetheless, numerous studies have suggested that male sex may be a dominating risk factor for dementia and cognitive impairment (53, 121, 126, 142–144). In keeping, male PwP have been shown to develop a more rapid and severe cognitive decline by comparison to female PwP (53, 72, 113, 121). In a recent 5-year longitudinal study in *de novo* PD population, male PwP experienced a steeper decline in both motor ($p = 0.009$) and non-motor ($p = 0.009$) symptoms, with a yearly increase in self-assessed UPDRS I by a multiplicative factor of 0.98, as compared to 0.67 in female PwP (113). Sex differences were also noted in differential phenotypes of deficits in executive functioning (53, 121, 122, 126, 148, 149). Both healthy males and male PwP groups performed significantly worse than females in semantic verbal fluency and delayed recall, while healthy females and female PwP groups performed worse in visuospatial function (126).

Clear sex differences in sleep have also been reported (127, 128, 130). Male PwP were more likely to experience increased daytime sleepiness, higher motor impairment and lower mini-mental score in tandem with abnormal sleep-related motor-behavioral episodes (127, 128, 130). In line with this, RBD and PD studies have also shown that male PwP have a higher prevalence of RBD and display greater global cortical and subcortical gray matter atrophy even when compared with females in PD-RBD group (125, 126, 143, 158). This suggests distinct sex-specific heterogenous profiling of RBD and other sleep parameters in PD.

Across studies using different cohorts' groups, male PwP consistently presented with more prominent sexual and urinary dysfunction than females (8, 131, 150). For instance, Martinez-Martin et al. reported a lower prevalence of sexual dysfunction in female PwP (~28%) as compared to males (~50%). This could be due to distinct biological features between sexes (8). The autonomic nervous system itself is sexually dimorphic with differences in urinary tracts (159, 160), brain anatomy (161, 162), and genital system (163).

Female PwP, on the other hand, have been reported to have a higher prevalence of mood disorders such as anxiety, depression and apathy, as well as to have a heightened experience of fatigue and pain (130–133, 139, 145–147, 154, 155). Zhu et al. reported higher scores on the Hamilton Rating Scale for Depression (HAMD) domains of anxiety/somatization, and hopelessness in female PwP (154), perhaps indicative of the functional role of estrogen in mood regulation (164). Specifically, affective regulation has been linked to neural structures rich in estrogen receptors and estrogenic regulation of neurotransmitters. Interestingly, even in healthy women, studies have reported a higher incidence of depression (165, 166) and anxiety (167) during peri/menopause – a period of drastic reduction in estrogen levels, which have been reported to coincide with the onset of PD (168, 169). Conversely, it has been shown that hormone therapy may prevent mood disorders during this period, and while the exact mechanism remains unknown, there is compelling evidence that supports neuromodulatory and neuroprotective effects of estrogen, which are directly relevant to mood symptomatology (164). In future, it would be important to elucidate the nature of postmenopausal exogenous hormone formulations in relation to premenopausal endogenous levels, as well as the ratio of estrone to estradiol, all of which warrants urgent consideration to address these debilitating non-motor symptoms in female PwP during the peri/menopause (164).

Moreover, impulse control disorders in PD, described as aberrant behaviors such as pathological gambling, hypersexuality, binge eating, and compulsive buying, which typically occur as a result of dopaminergic therapy, have all variably been shown to sport variable phenotypic sex-related expressions, e.g., with pathological gambling and hypersexuality more prevalent in men, whereas binge eating and compulsive buying occur more frequently in women (170). In that background, and given that specific impulse control disorders share clinical, phenomenological and biological features with obsessive–compulsive disorder (171), it is of note that sexually dimorphic pattern of genetic susceptibility to OCD's clinical heterogeneity has been

recently demonstrated, potentially requiring different specific therapeutic strategies (172). Further research is warranted to validate sex as one of the important determinants of the heterogeneity of impulse control disorders in PwP.

Pain is also more frequently reported in female PwP (133, 146, 173, 174). The mechanisms underlying this, and other mood phenomena, remain unclear. Arguably, however, they may reflect differential effect of the alpha-synucleinopathy process on distinct pain/mood centers in the female brain. For instance, one of the neuroanatomical candidates may be the dysfunction of the circuitry involving the posterior bed nucleus of the stria terminalis (BNST). The BNST is the center of the psychogenic circuit from the hippocampus to the paraventricular nucleus, this circuit is important in the stimulation of the hypothalamic–pituitary–adrenal axis, and its dysregulation may lead to mood, pain and anxiety disorders, social dysfunction and psychological trauma (175). It is known that oestradiol exerts its effects in the canonical pathway through the transcription factor estrogen receptor-α, the neuronal targets of which include the BNST for a review see (176). The BNST, is a sexually dimorphic structure, commonly approximately 1.5–2 times larger in men, compared to women (176). Of note, atrophy of the BNST has been demonstrated in *de novo* PD (177), possibly suggesting that in women, who have smaller BNST, any such neurodegenerative process may have proportionally larger negative impact on affective processing of pain.

3.2.2. Interventions

3.2.2.1. Pharmacological

One commonly used first-line PD treatment is levodopa (178). Several patterns were observed in levodopa pharmacokinetics and treatment outcome between sexes (79, 173, 178–180). Female PwP were more susceptible ("brittle response") to levodopa-induced dyskinesia and wearing-off phenomenon (115, 118, 173, 181, 182). Studies into intra-and inter-individual variability in levodopa's pharmacokinetics (PK) reported sex-specific treatment responses (178). Conti et al. measured plasma levodopa concentrations and pharmacokinetic parameters (Area under curve (AUC), Maximum plasma concentration (Cmax), time to reach Cmax (Tmax), half-life (t1/2)) in levodopa-naïve and levodopa-treated PD patients (178). Interestingly, AUC and Cmax were significantly higher in female PwP than in males, with body mass index (BMI) significantly predicting t1/2 only in female PwP ($p = 0.027$) (178). It is worth noting that in this study, female PwP had a longer duration of disease (59 ± 24.5 months) than male PwP (34 ± 28.5 months).

UA-level modification may also offer a tailored sex-specific PD treatment (183). Previous studies consistently reported the association of lower serum UA with higher disease severity, particularly in male PwP (85–88). This sex-specific profiling of UA also extends to urate-altering drugs (183). Schwarzschild et al. conducted a randomized, double-blinded clinical trial of the Safety Urate Elevation in PD (SURE-PD) trial and found that inosine elicited higher levels of serum urate that were 50% greater in female PwP (3.0 mg/dL) than in male PwP (2.0 mg/dL). CSF urate was also significantly higher on mild (+87%, $p < 0.001$) or moderate (+98%, $p < 0.001$) inosine than placebo, only in female PwP (183). Regarding motor severity, slower UPDRS progression was related to an increase in serum urate ($p = 0.001$) and plasma antioxidant capacity ($p = 0.006$). No relationship was found in male PwP, suggesting a protective effect of underlying female sex steroids interplay with urate (183).

Targeting a non-dopaminergic system may be effective in ameliorating motor and non-motor fluctuations that arise when on levodopa (184). One such treatment is safinamide (185). Safinamide acts on the reversible inhibition of the monoamine oxidase-B (MAO-B) enzyme and modulation of excessive glutamate release (186). In a recent study on the efficacy of safinamide on PwP, Pellechia et al. reported improvements in the total UPDRS score were 43.5% in males versus 39.1% in female PwP (185), further providing support for sex-specific treatment response in PD.

Surgical: Deep brain stimulation (DBS), a neurosurgical procedure that involves electrical stimulation of the global pallidus internus (GPi) or subthalamic nucleus (STN), is an alternative treatment for PD, particularly in advanced PD (187). In terms of sex disparities and treatment outcomes, three trends emerged: (1) sex disparities in DBS selection, particularly in the undertreatment, referral and follow-ups of female PwP, (2) similar surgical outcomes postoperatively after DBS between sexes, although males were more likely to display lasting improvements and (3) quality of life postoperatively depend on sex-specific symptoms phenotype (187–193).

Gender-specific disparities in treatment accessibility and patients' behavioral approach to mitigating PD symptoms are a primary concern, particularly for healthcare professionals (187, 190). In a cross-sectional, pseudo-randomized study in the United Kingdom, female PwP were disproportionally underrepresented in referral compared to the general PD population ($p = 0.002$), although they were more likely to be approved for DBS than males ($p = 0.029$) (187). Furthermore, female PwP were less likely to undergo DBS due to their preference ($p < 0.001$), while male PwP were more likely to be lost to follow-up ($p = 0.046$) (190). In terms of behavioral approach, female PwP were more likely to express strong fear of complications and were more likely to consult with immediate family members prior to deciding on DBS (194).

Although there was no sex differences in postsurgical outcomes improvements right after DBS (187, 190, 195), in subsequent follow-ups, female PwP showed a trend toward worsening in bradykinesia after 1 year and a lower score in non-dopaminergic features after 10 years (196). Furthermore, a recent study has also identified male sex as a significant predictor of DBS-induced improvement in camptocormia and global postural angle (193). Despite that, interestingly, in a mortality study assessing PwP treated with DBS, only male sex and disease duration were significant predictors of mortality (197).

Another controversial aspect of gender disparities after DBS is the quality of life in PwP (198, 199). While the long-term effect and short-term effect of DBS are similar in cognitive function and depressive symptoms, at 5-year follow-up post-DBS, physical quality of life is significantly more improved only in male PwP ($p < 0.001$) but not in female PwP ($p = 0.409$) (198). Despite that, there are also reports that suggest that female PwP experience greater improvements in activities of daily life (ADL) and positive effects on mobility, stigma and cognition than males (199).

3.2.2.2. Quality of life

Despite the higher prevalence and disease severity in male PwP, there seems to be a trend of lower quality of life in multiple aspects of female PwP (156, 174, 200–206). This could be attributable to several

gender, societal factors and the nature of clinical manifestation that contribute to lower quality of life in female PwP (174, 200, 207). In an Israeli study, lower quality of life in female PwP was attributable to the higher prevalence of depression and pain, while male PwP's quality of life only worsened in advanced stages (174, 208). These findings align with studies conducted worldwide, in which severe anxiety, lower nutritional status, lower emotional well-being, higher stigma, and psychosocial functioning were the most robust features of poorer quality of life in female PwP (201–203, 205, 207). This suggests that societal expectations of gender role factors are crucial in disease management and interventions in PD.

Furthermore, other environmental factors such as living conditions and visitation/seeking-care behavior could also account for lower quality of life in female PwP (201, 209). Female PwP were more likely to live alone (18% had no caregivers, compared to 2.4% of males) (201). Even if they utilized care services, female PwP were more likely to use home health and nursing facility care more often. They had less outpatient physician contact than male PwP throughout PD (204). For effective delivery of treatment, these societal expectations and gender patterns of seeking help should be considered by clinicians.

3.3. Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) is the second most common neurodegenerative dementia among the elderly (210). Core clinical features of DLB include neuropsychiatric symptoms (i.e., visual/auditory hallucinations), parkinsonism, and cognitive impairments (i.e., deficits in memory and executive functions) (211). On a pathological level, DLB is characterized by the presence of Lewy bodies (i.e., neuronal inclusions of alpha-synuclein) with differing degrees of co-existing Alzheimer's disease (AD)-related pathology (i.e., amyloid plaques and neurofibrillary tangles (NFT)) (212, 213). In addition, it has been suggested that inflammation may also play an important role in DLB, for instance PET imaging and blood biomarkers support an increase in cerebral and peripheral inflammation in the early phases of DLB, while these features appear reduced with disease progression (214, 215). Numerous studies have reported a greater male predominance in the incidence, prevalence, and mortality, although these findings are inconsistent (216–221) (please see Table 5).

In a retrospective study on Parkinson's Disease Dementia (PDD) and DLB in China, DLB was found to be more common in women in the age group 60 to 69 years but more balanced in younger age groups (217). In contrast, for age groups older than 70 years, males have a greater prevalence of DLB than females (217). Further severity-stratified analyzes revealed that males were more likely to visit their physician when experiencing mild symptoms in both PDD (63.6%) and DLB (56.9%), while females were more likely to visit only when experiencing moderate to severe symptoms levels (217), reiterating the need for more focus on early stages of DLB in females.

Other studies on sex distribution in DLB show inconsistent findings of DLB incidence between sexes (216, 221). In a cross-sectional study of DLB, AD, PD, and PDD, Mouton et al. reported a slight predominance of females with DLB, particularly in those older than 75 years and the sex ratio with a preference for females increased with age (216). These inconsistencies in sex distribution findings of DLB could be due to three reasons. Firstly, most DLB diagnoses were made by clinical judgments rather than pathological results. Nelson et al. posited that clinically suspected DLB was more likely to be over-diagnosed in females, which might explain this variation in the prevalence of DLB in different studies (222). Secondly, DLB shares similarities in pathological and clinical characteristics with AD, which may result in a higher proportion of females being diagnosed as AD is predominantly associated with female sex (223–225). For instance, a recent study reported that females with DLB had a higher Braak tau staging and less nigrostriatal loss than males with DLB, despite having similar Lewy body staging with males with DLB (226). Thirdly, there is also a genetic component to DLB (227, 228). For example, a clinical cohort study reported the association of GBA mutations with early onset DLB and male sex, although these findings have been somewhat inconsistent (228, 229).

Sex differences have also been reported in the initial symptoms of DLB diagnosis (13). In the initial stage of clinical manifestations, females with DLB exhibited a significantly higher overall rate of psychiatric symptoms ($p = 0.009$), particularly in auditory hallucinations (AHs) ($p = 0.012$), while males with DLB had a higher incidence of RBD ($p < 0.001$) (13). These findings align with Tsunoda et al., in which AHs were significantly associated with female sex ($p = 0.04$) (230).

Visual hallucinations have also been reported in DLB, with different symptomatology profiling between sexes (231–233). Cumulative and 1-month frequency analyzes of visual hallucinations of DLB patients found that the contents of visual hallucinations frequencies of non-family people, passed families, and nonchildren families were significantly higher (231), and earlier in women with DLB than men (232). Additionally, both sexes had distinct predisposing factors associated with visual hallucinations (231). More specifically, older age ($p = 0.003$) and higher neuropsychiatric inventory (NPI) score ($p = 0.009$) were associated with women with DLB, while severe dementia stage ($p = 0.008$) and higher rates of antipsychotics ($p < 0.047$) were associated with men with DLB (231). Furthermore, in a factorial analysis using the European DLB consortium, Abdelnour et al. parsed DLB clinical presentations into four subtypes and reported a greater predominance of females with DLB with characteristics such as higher MMSE scores, cognitive fluctuations and cerebrovascular pathology (234). This could indicate a distinct phenotype of DLB between sexes and age groups, although this remains elusive (233, 234).

Understanding sex differences also have significant implications in identifying biomarkers, neuropathology and evaluating the efficacy of pharmacological interventions in DLB (226, 227, 235–238). Lower cerebrospinal fluid (CSF) alpha synuclein and CSF amyloid levels were reported in women with DLB, accompanied by distinct sex-specific characteristics, such as more frequent hallucination and lower scores on a cognitive task (236). This aligns with previous study by Wennstrom et al. who reported lower levels of CSF alpha synuclein and CSF orexin concentration, particularly in women with DLB, as compared to AD and controls (238). In other brain biomarkers, females with DLB have also been associated with greater white-matter hyperintensities (WMHs), further reiterating sex-specific biomarker profiles in DLB (237). Finally, in a recent study on medication use history, a differential preference of medications between sexes was reported, with second-generation antipsychotics such as risperidone associated with females with DLB, while olanzapine, escitalopram and

TABLE 5 Sex differences in Dementia with Lewy Bodies (DLB) studies from 2012 to 2022.

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Disease diagnosis: epidemiology, prevalence, demographics, survival rate					
Mouton et al. (216) French National Alzheimer Database A repeated, cross-sectional study	DLB AD PD PDD	DLB: $N = 10,309$ (80.11 ± 7.84) $M = 4,674$\u00B0F = 5,635 AD: $N = 135,664$ (81.42 ± 7.98) $M = 40,566$\u00B0F = 95,098 PDD: $N = 3,198$ (79.45 ± 8.09) $M = 1746$\u00B0F = 1,452 PD: $N = 8,744$ (73.86 ± 10.79) $M = 4,979$\u00B0F = 3,765	Demographics and Clinical Assessments: 1. Variables such as gender, age, living conditions, education level, type of center, and location of patients were collected 2. Cognition: MMSE 3. Sex ratio and demographic data were compared using multinomial logistic regression and a Bayesian statistical model	1. Sex ratios (female percent/male percent) were different across the four groups; DLB: 1.21 (54.7%/45.3%); AD: 2.34 (70.1%/29.9%); PD: 0.76 (43.1%/56.9%) and PDD: 0.83 (45.4%/54.6%) 2. There were significant differences between each group (including DLB), but not between PDD and PD, which had a similar sex ratio	1. Large sample size 2. Diagnoses were made by clinical judgment and not according to anatomopathological results 3. Data entry by different physicians
Gan et al. (217) Beijing, Tianjin, China Retrospective, clinical study	DLB PDD	DLB & PDD: $N = 455$ $M = 239$ (age onset = 69.2 ± 8.1) $F = 216$ (age onset = 68 ± 8.8)	Clinical Assessments: 1. Cognitive fluctuations: The Mayo Fluctuations Composite Scale 2. Visual hallucinations: NPI 3. Delusions and depression from Parkinsonism: UPDRS III 4. RBD: RBDSQ/ Video-PSG 5. MRI/PET/DAT	1. There were slightly more males than females with DLB (50.9%) and PDD (57.9%) 2. Patients with DLB had a poorer performance compared to those with PDD on the MMSE ($p = 0.001$), the MoCA ($p < 0.001$), the CDR ($p = 0.002$) and the MTA (p = 0.002).	1. Retrospective study design which could introduce recall bias 2. Diagnoses of the patients were not subsequently validated by autopsy, which is the gold standard for a diagnosis 3. Not all patients were diagnosed using the updated protocols – inconsistencies 4. Gender differences were only focused on the prevalence not in other domains within PDD and DLB
Savica et al. (218) Minnesota, USA Epidemiologic study	DLB PDD	DLB: $N = 64$ PDD: $N = 46$	1. Diagnostic criteria included two steps: the definition of parkinsonism as a syndrome and the definition of the different types of parkinsonism within the syndrome 2. Reliability and validity of diagnosis checks	1. The incidence rate of DLB was 3.5 per 100,000 per person-years overall, and it increased steeply with age 2. Patients with DLB were younger at onset of symptoms than patients with PDD and had more hallucinations and cognitive fluctuations 3. Males had a higher incidence of DLB than females across the age spectrum. The pathology was consistent with the clinical diagnosis in 24 of 31 patients who underwent autopsy (77.4%)	1. It is possible that some patients with mild symptoms might go unrecognized and hence undiagnosed 2. Some of the clinical features (e.g., cognitive fluctuations) were not systematically recorded in medical records 3. Cognitive status was not systematically studied in all patients with parkinsonism

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Price et al. (219) Cambridge, United Kingdom Retrospective study	DLB AD	DLB: *N* = 251 (age at diagnosis = 79.3 ± 7.6) *M* = 122\u00B0*F* = 129 AD: *N* = 222 (age at diagnosis = 80.2 ± 8.8) *M* = 83\u00B0F = 139	1. Case identification: Searches of diagnosed DLB on electronic records across an 8-year period 2. Demographics, clinical and temporal data extracted 3. Other information: Medications, mortality	1. Median survival was 3.72 years for DLB and 6.95 years for AD 2. Controlling for age at diagnosis, comorbidity and antipsychotic prescribing, the model predicted median survival for DLB was 3.3 years for males and 4.0 years for females	1. The retrospective nature of the study meant that accurate estimation of the timing of symptom onset was not possible, limiting the ability to report the duration of illness accurately 2. The findings of this study do not reflect the total populations with these diagnoses–diagnosis in a secondary care setting may reflect greater symptom
Boot et al. (220) Rochester, USA Retrospective study	DLB AD	DLB: *N* = 147 (age at diagnosis = 72.5 ± 7.3) *M* = 113\u00B0F = 34 AD: *N* = 236 (age at diagnosis = 74.9 ± 10.1) *M* = 90\u00B0F = 146 Controls: *N* = 294 *M* = 226\u00B0F = 68	1. Demographics and clinical history 2. 19 Candidate risk factors (i.e., family history, depression, diabetes)	1. Compared to controls, DLB patients were significantly more likely to have a history of anxiety, depression, a family history of PD, and carry APOE4 alleles but less likely to have had cancer 2. Compared with AD patients, DLB patients were significantly younger and more likely to be male, have a history of depression, be more educated, and have a positive family history of PD.	1. Relatively small sample size 2. Some reports of missing data
Abdelnour et al. (234) European DLB (E-DLB) Consortium A multicentre, international study	DLB	*N* = 107 (68 ± 8.7) *M* = 77\u00B0F = 30	Clinical, neuroimaging and CSF assessments: 1. Assessments for parkinsonism, visual hallucinations, RBD and other clinical core features 2. Atrophy: MRI 3. Amyloid-b and tau neurofibrillary tangles were assessed through CSF levels of AB42 and phosphorylated tau (p-tau) using enzyme-linked immunosorbent assays (ELISAs)	1. Hierarchical clustering identified 4 clusters: (1) Cluster 1 was characterized by amyloid-b and cerebrovascular pathologies, medial temporal atrophy, and cognitive fluctuations; (2) Cluster 2 had posterior atrophy and showed lowest frequency of visual hallucinations and cognitive fluctuations and the worst cognitive performance; (3) Cluster 3 had the highest frequency of tau pathology, showed posterior atrophy, and had a lower frequency of parkinsonism; (4) Cluster 4 displayed normal AD biomarkers, the least region brain atrophy and cerebrovascular pathology, and the highest MMSE scores 2. Cluster 4 showed a slight predominance of females, while the whole cohort was mostly constituted by males	1. Relatively small sample size

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Jones and O'Brian (221) Newcastle, Cambridge, United Kingdom Systematic review	DLB	Total of 31 studies included in this review	1. Literature review of all relevant population and clinical studies conducted using PubMed	1. Only eight prevalence studies included the sex of those with DLB 2. Five of these studies reported disproportionately more females with the disease when controlling for the sex of DLB population (271–275) 3. The three remaining studies reported disproportionately more males (276–278).	1. Need more representative samples 2. There is a need to increase the likelihood of accurate diagnosis on a case-to-case basis.
Genetics					
Gámez-Valero et al. (228) Barcelona, Spain Post-mortem, clinical cohort study	DLB	Post-mortem: DLB = 50 PD = 43 Controls = 34 Clinical cohort: DLB = 47 (75.8) Controls = 131 (72.3)	1. Post-mortem brain samples with clinical and neuropathological diagnoses were obtained from tissue bank 2. GBA Mutation Screening: 11 DNA fragmentations and sequencing	1. 16 GBA mutation carriers were identified, 5 of which were brains with pure DLB 2. The most common mutation, E326K, was strongly associated with pure DLB and PD with dementia 3. 3. GBA mutations were overrepresented in males and associated with earlier DLB onset	1. There is lack of consideration of other factors such as clinical characteristics and lifestyle factors
Liu et al. (229) Jilin, China Meta-analysis	DLB	Total of 14 studies included in this review	1. PubMed, Cochrane and EMBASE databases were used to retrieve related studies 2. The odds ratios and 95% confidence interval were calculated to determine the association between GBA and DLB and between GBA and the clinical characteristics of DLB	1. This meta-analysis confirmed that the GBA variant rate was significantly higher in DLB group than in the control group, as were the variant rates of L444P, N370S, and E326K, whereas the variant rate of T369M showed no significant difference between the groups. 2. The GBA variant group had a younger age of onset and lower MoCA score than the GBA non-variant group in DLB patients 3. There were no significant sex differences in GBA variants between sexes	1. Lack of consideration of other factors that might affect occurrence and severity of DLB such as education level, smoking history and living habits

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Clinical Features: Non-motor Symptoms					
Utsumi et al. (13) Hokkaido, Japan Retrospective, clinical study	Probable DLB	*N* = 234 (age at diagnosis = 79 ± 7.5) *M* = 101 (age at diagnosis = 78.6 ± 6.7) *F* = 133 (age at diagnosis = 79.2 ± 8)	Initial symptoms assessment by an interview with patients and caregivers in nine initial symptoms: 1. Cognitive impairment 2. Visual hallucinations 3. Parkinsonism 4. RBD (e.g., frequent shouting) 5. Depression 6. Auditory hallucinations 7. Delusions 8. Disturbance of consciousness 9. Syncope DLB-related symptoms at diagnosis, all the above (except cognitive impairment) and four symptoms: 1. Fluctuations in attention and arousal levels 2. Orthostatic hypotension 3. Constipation 4. Hyposmia	Initial symptoms findings: 1. A larger proportion of females than males initially present with psychiatric symptoms. 2. For all assessed psychotic symptoms, females had higher rates than males, and there was a significantly higher rate of auditory hallucinations in females than in males 3. RBD was significantly more frequent in male than female patients DLB-related symptoms at diagnosis: 1. There were significantly higher rates in males than females in the incidence of RBD 2. There was also a significant difference between males and females in RBD, parkinsonism, hyposmia and syncope (higher rates in males) at diagnosis 3. Females experienced significantly more auditory hallucinations than males	1. No PSG was used to confirm RBD
Chiu et al. (231) Taiwan, China Cross-sectional, longitudinal clinical study	DLB	*N* = 152 *M* = 87\u00B0F = 65	Demographics and Clinical Assessments: 1. Patients were interviewed by a trained neuropsychologist for the assessment of the NPI domain of hallucinations that included ratings on eight individual forms of hallucinations 2. CDR 3. Cognitive function: MMSE, CASI 4. UPDRS 5. Cumulative frequency, 1-month frequency and phenomenology of VHs were summarized and compared between females and males with DLB.	1. Females had a higher frequency of visual hallucinations of nonfamily people, passed families and nonchildren families. 2. After adjusting for age and dementia severity, factors associated with VHs among all patients with DLB were female gender, longer duration of psychiatric disorder, higher total NPI score, a higher caregiver burden score and higher rates of antipsychotics	1. Comparison of the factors associated with VHs DLB in this study is cross-sectional. Hence, we cannot speculate on the causal relationship of factors with dementia 2. Diagnostic criteria: lack of dopamine transporter uptake imaging until 2010, the revised consensus criteria were not available in the hospital for the first two years; therefore, a lower diagnostic rate for probable DLB may be observed

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Tsunoda et al. (230) Kumamoto, Japan Cross-sectional, retrospective study	DLB	$N = 124$ (78.3 ± 5.6) $M = 54$\u00B0F = 70	Screening/Assessment: 1. Routine laboratory testing: Vitamin B1, Vitamin B12, thyroid function 2. Cognitive function: MMSE 3. NPI 4. MRI/Computed tomography and single-photon emission computed tomography for cerebral perfusion Neuropsychiatric Symptoms: 1. Hearing impairment 2. Semi-quantitative interview with primary caregivers using NPI: Auditory hallucinations, visual hallucinations	1. 35.5% of patients had AHs, and 60.5% had VHs 2. 90.9% with AHs also had VHs 3. 90% of patients hear the AHs in the form of a soundtrack of the scene 4. The presence of AHs was significantly more likely to be associated with female patients and those with hearing impairments	1. Internal psychiatric symptoms such as AHs cannot be directly studied because of patients' incomplete recollection 2. Selection bias because of clinical diagnostic criteria for DLB – makes the prevalence of DLB patients with pure AHs lower than it is 3. Multiple comparison problem: Type I error
Bayram et al. (233) Data obtained from the NACC Neuropathology Data Set, Genetic Data, and Uniform Data Set (UDS) Case-controlled retrospective study	Pathological confirmed DLB	$N = 211$ $M = 156$ (age at last visit = 75.9 ± 8.4) $F = 55$ (age at last visit = 80 ± 8.7)	Before death: 1. CDR-SOB 2. NPI-Q 3. UPDRS-III 4. Clinician report of DLB core features (i.e., cognitive fluctuations, VHs) at any visit during data collection Autopsy: LB pathology staging 1. Thal phase (amyloid-B plaque score) 2. Braak tau stage (neurofibrillary tangle stage) 3. CERAD (neuritic plaque score) 4. Level of substantia nigra	1. Females were more likely to die older, have fewer years of education, and had a higher tau burden 2. Females were also less likely with dementia and clinical DLB 3. Females reported lesser VHs than males	1. This study used a relatively small sample size of participants with limbic or neocortical stage LB pathology without cognitive impairment 2. No consideration of medications being taken for motor, behavioral, and cognitive symptoms 3. Pathological assessments recorded did not focus on regional severity – need finer grain comparisons

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Symptomology: non-motor symptoms; sleep					
Choudhury et al. (232) Minnesota, USA Longitudinal clinical study at the Mayo Clinic Alzheimer's Disease Research Center (ADRC)	DLB	*N* = 488 (age at first visit = 73) *M* = 370 (age at first visit = 72) *F* = 118 (age at first visit = 75)	Clinical assessments: 1. The clinician obtained information regarding each core feature's presence or absence 2. Recurrent episodes of dream enactment behavior during sleep with movements that appeared to match dream content Parkinsonism neurological examination: 1. Parkinsonism severity: UPDRS 2. 4-item Mayo Fluctuation Scale for cognition 3. GLDS 4. Cognition: MMSE and DRS Neuropathological examination	1. RBD is more apparent at a younger age in males than in females 2. Males were more likely to develop RBD before the onset of cognitive symptoms, while females were more likely to develop RBD and cognitive symptoms within the same time frame 3. Females met clinical criteria for probable DLB at an older age and after a longer latency from cognitive onset 4. Only half of the females in this study reported a history of RBD, compared to 84% of the males 5. At initial visit, females were older and more cognitively impaired than males 6. Females were also more likely to have visual hallucinations than males. 7. In males, the clinical cohort and autopsy subset showed that visual hallucinations were more likely to emerge after the other core features in men, while females did not demonstrate this time lag	1. This study was carried out in a tertiary care setting with referral patterns that may limit generalizability to other settings 2. This study did not include biomarkers, clinical symptoms
Mechanisms: inflammatory responses, brain structures etc.					
Van de Beek et al. (236) Amsterdam, Netherlands; Amsterdam Dementia Cohort Retrospective, clinical study	DLB	*N* = 223 *M* = 184 (67.7 ± 7.3) *F* = 39 (70.1 ± 6)	Clinical and cognitive features: 1. Hallucinations: NPI 2. Neurological examination: i.e., tremor/bradykinesia and/or rigidity 3. Semi-structured patient history interview 4. RBD 5. Depression: GDS 6. MMSE 7. Memory: Verbal learning test (RAVLT) 8. Attention and speed: TMT-A, TMT-B Apolipoprotein E genotyping 1. QIAamp DNA blood isolation kit CSF Analysis	1. Females had lower CSF alpha-synuclein and CSF AB42 levels compared with male 2. Females were significantly older, had a shorter duration of complaints, more frequent hallucinations and scored lower on MMSE and fluency task 3. No significant differences were found for fluctuations, RBD, parkinsonism, other cognitive tests, or tau concentrations	1. Well-defined, large sample of DLB patients with a clinical diagnosis of DLB supported by DAT 2. Retrospective design – not all features reported for all patients 3. CSF total alpha-synuclein is not yet validated as a clinically useful marker in DLB – there may be differences in sensitivity between different alpha-synuclein species 4. A small number of patients had normal DAT imaging, which is not supportive of DLB diagnosis, but clinical diagnosis made in tertiary centers

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Ferreira et al. (227) Multicentre cohort (Combination of E-DLB and the Mayo Clinic DLB Cohort) Prospective study	DLB	*N* = 417 *M* = 287 (70.2 ± 8.6) F = 129 (72.5 ± 8.2)	Demographics and clinical assessments: 1. Medical history review, informant interview, neurological examination, and neuropsychological assessment (i.e., MMSE) B-amyloid and tau biomarkers: 1. B-Amyloids (A+) and tau NFT (T+) were measured with CSF biomarkers and PET imaging 2. Patients were stratified into 4 groups: A-T-, A + T-, A-T+, and A + T+	1. The percentage of A-T-decreased with age, and A+ and T+ increased with age in both males and females 2. A+ increased more in APOE e4 carriers with age than in noncarriers 3. A+ was the main predictor of lower cognitive performance when considered together with T+ 4. T+ was associated with a lower frequency of parkinsonism and probable RBD 5. A + T+ was more common in females than males compared with the A − T− and A − T+ groups.	1. Multicentre study added the value of increased statistical power and ability to generalize the findings
Bayram et al. (226) NACC Uniform Data Set (UDS) Retrospective study	DLB	*N* = 691 *M* = 468 (Age at last visit = 76.4 ± 8.9) *F* = 223 (Age at last visit = 79.9 ± 10)	Clinical and neuropathological assessments: 1. Males and females were divided into two groups based on the staging of LB and AD pathologies 2. CDR-Dementia Staging Instrument-Sum of Boxes 3. Thal phase (amyloid-B plaque score), Braak tau stage (neurofibrillary tangle stage) and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) score (neuritic plaque score)	1. Females with more severe AD copathology and tau had worse cognitive decline and higher likelihood of AD clinical phenotype than males 2. Males with more severe AD copathology had lower likelihood of LB clinical phenotype than females 3. Interaction of sex and pathology was more prominent in those aged between 70 and 80 years	1. Analyzes included only clinician reports of LB core clinical features, because of significant amounts of missing data for other features that may help with clinical identification of LB disease 2. Clinical diagnosis and cognitive status of NACC were determined by a single clinician, a group of clinicians or an *ad hoc* consensus group which may include a combination of detailed examination
Sarro et al. (237) NACC; Rochester, USA Retrospective study	DLB AD Dementia	DLB: *N* = 81 (Age at MRI = 72 ± 8) *M* = 67\u00B0F = 14 AD Dementia: *N* = 240 (Age at MRI = 75 ± 10) *M* = 135\u00B0F = 105	Clinical and neuropathological assessments: 1. MMSE, DRS, CDR-Sum of Boxes, UPDRS-III, Mayo Fluctuations Questionnaire 2. Neuropathology assessment: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) MRI	1. DLB patients had a higher white matter hyperintensities (WMHs) volume compared to controls, and WMH volume was higher in the occipital and posterior periventricular regions in DLB compared to AD 2. Female sex and older age were associated with higher WMH volumes in both DLB and AD dementia groups	1. Relatively smaller sample size 2. There is lack of consideration of other clinical characteristics and lifestyle factors

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TABLE 5 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Wennström et al. (238) Malmö, Sweden Retrospective study	DLB AD	DLB: $N = 18$ (74 ± 7) AD: $N = 26$ (73 ± 6) Non-demented controls: $N = 24$ (72 ± 8)	Clinical assessments and CSF profile: 1. Demographics and neuropsychological assessments (i.e., MMSE) 2. a1-antichymotrypsin (ACT) concentrations in CSF and the basic CSF AD-biomarker profile (AB1-42, T-Tau, P-Tau181) 3. CSF Orexin samples were determined using radioimmunoassay 4. CSF alphasynuclein was determined using enzyme-linked immunosorbent assay (ELISA)	1. There was a decrease in CSF orexin concentrations in DLB as compared to AD patients and controls. The observed differences in orexin levels were found to be specific to females with DLB patients 2. Females with DLB also exclusively displayed lower levels of alphasynuclein compared to AD patients and controls 3. Orexin was associated to alphasynuclein and total Tau in female non-demented controls whereas associations between orexin and AB1-42 concentrations were absent in all groups regardless of gender	1. Very small sample size
Interventions: pharmacological					
Agbomi et al. (235) South Carolina, USA: PRISMA Health Registry Retrospective study	DLB PDD	DLB: $N = 608$ $M = 332$ (75.93 ± 9.18) $F = 276$ (81.74 ± 9.24) PDD: $N = 7{,}594$	From PRISMA Health registry: 1. Cognition: MMSE, MoCA, Saint Louise University Mental Status Examination 2. History of alcohol, tobacco, and length of stay in the hospital 3. Medication use: ChEIs, SGAs, or SSRIs	1. ChEIs, including donepezil, galantamine, and rivastigmine, were associated with DLB 2. SGAs such as risperidone were associated with females with DLB 3. Olanzapine, escitalopram, and tobacco use were associated with males with DLB	1. Data entry by different physicians – no external validation that standard criteria were met 2. No differentiation was made for patients with early and late DLB 3. PRISMA patients are not fully representative of the total DLB/PDD population 4. No outcomes of tests mentioned, i.e., MMSE 5. Retrospective study

AD, Alzheimer's Disease; CASI, Cognitive Abilities Screening Instrument; ChEIs, Central Acetylcholinesterase inhibitors; CDR, Clinical Dementia Rating; CSF, Cerebrospinal Fluid; DAT, Dopamine Active Transporter; DLB, Dementia with Lewy Bodies; DRS, Mattis Dementia Rating Scale; F, Females; GDS, Geriatric Depression Scale; GLDS, Global Deterioration Scale; LB, Lewy Body; M, Males; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, Magnetic Reasonance Imaging; N, Total Sample Size; NPI, Neuropsychiatric Inventory; PET, Positron Emission Tomography; PD, Parkinson's Disease; PDD, Parkinson's Disease Dementia; PSG, Polysomnography; RBD, Rapid Eye Movement Behavior Disorder; RBDSQ, REM Behavior Sleep Disorder questionnaire; SGAs, Second Generation Antipsychotics; SSRIs, Selective Serotonin Reuptake Inhibitors; TMT, Trail Making Test; UPDRS, Unified Parkinson's Disease Rating Scale; VHs, Visual Hallucinations.

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tobacco use were associated with males with DLB (235). The pathomechanism behind this diversity is currently unclear.

3.4. Multiple system atrophy

Multiple system atrophy (MSA) is an uncommon progressive neurodegenerative disorder characterized by autonomic failure and motor involvement of parkinsonism (MSA-P) or cerebellar ataxia (MSA-C) (11, 239). Autonomic failure in MSA includes orthostatic hypotension, constipation, and sexual and urinary dysfunction (239). In MSA, an astrocytic and microglial activation, along with a significant change in the expression of a subset of inflammation-associated genes, have all been reported in the MSA brain, suggesting that targeting inflammation-related processes might limit the disease progression (240, 241). Sex differences in MSA have been reported in many studies focusing on gender distribution, survival, and clinical features studies (11, 242, 243) (as summarized in Table 6). MSA is known to be more prevalent in men (11, 244), however, other studies focusing on sex-differences report oppositional findings. For instance, some studies quote longer survival in women (11, 242), others report longer survival in men (243, 245, 246) or no differences between sexes (247–253).

Several differences have been similarly reported regarding clinical presentation at disease onset (11). Women with MSA are more likely to have motor symptoms at onset, while men are more likely to experience severe autonomic symptoms (11). Men with MSA are also more likely to have orthostatic intolerance ($p = 0.0156$) and early

TABLE 6 Sex differences in Multiple System Atrophy (MSA) from 2012 to 2022.

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Demographics, clinical features, and mortality					
Coon et al. (11) Minnesota, USA Retrospective clinical study	MSA-P MSA-C	$N = 685$ $M = 356$ (age onset = 60.6 ± 9.8 $F = 329$ (61.3 ± 9.3) Alive = 100 $M = 52$\u00B0F = 48	1. Information of patients' demographics (i.e., Age onset), clinical features (i.e., ataxia, dream enactment, parkinsonism) and autonomic tests (i.e., Systolic blood pressure) were obtained 2. Living patients were called and examined for symptoms development since last neurologic examination	There are sex and gender differences in MSA in terms of symptoms onset, presentation, and survival: 1. Symptoms: Females were more likely to have a motor onset of symptoms than males. Males were more likely to have autonomic symptoms at onset, which is more severe 2. Age onset: Females were more likely to receive a diagnosis of MSA earlier than males 3. Survival: The difference in time of diagnosis to death is almost one year between males and females, with 3.6 months benefit in females (using a cohort of patients who had died data) Other clinical features: 1. Urinary dysfunction: Less severe urinary dysfunction in females 2. Sexual dysfunction: Rarely addressed in females	1. The retrospective nature of this study with different providers makes it hard to ascertain patient reporting of symptoms relating to confounding sex-specific factors such as childbirth, menopause etc. 2. Using a large number of patients and standardized questionnaires helped reduce bias and statistical power.
Coon et al. (253) Minnesota, USA Retrospective, clinical study	MSA-P MSA-C	$N = 685$ (60.9 ± 9.6) $M = 355$\ u00B0F = 330	Demographics and clinical assessments: 1. Motor and autonomic symptoms were obtained from recorded clinical history, neurological examination, and standardized patient-completed symptom questionnaire 2. Autonomic testing: Autonomic Reflex Screen 3. Survival data were obtained from the clinical record Imaging: 1. MRI scan	1. Neither MSA subtype, classification as probable or possible MSA, nor sex was significantly associated with survival	1. Retrospective nature of this study 2. Patients were seen by different providers over a long time, which may account for a difference in the recording of symptoms

(Continued)

TABLE 6 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Clinical Features: Non-motor Symptoms; Cognition					
Cuoco et al. (258) Salerno, Italy Case-controlled prospective, longitudinal clinical study	MSA-P MSA-C	Start: *N* = 55 *M* = 29 (61.79 ± 8.43) *F* = 26 (62.57 ± 7.51) After one year: *N* = 26/55 Attrition = 29/55 (10 died (4 M, 6F), 19 were unable to return due to worsening of disease (11 M, 8F)	Neuropsychological and neuropsychiatry battery at the start and after one-year follow-up: 1. UMSARS 2. MoCA 3. Memory: Rey auditory verbal learning test (15-RAWLT), the prose memory test, and recall of Rey-Osterrieth figure 4. Attention: TMT-A and Stroop color word test 5. Executive function: Clock design test, SVF, and the copy of Rey-Osterrieth figure 6. Visuospatial: Constructional apraxia test and BJLO 7. Language: two subtests from ENPA, the non-word repetition test and the hearing comprehension test of sentences 8. Functional autonomy: IADL, ADL 9. Mood: BDI-II, AES	At baseline: 1. Females with MSA had lower performance on global cognition abilities and visuospatial abilities 2. Females with MSA exhibited a higher prevalence of depression and apathy than males At follow-up: 1. Females with MSA deteriorated more than males in attention abilities and motor functions and had a higher prevalence of depression than males 2. Mild Cognitive Impairment was more pronounced in females than males 3. Females with MSA deteriorated more than males over time for motor functions and attention	1. Small sample size 2. The attrition rate at follow-up is high 3. No account of any sex hormones or menstrual cycle in females' hormones
Clinical Features: Non-motor symptoms; Others					
Yamamoto et al. (12) Chiba, Japan Retrospective, clinical study	MSA-P MSA-C MSA-mixed	*N* = 66 (62.2) *M* = 39\u00B0F = 27	Patients responded to a urinary symptoms questionnaire and underwent urodynamic examination twice: 1. Urinary Symptoms Questionnaire 2. Urodynamic Examination 3. EMG: Performed standard EMG and a motor unit potential (MUP) analysis using an EMG computer, inserted into the most superficial layer of the anal sphincter muscle	1. There were significant sex differences in reduced urine flow, increased post-void residuals, and decreased contractility at the second examination. 2. At the first examination, night-time urinary frequency and voiding symptoms were significantly more severe in males than in females; however, at the second examination, except for urinary urgency, sex differences were not observed for any other symptoms 3. Urodynamic examination: the degree of detrusor contraction was significantly less in males at the first examination. At the second examination, no significant differences were found in the urodynamic examination	1. Selection bias: It is known that MSA patients ultimately become bedridden and need urethral catheterization. However, it is not possible to examine such patients 2. The urodynamic examination is the only application to assess MSA patients whose daily living is not severely impaired 3. Not much validation in the urodynamic measure used

(Continued)

TABLE 6 (Continued)

Author/year country type of study	Subtype	Sample size	Methods	Main findings	Critical evaluation
Mechanisms: Biomarkers, neurochemical or Inflammatory responses					
Chen et al. (259) Guangzhou, China Cross-sectional clinical study	MSA-P	MSA: $N = 47$ (58.74 ± 10.18) $M = 31$\u00B0F = 16 Controls: $N = 50$	Clinical Assessments: 1. UMSARS 2. Detailed motor examination 3. Global disability scale (IV) 4. H&Y & ADL 5. Webster scale: Assess the degree of motor disability 6. Non-motor symptoms: NMS and PDSS 7. MMSE: Cognitive abilities Blood Sampling - Serum levels of: 1. Hcy 2. UA 3. CRP	1. Serum Hcy was found to be higher in MSA patients compared to healthy controls, especially in male patients 2. Serum UA was found to be lower in MSA patients when compared to healthy controls, especially in males 3. Levels of Serum Hcy were positively associated with the severity of MSA, such as movement dysfunction, declined cognition, and cardiovascular symptoms	1. Small sample size 2. Most patients with MSA are at the early stages of the disease – not representative 3. No consideration of sex factors (hormones) or genetic factors
Cao et al. (260) Sichuan, China Clinical, longitudinal study	MSA-C MSA-P	MSA: $N = 234$ $M = 121$\u00B0F = 113 Controls: $N = 240$ Follow-up (longitudinal): $N = 107$ $M = 56$\u00B0F = 51	1. Clinical information including gender, age, BMI, histories of hypertension and diabetes mellitus (i.e., UMSARS) 2. Fasting serum uric acid concentrations of the MSA patients and controls were measured in the clinical laboratory	1. Serum acid levels were lower in all MSA patients than that in controls. However, in a gender-specific analysis, this difference was only found in males compared with controls 2. However, the serum uric acid levels were not associated with either increased or decreased occurrence of MSA in females Longitudinal study: 1. The level of uric acid, age, disease duration at initial visit, BMI, gender, and the subtype of MSA did not significantly correlate with the mean rate of annualized changes in the UMSARS	1. Case controls design – results did not reflect the longitudinal effects of uric acid

ADL, Activities of Daily Living; BDI-II, Beck Depression Inventory-II; BJLO, Benton's Judgment of Line Orientation; BMI, Body Mass Index; CRP, C-reactive protein; EMG, Electromyography; F, Females; Hcy, Homocysteine; H&Y, Hoehn and Yahr Scale; M, Males; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MRI, Magnetic Resonance Imaging; MSA, Multiple System Atrophy; N, Total Sample Size; NMS, Non-Motor Scale; PDSS, Parkinson's Disease Sleep Scale; SVF, Semantic Verbal Fluency Test; TMT, Trail Making Test; UA, Uric Acid; UMSARS, Unified Multiple System Atrophy Rating Scale.

catheterization ($p = 0.0396$), which may contribute to worse survival rates (11, 247, 251, 254). The distinct symptoms at onset may prompt women to seek an earlier referral to a neurologist, which could explain an earlier diagnosis of MSA in women (11). Women with MSA were also less likely to experience severe urinary and sexual dysfunction (11, 12, 255). However, there is also a possibility that these autonomic symptoms, such as urinary and sexual dysfunction, are underdiagnosed in women. For example, sexual dysfunction was addressed differently, with a significantly higher number of male patients with documented sexual dysfunction ($p = 0.0001$) than female patients (11). This could be due to a lack of appropriate scales for measuring sexual and urinary dysfunction in women (256, 257).

In line with other subtypes of alpha-synucleinopathies, sex differences in other non-motor symptoms and biomarkers in MSA also displayed a distinct sex-specific phenotype (258, 259). In cognitive abilities of MSA patients, Cuoco et al. demonstrated that at the start of the study, women with MSA had significantly lower performance on global cognitive abilities, language, visuospatial ability, and attention (258). Additionally, at follow-up, women with MSA deteriorated more than men with MSA, particularly in motor functions and their attention abilities, and they had higher prevalence of depression (258). Mirroring this, elevated serum homocysteine levels and lower UA levels have also been reported MSA patients, particularly in males (259, 260). Furthermore, these markers are positively correlated with the severity of MSA, such as movement dysfunction and declined cognition (259). This further corroborates the notion of sex-specific profiling in alpha-synucleinopathies.

4. Discussion

We have critically analyzed a body of work to date that investigated sex and gender differences in alpha-synucleinopathies. Our findings simultaneously demonstrate (1) a scarcity of studies that systematically focused on sex and gender differences, and (2) clear phenotypical differences in multiple aspects of alpha-synucleinopathies, solely driven by sex and gender differences. In addition, very little appears to be known about the specific interplay of various sex hormones in

humans. Moreover, past clinical studies predominantly focus on the role of estrogen, and its potential protective role against the process of alpha-synucleinopathy, the argument for this is somewhat supported by higher incidence of PD in peri/and menopausal period (168, 169, 261). In preclinical studies, oestradiol and progesterone manipulation in ovariectomised, or gonadectomised mice, has demonstrated distinct sex differences in multiple aspects of alpha-synucleinopathy process (17, 262–267). Importantly, several of these animal models suggest that estrogen deprivation may results in dopaminergic neuron loss and lower dopaminergic binding (268).

Clinical studies on estrogen replacement therapy demonstrate a clear role for the estrogen in improving motor symptoms in post-menopausal women (269, 270). Nevertheless, many pieces of this pathomechanistic puzzle are missing; we are yet to clarify the importance of endogenous versus exogenous estrogen exposure, the causality of estrogen effects on multiple aspects of a disease (i.e., genetics) and the interplay between hormonal changes and the progression of alpha-synucleinopathies. Moreover, the threshold, the time-window (e.g., perimenopause versus postmenopause), and all other potentially modifying factors, to which estrogen confer a neuroprotective effect, remain unknown.

Similarly, there are several methodological caveats that should be considered while evaluating preclinical and clinical studies, all of which are rarely systematically considered in their translational importance. For example, in majority, if not in all, analyzed clinical and preclinical studies, there is a lack of focus on the synergistic and antagonistic effects of different sex hormones on various aspects of alpha-synucleinopathies. Most studies predominantly focus on one specific hormone (i.e., estrogen/progesterone), which makes it impossible to fully understand the pathomechanistic complexity. Additionally, even in clinical studies that included multiple hormone measures, women were frequently excluded (46, 47). Moreover, the stage of their menstrual cycle (e.g., follicular versus luteal stage, or and other endocrinology measures was rarely reported).

In conclusion, there is urgent need for future prospective multi-center studies that will account for a more integrated, representative account of sex differences in alpha-synucleinopathies. We suggest that the ideal research framework should systematically account for (1) a specific subtype and distinct phenotype of alpha-synucleinopathies (2) ethnicity and geographical location, (3) disease progression, rate and severity (i.e., early versus late onset), (4) monitoring menstrual cycle and endocrinology health in women, (5) direct quantification of sex hormones in both sexes, (6) medication history and responses (i.e., hormones replacement therapy) and (7) consideration of societal, cultural and gender factors that could impact treatment of PD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

KR selected and reviewed. KR and GD assessed all the eligible studies. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1204104/full#supplementary-material

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Type A personality, sleep quality, and cerebral small vessel disease: investigating the mediating role of sleep in a community-based study

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Purpose: Type A behavior pattern (TABP) is a personality type characterized by rapid speech, impatience, competition, and hostility. Asymptomatic cerebral small vessel disease (CSVD) is often endemic in older adults. Individuals with TABP commonly experience suboptimal sleep quality, and a correlation exists between sleep disturbances and CSVD. We investigated the relationship between TABP and CSVD markers and further explored the mediating role of sleep quality in the relationship between TABP and CSVD.

Methods: A cross-sectional survey included 764 community-dwelling adults aged 55–85 years. The TABP Scale and the Pittsburgh Sleep Quality Index (PSQI) were used to assess personality and sleep quality, respectively. Linear and logistic regression analyses were used to examine relationships between variables of interest. In addition, mediation analyses with bootstrapping were used to test whether sleep quality mediated the relationship between TABP and CSVD.

Results: Of the 764 participants [median age 65 (61–69) years, 59.9% female], the population with type A personality accounted for 44.8%. After adjusting for covariates, TABP scores ($p = 0.03$) and PSQI scores ($p < 0.001$) were significantly correlated with CSVD. In addition, sleep quality partially mediated the association between type A behavior and CSVD, and the mediating effect was 10.67%.

Conclusion: This study showed that type A behavior was a risk factor for CSVD among older community-dwelling adults and that sleep quality mediated the relationship between type A behavior and CSVD. Changing type A behavior may help improve sleep quality, which may in turn reduce the prevalence of CSVD.

KEYWORDS

cerebral small vessel disease, type A behavior pattern, sleep quality, mediation effect, white matter hyperintensity

1. Introduction

Cerebral small vessel disease (CSVD), common in the elderly, is a complex disease characterized by clinical, imaging, and pathological manifestations associated with small blood vessels in the brain (1). The imaging markers of CSVD include white matter hyperintensity (WMH), lacune (LA), enlarged perivascular space (EPVS), and cerebral microbleed (CMB) (2).

Furthermore, CSVD may lead to adverse health events, including stroke, urinary disorders, dementia, and gait disturbances. Given that the population is aging, the burden of CSVD will increase rapidly. Therefore, it is urgent to clarify the pathogenesis of CSVD.

Type A behavior pattern (TABP) is an emotional complex characterized by time urgency, impatience, competition, and hostility and has high stability over the lifetime (3). Additionally, TABP may lead to sleep disturbances (4), mood disorders (5), and fall risk (6). Prior studies have also found that TABP is associated with cardiovascular disease (7) and multiple sclerosis (8). However, to the best of our knowledge, no study has examined whether TABP is associated with neuroimaging features of CSVD.

Physiological sleep is characterized by a cyclical progression of non-rapid eye movement (NREM) and rapid eye movement (REM) phases. NREM is characterized by a gradual reduction in neural sympathetic activity with parasympathetic predominance. Autonomic function during REM is comparable to that during wakefulness. Sleep disorders may have an impact on the autonomic nervous system, systemic hemodynamics, and endothelial function (9). Obstructive sleep apnea (OSA) is a prevalent primary sleep disorder, characterized by frequent episodes of upper airway obstruction during sleep and resulting in significant sleep fragmentation and deprivation (10). There is a potential causal association between OSA and hypertension, atherosclerosis, stroke, obesity, and metabolic syndrome (9).

Poor sleep is a common health problem in older adults. The quality of sleep affects both physiological and psychological processes in the body, and vice versa (11). A study demonstrated a significant correlation between physical activity, dietary habits, and sleep quality among athletes (12). Aerobic exercise has a beneficial impact on the sleep quality of individuals who are obese (13). In addition, there is a correlation between cognitive performance and sleep, both of which affect personality. One study showed that athletes may experience cognitive impairment as a result of partial sleep deprivation (14). Recently, several studies have demonstrated that insomnia, sleep apnea, and other sleep-related problems are positively related to CSVD characteristics, especially WMH (15, 16). In addition, prior research suggests that adults with TABP tend to have trouble falling asleep, experience more nightmares, and sleep less in comparison with those with type B behavior patterns (4). These studies suggest that sleep quality is associated with type A behavior and CSVD independently; however, the relationship between type A behavior, sleep quality, and CSVD is unclear.

In this study, we hypothesized that poor sleep quality would mediate the association between TABP and CSVD. A significant mediation effect would suggest that TABP contributes to the risk of CSVD due to sleep quality.

2. Materials and methods

2.1. Study population

The study population was selected from an ongoing community-based prospective cohort project aimed at investigating sporadic CSVD in the elderly population of Wuhan, China. The selection criteria for this project were based on previous cohort studies on CSVD (17–19). CSVD is a disease that exhibits age-related characteristics, and its incidence demonstrates an upward trend with increasing age. Therefore, the inclusion criteria were as follows (20): (1) aged 55–85 years; (2) able to complete the self-reported written questionnaire; (3) willing to participate in this study and provide informed consent. The cohort project aimed to investigate imaging biomarkers, cognitive function, gait performance, and emotional status in the elderly population with sporadic CSVD. Therefore, the exclusion criteria were as follows (21): (1) Parkinson's disease, Alzheimer's disease, or other neurodegenerative diseases; (2) severe mental disorders such as major depression and schizophrenia; (3) non-vascular diseases causing white matter lesions, carbon monoxide poisoning, multiple sclerosis, and adrenoleukodystrophy; (4) presence of cerebral hemorrhage, subarachnoid hemorrhage, intracranial space-occupying lesions, or acute ischemic cerebral infarction; (5) life expectancy < 3 years; (6) unable to complete the magnetic resonance imaging (MRI) examination due to MRI contraindications. We recruited the elderly population of the community through leaflet distribution, media publicity, and door-to-door outreach efforts. The head MRI and questionnaire assessment were completed within 1 day. A total of 764 community residents participated in this study. This study was approved by the Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (No. 2019-S105).

2.2. TABP and sleep quality assessment

TABP was measured using the Chinese version of the TABP scale (22). The TABP scale, developed by the National Collaborative Group on Psychosomatic Medicine, consists of 60 items where participants are asked to answer "yes" or "no" to each item (5). The scale consists of three dimensions. First, the time hurry (TH) dimension reflects a sense of time urgency and speed of work. Second, the competition and hostility (CH) dimension represents competitiveness, hostility, and impatience. Third, the lie dimension score ≥ 7 indicates that the results of the scale are invalid (5). The overall score is significantly positively correlated with type A personality (5). A total score of ≥ 27 indicates TABP (22). Internal consistency reliability for the Chinese version of the TABP scale was 0.98, indicating good discriminant validity (22). Sleep quality was assessed using the Chinese version of the Pittsburgh Sleep Quality Index (PSQI) (23). The PSQI scale consists of 19 items, with a total score of 0–21. A PSQI score of >5 is considered poor sleep quality (24).

2.3. Covariate assessment

Demographic information and medical history were collected from all participants, including age, gender, body mass index (BMI), education level, smoking history, drinking history, stroke history, and whether they were diagnosed with hypertension, diabetes, hyperlipidemia, coronary heart disease, kidney disease, or any other disease (23). Symptoms of anxiety were measured using the Hamilton Anxiety Scale (HAMA). The Mini-Mental State Examination (MMSE) was used to assess cognitive functioning.

2.4. Magnetic resonance imaging

Brain MRI was obtained using a single 3T MRI scanner (United Imaging, Shanghai, China; see Supplementary Table 1 for detailed MRI protocols). Brain MRI included five sequences: T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), and susceptibility-weighted imaging (SWI). Two radiologists scored the neuroimaging markers for CSVD. Any disagreements were resolved by discussion with a superior physician. According to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) (2): (1) WMH is characterized by irregular hyperintensity under the overlying cortex on the T2-weighted and FLAIR sequences. According to the Fazekas score, moderate-to-severe WMH included confluent lesions. (2) LA was defined as a subcortical ovoid with a cerebrospinal fluid-like signal ranging from 3 mm to 15 mm in diameter on all sequences. (3) CMB was characterized by a round low-signal void with a diameter of 2–10 mm on the SWI sequence. (4) EPVS was defined as an oval or linear cerebrospinal fluid-like signal <3 mm in diameter on T2-weighted images. Grading was based on the number of gaps containing the largest EPVS in a unilateral basal segment (BG) section: 0 = no EPVS, 1 = 1–10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, 4 = ≥40 EPVS (25). A score of ≥2 was defined as moderate-to-severe EPVS. Total CSVD burden (0–4 points): moderate-to-severe WMH, any LA, any CMB, and moderate-to-severe EPVS (26) (Figure 1). A total burden of 0 indicates that CSVD is not present; otherwise, it is present (27).

2.5. Statistical analysis

Data were analyzed using SPSS version 23.0 software (SPSS Inc., Chicago, Illinois, USA). Variables with non-normal distribution were expressed as median values and quartiles (Q1–Q3), and count data were presented as percentages (%). The Mann–Whitney *U*-test or chi-square test was used to compare the differences between the two groups (TABP and non-TABP). Binary logistic regression was used to analyze the relationship between the TABP and PSQI scores with the presence of CSVD. Among them, the TABP or PSQI score was the independent variable, and the presence of CSVD (moderate-to-severe WMH, lacunar, CMB, and moderate-to-severe EPVS) was the dependent variable. Ordinal logistic regression was used to analyze the relationship between the TABP and PSQI scores and CSVD burden. Among them, the TABP or PSQI score was the independent variable, and the CSVD burden was the dependent variable. Linear regression was used to analyze the relationship between the TABP and PSQI scores. TABP was the independent variable, and the PSQI score was the dependent variable. Finally, the mediation analysis was performed using mediation packages in R, version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) (28). Among them, TABP was the independent variable, the PSQI score was the mediator variable, and the presence of CSVD (moderate-to-severe WMH, lacunar, CMB, and moderate-to-severe EPVS) was the dependent variable. To obtain robust effect estimates, the number of bootstrap samples was set to 5,000. Age, sex, education, HAMA score, and vascular risk factors (hypertension, diabetes, hyperlipidemia, and BMI) were entered as covariates. A p-value of <0.05 was defined as statistically significant.

3. Results

3.1. Demographic and clinical data

A total of 764 subjects were included in this study (Figure 2). The overall median age was 65 (range: 61–69) years, 458 cases (59.9%) were female, and 342 cases (44.76%) were TABP. The TABP group had a lower education level, higher BMI, a higher proportion of CSVD and diabetes, higher HAMA scores, lower MMSE scores, and poorer sleep quality (Table 1). There were no significant differences in age, hypertension, hyperlipidemia, smoking, and drinking history between the two groups (Table 1).

3.2. Associations between key variables

After adjustment for age, sex, education, HAMA score, and vascular risk factors, an ordinal regression analysis showed that the TABP score and the PSQI score were positively associated with CSVD burden, indicating that participants with higher TABP scores or poorer sleep quality had a greater CSVD burden (Table 2). Linear regression analyses showed that the higher the TABP score, the worse the sleep quality (Table 3). In addition, binary logistic regression analyses showed that TABP and sleep quality were associated with the presence of CSVD (Table 4), moderate-to-severe WMH (Supplementary Table 2), and moderate-to-severe EPVS (Supplementary Table 2). However, TABP was not associated with the presence of LA and CMB (Supplementary Table 2).

3.3. Mediating effect of sleep quality on TABP and CSVD

The total effect ($c = 0.0056$, $p < 0.01$), direct effect ($c' = 0.0050$, $p = 0.01$), and indirect effect (path $a \times$ path $b = 0.0006$, $p = 0.02$) of TABP on the presence of CSVD were statistically significant, after adjusting for age, gender, education level, HAMA score, and vascular risk factors (Figure 3A). The mediating effect ab/c was 10.67% (Figure 3A). Furthermore, sleep quality mediated the relationship between the CH dimension and CSVD (Figure 3C) but not the relationship between TH and CSVD (Figure 3B). Additionally, sleep quality mediated the relationship between TABP and WMH (Figure 4A) but did not mediate the relationship between TABP and other CSVD imaging markers (Figure 4).

4. Discussion

The results from the present study demonstrated a positive association between TABP and CSVD in community-dwelling

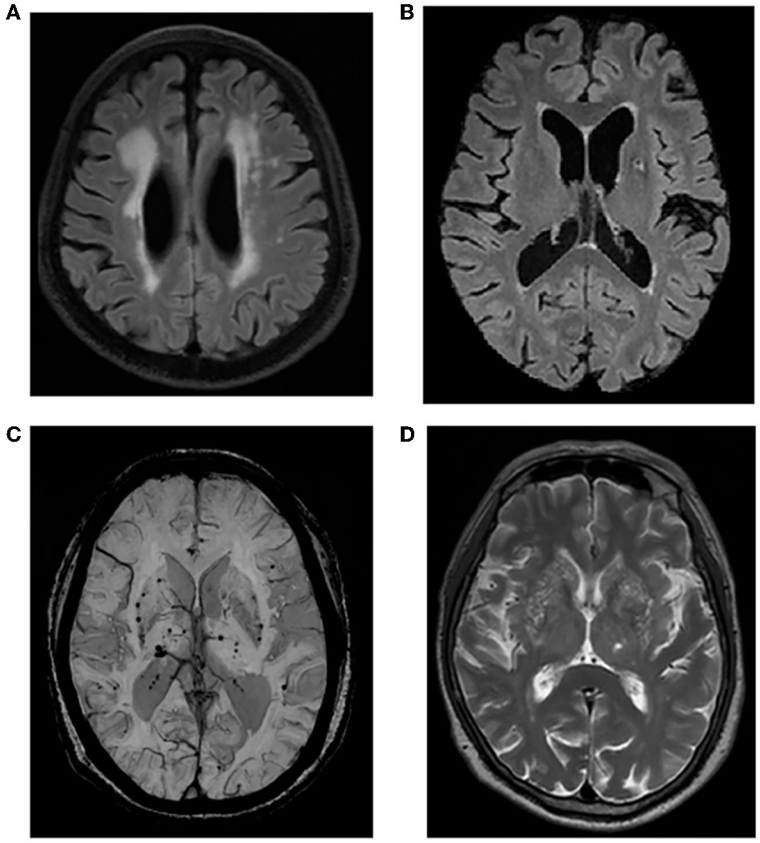

FIGURE 1
Representative imaging markers of CSVD. **(A)** Moderate-to-severe WMH; **(B)** LA in the left basal ganglia region; **(C)** CMBs in the basal ganglia; **(D)** moderate-to-severe EPVS in the basal ganglia. CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; LA, lacune; CMB, cerebral microbleed; EPVS, enlarged perivascular space.

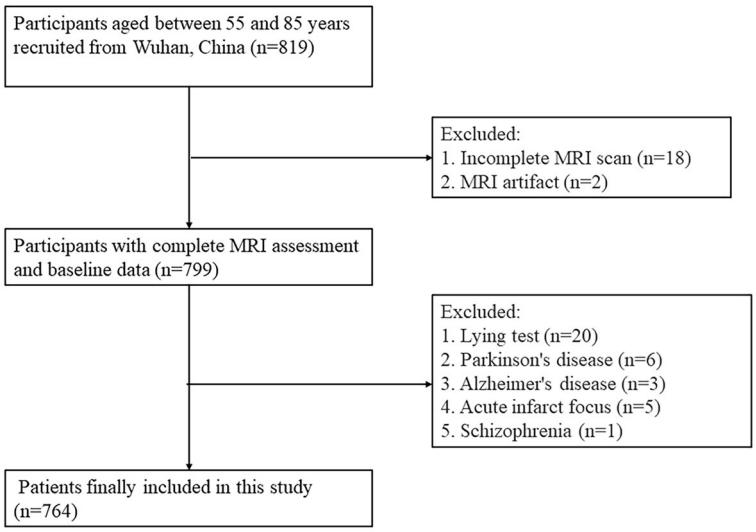

FIGURE 2
Flowchart of the study.

older adults, and sleep quality mediated this association. The findings of this study suggest that older adults with TABP, especially those with higher CH scores, may be at risk for sleep disorders, which may further influence CSVD. Furthermore, worse sleep quality partially mediated the association between TABP and moderate-to-severe WMH.

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TABLE 1 Comparison of clinical variables in TABP patients.

	Total (764)	No-TABP (422)	TABP (342)	*p*-value
Age, years, median (IQR)	65 (61–69)	65 (61–69)	66 (61–70)	0.494
Female, *n* (%)	458 (59.9%)	267 (63.3%)	191 (55.8%)	**0.037**
Education level, median (IQR)	12 (11–16)	12 (12–16)	12 (9–15)	**<0.001**
TABP score, median (IQR)	26 (20–32)	20 (17–24)	30 (30–37)	**<0.001**
TH score, median (IQR)	13 (10–16)	10 (8–12)	17 (15–19)	**<0.001**
CH score, median (IQR)	13 (10–16)	10 (8–12)	16 (15–18)	**<0.001**
MMSE, median (IQR)	28 (27–29)	29 (28–29)	28 (27–29)	**<0.001**
PSQI score, median (IQR)	7 (4–10)	6 (4–9)	7 (5–11)	**<0.001**
Vascular risk factors				
BMI, median (IQR)	24 (22–26)	23 (21–25)	24 (22–26)	**0.006**
Smoking history, *n* (%)	85 (11.1%)	41 (9.7%)	44 (12.9%)	0.169
Drinking history, *n* (%)	83 (10.9%)	42 (10.0%)	41 (12.0%)	0.369
Diabetes, *n* (%)	119 (15.6%)	49 (11.6%)	70 (20.5%)	**0.001**
Hypertension, *n* (%)	343 (44.9%)	178 (42.2%)	165 (48.2%)	0.094
Hyperlipidemia, *n* (%)	238 (31.2%)	126 (29.9%)	112 (32.7%)	0.391
HAMA, median (IQR)	3 (1–5)	3 (1–4)	2 (3–5)	**<0.001**
Neuroimaging characteristics				
CSVD, *n* (%)	317 (41.5%)	144 (34.1%)	173 (50.6%)	**<0.001**
Moderate-to-severe WMH, *n* (%)	144 (18.8%)	52 (12.3%)	92 (26.9%)	**<0.001**
Presence of LA, *n* (%)	88 (11.5%)	40 (9.5%)	48 (14.0%)	0.050
Presence of CMB, *n* (%)	150 (19.6%)	71 (16.8%)	79 (23.1%)	**0.030**
>10 EPVS-BG, *n* (%)	134 (17.5%)	61 (14.5%)	73 (21.3%)	**0.013**

TABP, type A behavior pattern; SD, standard deviation; TH, time hurry; CH, competition and hostility; MMSE, Mini-Mental state examination; PSQI, Pittsburgh sleep quality index; BMI, body mass index; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; LA, lacune; CMB, cerebral microbleed; EPVS-BG, enlarged perivascular space—basal ganglia.
Bold values mean *p*-value of < 0.05.

TABLE 2 Ordinal logistic regression analyses with CSVD burden as the DV.

	Unadjusted model			Adjusted model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
TABP score	1.039	1.020–1.057	**<0.001**	1.030	1.011–1.049	**0.002**
TH score	1.053	1.020–1.087	**0.001**	1.040	1.005–1.075	**0.024**
CH score	1.074	1.040–1.108	**<0.001**	1.058	1.022–1.094	**0.001**
PSQI score	1.080	1.040–1.121	**<0.001**	1.116	1.066–1.168	**<0.001**

Adjusted for age, gender, education level, HAMA scale, BMI, hypertension, diabetes, and hyperlipidemia.
CSVD, cerebral small vessel disease; DV, dependent variable; CI, confidence interval; TABP, type A behavior pattern; TH, time hurry; CH, competition and hostility; PSQI, Pittsburgh sleep quality index.
Bold values mean *p*-value < 0.05.

CSVD burden has been widely used to assess the severity of CSVD (26, 29). In the present study, the CSVD group (scores 1–4) accounted for 41.5% of the total population. This prevalence was slightly higher than the results of a previous study (33.8%) that included 1,586 community adults over the age of 35 in China (29). A possible reason for the different findings is that the present study enrolled older adults. The TABP scale is a widely used scale to assess type A behavior (5, 30). Individuals with high TABP scores have been found to be quick and diligent but often irritable, impatient, and aggressive (30). Higher TABP scores were significantly associated with more severe depressive disorders, higher frustration, and higher work stress (31, 32).

Although TABP was associated with coronary heart disease and multiple sclerosis (8, 33), no study has examined the relationship between TABP and CSVD burden. The present study found that TABP was significantly associated with CSVD burden. Many

TABLE 3 Multivariate linear regression models with the PSQI score as the DV.

	Unadjusted model			Adjusted model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
TABP score	1.092	1.058–1.127	**<0.001**	1.040	1.010–1.070	**0.009**
TH score	1.164	1.100–1.234	**<0.001**	1.064	1.010–1.120	**0.020**
CH score	1.143	1.079–1.213	**<0.001**	1.065	1.011–1.122	**0.018**

Adjusted for age, gender, education level, HAMA scale, BMI, hypertension, diabetes, and hyperlipidemia.
PSQI, Pittsburgh sleep quality index; DV, dependent variable; CI, confidence interval; TABP, type A behavior pattern; TH, time hurry; CH, competition and hostility.
Bold values mean p-value < 0.05.

TABLE 4 Binary logistic regression analyses with the presence of CSVD as the DV.

	Unadjusted model			Adjusted model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value
TABP score	1.036	1.018–1.056	**<0.001**	1.031	1.010–1.052	**0.003**
TH score	1.048	1.014–1.083	**0.005**	1.037	1.001–1.075	**0.044**
CH score	1.073	1.037–1.109	**<0.001**	1.063	1.025–1.102	**0.001**
PSQI score	1.069	1.027–1.112	**0.001**	1.097	1.044–1.153	**<0.001**

Adjusted for age, gender, education level, HAMA scale, BMI, hypertension, diabetes, and hyperlipidemia.
CSVD, cerebral small vessel disease; DV, dependent variable; CI, confidence interval; TABP, type A behavior pattern; TH, time hurry; CH, competition and hostility; PSQI, Pittsburgh sleep quality index.
Bold values mean p-value < 0.05.

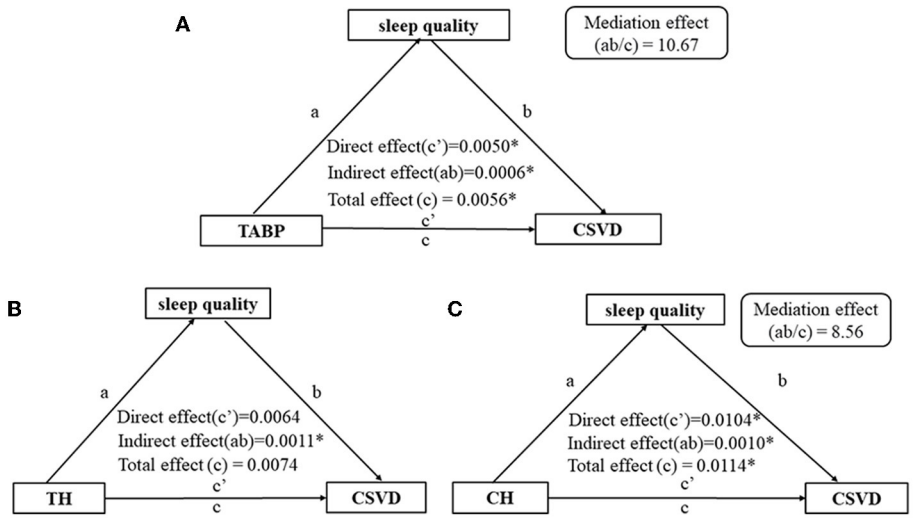

FIGURE 3
Path diagram of the relationship between type A behavior and the presence of CSVD, with sleep quality as the mediator. **(A)** Path diagram of the relationship between TABP and CSVD, with sleep quality as the mediator. **(B)** Path diagram of the relationship between TH and CSVD, with sleep quality as the mediator. **(C)** Path diagram of the relationship between CH and CSVD, with sleep quality as the mediator. *p-value of < 0.05. Control variables: age, gender, education level, HAMA scale, BMI, hypertension, diabetes, and hyperlipidemia. CSVD, cerebral small vessel disease; TABP, type A behavior pattern; TH, time hurry; CH, competition and hostility.

studies have found that TABP was associated with hypertension (34), hyperlipidemia (35), diabetes (36), alcohol consumption (37), and atherosclerosis (35), all of which may increase the risk of CSVD burden. We also found that TABP was positively correlated with WMH and EPVS but not LA and CMB, which may be due to the different pathogenesis of the four CSVD markers. The current literature describes WMH as a demyelinating lesion with chronic hypoperfusion of blood flow due to atherosclerosis of the vessel wall and restriction of the lumen (38). The mechanism of EPVS remains unclear. Furthermore, EPVS has been described as an indicator of inadequate drainage of the glymphatic system, elevated cerebral venous pressure, and neuroinflammation (39). EPVS and WMH may overlap in pathogenesis (39). Additionally, LA has been proposed to originate from an ischemic or hemorrhagic stroke but lacked definitive symptoms and may be associated with cerebral amyloid lesions (39). Finally, CMB has been described as a

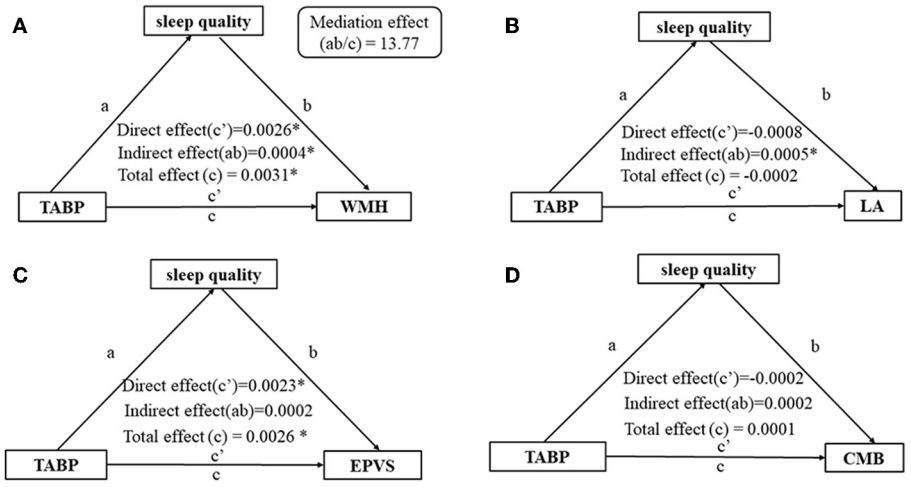

FIGURE 4
Analysis of the mediating effect of sleep quality on the relationship between TABP and the presence of CSVD markers. **(A)** Analysis of the mediating effect of sleep quality on the relationship between TABP and moderate-to-severe WMH. **(B)** Analysis of the mediating effect of sleep quality on the relationship between TABP and the presence of LA. **(C)** Analysis of the mediating effect of sleep quality on the relationship between TABP and moderate-to-severe EPVS. **(D)** Analysis of the mediating effect of sleep quality on the relationship between TABP and the presence of CMB. $^{*}p$-value of < 0.05. Control variables: age, gender, education level, HAMA scale, BMI, hypertension, diabetes, and hyperlipidemia. TABP, type A behavior pattern; CSVD, cerebral small vessel disease; WMH, white matter hyperintensity; LA, lacune; CMB, cerebral microbleed; EPVS, enlarged perivascular space.

perivascular hemosiderin deposition, indicating that inflammation and endothelial dysfunction are important parts of the pathogenesis (39). Type A personality is associated with chronic stress, which has adverse effects on health behavior, contributes to cerebrovascular atherosclerosis (35), and promotes the development of WMH and EPVS.

Consistent with previous studies, our results suggested that sleep quality was associated with TABP (5, 32, 40) and CSVD (16, 41–43). Several previous studies have suggested that sleep quality may lead to CSVD through decreased cerebral perfusion, increased cerebrovascular resistance, impaired vasomotor responsiveness, sympathetic tone, insulin resistance, inflammatory activation, and increased blood–brain barrier permeability (43, 44). Some studies have shown that adults with higher TABP scores have worse sleep quality (4, 5, 32, 40). TABP may contribute to sleep disorders due to impaired self-regulatory stress systems, abnormal dopamine expression, and other factors (4, 5, 32, 40). Another study demonstrated that high TABP scores were significantly associated with depressive symptoms, high frustration levels, and high levels of work-related stress (3). High TABP may contribute to small vessel ischemia and hypoxia by stimulating the neuroendocrine system and activating the sympathetic nervous system, resulting in active catecholamine secretion, increased vascular resistance, and elevated blood pressure level (45). The results from our study suggest that sleep quality mediated the relationship between competition and hostility (CH) and CSVD but not time urgency (TH) and CSVD, possibly due to different pathogenesis.

This study highlights the critical role of TABP in the development of sleep quality and CSVD in community-dwelling older adults. There is a need for TABP assessment in older adults in the community because TABP can be treated. A twin study of type A behavior suggests that TABP comprises 45% genetic and 55% environmental factors, which would be valuable for prevention and treatment (46). First, cognitive behavioral therapy and health education may help TABP populations identify adverse and maladaptive behaviors and replace them with more adaptive behaviors (34). Second, those with TABP may relieve stress and bad moods through meditation or music therapy. Alternatively, β-blockers alter adrenergic responsiveness, which is considered an important physiological trait of type A personality (47). Finally, trazodone may treat sleep disorders, thereby alleviating the cognitive impairment caused by CSVD (42).

There were several limitations in the present study. First, this study was cross-sectional and therefore cannot establish a causal association between TABP and CSVD. Second, the TABP self-rated scale was completed by participants; therefore, the data may include recall bias. Future studies with stronger research designs should explore the relationship between personality traits and CSVD. Third, the primary limitation of this study is the lack of use of precise sleep measurement tools such as polysomnography. Sleep quality was measured using a self-rated scale and thus may be affected by self-report. Fourth, the generalization to the overall population should be approached with caution due to the lack of random sampling in this project. Finally, future researchers should conduct longitudinal studies on the relationship between TABP, sleep quality, and CSVD.

5. Conclusion

This study demonstrated that markers of CSVD, moderate-to-severe WMH and EPVS, were more prevalent in individuals with higher TABP scores among community-dwelling older adults. In addition, sleep quality mediated the association between TABP and CSVD. We did not investigate the effectiveness of behavioral

interventions on sleep quality or CSVD prevention, therefore, further research is needed in this area.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Hospital (No. 2019-S105). The patients/participants provided their written informed consent to participate in this study.

Author contributions

XZ drafted and revised the manuscript. HH and WQ studied concept and design. ZY revised the manuscript. JZ and LW processed the statistical data. YZ, QK, and ZW collected the clinical data. XL designed and guided the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1236670/full#supplementary-material

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Sleep in marathon and ultramarathon runners: a brief narrative review

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Introduction: Sleep is considered a fundamental biological function in humans necessary for recovery from daily physical activities. Considering the increasing popularity of long-distance running and participation in races such as marathons and ultramarathons, the aim of the present study was to review the relationship of such strenuous physical activities with sleep.

Methods: A search of Scopus was performed on 24/6/2023 using the syntax [ABS (sleep) AND ABS (marathon)] to identify relevant papers, the references of which were hand-searched to find additional sources.

Results: Optimal sleep has been shown to affect injury prevention and susceptibility to infection positively. In turn, participation in a marathon race may influence nocturnal autonomic modulation and disturb homeostasis. Ultramarathon races may have such a long duration that results in sleep deprivation even for several days, where sleep duration is quite below the physiological range. It seems that for ultramarathons of short duration, continuous running and sleep deprivation are beneficial for performance. In contrast, for races longer than 200 miles, it is necessary to develop sleep strategies to sustain performance.

Conclusion: In summary, the longer the distance of a running race, the greater the importance of an optimal sleep for race performance as well as the impact of a race on sleep.

KEYWORDS

exercise, athletic performance, marathon running, sleep deprivation disorders, sleep extension duration

Introduction

Sleep is considered a fundamental biological function in humans necessary for the recovery of energy loss resulting from daily physical activities including exercise and sports (1). Driller et al. (2) highlighted the importance of sleep in an athlete's recovery process and performance, which may explain the increase in sleep monitoring in sports. In the context of daily energy expenditure, sport practice has been a subcategory of physical activity characterized by regular exercise training and often high metabolic demands (3). Sleep has been widely acknowledged as one of the foundations of sports performance, considering its impact on illness, injury, metabolism, cognition, memory, learning, and mood (4, 5). An explanation of the beneficial role of sleep on performance might be the restorative function of slow-wave sleep, allowing

recovery from previous wakefulness and fatigue (4). Considering the increasing popularity of long-distance running and participation in races such as marathons and ultramarathons (6, 7), it would be interesting to examine the relationship of such strenuous physical activities with sleep. Therefore, the aim of the present study was to review sleep aspects of marathon and ultramarathon runners. For the purpose of our brief narrative review, a search of Scopus was performed on 24/6/2023 using the syntax [ABS (sleep) AND ABS (marathon)] to identify relevant papers, the references of which were hand-searched to find additional sources. The search did not have any time restriction resulting in 42 entries. The references of these studies were hand-searched to identify further literature. We considered the impact of sleep on marathon/ultramarathon performance and vice versa. First, the role of sleep in athletes generally was introduced, and second, thereafter, there was a focus on marathon and ultramarathon runners.

Sleep and athletes

The model of sleep deprivation or partial sleep loss, observed in athletes traveling crossing several time zones or participating in prolonged races such as ultramarathons and triathlon races, was used as a methodological approach to examine the role of sleep (8). Compared with the general population, few studies have been conducted on the effects of sleep deprivation on athletes (9). Compared to the general population, elite athletes have poor quality and quantity of sleep due to training times, competition stress/anxiety, muscle soreness, caffeine use, and travel (4). There were several factors—including changes in nutrition, environmental aspects (e.g., temperature and altitude), crossing time zones and stress—that may exert detrimental effect on sleep, and consequently, on sports performance (10).

The beneficial role of exercise on sleep duration and delayed rapid-eye movement (REM) sleep onset, enhanced slow-wave sleep, and decreased REM sleep has been previously reported (11). Driver and Taylor (11) addressed methodological concerns about research on exercise and sleep with regard to differences in the study design (e.g., exercise protocols) and interactions between individual characteristics. Occasionally, athletes may be in a state of low energy availability (e.g., sudden decrease of energy intake in case of weight loss). A case study reported that weight loss practices did not compromise the sleep of martial sports athletes (12). Research on sleep patterns of athletes during the early coronavirus disease lockdown showed that sleep quality and quantity were characterized as "normal" for half of them, followed by those reporting "improved" and "worsened" sleep (13). In turn, sleep quality and quantity may relate to variability in sleep onset and offset (14) assessed by the sleep regularity index (SRI). A comparative study showed that SRI recorded for 5 days in athletes was better in competitive athletes, women, and athletes of individual sports (15). Driller et al. (16) found in a comparative study that individual-sport (e.g., badminton, boxing, cycling and rowing) athletes had greater total sleep time and higher sleep efficiency than team-sport (e.g., basketball, soccer, cricket, and hockey) athletes. In another study, SRI was monitored for 7 days and suggested that—compared to irregular sleepers—regular sleepers had greater sleep efficiency, less variability in total sleep time and sleep efficiency, similar total sleep time, and less variation in sleep onset times (14).

The feeling of stress before a sports competition may affect sleep. For instance, Vitale et al. monitored two nights before and two nights after an evening soccer game, and concluded that the athletes had a late bedtime and wake-up time after a game, whereas no alteration in sleep quality and duration was shown (17). Nevertheless, adolescent basketball players' sleep quality did not differ in the competitive period compared to off-season (18).

In adolescent basketball players, the majority had sleep duration less than the suggested 8 h (19). Gupta et al. (20) reviewed 37 studies that showed an increased number of sleep complications in high-level athletes, and sleep disturbances were due to training, travel, and competition. They also highlighted the high incidence of insomnia symptoms such as increased sleep latencies, larger sleep fragmentation, non-restorative sleep, and disproportionate daytime fatigue. Regarding the role of traveling across several time zones, Fowler et al. (21) recorded sleep in physically active men who traveled from Australia (East) to Qatar (West) and vice versa and observed that sleep onset and offset occurred in a later time, and resting in bed as well as total sleep time were decreased during 4 days in Australia compared with baseline and Qatar.

Sleep in marathon and ultramarathon runners

Marathon

A methodological approach to examine the relationship between sleep and marathon was to investigate (a) the effect of different levels of sleep quality and quantity on marathoner runners' physiology (e.g., immunity, musculoskeletal system), and (b) the effect of a marathon race on sleep quality and quantity. With regards to the relationship of sleep and immunity system in marathon runners, there has been a concern that strenuous and lengthy training or competing in endurance events (e.g., marathon races) may result in a high incidence of infections (e.g., upper respiratory tract infections) (22). For instance, Sparling et al. (23) reviewed selected scientific aspects of marathon running, and found that adequate sleep—in addition to proper nutrition, rest between intense training sessions, and the control of contact with sick people—may reduce susceptibility to infection. In addition to the immunity system, another health concern of marathon runners was the occurrence of musculoskeletal injuries. Marathon runners were subject to injuries, mostly in the lower limbs, related to overuse (24). Ashcroft (25) highlighted the role of adequate sleep in the context of the prevention of injuries in distance runners. In summary, there was evidence of a beneficial role of sleep for the immunity (infections) and musculoskeletal system (injuries).

The effect of a marathon race on sleep has been examined in studies that compared the condition of the race with training and rest (26–28). Montgomery et al. (26) investigated the effect of three circumstances (no exercise, a 90 min running, and a marathon race) on the sleep of recreational marathon runners. They showed a sleep disorder, consisted of an inhibition of REM sleep and a reduced in sleep duration after the marathon race, whereas sleep was unaffected by the 90 min training running. These authors attributed the sleep disruption after the marathon race to stress, as noted by the elevated cortisol levels (26). A similar study design (i.e., comparison of marathon race with training and rest) was adopted by Hynynen et al.

(28) who studied the influence of a rest day, moderate endurance exercise, and marathon run on healthy, physically active men's nocturnal heart rate (HR) variability. They observed that compared to a rest day, the intervals between consecutive heart beats increased to 109 and 130% after moderate endurance exercise and a marathon, respectively, whereas the standard deviation of these intervals decreased to 90 and 64%. These findings proposed a prolonged dose–response effect on autonomic modulation after exercises influencing nocturnal autonomic modulation and causing disturbance to homeostasis (28). Moreover, Cecchetti et al. (27) compared sleep HR after a habitual training session and a marathon race, separated by 2 weeks in senior marathon runners. They showed that HR was higher during marathon and post-marathon waking time than on the training day; however, no difference was found in sleep HR. The authors attribute this pattern to the decrease of adrenergic activation during night sleep (27). In summary, a marathon race likely would induce more sleep disturbances than a training session or no exercise; however, more research was needed in this field considering controversial findings (26–28).

Another aspect of practical significance was the traveling across time zones to participate in a marathon race (29). As it has been shown recently, a small number of participants in marathon races was from other countries and continents, and this observation concerned both elite and recreational runners (7, 30). For instance, from 1970 to 2017 in the New York City Marathon, ~530,000 out of ~1.2 M participants were not from USA (7). Traveling to the city of a marathon race might involve covering a large distance in a short time by plane resulting in circadian change and sleep loss (31). Moreover, sleep loss would also result from the spring version of daylight savings transition (DST), i.e., setting the clock 1 h forward (32), and might impair performance in case of a race in the day after a spring-DST (33). In this topic, O'Connor and Kancheva (33) examined the effect of DST on endurance performance and observed that the spring-DST marathon race time was slower by ~12 min while autumn-DST was slower by ~1 min compared to control marathon times. The authors proposed that their results indicate a deterioration of marathon running occurred on the spring-DST, which was attributed to a forced circadian change and sleep loss (33).

Ultramarathon

It should be noted that a marathon race referred to running a distance of 42 km, whereas an ultramarathon race denoted any distance longer than 42 km or lasting more than 6 h (34). Thus, by definition, an ultramarathon race might cover a wide range of distances and durations (35), and the characteristics of ultramarathon runners might differ from marathon runners in terms of participation rates (e.g., fewer participants in ultramarathon than in marathon races) and performance (e.g., slower running speed in the former than in the latter races) (35). The effect of a race on sleep has been studied in ultramarathon races (36, 37). Bianchi et al. (36) examined the sleep–wake behavior of 200-mile (~82.5 h) ultramarathon runners before (for 7 days), during, and after a race (for 7 days). They reported that runners had ~5 h of sleep from ~5 sleep episodes (i.e., ~1 h of sleep per episode), and the sleep duration was 6.0 h before the ultramarathon, and 6.3 h in the week after the race. The authors concluded that runners drastically restricted their sleep, the importance of sleep increased during the days of the race, and the ultramarathoners had less sleep duration than the suggested ~8 h in both pre-race and post-race periods of the race (36). In another study of the same research group, Miller et al. (37) investigated sleep/wake behavior before, during, and after ultramarathon races lasting more than 161 km. The majority of runners of such distances usually had no sleeping during races, whereas, for races longer than 322 km, runners had more sleep episodes, more sleep time per episode and in total than races of 161–240 km. The authors concluded that for events lasting less than 161 km, the advantage of constant running values more than the disadvantage of unceasing wakefulness/sleep deprivation. On the contrary, for events lasting more than 322 km, there is an apparent compromise between sleep deprivation and race strategy, whereby runners may not tolerate an intended performance without sleep (37). In addition, they attributed this finding to the conventional sleep/wake behavior models indicating that sleep requirement increases as wakefulness increases, or in this case, as race duration increases. To sum up, ultramarathon runners sleep inadequately even in pre-and post-race periods, sleep duration decreases during race days, and the longer the race distance, the lower the sleep duration (36, 37).

Graham et al. (38) examined sleep during a 120-mile, three-day Arctic ultramarathon. Sleep—assessed by the Brunel Mood Scale questionnaire—was 4.07 h per day and correlated neither with injury rate nor mood changes. The authors interpreted these findings as suggesting that this demanding race involves significant psychological and physiological preparation that minimizes the effects of sleep deprivation (38). In another research, Huang et al. (39) studied the aspect of visual hallucinations commonly reported by adventure-race competitors (e.g., ultramarathons in the mountains and deserts) in a 245 km race with an altitude difference of 3,266 m (duration 44 h). All eight runners in this study slept for <30 min during the race and three had visual hallucinations, which the authors assumed may be associated with excessive physical exertion and sleep deprivation. Sleep deprivation may influence ultramarathon performance within a holistic model, including environmental conditions, painkillers or psychostimulants, and cognitive and nutritional strategies (40). During ultramarathon training and competing, to sustain performance and offset the compromise of athlete safety due to sleep deprivation, a consensus supports the strategic use of caffeine (41). Poussel et al. (42) observed that all runners in the North-Face UltraTrail du Mont-Blanc 2013 adopted pre-race sleep management strategies, the majority of runners did not sleep during the race and non-sleepers were faster than sleepers. In addition, ultramarathon finishers of the abovementioned race, who used a sleep management strategy based on increased sleep time before the race, were faster than those who did not use such strategy.

Other aspects

In addition to the effect of marathon and ultramarathon races on sleep, a few studies examined the role of relevant aspects such as sleeping after traveling across different time zones (43), preparation for an endurance race (44), night running (45), post-marathon recovery (46), and sex differences (47). Montaruli et al. (43) studied the effect of a flight across different time zones (from Milan to

New York) on the sleep of marathon runners divided into the morning training group, evening training group, and control group. Sleep patterns were continuously monitored using an actometer on the wrist of the non-dominant hand. They concluded that physical activity could positively affect sleep by improving quality and encouraging re-synchronization after the flight (43). In addition, Meijer et al. (44) examined the effect of a 20 week program on sleeping metabolic rate in athletes preparing for a half-marathon, where they measured sleeping metabolic rate from 3 to 6 am in a respiration chamber. No changes in SMR were found, either in absolute terms or when normalized for body mass or fat-free mass, concluding that exercise training has no chronic, long-term effect on sleeping metabolic rate (44). Furthermore, Rozmiarek et al. (45) contacted research in night runners and observed that night running makes it easier to fall asleep and improves the quality of sleep. However, Castell (48) proposed that in endurance athletes, one night's sleep loss would induce changes in parameters related to immune function and cognitive ability. Polak et al. (46) analyzed Rotterdam Marathon runners for information concerning total recovery and recovery from pain, stiffness, loss of appetite, sleep disturbance and fatigue. They showed that the immediate replacement of 2.5 L of fluid had no significant influence on the total recovery rate, the number of days with pain or stiffness, the appetite, sleep, or fatigue (46). With regard to sex differences, Roberts et al. (47) studied endurance athletes in pre-race relationships between sleep, perceived stress and recovery. They monitored sleep using actigraphy over four consecutive days before an ultramarathon and showed that—compared with men—women had shorter wake after sleep onset (50 vs. 65 min), and experienced greater pre-race stress, and their sleep duration was associated with emotional factors (47). Swain and Rosencrance (49) focused on headaches in half-marathon and 5 km runners. They observed a higher proportion of distance runners with migraine headaches compared to the regular population (36% vs. 17%). An interesting finding was that running reduced the severity and frequency of all types of headaches, and sleep eliminated headaches in most headache patients (49). It was acknowledged that being a narrative review the present study could not draw quantitative conclusions. As the body of relevant literature increases, systematic reviews and meta-analyses are expected in the near future to provide complimentary knowledge.

Conclusion

In summary, optimal sleep has been shown to positively affect injury prevention and susceptibility to infection. In turn, participation in a marathon race may influence nocturnal autonomic modulation and disturb homeostasis. Ultramarathon races may have such a long duration resulting in sleep deprivation even for several days, where sleep duration would be quite below the physiological range. It seemed that for ultramarathons of short duration, continuous running and sleep deprivation were beneficial for performance, whereas for races longer than 200 miles it was necessary to develop sleep strategies to sustain performance.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Fabry disease and sleep disorders: a systematic review

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Background: Fabry disease (FD) is an X-chromosome-linked disorder characterized by a reduced or complete absence of the enzyme α-galactosidase, resulting in the accumulation of lysosomal globotriaosylceramide. Despite the presence of these deposits in multiple organs, the problem of sleep disorders within this population has very rarely been documented.

Objective: This study aimed to investigate the types and prevalence of sleep disorders among patients with FD.

Methods: Screening of the following medical databases using key terms was performed on 10 February 2023: PubMed, Scopus, and Embase. A total of 136 records were identified. The quality assessment of the studies was conducted by using tools from the National Institutes of Health (NIH) and critical appraisal tools from the Joanna Briggs Institute (JBI).

Results: The study included nine studies on sleep disorders in patients with FD. The overall quality of the majority of these studies was assessed as either poor or fair. Among 330 patients, there was a slightly higher representation of female patients (56%). Sleep problems manifested 4–5 years after the onset of FD and sometimes even after 10–11 years. Genotypes of disease associated with sleep problems were rarely described. Within the FD population, the most commonly reported conditions were excessive daytime sleepiness (EDS) as well as obstructive and central sleep apnea (OSA, CSA). However, EDS occurred more frequently in FD patients, while the prevalence of OSA and CSA was within the ranges observed in the general population. The studies included indicated a lack of association between organ impairment by primary disease and EDS and OSA. The effectiveness of enzyme replacement therapy (ERT) in treating sleep disorders was not demonstrated.

Conclusion: The findings of this report revealed the presence of many sleep-related disorders within the FD population. However, very few studies on this subject are available, and their limited results make it difficult to truly assess the real extent of the prevalence of sleep disturbances among these individuals. There is a need to conduct further studies on this topic, involving a larger group of patients. It is important to note that there are no guidelines available for the treatment of sleep disorders in patients with FD.

KEYWORDS

Fabry disease (FD), sleep disorders, excessive daytime sleepiness (EDS), obstructive sleep apnea (OSA), central sleep apnea (CSA)

1. Introduction

Lysosomal storage diseases (LSDs) are congenital metabolic defects that impair lysosome function. LSDs are autosomal recessive disorders, several of which are linked to the X-chromosome. In general, mutations of lysosomal genes result in the accumulation of sphingolipids, mucopolysaccharides, or glycoproteins inside the lysosome, ultimately leading to cell damage and death. LSDs cover a group of 70 disorders, with Fabry disease (FD) being the most prevalent manifestation (1).

FD is an X-chromosome-linked disease that is marked by a reduced or complete absence of the α-galactosidase enzyme, resulting in the accumulation of lysosomal globotriaosylceramide (Gb3). In Europe, the disease affects between 1/3,100 and 1/117,000 individuals (2). However, these data may not reflect the actual prevalence as instances of the disease exist with partially active enzymes or within female patients carrying a defective gene (3). The disease manifests in different forms based on enzyme activity levels and the extent of mutation of the galactosidase alpha gene (GLA). The classic, severe clinical form is found only in men and manifests itself as early as childhood/teenage years (4). Atypical variants of the disease retain some residual α-galactosidase A activity, leading to these patients not exhibiting all of the described symptoms. The non-classic form affects both men and women and is characterized by a late clinical onset or even an asymptomatic course. This disease further distinguishes between cardiac and renal variations, involving specific organs only (5). It should be kept in mind that regardless of the variant, FD is a progressive disease with a reduced life expectancy. The median survival age for men is 50–55 years, while for women, it is 70 years (6).

Usually, the initial reason for seeking medical help is the presence of acute burning pain in the distal parts of the limbs, a condition referred to, in literature, as acroparesthesia. This neuropathic pain, however, may occur anywhere in the body. These pain episodes can be triggered by factors such as physical activity, ambient temperature, stress, or meals (7). In the classic presentation of the disease, characteristic reddish–purple skin lesions known as angiokeratoma are also observed, usually in the area around the umbilicus, trunk, and thighs. These lesions may spread to the facial area, impacting the appearance, which can be even more affected by occasional bleeding from the lesions (8). Tubulointerstitial kidney injury develops progressively, leading to renal failure and necessitating dialysis therapy (9). Cardiovascular symptoms are present in most patients who tend to develop left ventricular hypertrophy, myocardial fibrosis, and conduction abnormalities leading to arrhythmias (10). Neurological complications of the disease include memory impairment and headaches. The prevalence of vascular incidents including transient ischemic attacks (TIA), vascular dementia, and ischemic strokes is significantly higher in this group of patients (11).

Despite lysosomal deposits impacting many organs, the problem of sleep disorders in these patients has rarely been documented in studies on FD. Studies examining the quality of life in this patient group have reported daytime fatigue and sleep problems (12, 13). Furthermore, it is worth noting that no systematic reviews related to this clinical issue were found. Given these aspects, the aim of this systematic review was to investigate the type and prevalence of sleep disorders in patients with FD.

2. Methods

To write this systematic review, we conducted a literature search following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) (14, 15). However, it is important to note that this systematic review was not registered.

2.1. Eligibility criteria

To be incorporated into this systematic review, studies needed to involve patients with FD, along with a description of their sleep disorders. Sleep disorders can be assessed by a wide range of medical methodologies, ranging from interviews or appropriate questionnaires to instrumental examinations. All age groups, genders, and FD variations were taken into consideration. Only original research was sought, and thus, reviews, book chapters, or comments were excluded. The following exclusion criteria as also applied: non-English records and the absence of sleep problems in FD patient groups.

2.2. Search strategy and study selection

Our search strategy was based on screening three medical databases, namely, PubMed, Scopus, and Embase (MEDLINE) by using key terms such as "Fabry disease" OR "Anderson–Fabry disease" AND "sleep" OR "insomnia" OR "sleeping problems" OR "restless leg syndrome" OR "snoring" OR "night." On 10 February 2023, two authors (BB and HM) independently identified relevant records. Once studies were identified, duplicate studies were excluded from the review. To determine the content of each article, the same authors studied the titles and abstracts. By using this method, we excluded studies that were seen to be irrelevant for the purpose of our review. All identified reports were made available for retrieval. In the process of determining eligibility for inclusion in the final systematic review, the full texts of the remaining articles were read, and the results were compared by the authors. The third author (MW) was responsible for solving potential conflicts. As per the exclusion criteria outlined in Section 2.1, ultimately, only nine studies met the requirements for inclusion in this systematic review.

2.3. Data extraction and quality assessment

After the qualification of the final chosen studies for this review, two authors (BB and HM) extracted relevant data. The following information from the studies was taken into account: study authors, country of residence of patients diagnosed with FD, number of groups tested, patients' ages and genders, types of sleep disturbances, methods used to confirm the presence of sleep disorder, and FD variants. These data are shown in Table 1.

TABLE 1 General information of included studies demonstrating sleep disorders in Fabry disease patients.

References	Country where the study was conducted	Patients' gender and number of cases	Patients' age	Patients' BMI	Enzyme replacement therapy receiving	Fabry disease variants	Sleep disturbances	Methods to confirm sleep problems
Rosa Neto et al. (16)	Brazil	21 female and 16 male participants	42.1 ± 17.7 years old in female participants, 44.4 ± 11.6 years old in male participant	None	22 patients	Classic variants embraced: C142R, A156D, L180F, R227X, W262X, G271A, P293S, Y264SX mutations	17x insomnia/unrefreshing sleep, 22× quality sleep disturbances	Medical interview, Pittsburgh, Sleep Quality Index
Gaisl et al. (17)	Switzerland	35 female and 17 male participants	42.1 ± 14.2 years old	23.3 ± 3.5 kg/m^2	32 patients	Not reported	10× obstructive sleep apnea, 7.9 ± 4.0 points for excessive daytime sleepiness	Respiratory polygraphy, Epworth Sleepiness Scale
Vallim et al. (18)	Brazil	10 female and 6 male participants	40.1 ± 12.9 years old	None	11 patients	Not reported	10× poor sleep quality	Actigraphy, Pittsburgh Sleep Quality Index
Talbot et al. (19)	Australia	20 male participants	43.9 ± 10.7 years old	24.3 ± 3.8 kg/m^2	16 patients	Phenotypes: 59% having cardiomyopathy and 37% cerebrovascular disease	8× obstructive sleep apnea, 15× restless legs syndrome, 19× periodic limb movement in sleep, 7× excessive daytime sleepiness	Polysomnography, Epworth Sleepiness Scale
Franzen et al. (20)	Switzerland	35 female and 17 male participants	42.8 ± 14.7 years old	23.4 ± 3.6 kg/m^2	32 patients	Not reported	10× obstructive sleep apnea, 3× central sleep apnea, 7× excessive daytime sleepiness	Respiratory polygraphy, Epworth Sleepiness Scale
Löhle et al. (21)	England	60 female and 50 male participants	49.0 ± 16.0 years old	None	80 patients	Not reported	29× REM sleep behavior disorder, 28× excessive daytime sleepiness	REM Sleep Behavior Disorder Screening Questionnaire, Epworth Sleepiness Scale
Duning et al. (22)	Germany	11 female and 12 male participants	48 ± 19 years old with sleep apnea, 46.0 ± 22.0 years old without sleep apnea	24.2 ± 8.2 kg/m^2 with sleep apnea, 26.2 ± 9.8 kg/m^2 without sleep apnea	23 patients	Not reported	5× central sleep apnea with Cheyne–Stokes respiration, 2× obstructive sleep apnea, 2× above disorders together, 13.5 ± 8.1 points for excessive daytime sleepiness in CSA group, 9.4 ± 9.2 points for excessive daytime sleepiness without in group without CSA	Polysomnography, Medical interview, Epworth Sleepiness Scale

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TABLE 1 (Continued)

References	Country where the study was conducted	Patients' gender and number of cases	Patients' age	Patients' BMI	Enzyme replacement therapy receiving	Fabry disease variants	Sleep disturbances	Methods to confirm sleep problems
Rosa Neto et al. (23)	Brazil	11 female and 8 male participants	40.7 ± 15.1 years old	None	2 patients	Non-classic mutations: A143T and R118C.	9× insomnia/unrefreshing sleep, 10× quality sleep disturbances	Medical interview, Pittsburgh Sleep Quality Index
Duning et al. (24)	Germany	1 female participant	56 years old	None	1 patient	Not reported	1× central sleep apnea with Cheyne–Stokes respiration, 1× excessive daytime sleepiness	Polysomnography, Epworth Sleepiness Scale, Multiple sleep latency test

BMI, body mass index; REM, rapid eye movement; CSA, central sleep apnea.

The inclusion criteria encompassed a wide range of study types. Therefore, a number of tools were used to assess the quality of the studies. Tools established by the National Institutes of Health (NIH) were used to evaluate cohort and cross-sectional studies (25). Case–control studies were assessed using methodologies from the same institution. For cohort and cross-sectional research, a critical appraisal was done on the basis of 14 questions pertaining to study the conduct. Meanwhile, case–control studies were examined for bias on the basis of 12 different categories. Responses to each question could range from "yes," "no," "cannot determine," "not applicable," to "not reported." The overall quality of the studies could be categorized as one of the following: "good" which indicates a low risk of bias, "poor" which equates to a high risk of bias, and "fair" which indicates a moderate risk of bias. Specific criteria for overall assessment were not formulated, considering each study's unique details requiring individual assessment. The assessment for bias in the case report was done according to the Joanna Briggs Institute (JBI) critical appraisal tool (16). Quality assessment was done with a designation of "high" assigned if the study received 7 or more "yes" answers out of the 8 designated criteria. "Moderate" quality was attributed to studies that received 5–6 "yes" responses, while quality was considered to be "low" when ≤4 positive answers were received. Two researchers (BB and HM) performed the above procedure and compared the final results during the discussion.

3. Results

3.1. Search results

After the search for key terms was carried out, a total of 136 records were identified: 18 records from PubMed, 68 from Scopus, and 50 from Embase (MEDLINE). Of these, 55 were duplicate studies, 54 articles were deemed unrelated to the purpose of our review, and five non-English studies were excluded from our analysis. The remaining 22 articles were assessed for eligibility. Of these 22 publications, eight review studies and four records did not contain a description of sleep disturbances in patients with FD, and one was a book chapter. Finally, nine studies were included in our review (16, 17, 19–24, 26). Figure 1 presents a summary of our search. The main characteristics of the included studies are outlined in Table 1.

3.2. Quality of studies

Of the publications included in this review, five articles were cohort studies (16, 17, 19, 20, 23), two were cross-sectional records (21, 22), one was a case–control study (18), and one was a case report (24). The evaluation of study quality was guided by the National Institute of Health (NIH) tools for cohort and cross-sectional studies. In the cohort category, three studies were assessed as fair in overall quality (17, 19, 20), while two were deemed poor (16, 23). The two cross-sectional studies were also evaluated as being of poor quality (21, 22). Further details are available in Supplementary Table 1. For the case–control study, an NIH tool specially curated for the evaluation of this type of research was used. This case–control study was ultimately (18) deemed to be of

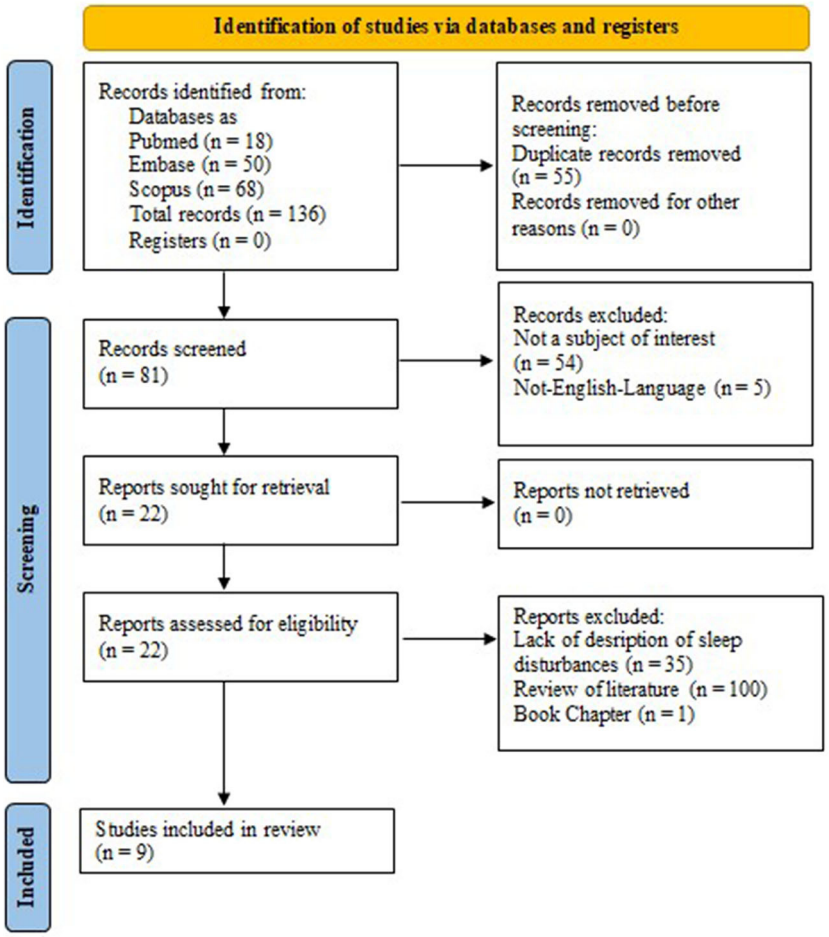

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses 2020 (PRISMA 2020) flow diagram.

poor quality. These ratings can be seen in Supplementary Table 2. Following the JBI checklist for case reports, the case report presented herein (24) received five "yes" marks and was rated as having moderate quality. A summary of this assessment is presented in Supplementary Table 3.

3.3. Included studies

3.3.1. Main characteristics

According to the methods described in Section 2.2, we identified nine studies detailing sleep disorders in patients with FD. These studies encompassed 330 FD patients, comprising 184 female and 146 male patients. Most studies included both male and female participants (16–18, 20, 21, 23). An exception was (19) which had solely focused on male participants and the case report (24) which had a female participant. Patients observed in the studies were of an average age of ∼40 years, with appropriate standard deviations. Only the female patient in the case report was in her 50s. The studies included patients whose FD was most commonly confirmed through genetic analysis of known mutations. However, a study (23) also analyzed patients with GLA gene variants that do not lead to substrate accumulation but do present with certain disease symptoms. In some of the studies, the body mass index (BMI) of patients was given along with the standard deviation; in three of the studies (17, 19, 20), the body weight of the observed subjects was within the normal range, while in one of them (22), it was possible to conclude that the study cohort was overweight. Within the collected data, 219 out of 330 patients (66.36%) were treated with enzyme replacement therapy (ERT).

3.3.2. Description and diagnostic methods of sleep disorders

Overall, sleep problems affected 213 out of 330 patients (64.5%). Excessive daytime sleepiness (EDS) was reported most frequently in six studies (17, 19–22, 24), assessed using the Epworth Sleepiness Scale (ESS). Two studies (17, 22) provided mean ESS scores, while the remaining studies (19–21, 24) mentioned the number of patients with EDS (scoring > 10 points). Hence, in these four studies, 43 out of 183 FD patients (23.5%) were diagnosed with EDS. In addition to the aforementioned scale, the multiple sleep latency test (MSLT) was also used for the diagnosis of EDS in one study (24).

Using the Pittsburgh Sleep Quality Index (PSQI) questionnaire (16, 23, 26), sleep quality over the previous month was measured and assessed through patient responses. Poor sleep quality was diagnosed in 42 out of 72 subjects (58.3%) included in these studies. The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) was used to diagnose disturbed muscle atonia and nightmares occurring during the rapid eye movement (REM) sleep stage (21), which is common in people with neurodegenerative disorders; 29 cases of REM sleep behavior disorder (RBD) were identified among 110 participants (26.4%) (21). Medical interviews conducted in studies by Rosa Neto et al. (16, 23) identified insomnia or unrefreshing sleep, affecting 26 out of 56 subjects (46.4%).

More objective and reliable approaches, such as polysomnography (PSG) or respiratory polygraphy, were utilized to evaluate sleep apnea in specific studies. This involved examining obstructive sleep apnea (OSA) in studies (17, 19, 20, 22), central sleep apnea (CSA) with Cheyne–Stokes respiration in studies (22, 24), and CSA without Cheyne–Stokes respiration in Franzen et al. (20). Additionally, the occurrence of periodic limb movement in sleep (PLMS) was also noted in Talbot et al. (19). Across all subjects under observation, 10 cases each of obstructive sleep apnea were identified in Gaisl et al. (17) and in Franzen et al. (20), eight were documented in Talbot et al. (19), and four cases were identified in Duning et al. (22) amounting to 32 instances among 147 patients (20.4%). Moreover, central sleep apnea accompanied by Cheyne–Stokes respiration was reported in five out of 23 patients in the study conducted by Duning et al. (22, 24). Franzen et al. (20) found three cases of central sleep apnea in a group of 52 patients. In Duning et al. (22), two participants were found to simultaneously exhibit the aforementioned disorders, resulting in CSA comprising 11.8%. Talbot et al., using polysomnography, diagnosed periodic limb movement in sleep in 19 male subjects out of a total of 20 participants (95%) (19). Furthermore, actigraphy was performed, detecting sleep parameters including time in bed (TIB), total sleep time, sleep efficiency, and the awakening index in Vallim et al. (26). However, no significant differences in these parameters were observed between FD patients and the healthy population.

4. Discussion

Several studies in recent years have focused on the quality of life experienced by FD patients. These studies revealed that, in addition to the characteristic symptoms of the disease, sleep disturbances are also common in this group. Despite this revelation, sleep-related problems are scarcely acknowledged within the description of the disease itself. Therefore, our systematic review focused on determining the prevalence of sleep-related disorders and sought to identify the specific sleep-related conditions diagnosed among FD patients. Although the majority of the studies were assessed to be of poor or fair quality, several conclusions can still be drawn.

A majority of the reviewed research originated from five specific countries. The largest studies came from Brazil, Switzerland, and Germany (16–18, 20, 22, 23). There were also individual reports from England and Australia (19, 21). It is unclear to us as to why there are no reports on this subject from other countries, especially highly developed ones such as the USA or Japan. Arguably, the prevalence of this X-chromosome-linked recessively inherited disease varies across different countries, and the studies mentioned above originated from regions with the highest concentration of FD patients. Additionally, in these areas, sleep problems were beginning to pose a serious medical challenge. It is also interesting to note that in the reviewed studies, 184 of 330 patients were women (56%) (27, 28). This is consistent with data from Japan, where a population screening for undiagnosed cardiac, renal, and cerebrovascular diseases showed that nearly 59% of new FD diagnoses were in women (29). In contrast, Arends et al. suggested that men with the classic form of the disease experience a more severe disease trajectory compared to men with the non-classic form and women with any form of the disease (30). Therefore, it remains unclear whether the prevalence of sleep disorders is higher among women, or it appears so because men did not want to participate in conducted studies. Thus, the true prevalence of sleep disturbances is yet to be accurately estimated.

Approximately 65% of patients diagnosed with Fabry disease experienced sleep problems. In terms of age, only three of the included studies provided data on the onset of FD and the age at which sleep problems were diagnosed. Gaisl et al. (17) and Löhle et al. (21) reported that the onset of FD occurred at 15.5 ± 7.8 years and ∼10–11 years before the manifestation of sleep disorders. On the other hand, Duning et al. (22, 24) indicated an onset range of 4–5 years before they conducted their studies. Therefore, these data remain inconclusive; while FD variants might provide an answer, only three articles (16, 19, 23) addressed this aspect. Unfortunately, some articles lacked a detailed diagnosis of sleep disturbances (16, 23, 26), and some of them presented inaccurate results, offering mean scores for EDS diagnosis instead of specifying the exact number of affected patients (17, 22). Notably, excessive daytime sleepiness (EDS) emerged as the most frequently reported complaint in the included studies, and it featured in six out of the nine studies. This is consistent with findings in other research studies (24), where the prevalence of this condition was estimated to be as high as 68%, whereas our calculation placed the prevalence of EDS at 23.5%. In contrast, within the European population, EDS occurs in approximately 18% of healthy individuals (20). The causes of EDS in the general population include factors such as sleep deprivation, circadian rhythm disorders, depression, nervous system abnormalities, obesity, narcolepsy, or sleep apnea (31). Notably, a study measuring body temperature and melatonin metabolite excretion revealed changes in the circadian rhythm of FD patients (26, 32). Furthermore, within this cohort, EDS was found to be more frequently associated with depression rather than with sleep-disordered breathing (especially with obstructive sleep apnea (20). While there is a well-proven association between increased EDS and a heightened risk for cardiovascular diseases and even cardiovascular mortality (33, 34), the FD studies (19, 20, 22) that encompassed sleep problems and cardiovascular patients' presentation did not establish a connection between cardiovascular system impairment and an increased prevalence of sleep problems. This implies the presence of other factors contributing to the occurrence of sleep problems, but this would require further studies. However, the included studies did not specifically indicate reported symptoms in particular patients. Even though these symptoms were described in a few articles, there were differences among the studies. Gaisl et al. (17) highlighted poor sleep quality and daytime sleepiness, Talbot et al. (19) reported

symptoms consistent with restless leg syndrome, Rosa Neto et al. (23) described insomnia and unrefreshing sleep, and Löhle et al. (21) presented a range of unrelated sleep disorder symptoms such as orthostatic problems, urinary dysfunction, constipation, depression, neuropathic pain, and impaired hearing. Therefore, it is hard to define primary symptoms apart from those characteristics of FD. This diversity of symptoms may arise from genotype–phenotype variations, distinct disease processes between males and females, and other organ impairments.

Sleep-related breathing disorders (SRBD) encompass a group of conditions characterized by the occurrence of respiratory arousals, which ultimately cause disturbances in sleep architecture and sleep fragmentation (35). There are four main types of SRBD, namely, obstructive apnea, central apnea, sleep-related hypoventilation, and sleep-related hypoxemia (36). Among the reviewed studies, five out of nine reported the presence of the first two conditions, with a prevalence of 20.4% for OSA and 11.8% for CSA. OSA is a breathing disorder characterized by intermittent reduction in airway patency due to airway collapse during sleep which leads, leading to hypoxemia, arousal, and sleep fragmentation, which can cause EDS (37). Its prevalence in the general population ranges from 9 to 38% (38). The causes of OSA include abnormalities in the activation and function of upper airway dilating muscles, a large tongue, tonsillar hypertrophy, or a large neck circumference, most often associated with obesity (39). Interestingly, most FD patients in certain studies had a body mass index (BMI) within the normal range. In cases where oral anatomy was taken into account by using the Mallampati score, no significant difference between FD patients and the control group was observed (17). Furthermore, throat diameters of FD patients were found to be within the normal range (19). It is worth noting that OSA is more prevalent in men (40), while the majority of the reviewed studies included women. The prevalence of OSA increases with age in both sexes (40) with an average age of patients, upon diagnosis of OSA, being approximately 40 years (with appropriate standard deviations). However, there are no available studies on OSA in FD patients who significantly differ in age. The hypothesis that glycosphingolipid deposition in upper respiratory muscles could disrupt their function and lead to nocturnal respiratory abnormalities has also not been confirmed (20). Nevertheless, deposits do accumulate in lung lysosomes, causing smooth muscle hyperplasia in the lower end of the bronchi, resulting in obstructive lung disease (41). The statistical analysis showed no association between the involved organs in FD and the presence of OSA (19) in contrast to the normal population where cardiac and cerebrovascular diseases are associated with OSA and CSA (42, 43).

In contrast, in CSA, the cause of sleep apnea is a transient decrease or temporary cessation of the respiratory drive originating in the respiratory center of the brain (44). The prevalence of CSA varies from 5 to 10% among clinic patients (45), with 11.8% of FD patients experiencing this condition. Risk factors for CSA include male sex, a history of stroke, opioid use, or heart failure. These factors are especially linked to CSA when it coexists with Cheyne–Stokes respiration (CSR) (45). Other causes can be physiological factors, muscle, endocrine, brainstem, or spinal cord disorders (46). In the study by Duning et al., there was no association between heart failure and CSA (22). Similar conclusions were drawn by Franzen et al. (20). Because of overlapping pathophysiological causes, clinical OSA and CSA can coexist (47), as observed in FD patients in the study by Duning et al. (22).

Given the pathomechanism of FD, changes in the central nervous system could also be expected. Indeed, using "gold-standard" imaging techniques such as magnetic resonance imaging (MRI), small vessel microangiopathy-induced white matter hyperintensities (WMH) were detected, emerging as the most frequent brain lesions in this patient group (48). Additionally, reduced brain volume and the presence of the pulvinar sign were mentioned (49). However, these neurological lesions are not distinct or specific to this syndrome (50). For example, WMH can manifest in aging populations and individuals with Parkinson's disease (51, 52), and the pulvinar sign has also been noted in conditions such as Creutzfeldt–Jakob disease and antiCV2 encephalitis (53). Given these considerations, brain lesions may have a link to sleep issues. Dunning et al. (22) used a diffusion tensor imaging (DTI)-based sequence that can detect even the smallest damage to brainstem neuronal networks on MRI. They found that there is a correlation between the extent of brainstem damage in FD patients and the severity of central sleep apnea with Cheyne–Stokes respiration (CSA–CSR). Moreover, similar changes in the white matter as seen in FD have been associated with sleep disturbances in Parkinson's disease resulting in shorter sleep duration among middle-aged adults (54, 55). However, the most recent studies by Kocevska et al. (56) and Li et al. (57) demonstrated a lack of association between global white matter lesions and sleep problems. It is worth mentioning that all participants in the Duning et al. (22) study had, including non-CSA patients, white matter lesions in the brain. The studies (22, 54, 55) comprised relatively small patient groups and were published before those of Kocevska et al. and Li et al. Additionally, the specific brain regions where these lesions occur could potentially influence the outcomes related to sleep problems. Therefore, more studies assessing brain changes and sleep quality, particularly in Fabry disease, are needed.

The genotypes of the disease play an important role in treatment, and ∼700 variants of FD have been identified to date. However, novel types and variants of unknown significance (VOUS) continue to be discovered (58, 59). Within the gathered group of patients, only two studies presented patient genotypes (16, 23), and one clearly showed the phenotypes (19). However, one of them (23) included variants that are not entirely associated with FD. As a result, we were unable to ascertain the relationship between specific FD variants and sleep problems or to indicate any particular trend in a certain type causing sleep problems. More studies are required to provide a comprehensive understanding of FD and its relationship with sleep problems. Thanks to genetic engineering, ERT is available for the treatment of FD. This therapy involves intravenous infusion of the missing enzyme α-galactosidase to patients. However, the amenable GLA variant could also be treated by pharmacological chaperone therapy (Migalastat), which is one of the oral regimens used for FD treatment (60). The indication for this treatment is determined by the manifestation of the disease and the accompanying symptoms of organ damage. However, in general, this therapy is recommended for all FD patients as it can reverse the organ changes caused by the disease (61). The included studies indicated that either all participants (22) or a smaller subset

(23) had received such treatment. It should, however, be noted that despite receiving treatment, sleep-related symptoms such as EDS persisted (22, 24), along with other sleep disorders. Duning et al. (24) also reported a lack of correlation between years of ERT and ESS results. Moreover, no guidelines for treating sleep disorders are included in the recommendations for adjunctive treatment of disease symptoms (62). Additionally, treatment options for affected patients were not presented in the included studies. Only Gaisl et al. (17) reported the use of continuous positive airway pressure (CPAP) therapy for OSA, but without follow-up information, the results remain unknown. There are pharmacological options for treating EDS (31) as well as the "gold-standard" CPAP therapy for OSA treatment. In cases of mild OSA, mandibular advancement devices (MAD), positional therapy, and weight loss therapy are used (63). However, there is a lack of evidence in the literature regarding the effectiveness of these treatment options for this specific patient group. Therefore, there is a need for further studies to explore the response of FD patients with sleep problems to these treatment approaches.

Various methods were used for the diagnosis of sleep disorders in patients within the reviewed studies. Polysomnography (PSG) serves as the "gold-standard" technique for identifying sleep disorders (64). PSG uses various techniques to measure sleep parameters, respiratory effort and airflow, oxygen saturation, heart rate and rhythm, limb movements, body position, and comprehensive behavioral monitoring using cameras (65). Unfortunately, only three out of nine studies used this objective examination to diagnose their patients. Two studies used respiratory polygraphy instead of PSG, while one study used actigraphy. However, compared to PSG, polygraphy may be inadequate for measuring OSA as it has limitations in detecting respiratory events associated with sleep arousal (66). On the other hand, actigraphy poorly identifies awake states and periodic limb movements, making it unsuitable as a substitute for PSG (67–69). Additionally, actigraphy cannot replace the multiple sleep latency test for evaluating EDS (70). During medical interviews, data were collected using scales that assess sleep problems, such as ESS or PSQI. The PSQI is used for the assessment of sleep quality and insomnia and is an important clinical tool for diagnosing these conditions (71, 72). Similarly, the ESS is effective in detecting EDS (73). However, the use of questionnaires and medical history alone, without the use of objective supplementary tests, only allows for the detection of vaguely defined medical conditions (16, 23, 26) and deprives the patient of an accurate diagnosis and numerous treatment options. Furthermore, the use of RBDSQ in Löhle et al. (21) identified the presence of REM sleep behavior disorder in FD patients although its prevalence was not higher than in the general population. While this questionnaire is efficient for population screening, neurological conditions such as Parkinson's disease require alternative diagnostic methods (57). In Talbot et al. (19), the medical history revealed that 15 out of 20 patients reported symptoms of restless leg syndrome (RLS), while PSG indicated abnormal periodic leg movements (PLMS) in 19 out of 20 subjects. However, it is also important to note that the two conditions are not the same. PLMS occurs in 80% of RLS patients and is often present without the typical symptoms of RLS (74). In FD patients, PLMS was associated with cardiac dysfunction and was not dependent on other risk factors such as anemia, iron deficiency, or neurological diseases (75).

Unfortunately, despite conducting a comprehensive systematic review of the available literature, this study does have certain limitations. First, only a limited number of studies, encompassing just five countries, have addressed the topic of sleep disorders in FD. Moreover, the included studies had a high or moderate risk of bias. Several of these studies lacked detailed diagnoses of sleep disturbances or provided inaccurate results, such as reporting mean scores for EDS diagnosis instead of specifying the exact number of affected patients. As a result, our analysis is restricted in its scope. Given these constraints, it is recommended that further studies on this topic be carried out with a larger group of patients by using objective diagnostic techniques. Additionally, further studies will help explain the response of FD patients with sleep problems to standard treatment, timeframe between FD onset and occurring sleep diseases, and relationship between sleep problems and FD genotypes and reported symptoms related to sleep problems in particular FD patients and correlation between gender and sleep disturbances. There is also a need to develop guidelines for the treatment of sleep disorders in FD patients, given that our review shows the prevalence of these issues among these patients.

5. Conclusion

This review has revealed the presence of many sleep-related conditions that significantly affect the quality of life of FD patients. Despite sleep disorders being more prevalent in the general population than in patients with FD, only a few studies on this subject are available in the literature. Moreover, existing results related to this topic are limited, which makes it difficult to accurately assess its true prevalence among patients with FD. Therefore, the attention of clinicians caring for these patients should be drawn to the careful assessment of potential sleep disorders in patients diagnosed with this condition. The authors would also like to emphasize the need for further research on this topic involving a larger group of subjects, explaining reported symptoms related to sleep problems, relationship between FD onset and age when sleep disturbances occurred, ERT action on sleep problems and, above all, for the creation of guidelines for the treatment of sleep disorders in patients with FD.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

BB and HM contributed to the study conceptualization and prepared the manuscript. BB, MK, HM, MW, and GL collected the data. BB, HM, and MW performed data analysis. GM supervised the study. HM and MW revised the final version

of the manuscript. All authors have reviewed and approved the manuscript for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Recovery from shift work

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One fifth of today's workforce is engaged in shift work and exposed to various mental and physical health risks including shift work disorder. Efficiently recovering from shift work through physical and mental interventions allows us to mitigate negative effects on health, enables a better work-life balance and enhances our overall wellbeing. The aim of this review is to provide a state-of-the-art overview of the available literature. The role of sleep timing and naps, light therapy and psychotherapy, diet and exercise in recovery from shift work is presented here. We further review the impact of shift schedules and social support on post-shift unwinding.

KEYWORDS

shift work, shift work disorder, circadian rhythm disorder, recovery, interventions

1. Introduction

Shift work plays an important role in today's workforce due to the continuous demand for availability and customer service in our economy as well as its role in public safety and health while offering various financial benefits. It's an essential work format in the health, transport, industry, commerce, and hospitality sectors (1). In total 21% of workers included in the sixth European Working Conditions Survey in 2015 reported engaging in shift work (1). The percentage of European workers aged 20 to 64 years old who regularly performed shift work in 2021 ranged from 6.8 to 33.6% (2) and thus stays somewhat similar to 2015. An increase in shift work in the Benelux over the last 10 years has also been observed (2). Shift work is defined in literature as work conducted outside the standard daylight working hours (7/8 am to 5/6 pm) and can entrail fixed or rotating shifts (1, 3). Shift work may thus expose workers to light during normal sleeping hours which disrupts normal sleeping patterns and causes circadian misalignment (4, 5). The change in the interaction between circadian and homeostatic processes when working a night shift leads to sleep loss, excessive sleepiness, and impaired alertness during work (6). Not surprisingly, an increased occupational and motor accident risk, the latter especially after night shifts, has been found, which can negatively impact the health of the shift worker and others involved (7, 8). A plethora of other health issues have been described concerning shift work as well.

Shift work disorder, a specific sleep disorder related to irregular work schedules, may affect up to 10% of shift workers (9). According to the International Classification of Sleep Disorders the prevalence of shift work sleep disorder is estimated to be 10 to 38% of workforce (10, 11). This disorder encompasses a persistent circadian-related sleep problem resulting in insomnia and/or excessive sleepiness in shift workers for at least 3 months, accompanied by a reduction in total sleep time. Moreover an increased risk of poor mental health (12), as well as a higher risk for the development of metabolic syndrome (13, 14), cardiovascular disease, in particular coronary heart disease (15), and gastrointestinal disease such as peptic ulcers (16, 17) have been reported. It seems vital that we seek interventions to limit or erase the negative impact of shift work on health. In this review, we will describe the recent literature on non-pharmacological as well as pharmacological (melatonin) interventions that can aid shift workers in their recovery from work.

Recovery from work has been defined as the process of psychophysiological unwinding after effort expenditure and has been described to mitigate some of the negative health risks mentioned above (18). As health professionals, it's important to minimize negative health outcomes for such a large proportion of our workforce including our colleagues.

2. Role of sleep and circadian rhythms

Sleep regulation is guided by the interaction between a homeostatic process, reflected in the amount of slow wave sleep, representing the sleep pressure accumulated during wakefulness, and a circadian process showing 24-h rhythmicity entrained to the light-dark cycle. Shift work induces sleep disturbances by disrupting the temporal relation between the two processes due to the adoption of irregular sleep schedules that are not aligned with the internal circadian clock and the external light-dark cycle (5). Shift workers suffer from chronic sleep deprivation, impaired sleep quality, and symptoms of insomnia or excessive daytime sleepiness that eventually could lead to alertness or cognitive deficits (19, 20). Obtaining sufficient and high-quality sleep after night shifts has been shown to enhance post-work recovery from fatigue in nurses (21, 22).

2.1. Traditional countermeasures

2.1.1. Recovery from sleep debt

Hypnotics and melatonin have been studied as means to extend sleep duration after night shifts. Although these drugs increased daytime sleep among shift workers, no significant effect on sleepiness and alertness during the shift was found, while their long-term efficacy and tolerance is a matter of debate (23, 24). However, they can be considered on an intermittent basis to counterbalance the cumulative sleep debt in shift workers with insomnia complaints.

2.1.2. Naps

Napping before or during the night shift may increase the total amount of sleep time obtained throughout the day and also improve performance and decrease fatigue during the shift (25). Moreover, napping during the shift resulted in a lower need for recovery after work, as has been shown in studies with nursing personnel (26–28). However, the phenomenon of sleep inertia and its negative effect on alertness immediately after waking from such naps could be a hindering factor, especially in professions where operational readiness is crucial (29).

2.1.3. Stimulants

Caffeine has been extensively studied as a stimulant for consumption during night shifts to promote vigilance and performance (30). Caution is required to avoid consuming it too late in the shift as it may interfere with the daytime recovery of sleep. Other stimulants, such as modafinil and armodafinil, have also been tested with favorable results (31, 32). While all these measures may reduce performance deficits during shifts, some level of residual sleepiness may persist, especially close to the circadian temperature nadir that usually occurs at about 4 a.m.

2.2. Sleep timing and circadian adaptation

A crucial factor that contributes to sleep and daytime complaints of shift workers is the desynchrony between the sleep-wake schedule forced by the socio-economical commitments and the internal circadian rhythm. Although there is significant inter-individual variability regarding tolerance to shift work, with influences from genetic-epigenetic factors (33, 34), age, and chronotype (35), the diurnal nature of the circadian system drives us to be alert at daytime and sleepy at night.

For shift workers on fixed schedules (night shifts only or rotating between evening and night shifts), chronotherapeutic approaches can be employed to phase shift the internal circadian clock and reduce the circadian misalignment (36). With this approach, the night-shift worker should aim to go to bed as early as possible after the shift to avoid longer exposure to morning light and excessive delay of the temperature nadir. A shift worker should try to obtain at least 7 h of sleep in a dark and quiet environment, except for the morning on his 1st day off after consecutive night shifts, when he should sleep somewhat shorter to build up sleep pressure for the following night. On days off, the worker should adopt a later bedtime and rise time, so the shifted temperature nadir remains inside the sleep period, and aim for nearly 9 h of continuous sleep, based on individual needs (Figure 1) (37). Apart from sleep timing, phase shifting of the light-dark cycle, using timed exposure to bright light during the night shift, is additionally important to facilitate circadian adaptation (37). In the same context, melatonin can also be used for phase shifting along with its soporific properties. Melatonin advances the circadian clock when taken in the afternoon/evening (for night workers who prefer to sleep before the shift) and delays it when consumed in the morning (for those who prefer to sleep after the shift) (38).

Chronotherapy, however, is not an option for shift workers on fast-rotating schedules that include day and night shifts and constitute the majority of shift systems in modern workplaces, especially in the health sector. For these workers, a combination of general behavioral approaches (sleep hygiene practices, scheduled naps, caffeine), timed light exposure and avoidance, melatonin use, and adequate planning of days off for recovery could apply to reduce the adverse effects of the shift work-induced circadian misalignment (39).

3. The effect of shift schedules on recovery

Apart from individual differences in adaptability to shift work, the specific shift schedules can also have an impact on the recovery process. Recovery can be defined as "the period of time that an individual requires to return to a normal or pre-stressor level of functioning following the termination of a stressor" (40). It can be assessed either behaviorally (performance, sleep, mood, wellbeing) or biologically (autonomic activity indicators, such as

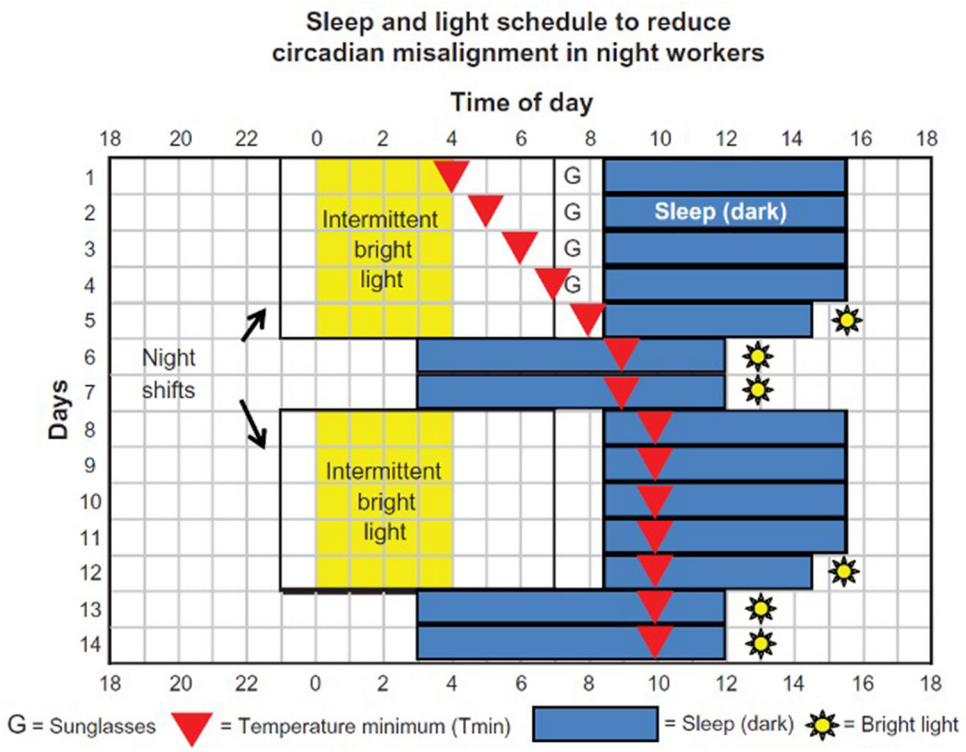

FIGURE 1
Process of phase shifting in permanent night shift workers using chronotherapy (37).

blood pressure and heart rate variability). An early report from Totterdell et al. (40) highlighted that most behavioral recovery measures were at their worst on the first rest day after a night shift in nurses and gradually improved on subsequent days, highlighting the need for two recovery days following 1 or more night shifts. Similarly, Malmberg et al. (41) concluded that physicians require two nights' sleep for a full recovery from a night call. Chung et al. (42) measured heart rate variability during sleep in nurses working on a rapidly rotating 3-shift schedule and found that 2 consecutive days off were needed to restore sleep-related autonomic regulation. However, other studies have reported shorter (43) or longer (44) periods for recovery than the conventional rule of having 2 days off. The direction of the rotating shift system has also been found to play a role in the recovery process, favoring forward over backward rotating schedules (45).

Past research has also tried to identify differences in recovery between various permanent night shift systems, namely the 2 + 2, 4 + 4, and 7 + 7 (night shifts + recovery days) schedules: while behavioral recovery measures favored the 7 + 7 schedule (46), autonomic function restoration was higher in the 2 + 2 schedule (47). More studies are needed to clarify which night shift schedule is more appropriate in terms of recovery.

4. The effect of other sleep disorders on recovery

Recovery from shift work can be more challenging when comorbid sleep disorders, causing excessive sleepiness, such as obstructive sleep apnea (OSA) and narcolepsy, are present or when maladaptive behaviors and cognitions about sleep lead to insomnia (10). Referral to a sleep specialist is crucial to differentiate between OSA and shift work sleep disorder, especially since both patient groups can score equally high on the Epworth Sleepiness Scale (ESS) questionnaire (48). Prevalence of OSA in shift workers is estimated in a recent systematic review between 14.3 and 38.1%, while only between 1 and 14% in the general adult population (49, 50). We note that another recent meta-analysis could not find an increased OSA prevalence in shift workers, although this finding was limited as not all included studies used polysomnography to diagnose OSA (9). To fully observe this effect, polysomnography during the daytime after a night shift is more meaningful than a classical nighttime polysomnography (51). Underdiagnosing OSA by performing a study during an unusual for the patient sleep period, may lead to under treatment. The effect of OSA treatment in this group needs to be monitored because remaining sleepiness might be caused by shift work sleep disorder.

5. Light and need for recovery from shift work

Light is the strongest synchronizing agent (zeitgeber) for the circadian system and the most important and effective factor affecting the health of shift workers (52). Light exposure history has been shown to have an impact on light sensitivity in humans, as assessed by the magnitude of the suppression of melatonin secretion by nocturnal light (53). Shift workers and especially night

workers are exposed to a substantial amount of unnatural light, which has been shown to suppress melatonin and aggravate the circadian misalignment between the internal circadian clock and activities (54).

Workers on long-lasting night shift schedules often experience a stabilized misalignment of the circadian rhythm with the day-night cycle and they appear to be less susceptible to the health risks associated with shift work (19). For these workers, attention should be paid to their nighttime alertness and preservation of their daytime recovery. According to the National Institute for Occupational Safety and Health (NIOSH) (55), increased light exposure during the first half of the shift can improve the alertness in this group. There is less concern regarding further phase delay through light exposure since their sleep period is constantly delayed. Moreover, bright light during the night shift could help preserve a stable pattern of melatonin secretion by assisting in the delay of circadian rhythms. In theory, melatonin can be secreted later to help initialize day sleep in a dark bedroom, but there is inconsistent data regarding this theory. Previous research has found that controlling light exposure can improve circadian alignment in individuals who work permanent night shifts (56). A recommended sleep-and-light schedule by Smith et al. (57) has these workers exposed to intermittent bright light during their night shifts, especially between midnight and 4:00 am, to gradually achieve through phase delay, a stable circadian rhythm. This stability is then preserved, even during the 2-day recuperation period of the weekend.

Scheduling and timing can get more complicated for employees working rotating shift schedules that cycle through progressions or who have on-call duties, including sporadic or rapidly rotating night work. In these cases, light-based intervention has been studied for both preventive and restorative purposes. A week of "preparation" with bright light during the day could alleviate the effect of light exposure during the late shift. Other studies demonstrated the same stabilizing effect after a duration of light exposure that ranged from 2 weeks to even a couple of days prior to the shift (58, 59). Studies have shown that exposure to additional light throughout the day before the shift can reduce the negative effects of evening and nocturnal light on sleep quality, melatonin levels, and circadian phase delays in healthy adults (60, 61).

Bright light can also act as a stimulant and improve alertness during evening or night shifts. A recently published systematic review and meta-analysis of 14 studies from 7 countries showed that lighting interventions, especially blue-enriched white light significantly improved the sleepiness of night-shift workers (62). A recent randomized controlled trial used the combination of evening light exposure and morning light avoidance in a group of healthy nurses who worked full-time rapidly rotating shift schedules. The researchers used the improvement of diet as a control intervention. Besides improvements in fatigue, sleepiness, and sleep duration, light interventions improved the mood and reduced the number of work errors (63).

NIOSH advises reducing light exposure during the second half of the shift, to facilitate sleep when workers get home (55). Sunglasses can block the alerting effect of daylight on the ride home and can facilitate the secretion of melatonin. On the other hand, strategies to improve health through the management of light for circadian (re) adaptation have been broadly explored. In 2019 the Working Time Society (WTS) and International Committee on Occupational Health (ICOH) published their consensus statements regarding evidence-based interventions using light to improve circadian adaptation to working hours (64). Interventions using natural or artificial light should be done extremely carefully to avoid further circadian disruption and should consider the type of shiftwork and the chronicity of time misalignment.

6. Diet and need for recovery after shift work

There is increasing evidence suggesting that eating time and frequency may significantly influence health of the general population, particularly in shift workers (65). Due to several factors ranging from voluntary to involuntary busy schedules, many shift workers eat at non-optimal times (66). The unpredictable nature of their work schedules can disrupt regular mealtimes, resulting in skipped or missed meals. This disruption of the circadian feeding timing can lead to erratic eating patterns and an increased tendency to opt for unhealthy food choices; many shift workers reach for convenience foods, which are often high in sugar, unhealthy fats, and lacking essential nutrients. These irregular dietary patterns of rotating shift workers were recently presented in a systematic review and meta-analysis (67).

Research indicates that shift workers tend to consume more junk food and sugary snacks compared to those on a regular 9-to-5 schedule (68). The consequences of these poor eating habits extend beyond weight gain and energy fluctuations. Irregular eating patterns have been associated with an increased risk of obesity, diabetes, cardiovascular diseases, and gastrointestinal issues (69, 70). Furthermore, inadequate nutrition can impact cognitive function, mood, and overall wellbeing. Lately, there are more data regarding the connection between nutritional circadian regulation and cancer prevention (71). Although described in the literature and widely assumed to be true, there is scarce evidence for food zeitgeber effects in human studies, as demonstrated in the recent review by Lewis et al. (72). In one study (73) the researchers succeeded in showing that meal timing has the capability of regulating the human circadian system and fulfills at least one of the zeitgeber criteria proposed by Aschoff (74).

Considering this low-grade evidence, the question remains whether adjustments to meal timing and composition could potentially reduce chronobiological strain and recovery from modern 24/7 lifestyles, such as shift work, in humans. It is accepted that timing of meals plays a vital role in optimizing energy levels and sleep quality, but when should the last meal be in relation to the first sleep period after a shift? Kogevinas et al. (75) studied the negative health outcomes of mistimed eating patterns and concluded that we should generally avoid eating 2 h or less before initiating sleep. This could be very important to the evening shift workers when they return home, to leave enough time between their last meal and the recovering sleep. Implementing this habit could be more difficult though for the night shift, because daytime sleep could be shorter and interrupted from hunger (76, 77). In a population of overweighted fixed night-shift workers, longer time interval between the last meal and sleep onset appeared to

be protective against dyslipidemia (78). Unfortunately, it is an unhealthy habit of night workers to shorten the interval till the sleep recovery of the shift and this has been shown to increase the total duration of diurnal sleep (79). In a research study of nighttime nurses, every hour decrease in the interval between the last meal and sleep onset there was an increase of 0.39 h on diurnal sleep duration. This nutritional misalignment has also been connected to increased risk for obesity (80).

Besides timing, shift workers are advised to thoughtfully schedule food intake during the evening and the night and opt for a healthy snack. Eating a large meal during the nightshift could impair cognitive performance and sleepiness above the effects of time of night alone (81, 82). The feasibility of fasting during the shift remains debatable, despite the possible positive effects (83). Shift workers could benefit from a short meal or a snack for social, hedonic, and stress-related factors. Scheduling and planning of meals are more important than dramatic measures like strict fasting because shift work and especially night schedules lead to a high caloric intake, even during the recovery days.

A healthy and balanced diet is crucial for mitigating health risks and enhancing the overall quality of life for shift workers. Their diet should focus on providing sustained energy throughout their shifts. Hence, consuming nutrient-dense meals that balance carbohydrates, proteins, and healthy fats is extremely important (84). This can be challenging because studies have shown that satiety decreases after a night shift (85) leading to the described tendency to overeat and turn to junk food. The study in the group of night nurses showed that an unbalanced diet can also affect recovery as every 1 g of fat and 1 g of carbohydrate consumed in the last meal before sleep was associated with an increase in diurnal sleep onset latency of 0.13 h (79). In addition to proper nutrition, hydration is crucial for shift workers. Staying hydrated throughout the shift can help combat fatigue, maintain alertness, and support overall health (86). It is essential to prioritize water intake and limit caffeine consumption and sugary drinks, as these can disrupt sleep patterns and lead to dehydration.

Given the negative impacts of irregular shiftwork eating behaviors, correcting these habits for a healthy lifestyle is essential. Healthcare specialists have proposed different methodologies ranging from psychological to medical interventions. The self-determination theory is the foremost step in correcting such disorders (87). Setting specific goals, planning meals in advance, and incorporating healthy snacks can promote adherence to a nutritious diet (88). The Centers for Disease Control and Prevention (CDC) (55) recommends several strategies for managing work hours, including meal planning, consuming high-protein meals during the shift, and avoiding heavy meals close to bedtime. These guidelines can help shift workers optimize their nutrition, maintain energy levels, and promote better sleep quality.

7. Role of exercise in recovery from shift work

Shift workers face significant challenges in maintaining a healthy lifestyle due to the lack of a proper exercise routine. Factors such as irregular work schedules and consequently sleep disruptions make it difficult for individuals to find the time and motivation for physical activity (89). Shift workers often experience higher levels of acute fatigue due to irregular sleep patterns and disrupted circadian rhythms. It has been documented, for example, that nurses struggle with moderate to high fatigue during inter-shift recovery, and the situation is even worse for the nurses working 12 h shifts (90). As an individual grows older, the combination of a sedentary lifestyle and the demands of shift work can further contribute to increased fatigue, reduced cognitive function, and decreased physical performance (90). These symptoms can also be present during days-off, creating a vicious circle (43).

Physical inactivity can exacerbate fatigue among shift workers, negatively impacting their performance, productivity, and overall wellbeing. A recent systematic review and meta-analysis aimed to compare physical activity and sedentary behavior in shift workers with non-shift workers (91). Interestingly, habitual levels of physical activity were similar for shift and non-shift workers, with only 41% of shift workers meeting physical activity guidelines. The writers pointed out the heterogeneity of the included studies regarding measurement and scoring of physical activity and the population bias: 50% of the scientific work included in the review studied nurses, which might explain the relatively comparable physical activity and the low sedentary time. In reality, sedentary time is prevalent in most workplaces that involve shift work (92). Moreover, the difference between physical activity and exercise needs to be highlighted.

According to Caspersen et al. (93) exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective to improve or maintain physical fitness. Due to disturbed natural circadian rhythm various physiological processes and lifestyle habits like exercise also become affected (94). The lack of regular exercise among shift workers has significant physical and mental health consequences (95). On the other hand, regular exercise could act in a preventive and recuperating way by helping shift workers establish a more stable circadian rhythm by promoting better sleep-wake patterns.

First and foremost, exercise could serve as a non-photic synchronizer of circadian rhythmicity, or a zeitgeber (96). Back et al. (97) have shown that physical exercises have non-photic effects that can positively impact the circadian timing system, thereby benefiting the health of individuals in various situations. The systematic review of Lewis et al. (98) showed that correctly timed exercise could help in maintenance of chronobiological homeostasis and improve general health in the unnatural modern work- and living environment. In this way, exercise could keep "winding" the internal clock, promoting better synchronization and improving sleep quality among shift workers. Appropriate timing of exercise may help adapt to a specific shift schedule or facilitate readaptation to a daytime schedule after the end of a shift (99).

A systematic review of physical activity-based interventions in shift workers in 2018 studied the efficacy of exercise promoting initiatives in this occupational group (100). The findings suggested that physical activity could mitigate intermediate health-risk factors in shift workers. More specific, a randomized controlled trial showed that the combination of a worksite exercise and behavioral intervention improved sleep duration and quality in shift workers (101). Regarding the timing of the intervention, it is important to mention that in this study the participant could choose from

several suitable time-windows for their exercise. This is important because a lot of workers struggle to incorporate physical exercises into daily routines.

Different studies have recently tried to objectify the recovery effect of such an intervention before the shiftwork. It is generally accepted that regular exercise improves cardiovascular health and enhances physical performance, allowing shift workers to better cope with the demands of their work. High-intensity interval training prior to night shift work has shown to improve physical work capacity and endothelial and vascular function (102). These results were not reproduced though in a larger study after an 8-week intervention with supervised high intensity physical activity three times a week. Another study also failed to show that general aerobic fitness is associated with the recovery after a 24 h shift, as shown from the parasympathetic cardiac control and heart rate variability (103). There is also a concern regarding the effect of training on the sleep schedule and the recovery during the days-off, especially in a rapidly rotating shift schedule. Incorporating a dense exercise schedule into the shift rotation could further exacerbate the circadian disruptions and impair the recovery (104). While there is literature showing no disturbance of sleep quality from close-to-bedtime exercise (105, 106), a recent systematic review and meta-analysis showed that sleep could be affected after vigorous exercise ending $\leq$1 h before bedtime (107). It is generally advised that extremely intense physical exertion should be avoided before the work shift so that recovery before the upcoming shift would be optimized.

Several national health organizations suggest prioritizing recovery and rest days by exploring different exercise options: considering a workout partner, following a flexible work-out plan, incorporating shorter workouts, utilizing breaks, and even finding opportunities at work (108, 109). A recent study (110) showed that a short but continuous training of moderate intensity elicited an anti-inflammatory effect and significantly reduced sleep fragmentation in shift workers. Lack of free time due to the particularities of shift working, is a factor that keeps many employees away from frequent training. Training facilities within the workplace and exercise during the shift-breaks could be a viable alternate (111). For example, isometric and isotonic exercises during the inter-shift break positively affected fatigue recovery of the control room staff of an urban railway (111). Another possibility is a smartphone-based home workout program. Such a program for shift-work nurses implemented by Baek et al. showed statistically significant improvements in physical and psychological health (112).

Thus, while there is a lack of solid evidence about the effect of exercise on recovery, incorporating training into the daily routine of shift workers can positively impact their overall wellbeing and ability to adapt to shift work schedules.

8. Effect of social support on burden of shift work

Sacrificing recuperative sleep for social obligations, such as childcare or planned activities, can be challenging and is even discouraged in the literature (113), in an effort to reduce the health and safety risks of a night shift. More often, social networking and activities are sacrificed due to rotating working hours, in an effort to create free time (114). Shift work can be inherently stressful due to irregular schedules, work demands, and the disruption of personal routines. Shift work can thus often lead to social isolation due to working unconventional hours. For a shift worker, the social consequences for their partner, their family and their social circle can be even more important than the biological ones they experience themselves (115). Not every worker is affected in the same way. Certain personality traits are a better match for shift work such as flexibility, extraversion, self-esteem and hardiness (116). Everyone though, can be, to a level, impacted by the fatigue and the stress in the modern 24/7 world. Up to 88% of night shift working nurses were impacted by negative psychological effects of their work, especially females with domestic responsibilities (117). Shift work can also have severe direct implications on a worker's family life, even leading to an increased risk for divorce. The absence of availability during normal social hours defined by our Western society can cause social desynchronization and work-family conflict (118).

The personal and social habits of shift workers can significantly impact their sleep patterns and overall wellbeing. This is true across different age ranges, although specific challenges may vary. Additionally, individual and social determinants of shift work tolerance change with the age of the worker. Younger individuals (18–30) may be more likely to engage in active social lives and late-night social activities, which can sometimes conflict with their shift schedules and the structured recuperation. A marginally elevated risk of excessive drinking among shift workers was often correlated with younger age (119). Younger shift-workers might be more prone to using caffeine and other stimulants to cope with irregular sleep schedules. Moreover, excessive use of screens before bedtime, which is common among younger generations, can contribute to sleep disturbances (120). Due to these displays emitting blue light of around 460 nm spectrum, which suppresses melatonin, release of melatonin is delayed and thus sleep onset as well in the general population as well as in shift workers (121–124). This effect can even last for more than 1 h after discontinuing use (121). When combining display light with general room lighting the side effects worsen. Night mode, meaning reduced brightness, on smartphones might prevent the suppression of melatonin (122). Limited evidence suggests that wearing blue-blocking glasses before bed might aid in diminishing sleep onset latency in workers with variable shift work schedules (125). On the other hand sleep time in general is decreased when using these devices before bedtime through bedtime procrastination (121, 122). Besides, depending on the contents watched, wakefulness might be increased (126). Sleep hygiene with limited and preferably no screen time before bed should thus be advised.

Smartphone apps however can be, thanks to their widespread use, of interest to aid in recovery from shift work through health self-management. Nunes et al. designed a smartphone application, "The Clockwork app" especially made for shift workers that allows them to visualize their sleeping habits, activity level and light exposure at work, but also provides recommendations to promote healthy habits and has a feature to enter their own shift schedule and swap shifts with colleagues (127).

Middle-aged workers (31–50) are more likely to have family responsibilities, such as caring for children or aging parents.

Juggling these responsibilities with shift work can lead to disrupted sleep. Older individuals (51+) often experience natural changes in their sleep patterns (128) and shift work can exacerbate these circadian clock changes, making it harder for them to get quality rest (129).

However, social networks are considered an independent determinant of health (114) and there is scientific evidence that social support could play a crucial role in mitigating some of the negative effects of shift work. Having a strong support network, such as friends, family, or colleagues, who understand and empathize with the challenges of shift work can provide emotional support (116, 117, 130, 131). They can offer a listening ear, encouragement and understanding, which can alleviate stress and help individuals cope better. Social support from family to optimize sleeping conditions at home is important as well (132). Additionally, workers who find comfort in religion cope better with the negative effects of shift work as well (130). This support reduces the burden on the individual, allowing them to better manage their responsibilities and reduce stress. Support can also be provided through opportunities for social interaction, reducing feelings of loneliness and enhancing overall wellbeing. Coping with loss of participation can include staying connected by social media and making new friends at work (133). Engaging in activities with friends or participating in social events organized by colleagues can help shift workers maintain a sense of connection and belonging.

Social support can also involve practical assistance, to further ease the combination of family and social life with shift work. Easy access to childcare facilities via the employer or the state, especially when both parents are at work, is vital (118). Family and friends can also step in to help with childcare and household chores. Further practical support via the employer, such as allowing employees to have a say in changes to their shift schedule may also be beneficial. Schedules with fast rotation in contrary to slow rotation may allow regain of social rhythm during parts of the week. There is no hard evidence available pointing to forward or backward rotation as the better choice. Having control over the work schedule improves the ability to attend and participate in social activities and balance the work-family interaction, even when working times are highly irregular and/or no actual change in working hours is observed (118).

Additional social support can be provided in the form of valuable information and advice. Colleagues who have experience with shift work can share strategies for managing sleep, staying healthy, and maintaining work-life balance. This exchange of information can be helpful in adapting to the challenges of shift work and finding effective coping mechanisms (130). Establishing peer support groups specifically for shift workers could be highly beneficial (116, 117). These groups provide a platform for individuals to share their experiences, exchange coping strategies, and offer mutual support. Being part of a community that understands the unique challenges of shift work can significantly improve wellbeing and resilience (130). It's important to note that social support is a two-way street. Individuals must actively seek and foster these connections by reaching out, communicating their needs, and reciprocating support when possible. Building and maintaining a robust social support network can go a long way in mitigating the negative effects of shift work and promoting overall wellbeing.

9. Psychotherapy and recovery from shift work

Psychotherapy can be valuable to mitigate some of the negative effects of shift work by addressing the psychological and emotional challenges that can arise from working non-traditional hours. Psychotherapy can provide support and strategies to cope with the challenges associated with shift work and facilitate the recuperation process. It's important to note that psychotherapy should be tailored to an individual's specific needs and circumstances. Consulting with a mental health professional, such as a psychologist or therapist, can help determine the most suitable therapeutic approach to support recovery from the effects of shift work. A therapist can help individuals develop effective coping strategies to manage the unique stressors associated with shift work. This may involve teaching relaxation techniques, stress management skills, and problem-solving techniques. Psychotherapy can also teach stress management techniques, such as mindfulness, cognitive-behavioral therapy (CBT), and problem-solving skills, to help individuals effectively cope with work-related stressors.

As mentioned before, shift work often disrupts the sleep-wake cycle, leading to sleep disturbances and insomnia (131). A higher workload and emotional work can more easily induce these symptoms (134). Psychotherapy can address sleep-related issues by implementing cognitive-behavioral techniques, such as sleep hygiene education, relaxation training, and addressing any underlying anxiety or depression that may contribute to sleep problems. A recent meta-analysis by Reynolds et al. (135) however showed a not significant decrease in mean symptom scores for Insomnia Severity Index (ISI) and Pitsburg Sleep Quality Index (PSQI) after cognitive-behavioral therapy for insomnia (CBTi). This may be explained by the importance of a strict and consistent schedule for behavioral therapy (including sleep restriction and stimulus control therapies) to succeed, which is hard to adhere to when working a rotating schedule. Increased somnolence and reduced vigilance during working hours due to sleep restriction might also pose health risks for workers and diminish adherence even further. Increased compliance can be reached when we take these considerations into account. There is a need for studies that implement tailored CBTi interventions for this specific population. On the one hand study design might benefit from patients' input, on the other hand types of CBTi that work faster such as Intensive Sleep Retraining need to be investigated (135). Sleep restriction therapy could also be implemented in a stepwise manner and patients that suffer from increased somnolence as stated above might benefit from a more flexible sleep window (132).

In a recent study, Li et al. (136) found that nurses that work in shifts are at greater risk for depression and anxiety. A meta-analysis by Lee et al. (137) showed a 40% risk increase for depression for night shift workers regardless of gender, occupation or shift duration. Psychotherapy can provide a safe space for individuals to express their emotions, process work-related challenges, and develop emotional regulation skills. There is very limited evidence showing a positive effect of mental health interventions such as mindfulness and meditation-based interventions available for workers in general (138, 139). Sadly, there is no data available for shift workers in particular.

As shift work has been associated with increased risk of various health issues, such as cardiovascular problems, obesity, and gastrointestinal disorders (16, 140–142) psychotherapy can help promote health and improve work-life balance by guiding individuals to adopt healthier lifestyle habits, such as proper nutrition, regular exercise, and stress reduction. Furthermore, balancing work and personal life can be particularly challenging for shift workers. Shift work requires significant adjustments in one's lifestyle and social interactions. A therapist can assist in navigating these adjustments and provide guidance on maintaining work-life balance, managing relationships and time effectively, setting boundaries to ensure overall wellbeing and developing strategies to create a more balanced and fulfilling lifestyle.

There is very scarce literature about health promotion in shift workers. Data about a consultancy agency providing a 4-h workshop including advice about healthy food options and advice on work-life balance as well as how to improve alertness and sleep quality and reduce sleepiness, showed a higher number of participants reporting an improved feeling of overall health, mainly less gastrointestinal complaints, believing to have found a better work-life balance and having more sleep time, after the course. The data that is available is promising though only related to at work health promotion courses (143). Psychotherapy can offer the patient more than only health promotion as stated in this review and can offer anonymity. Therapeutic interventions, such as cognitive training exercises and techniques to improve focus and mental clarity, can be incorporated into the treatment plan. Scientific data to support this advice in shift workers are to our knowledge not available and are therefore needed in the future. Psychotherapy can help in managing and treating shift-work disorder through a combination of behavioral interventions, sleep hygiene strategies, and possibly referral to a sleep specialist if necessary. Online and in-patient formats can be equally successful. An online CBT-I treatment course would benefit workers who would prefer to stay anonymous and have difficulties attending therapy sessions at certain daytime hours (144).

It's important to note that the specific approach and techniques used in psychotherapy will depend on the individual's needs and the therapist's expertise. Consulting with a qualified mental health professional will ensure personalized and effective support for managing the challenges associated with shift work.

10. Conclusion

Shift work often involves irregular working hours, disrupting the body's natural circadian rhythm and placing significant strain on individuals. As a result, there is a pressing need for recuperation after engaging in such work. The human body thrives on stability and routine, and when this balance is disrupted, it can lead to a myriad of physical and mental health issues. Post-shift recuperation is essential to allow workers to restore their energy levels, promote restorative sleep, and maintain overall wellbeing. It provides a valuable opportunity for individuals to engage in activities that promote relaxation, self-care, and stress reduction, helping them recover from the physical and psychological demands of shift work. Recuperation periods also allow workers to spend quality time with family and friends, fostering social connections and enhancing their overall quality of life. Furthermore, adequate rest and recovery enable individuals to return to work feeling refreshed, rejuvenated, and better equipped to perform at their best, ultimately improving productivity and job satisfaction. In conclusion, the need for recuperation after shift work is undeniable, as it plays a crucial role in maintaining the health, wellbeing, and overall effectiveness of shift workers.

Author contributions

SD: Data curation, Writing—original draft, Writing—review & editing. AK: Conceptualization, Data curation, Methodology, Supervision, Writing—original draft, Writing—review & editing. DP: Data curation, Writing—original draft, Writing—review & editing. DT: Supervision, Writing—review & editing. BB: Supervision, Writing—review & editing.

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Heart rate variability during sleep in synucleinopathies: a review

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Synucleinopathies are a group of neurodegenerative diseases characterized by abnormal accumulations of insoluble alpha-synuclein in neurons or glial cells. These consist of Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA). Moreover, idiopathic REM sleep behavior disorder (iRBD) is often the first manifestation of synucleinopathies, demonstrating a pathophysiological continuum. While these disorders vary in prevalence, symptom patterns, and severity, they can all include autonomic nervous system (ANS) dysfunction, which significantly reduces quality of life and worsens prognosis. Consequently, identifying abnormalities of the ANS can provide opportunities for improving quality of life through symptomatic treatments that are tailored to the individual's symptoms. An exciting development is using heart rate variability (HRV) as a non-invasive research tool for analyzing how the ANS regulates physiological processes. HRV during sleep, however, may provide a more accurate and reliable measure of ANS activity than during wakefulness, as during awake time, ANS activity is influenced by a variety of factors, including physical activity, stress, and emotions, which may mask or confound the underlying patterns of ANS activity. This review aims to provide an overview of the current knowledge regarding sleep-related HRV in synucleinopathies and to discuss contributing mechanisms. Evidence suggests that iRBD, PD, and MSA are associated with nocturnal ANS dysfunction. Further, comparative studies indicate that the presence of RBD could exacerbate this abnormality. In contrast, no studies have been conducted in patients with DLB. Overall, this review provides new insight into the complex interplay between the ANS and synucleinopathies and underscores the need for further research in this area to develop effective therapies to improve sleep and overall quality of life in patients with synucleinopathies.

KEYWORDS

heart rate variability (HRV), synucleinopathies, Parkinson's disease, sleep, Alzheimer's disease, Lewy body dementia, multiple system atrophy, rapid-eye-movement sleep behavior disorder (RBD)

Introduction

Synucleinopathies are a group of neurodegenerative disorders characterized by abnormal aggregation of alpha-synuclein protein in the brain. These conditions include Parkinson's disease (PD), multiple system atrophy (MSA), and dementia with Lewy bodies (DLB). Rapid eye movement (REM) sleep behavior disorder (RBD) is an early manifestation of synucleinopathies (1–4). Sleep disorders including RBD are common in synucleinopathies, and can significantly impact quality of life (5, 6). In PD, RBD prevalence ranges from 35%

to 50%, while in MSA it can be as high as 90% (7–9). Currently, however, there is no evidence that juvenile-onset RBD, such as would be associated with narcolepsy, is associated with synucleinopathies. Due to the lack of non-invasive biomarkers, there are no good treatment options, resulting in worsened quality of life (5).

During sleep, heart rate variability (HRV) serves as an objective, non-invasive assessment of autonomic nervous system (ANS) function in people with neurodegenerative disorders (10). HRV reflects beat-to-beat heart rate variation and is regulated by the ANS. Sleep stages and circadian rhythms influence HRV. For example, the parasympathetic nervous system (PNS) dominates during non-REM (NREM) sleep, particularly during deep sleep (slow-wave sleep), resulting in increased HRV (11). Conversely, during REM sleep, the sympathetic nervous system dominates, reducing HRV (12). Furthermore, circadian factors influence HRV, with HRV being highest during the nighttime and lowest during the daytime (13). Synucleinopathies reduce HRV during sleep, possibly related to the degeneration of brain regions controlling the ANS (14, 15). Thus, HRV analysis during sleep may provide insights into potential biomarkers, therapeutic interventions, underlying mechanisms of autonomic dysfunction, and early warning signs for disease progression and complications.

Sleep-related heart rate variability (HRV) can be analyzed in several ways, including time-domain, frequency-domain, and non-linear analyses (14). Time-domain analysis measures the variation in intervals between successive heartbeats. Commonly used time-domain measures of HRV during sleep, which provide general information about ANS activity, are the standard deviation of normal-to-normal (NN) intervals (SDNN), root mean square of successive differences (RMSSD), and percent of NN intervals that differ by more than 50 ms (pNN50). Frequency-domain analysis uses Fourier transform to convert time-domain signals into frequency components. The three standard frequency-domain measures of HRV during sleep are low-frequency power (LF; 0.04–0.15 Hz, proposed to represent combined sympathetic and parasympathetic influences and baroreflex modulation), high-frequency power (HF; 0.15–0.4 Hz, proposed to represent parasympathetic influences), and the ratio of LF to HF, which is thought to represent sympathovagal balance (16). Table 1 describes these and additional HRV measures. Non-linear analysis measures the complexity of heart rate signals using complex mathematical models. Non-linear measures of HRV during sleep include approximate entropy (ApEn), sample entropy (SampEn), and detrended fluctuation analysis (DFA). Despite non-linear analyses providing new insights into HRV, applications to clinical outcomes are unclear and therefore this analysis will not be discussed further in this review. Rather, this review will summarize available literature exploring HRV during sleep in patients with synucleinopathies including RBD (Table 2).

As previous meta-analysis (36) has synthesized differences in HRV between patients with PD, mostly during awake studies, this narrative review aims to provide an overview of the current knowledge concerning sleep-related HRV in synucleinopathies and discuss potential contributing mechanisms. The PubMed database was searched by using the keywords "Heart rate variability" AND "sleep," AND "alpha synucleinopathies," OR "Parkinson's disease," OR "Alzheimer's disease," OR "Rapid eye movement sleep behavior disorder," OR "multiple system atrophy" OR "dementia with Lewy Bodies." We selected only those articles that measured HRV during sleep in synucleinopathies based on the title and abstract.

TABLE 1 Heart rate variability measures and abbreviations.

Metric (Abbreviation)	Relevance
Temporal domain analysis	
RR Interval (RR)	Interval between successive R waves in the QRS complex measured in time
RR50	Represents the number of subsequent RR intervals that differ by more than 50 ms
Normal-normal interval (NN)	Interval between normal/normalized successive R waves in the QRS complex measured in time
Standard deviation of NN intervals (SDNN)	The standard deviation of NN intervals during a period of interest
Standard deviation of the average NN intervals (SDANN)	The standard deviation of the averages of NN intervals during 5 min segments of the entire recording
Number of adjacent NN intervals differing > 50 ms from previous (NN50)	Requiring a 2 min epoch, NN50 notes the number of adjacent NN intervals that differ from each other >50 ms
Percent of NN intervals differing > 50 ms from previous (pNN50)	Requiring a 2 min epoch, pNN50 notes the percentage of adjacent NN intervals that differ from each other >50 ms
Root mean square of successive differences of NN intervals for period of interest (RMSSD)	Reflecting beat-to-beat variance in heart rate, RMSSD is the root mean square of successive differences between normal heartbeats.
Frequency domain analysis	
High frequency power (HF)	HF band (0.15–0.40 Hz) reflects parasympathetic activity
High frequency power normalized units (HFnu)	HF power normalized to total power
Low frequency power (LF)	LF band (0.04–0.15 Hz) reflects both sympathetic and parasympathetic activity
Low frequency power normalized units (LFnu)	LF power normalized to total power
Very low frequency power (VLF)	VLF band (0.0033–0.04 Hz) reflects parasympathetic activity and denotes non-autonomic renin-angiotensin system effects
Ultra-low frequency power (ULF)	ULF band (≤0.0033 Hz) implicated in very slow-acting biological processes
Ratio of LF to HF (LF/HF)	LF/HF ratio is associated with sympathovagal balance. A low LF/HF ratio reflects parasympathetic predominance; a high LF/HF ratio reflects sympathetic predominance.
Total power (TP)	Reflects total HRV through variance of all NN intervals. TP is the sum of energies in the ULF, VLF, LF, and HF bands during a 24 h period and the VLF, LF, and HF bands for short-term recordings.

TABLE 2 Available literature investigating heart rate variability in synucleinopathies.

References	Country	Disease	N	Study design	Methods	Results/Findings
Abele et al. (17)	Germany	SAOCA and MSA	Sleep study: 7 MSA 3 SAOCA 5 Controls Wakefulness study: 17 MSA 17 SAOCA 17 Controls	Case-control	• Analyzed standard 8-h PSG in sleep for two consecutive nights • Analyzed 300 second body-movement-free periods from stages: NREM2, NREM3/4, REM, and wakefulness prior to sleep • Frequency domain values computed: HF, LF, HF/LF	• Significantly increased HFnu in MSA compared with SAOCA during-REM sleep and compared with controls while awake, during REM-sleep, and during NREM3/4.
Bugalho et al. (18)	Portugal	iRBD and PD	10 iRBD 18 PD with RBD 8 PD without RBD	Comparative	• Analyzed 5-min epochs selected from wake, NREM, and REM • Time domain values computed: NN, SDNN, and RMSSD • Frequency domain values computed: LF and HF	• No HRV differences found between PD and iRBD groups. • Lower HF values found in patients with IRBD compared to patients without iRBD
Brisinda et al. (19)	Italy	PD, MSA	23 PD 13 MSA 40 Controls	Case-control	• Frequency domain values computed: LF, HF, and LF/HF ratio	• Both PD and MSA patients had significantly lower LF and HF during sleep and wakefulness
Covassin et al. (20)	USA	PD	18 PD with RBD	Retrospective	• Analyzed 2 min from every sleep stage • Frequency domain values computed: LF, HF, and LF/HF ratio • HRV measures were averaged for NREM and REM sleep periods. Average overnight values were also calculated.	• Significant negative relationships between the HF during REM and the H&Y Score and UPDRS total score • Overnight LF/HF ratio was positively related to the H&Y staging, UPDRS total score, rigidity, and hypokinesia
Dijkstra et al. (21)	Belgium	iRSWA	49 iRSWA 41 Controls	Case-control	• Analyzed 5-min epochs of ECG data during wake (at rest), N2, and REM • Time domain values computed: NN and SDNN • Frequency domain values computed: VLF, LF, HF, and LF/HF ratio	• Median NN intervals were smaller in the iRSWA group than in the control group during all stages of sleep, but the difference was not statistically significant.
Ferini-Strambi and Smirne (22)	Italy	PD, AD, MS, and RBD	26 PD 16 AD 25 MSA 14 RBD 15 Controls	Case-control	• Standard 8-h PSG from two consecutive nights. • Sleep stages scored according to Rechtschaffen and Kales • Evaluated RR interval., $R_{s/w}$, R_{bm}	• More than one third of patients with presenile AD had defective cardiac control. • Untreated PD patients showed predominantly defective parasympathetic (decrease $R_{s/w}$), and to a lesser extent sympathetic (decrease R_{bm}), function during sleep.
Haapaniemi et al. (23)	Finland	PD	54 Untreated PD 47 Controls	Case-control	• HRV analysis conducted using 24-h ambulatory ECG • Frequency domain values computed: LF, VLF, and HF	• Patients with PD had significantly lower SDNN, VLF, LF, and HF values compared to controls. • Patients with mild hypokinesia had higher HF values than patients with more severe hypokinesia
Kitae et al. (24)	Japan	MSA	7 MSA 7 Controls	Case-control	• Time domain value computed: RR50 • Frequency domain values computed: LF, HF power (measured every 5 min) • Differences in the averages between SBP, DBP, PR, HR, RR50, LF and HF between waking and sleeping periods were also computed.	• Compared to controls, MSA patients had lower RR50, LF, and HF values during sleep • Controls had significantly lower LF/HF ratio during sleep than during the waking period, but patients with MSA did not

(Continued)

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TABLE 2 (Continued)

References	Country	Disease	N	Study design	Methods	Results/Findings
Kasanuki et al. (25)	Japan	DLB, AD	30 Probable DLB 30 Probable AD 20 Controls	Case-control	• HRV determined through 5-min EEG recording of RR intervals. • Time domain values computed: NN, SDNN, pNN50, and RMSSD • Frequency domain values computed: VLF, LF, HF, and total spectral power	• DLB group showed significant decreases compared to AD group in almost all HRV parameters including SDNN, pNN50, RMSSD, VLF, LF, HF, and total power.
Lanfranchi et al. (26)	Canada	iRBD	10 iRBD 10 Controls	Case-control	• Analyzed 5-min segments from stages NREM, and REM • Time domain values computed: NN, SDNN, and pNN50 • Frequency domain values computed: LF, HF, total power, and LF/HF ratio	• HF, and HFnu components decreased from NREM to REM in controls but did not change in RBD subjects • LFnu and LF/HF increased from NREM to REM sleep in controls but remained stable in RBD subjects.
Mastrocola et al. (27)	Italy	PD	13 PD 13 Controls	Case-control	• HRV analysis conducted using a continuous 24-h ECG • Time domain value computed: mean SDNN intervals • Frequency domain values computed: LF and HF	• PD patients had reduced SDNN and LF during the full 24-h period compared to controls • PD patients had reduced SDNN, LF, and HF during the night compared to controls
Niwa et al. (28)	Japan	PD	27 PD 30 Controls	Case-control	• HRV analysis conducted using 24-h ambulatory ECG • Frequency domain values computed: total frequency LF, HF, and LF/HF ratio	• Total frequency component and LF/HF ratio were lower in PD patients • Compared to controls, PD patients had lower HF in bed, but higher HF out of bed
Palma et al. (16)	Spain	PD	33 PD 29 Controls	Case-control	• Analyzed 10-min transformed and averaged epochs throughout sleep periods: REM, N1–N2, N3, wakefulness before sleep (W-pre), and wakefulness after sleep (W-post). • Time domain values computed: NN and SDNN • Frequency domain values computed: ULF, VLF, LF, HF, and LF/HF	• Mean RR intervals were significantly lower in PD patients than control subjects in all sleep stages, except in N1–N2. • There were no significant differences in the SDNN parameter in any sleep stage. • For PD Patients: ULF was lower during N3, VLF and LF were lower during REM, and HF was lower during N1–N2 • In PD patients, UDPRS-ON and UPDRS-OFF were inversely correlated with VLF and LF during REM
Pyatigorskaya et al. (29)	France	PD	52 PD 24 Controls	Case-control	• HRV analysis conducted using continuous overnight ECG monitoring • Frequency domain values computed: LF, LFnu, HF, and HFnu	• PD patients had significantly lower LF and higher HF compared to controls during REM sleep.
Pursiainen et al. (30)	Finland	PD	44 PD 43 Controls	Case-control	• Time domain values computed: SD intervals • Frequency domain values computed: LF and HF	• PD patients had reduced LF and HF during the night compared to controls • The night-to-day ratios of HRV measures did not differ significantly between patients and controls.

(Continued)

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TABLE 2 (Continued)

References	Country	Disease	N	Study design	Methods	Results/Findings
Sauvageot et al. (31)	Luxembourg	PD	35 PD 35 Controls	Case-control	• HRV analyzed in stages: NREM 1–4 and REM • Time domain values computed: NN and pNN50 • Frequency domain values computed: VLF, LF, HF, and LF/HF ratio	• RR intervals and pNN50 did not change significantly from NREM to REM sleep or between PD patients and controls. • Compared to controls, PD patients had significantly lower LF values and higher HF values in both NREM and REM • LF/HF ratio remained significantly lower in PD patients than in control subjects, both in NREM and REM
Sorensen et al. (32)	Denmark	iRBD, PD	11 iRBD 14 PD with RBD 16 PD without RBD 17 Controls	Case-control	• Heart rate response (HRR) was measured instead of typical time or freq domains • HRR to arousals or Leg Movement was estimated by calculating the change in RR intervals in the ECG signal and determining the area under the curve (AUC) for the HR change (HRC) from 10 beats before to 15 beats after the onset of the events. • Heart rate response associated with arousal or leg movement from all sleep stages were analyzed.	• The heart rate response to arousals was significantly lower in both Parkinsonian groups compared with the control group and the iRBD group in N2 and REM • The heart rate response to leg movement was significantly lower in both Parkinson's groups and in the iRBD group compared with the control group. In N2 and REM
Sorensen et al. (33)	Denmark	iRBD and PD	11 iRBD 10 PD with RBD 13 PD without RBD 10 Controls	Case-control	• 5-min ECG segments taken from wakefulness, and non-REM and REM sleep • The 5-min wake was selected from the pre-sleep period and the 5-min NREM 2 was selected from the beginning of the night. • Where possible, the 5-min REM sleep was selected from the last REM period, as this tended to be the longest period of REM in most subjects. • Time domain values computed: NN, SDNN, RMSDD, NN50, and pNN50 • Frequency domain values computed: VLF, LF, HF, and LF/HF ratio	• For the iRBD patients, only the VLF component in the wakefulness stage was significantly different (lower) from the control group. • For the PD patients, SDNN, VLF, and LF were significantly lower than the control group in the wakefulness stage.
Salsone et al. (34)	Italy	RBD and PD	20 PD with RBD 20 PD without RBD	Comparative	• A circadian (24-h) HRV recording was performed in all patients (patients were independent in their activities) • The mean values of the different measures of the nighttime (from 10 p.m. to 6 a.m.) and daytime (from 9 a.m. to 10 p.m. and from 6 a.m. to 9 a.m. of the next day) HRV were calculated • Frequency domain values computed: LF and HF	• Both nocturnal LF and HF spectral power values were significantly higher in PD-RBD patients than in PD patients • PD-RBD patients LF and HF values were higher at night than during the day while no difference between nighttime and daytime values was observed in patients with PD.
Yang et al. (35)	South Korea	iRBD (RSWA)	47 iRBD 26 Controls	Case-control	• Analyzed first 5 min with stable ECG in each stage: N2, Wake, and REM • Time domain values computed: NN, SDNN, and RMSDD • Frequency domain values computed: LF and HF	• iRBD group showed reductions in SDNN, RMSSD, and HF values. • Quantified tonic RSWA was negatively correlated with LFnu values and the LF/HF ratio and postively correlated with HFnu values.

AD, Alzheimer's disease; DBP, diastolic blood pressure; ECG, electrocardiogram; H&Y, Hoehn and Yahr score; HF, high frequency; HRV, heart rate variability; iRBD, idiopathic REM sleep behavior disorder; LF, low frequency; MSA, multiple systems atrophy; N2, non-rapid eye movement (NREM) stage 2; N3, NREM stage 3; NN, normal-to-normal; nu, normalized units; PD, Parkinson's disease; PSG, polysomnography; pNN50, percent of normal-normal intervals differing >50ms from previous; PR, pulse rate; REM, rapid eye movement sleep; RMSDD, root mean square of successive differences; RR interval, interval between successive R-wave in QRS complex on ECG, RSWA, REM sleep without atonia; $R_{s/w}$, an index of tonic heart rate decrease induced by sleep; R_{bm}, the ratio of longest RR interval before body movement to shortest RR interval after body movement; SBP, systolic blood pressure; SDNN, standard deviation of normal-to-normal (NN); SAOCA, sporadic adult onset cerebellar ataxia intervals; UPDRS, Unified Parkinson's Disease Rating Scale; ULF, ultra-low frequency power; VLF, very low frequency.

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Sleep-related heart rate variability in idiopathic REM sleep behavior disorder

RBD is characterized by REM sleep without atonia (RSWA) and dream-enactment behavior and is an early manifestation of synucleinopathies (37). RBD in individuals without a diagnosis of PD, DLB, or MSA is termed idiopathic RBD (iRBD), and termed symptomatic RBD in individuals with these diagnoses. Longitudinal cohort studies show that >80% of patients with iRBD diagnosed with a neurodegenerative disease over 12 years of follow up (3, 37, 38). Several case-control studies evaluated HRV comparing iRBD or RWSA to controls.

One case-control study showed that patients with iRBD had decreased cardiac autonomic function (35). The authors evaluated the first 5-min each of stages N2, REM, and wake recorded during video polysomnography (PSG). Compared to controls, the iRBD group showed reductions in SDNN, RMSSD, and HF values. Furthermore, quantified tonic EMG activity was inversely correlated with normalized LF values (LFnu) and LF/HF ratios and positively correlated with normalized HF values (HFnu). These results suggest that parasympathetic activity is disrupted in iRBD.

Another study (22) evaluated the ratio of R-R intervals preceding and following body movements during NREM and REM sleep in 14 patients with RBD compared to 14 matched controls. Notably, four of the RBD patients in this study had other neurodegenerative diseases (Alzheimer's disease, PD, or MSA). There was a decrease in the R-R interval ratio (reduced tachycardic response) related to body movements during REM sleep and NREM in RBD compared to controls. There were no differences between idiopathic RBD and symptomatic RBD.

One retrospective study evaluated 10 patients with iRBD compared to 10 matched controls (26). The expected increase in LF and LF/HF and the expected decrease in HF in the transition from NREM to REM sleep occurred only in controls but was absent in iRBD. Thus, the typical sympathetic predominance during REM sleep appears to be lost or decreased in iRBD.

One case-control study investigated individuals with iRWSA (21), finding no significant differences in HRV time or frequency domains during wakefulness or the first 5 min of the first N2 and last REM stages compared between 33 individuals with iRSWA and 28 controls (21). In addition, this study reported a non-significant reduction in NN during wake and NREM in individuals with iRSWA compared to controls. Taken together, case-control studies in iRBD suggest that there may be both sympathetic and parasympathetic dysfunction measurable during sleep through HRV. However, more research in larger cohorts is needed to fully understand sleep-related HRV changes in RBD.

Sleep-related heart rate variability in idiopathic Parkinson's disease

The prevalence of ANS dysfunction in PD patients, which includes constipation, urinary dysfunction, erectile dysfunction, and orthostatic hypotension, is estimated to be between 50% and 70% (15). Because dysautonomia can occur during prodromal stages of PD, monitoring HRV parameters may aid in earlier diagnosis (15). Several case-control studies assessed sleep-related HRV parameters in both time and frequency domains in PD. The studies found that PD patients have altered cardiac autonomic function during the night or during sleep compared to controls.

Three studies evaluated 24-h ECG for HRV in PD and matched controls. One study (27) compared 13 PD and 13 controls and found significantly reduced SDNN, LF, and HF in PD compared to controls during nighttime hours. PD patients also had reduced SDNN and LF during the full 24-h period and during the day compared to controls. A larger study (23) evaluated 54 dopaminergic-naïve PD patients and 47 age-matched controls. Over 24-h, SDNN, VLF, LF, and HF were significantly lower in PD than controls. The night-time HRV was not analyzed separately, but was reported in another paper (30), showing lower night time LF and HF in PD compared to controls. This group also showed negative correlations between total and motor UPDRS and 24-h LF and VLF, but no relationship between HRV and disease duration (23). Additionally, patients with less bradykinesia had significantly higher 24-h HF. Another study evaluated 24-h HRV and included actigraphy to distinguish between time in and out of bed (28), finding that PD patients had lower HF when in bed, but higher HF when out of bed. The LF/HF ratio was lower (parasympathetic predominance) in patients than controls both in and out of bed. A limitation of these studies was the absence of EEG identification of sleep or wake.

PD patients also had altered HRV in response to body movements during REM sleep in a study that compared 26 untreated PD patients to 15 controls (22). This study found reduced tachycardia response to body movements during REM sleep in PD compared to controls.

In another study, 35 PD patients demonstrated lower sympathetic influence on HRV during both REM and NREM compared to 35 matched controls. No differences were found in time domain HRV parameters (RR interval and pN50) for REM or NREM. However, in the frequency domain, LFnu was lower and HFnu was higher in PD compared to controls, representing reduced sympathetic influence. Similarly, LF/HF was lower (parasympathetic predominance) in PD patients than controls for REM and NREM. Dopaminergic medications did not influence the HRV parameters (31). The authors attributed the findings to partial post-ganglionic noradrenergic cardiac denervation corresponding to observed blunted sympathetic responses during dream enactment behavior.

Palma et al. (16) evaluated HRV during REM and NREM (N1-N2 combined, and separately N3) sleep in 33 PD participants compared to 29 matched controls. Time and frequency domain HRV parameters were analyzed by averaging 10-min epochs across REM, N1-N2, N3, and wake. RR intervals were lower in PD compared to controls in wake, N3, and REM, with no differences in SDNN in any sleep stage. ULF was lower in N3, VLF and LF were lower during REM sleep, and HF was lower in N1-N2 in PD compared to controls. Furthermore, Unified Parkinson's Disease Rating Scale (UDPRS) part III ON and OFF scores were inversely related to VLF and LF during

REM sleep. Similarly, Covassin et al. (20) found that lower HF (parasympathetic) HRV during REM sleep and higher LF/HF (sympathetic) during REM sleep were significantly correlated with disease severity in PD. These studies highlight the significance of cardiac autonomic dysfunction in PD and suggest utility in measuring disease severity.

Another study compared HRV and diffusion tensor imaging (DTI) in the medulla between 52 PD patients and 24 controls (29). PD patients did not demonstrate the expected sympathetic predominance during REM sleep, with significantly lower LF and higher HF compared to controls. In contrast to controls, there was no change from N3 to REM in either LF or HF. DTI measures in the medulla were negatively correlated with LF, HF, and LF/HF ratio in REM but not in N3, suggesting that neurodegeneration in the medulla influences loss of sympathovagal balance during REM sleep.

In addition to these case-control studies, Liu et al. (39) evaluated effects of subthalamic nucleus (STN) deep brain stimulation (DBS) on nighttime HRV in PD by comparing nights with DBS on vs. off. They found increased LF/HF ratio during the DBS-on night, suggesting that DBS may restore sympathetic regulation. However, a significant limitation of this study is that sleep and sleep stage were not confirmed during the recordings.

Thus, sleep-related HRV measures suggest alterations in sympathovagal balance and reduced sympathetic predominance in REM in people with PD. Additionally, these measures appear to be related to motor disease severity.

Heart rate variability and multiple system atrophy

Multiple system atrophy (MSA) is a neurodegenerative disorder with glial cytoplasmic synuclein inclusions that results in autonomic dysfunction and Parkinsonism or cerebellar ataxia (19). Only two small case-control studies have evaluated HRV during sleep in MSA and another study compared HRV in MSA, PD, and controls.

One study compared seven MSA patients and seven controls, showing lower RR50, LF, and HF during sleep in MSA compared to controls (24). In controls, the LF/HF ratio was lower (parasympathetic predominance) during sleep than wake; however, this variation was absent in MSA. Another case-control sleep study showed increased HFnu in 7 MSA patients compared with 5 controls during REM and NREM 3/4 sleep (17). These findings suggest relative abnormal predominance of parasympathetic activity in MSA during REM sleep.

Brisinda et al. (19) evaluated HRV during 24-h ECG in PD, MSA, and controls showing lower LF and HF power in PD and MSA during sleep and awake activity, although PD participants had more impairment in LF/HF (parasympathetic predominance) during sleep and activity, while MSA patients had impaired LF/HF (parasympathetic predominance) only during daytime activity. However, the study is difficult to interpret because it was unclear how sleep was defined and no EEG was performed. Larger studies of sleep-related HRV are needed to explore autonomic dysfunction during sleep in MSA.

Heart rate variability and Lewy body dementia

DLB is a synucleinopathy that manifests as progressive cognitive decline, cognitive and attentional fluctuations, visual hallucinations, RBD, and Parkinsonism. The neuronal synuclein deposits associated with DLB can affect various areas of the brain, including those that regulate the ANS. To the best of our knowledge, there have been no studies evaluating HRV during sleep in patients with DLB to date. In a study that evaluated 5-min EEG recordings of RR intervals during the day comparing DLB to Alzheimer's disease, lower values were found in DLB for most HRV parameters, including SDNN, pNN50, RMSSD, VLF, LF, HF, and total power (25). These findings suggest autonomic dysfunction in DLB and the authors proposed that HRV evaluation may be one way to distinguish between these two causes of dementia.

Comparative studies

Cardiac autonomic dysfunction is associated with both iRBD and PD. However, whether ANS dysfunction is specific to RBD or if PD patients without RBD also demonstrate this dysfunction remains unclear.

One study (32) found attenuated heart rate responses (HRR) to both leg movements and arousals during both REM and NREM in patients with iRBD, PD-RBD, and PD-noRBD compared to controls, but no difference between PD patients with and without RBD. Sub-analysis showed that the attenuated HRR was not caused by dopaminergic medications. The most pronounced attenuation was found in PD patients, with iRBD having findings intermediate between PD and controls. These changes may be related to degeneration of cortical and subcortical regions, which are thought to be involved in modulating sleep EEG, HRR, and motor activity (40). As iRBD often precedes PD, the ANS changes may be early manifestations of brainstem neurodegeneration. HRV parameters during wakefulness and during consolidated sleep (without arousals) were also evaluated in this cohort, showing no differences in LF, HF, or LF/HF during N2 or REM between controls, iRBD, PD with RBD, and PD without RBD (33).

Another study (34) conducted 24-h ambulatory ECG recordings to elucidate whether RBD might influence circadian cardiac autonomic activity. They found increased nocturnal (10 pm to 6 am) LF and HF in PD-RBD compared to patients with PD without RBD. Further, there was no difference between daytime and nighttime LF and HF in PD without RBD, but these HRV parameters were higher at night compared to daytime in PD-RBD. These findings are unexpected based on other studies finding suppression of these measures during sleep in RBD. Because EEG was not recorded in this study, it is possible that differences between the groups in terms of percentages of sleep stages and time spent awake during the night may have been responsible for these unexpected results.

These studies demonstrate the importance of identifying sleep stages when evaluating nocturnal autonomic fluctuations, although such methods have shown mixed results when evaluating the influence of RBD on ANS in PD patients. One study (33) found no

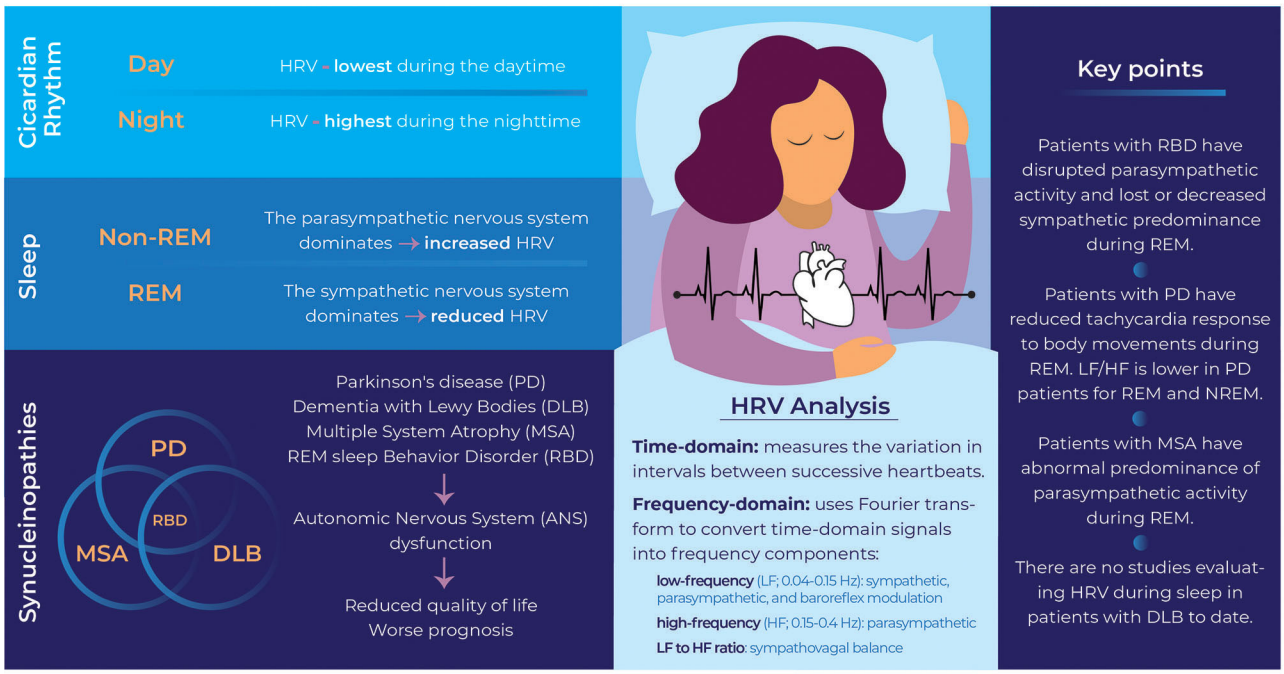

FIGURE 1
Infographic on sleep-related HRV in synucleinopathies.

frequency domain HRV differences during sleep between PD with and without RBD. However, Bugalho et al. (18) found significant attenuation of parasympathetic HRV values (HF) in all stages of sleep in RBD (iRBD and PD-RBD) compared to PD without RBD. Further, there was a blunting of the expected increase of HF in NREM. Divergent results in these studies may be related to demographics in that participants had a higher mean age in the Bugalho study. Additionally, the Bugalho study included both iRBD and PD-RBD in the RBD group and compared to PD without RBD, while the other study compared the groups to a control group. Further study is needed to definitely determine the influence of RBD on HRV in PD.

Discussion

This review summarizes available literature investigating sleep-related HRV in synucleinopathies, demonstrating nocturnal ANS dysfunction in these individuals. Studying HRV during sleep may provide clues as to potential biomarkers or therapeutic targets for these disorders. Figure 1 summarizes the key findings of the paper.

Many questions remain regarding the pathophysiological mechanisms of ANS dysfunction in iRBD and PD. However, neuropathological and imaging studies conducted in iRBD patients demonstrate abnormalities in several brainstem areas (41) that are important to autonomic network function of the central nervous system (CNS) (26). In PD, deposition of alpha-synuclein in both the PNS and CNS and post-ganglionic neuronal degeneration may lead to autonomic dysfunction (15). According to the Braak hypothesis (42), since iRBD often precedes PD clinical manifestations (8), the change in autonomic function may be an early manifestation of neurodegeneration in the brainstem.

There are also studies assessing whether ANS dysfunction is predominantly related to RBD or also influenced by PD pathology. There was a marked reduction in cardiac 123I-labeled meta-iodobenzylguanidine scintigraphy (a physiological norepinephrine analog used to assess sympathetic autonomic function) in patients with iRBD in the same range as PD (43, 44). However, another study found that the degree of MIBG dysfunction in iRBD was intermediately reduced between controls and patients with PD (33, 45). Using HRV as a marker, one study (34) found an increase in nocturnal sympathetic and parasympathetic activity in PD-RBD patients compared to PD-noRBD patients. Because the study lacked EEG sleep staging, it is difficult to speculate whether or how RBD may increase nocturnal ANS drive. ANS alterations could result from dream enactment behavior or microawakenings, or from cardiac nonadrenergic fiber involvement. Another proposed mechanism is spread of alpha-synuclein to pontomedullary structures, particularly the sublaterodorsal nucleus and subcoerulus complex (46). Additionally, the dorsal motor nucleus of the vagus, the nucleus solitarius, and the rostral ventrolateral medulla may be affected during the early disease stages, causing parasympathetic nervous system dysfunction (46). Future prospective studies are needed to clarify these conflicting results.

A few small studies suggest that ANS dysfunction occurs during sleep in MSA. Thus far, no studies have evaluated sleep-related HRV in DLB. More studies are needed to determine whether HRV may serve as an effective biomarker for earlier detection of MSA or DLB and provide further insight into the autonomic imbalance present in these disorders.

Although several case-control and/or retrospective studies of nocturnal HRV are available, much remains to be investigated. For example, longitudinal studies should examine how changes in sleep-related HRV impact health outcomes such as cognitive and motor decline in synuclein disorders. Additional areas of study should include wearable technology and sophisticated analytical methods. Moreover, HRV data from diverse populations should be collected to allow better understanding of normative values during sleep as well as the effects of age, sex, race/ethnicity, and comorbidities on HRV outcomes. Future research may identify clinical applications of HRV during sleep, such as its utility as a biomarker for various sleep or ANS disorders in synucleinopathies. In addition, interventional studies examining effects of sleep therapies such as cognitive-behavioral therapy, exercise, or pharmacological treatments on HRV during sleep could broaden treatment options for ANS dysfunction in neurodegenerative disorders. This review explored the nuances of HRV during sleep in synucleinopathies. Because this review is narrative, we did not follow PRISMA guidelines, and synthesizing evidence involves inherent subjectivity and potential for bias.

Conclusion

HRV during sleep is a non-invasive measure that can inform our understanding of ANS dysfunction in synuclein disorders. Available research in iRBD, PD, and MSA demonstrate alterations in parasympathetic and sympathetic function as well as sympathovagal balance. Additional work is needed to determine if sleep-related HRV can be used as a biomarker of early disease identification, prognosis, or progression and if guided therapies targeting ANS dysfunction in sleep could improve patient outcomes and quality of life.

Author contributions

AM: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. EG: Data curation, Methodology, Writing – review & editing. TN: Data curation, Methodology, Writing – review & editing. YS: Data curation, Methodology, Writing – review & editing. CC: Visualization, Writing – review & editing. AA: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Association of Barrett's esophagus with obstructive sleep apnea syndrome: a bidirectional analysis of Mendelian randomization

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Background: Observational studies have reported associations between Barrett's esophagus (BE) and obstructive sleep apnea syndrome (OSAS), but the causal relationship remained unclear due to potential confounding biases. Our study aimed to elucidate this causal relationship by deploying a two-sample Mendelian randomization (MR) methodology.

Methods: Instrumental variables (IVs) for Barrett's esophagus were obtained from a public database that comprised 13,358 cases and 43,071 controls. To investigate OSAS, we utilized summary statistics from a comprehensive genome-wide association study (GWAS) encompassing 38,998 cases of OSAS and 336,659 controls. Our MR analyses adopted multiple techniques, including inverse variance weighted (IVW), weighted median, weighted mode, MR-Egger, and simple mode.

Results: The IVW analysis established a causal relationship between Barrett's esophagus and OSAS, with an odds ratio (OR) of 1.19 and a 95% confidence interval (CI) of 1.11–1.28 (p = 8.88E-07). Furthermore, OSAS was identified as a contributing factor to the onset of Barrett's esophagus, with an OR of 1.44 and a 95% CI of 1.33–1.57 (p = 7.74E-19). Notably, the MR–Egger intercept test found no evidence of directional pleiotropy ($p > 0.05$).

Conclusion: This study identifies a potential association between BE and an increased occurrence of OSAS, as well as the reverse relationship. These insights could influence future screening protocols and prevention strategies for both conditions.

KEYWORDS

OSAS, Barrett's esophagus, Mendelian randomization, instrumental variables, GWAS

1 Introduction

Barrett's esophagus (BE) is characterized by replacing normal squamous epithelial cells in the lower part of the esophagus with columnar epithelial cells (1). BE with intestinal metaplasia represents a significant concern as it is closely linked with a substantially elevated risk of progressing to esophageal cancer (2). Approximately 1–2% of the worldwide population is believed to have BE, primarily due to chronic gastroesophageal reflux (3, 4). While gastroesophageal reflux disease (GERD) is often associated with BE, it is vital to understand that BE can occur in its absence (5).

The clinical manifestations of BE frequently include persistent heartburn, consistent acid reflux, dysphagia, and thoracic discomfort. Interestingly, some individuals with BE may not exhibit any symptoms (6). Obstructive sleep apnea syndrome (OSAS) is a prevalent sleep-related respiratory disorder impacting nearly a billion individuals globally. Its repercussions profoundly affect individual wellbeing and broader societal challenges (7). The hallmark of OSAS is the transient cessation or significant reduction of airflow during sleep. This phenomenon is primarily attributed to the relaxation of pharyngeal muscles, which leads to episodic airway obstructions (8). Clinically, OSAS is often accompanied by symptoms such as pronounced snoring, daytime lethargy, headaches upon awakening, diminished cognitive focus, and memory impairment (9). Interestingly, recent studies have revealed a bidirectional relationship between OSAS and BE. Lindam et al. demonstrated that individuals with excessive daytime sleepiness or symptoms related to sleep apnea show a higher prevalence of BE (10). Hadi et al. indicate that the risk of developing BE increases with the severity of OSAS, categorized in increments of 10 on the apnea-hypopnea index scale (11). Although there is an association between OSAS and BE, this association may either be mediated by GERD or independent of gastroesophageal reflux (12). Given the complexity of confounding factors such as GERD, any potential link between OSA and BE appears to have not been sufficiently explored.

GERD is commonly believed to be associated with OSAS and BE, but some studies and theories consider other potential pathways of connection (13). A prevailing hypothesis posits that OSAS might influence BE progression by initiating inflammatory cascades (14). It is well-acknowledged that OSAS is characterized by intermittent hypoxia, occurring due to periodic episodes of hypoxia followed by reoxygenation during sleep, which is associated with systemic inflammation (15). Elevated systemic inflammatory markers, observed in OSAS patients, are theorized to facilitate the onset of BE by inducing cellular injury, genetic aberrations, and heightened oncogenic risk (16). The main symptoms of BE include reflux symptoms such as heartburn and retrosternal pain, which may worsen at night, affecting sleep quality and potentially causing or exacerbating symptoms of OSAS (17, 18). Nevertheless, the current body of evidence does not conclusively indicate that BE directly aggravates or engenders OSAS.

Mendelian randomization (MR) stands as a robust analytical approach in observational research, seeking to elucidate causal associations between modifiable risk factors and disease outcomes by leveraging established functional genetic variants (19). There are numerous approaches within the two-sample methodology, and recently, the Mixture model Reciprocal Causation Inference (MRCI) has emerged as a novel statistical framework (20). Two-sample Mendelian randomization has emerged as a pivotal method within genetic epidemiology. This refers to a type of instrumental variable analysis in which genetic variations, notably single nucleotide polymorphisms (SNPs), serve as the instrumental variables. By employing known genetic markers, especially SNPs, as instrumental variables, this approach facilitates the estimation of causal associations between an exposure and a given outcome (21). Our study was designed to clarify the causal relationship between OSAS and BE by employing a two-sample MR approach.

2 Methods

2.1 Study design

The MR is underpinned by three cardinal assumptions: (1) the Instrumental variables (IVs) manifest a potent association with the exposure; (2) These IVs remain uncontaminated by potential confounders; and (3) the influence of the IVs on the outcome is channeled exclusively through their affiliation with the exposure, eschewing any ancillary pathways (22) (Figure 1A). The bidirectional Mendelian randomization methodology was executed to decipher the causative nexus between BE and OSAS, as delineated in Figure 1B.

2.2 Sources of data and selection of SNPs as IVs

Summary statistics of BE phenotypes were procured from the IEU GWAS database (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90000515/). The diagnosis of BE is established based on the ICD-10 code K22.7, primarily determined through a combination of patient self-reports and clinical diagnostic evaluations. This repository houses data from a cohort of 56,429 individuals of European descent, encompassing 13,358 diagnosed BE cases juxtaposed against 43,071 control subjects (23). For OSAS, pertinent genetic instruments were derived from the FinnGen database (https://storage.googleapis.com/finngen-public-data-r9/).

The diagnosis of OSAS is indicated by ICD-10 code G47.3.The confirmation of OSA involves the assessment of clinical symptoms and signs, along with the Apnea-Hypopnea Index (AHI) of $\geq$5 events per hour. This collection incorporates an aggregation of 38,998 OSAS cases and 336,659 control subjects. It's paramount to emphasize that the FinnGen dataset originates from individuals of European lineage (24).

In the process of choosing suitable instrumental variables, SNPs are required to fulfill a range of criteria. The selection of IVs necessitated SNPs to meet a rigorous set of criteria. Initially, SNPs must manifest a prominent association with the exposure on a genome-wide scale. This dictates that a statistically significant relationship between the SNPs and the exposure should be established, adhering to a p-value threshold of <5E-08. This stringent criterion bolsters confidence in the integrity of SNP exposure associations, mitigating potential false-positive results (25). Second, SNPs selection hinged on the PLINK algorithm to identify SNPs not in linkage disequilibrium, typified by an $r^2 < 0.001$. Within a clumping window of 10,000 kilobases, this procedure is designed to precisely identify genuinely independent SNPs, eliminating potential correlations from nearby genetic markers. Third, A meticulous curation was executed utilizing the PhenoScanner GWAS database (http://phenoscanner.medschl.cam.ac.uk) to omit IVs conceivably linked to the investigative outcome trait, including those potentially associated with GERD, smoking, and alcohol consumption (26). SNPs registering an F-Statistic < 10 were earmarked as weak IVs and were consequently sidelined from subsequent analyses (27). Ultimately, 8 SNPs

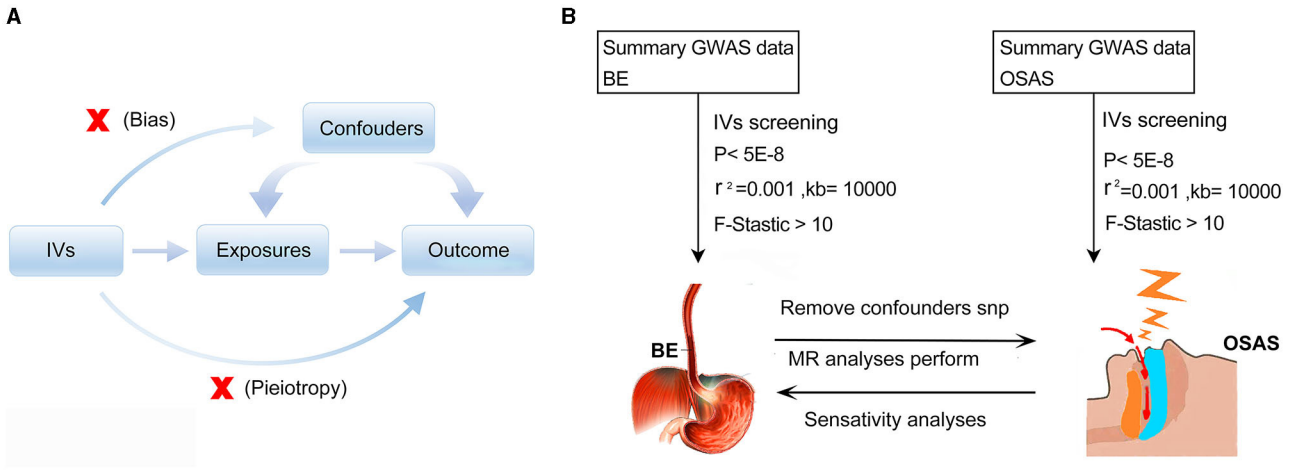

FIGURE 1
Schematic representations of the employed methodologies. **(A)** Illustration of Mendelian randomization principles. **(B)** Schematic diagram depicting the bidirectional Mendelian randomization methodology utilized to investigate the causal relationship between BE and OSAS. MR, Mendelian randomization; GWAS, genome-wide association study; IVs, Instrumental variables; BE, Barrett's esophagus; OSAS, Obstructive Sleep Apnea Syndrome.

were identified as instrumental variables for OSAS, and 11 SNPs emerged as instrumental variables for BE. This deliberate exclusion strategy was orchestrated to ensure the incorporation of robust and dependable IVs in the MR paradigm. In conclusion, the selection process systematically excluded palindromic SNPs and those demonstrating associations with the outcome at a genome-wide significance threshold.

2.3 Genetic correlation analysis

To assess the genetic correlations between BE and OSAS, our study employed the Linkage Disequilibrium Score Regression (LDSC) software package, accessible at (https://github.com/bulik/ldsc) (28). This methodological approach was instrumental in quantifying the extent of genetic overlap and potential shared etiological pathways between these two conditions.

2.4 Evaluation of OSAS and BE data overlap

To strictly adhere to established guidelines, we meticulously assessed the sample overlapping ratio between OSAS and BE (29). Our analysis showed that the BE GWAS data, derived from prominent databases including the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON), as well as the comprehensive datasets from Bonn, Cambridge, Oxford, and UKB, did not display potential overlap with the FinnGen database for OSAS (23, 30, 31). The observation reinforces the integrity of our two-sample MR approach.

2.5 Analyses based on Mendelian randomization

This investigation harnessed an array of MR methodologies, notably IVW, MR-Egger, weighted median, weighted mode, and simple mode, intending to elucidate the causative linkage between BE and OSAS (29). To leverage its higher statistical power compared to other MR methods, the IVW approach, assuming the validity of all SNPs used as IVs, was selected as this research's primary analysis and main analytical approach (32). This method capitalizes on the vigor of the genetic correlation IVs, amalgamating the precision of each estimation. Consequently, enhanced emphasis is accorded to more precise measures, facilitating a causal extrapolation between the exposure and the resultant outcome. Subsidiary methods acted in tandem with IVW, each entrenched in its unique set of assumptions concerning horizontal pleiotropy, with a collective objective to provide comprehensive and resilient MR estimates across various contexts.

2.6 Statistical analysis and sensitivity assessments

We performed statistical analyses with R software (version 4.1.2) and the "Two Sample MR" package. Cochran's *Q*-test, integral to the IVW methodology, probes the heterogeneity across instrumental variables. The *p*-value falling below 0.05 typically flags significant disparities across the scrutinized cohorts. Pleiotropy embodies the intriguing paradigm wherein an isolated gene influences multiple traits. In deciphering horizontal pleiotropy and pinpointing anomalous variants, the study turns to the MR Pleiotropy RESidual Sum and Outlier PRESSO methodology (33). Discarding these divergent SNPs generates a decontaminated causal inference via the outlier-corrected Mendelian randomization

TABLE 1 Genetic correlation estimates from LDSC regression.

Phenotype 1	Phenotype 2	Rg (SE)	Oval
BE	OSAS	0.35 (0.03)	1.36e-20

BE, Barrett's esophagus; OSAS, obstructive sleep apnea syndrome; Rg, genetic correlation; Pval, the p-value for rg; SE, the standard error of Rg.

assessment. The research employs the MR-Egger intercept examination to probe directional pleiotropy within the IVs. An intercept test bearing a non-zero magnitude intimates the manifestation of directional pleiotropy in the set of IVs (34). A leave-one-out diagnostic is orchestrated for a granular assessment of potential SNP-driven biases in MR outcomes, wherein each SNP is iteratively sidelined, and the consequent ramifications on analytical outputs are scrutinized (35).

3 Results

3.1 Genetic correlation analysis of BE and OSAS

In our analysis utilizing the LDSC methodology, we observed a notable genetic correlation between BE and OSAS. The results indicated a significant correlation coefficient (rg) of 0.35, with a highly significant *p*-value of 1.36e-20 (Table 1).

3.2 The influence of OSAS on the phenomenon of BE

Initially, SNPs manifesting a notable association with OSAS at the genome-wide threshold were delineated, with a concurrent emphasis on SNPs devoid of linkage disequilibrium. After meticulously excluding SNPs that exhibited pleiotropic tendencies, such as those related to reverse causation, reflux, and obesity, among other factors, a refined set of 8 SNPs emerged as IVs. These SNPs were characterized by an F-Statistic exceeding 10, underscoring their robust instrument strength (Supplementary Table 1). Employing the IVW method yielded an odds ratio (OR) of 1.647 (95% CI: 1.273–2.133, $p = 0.00015$). Similarly, the weighted median method produced an OR of 1.751 (95% CI: 1.304–2.353, $p = 0.00015$), while the weighted mode method indicated an OR of 1.796 (95% CI: 1.261–2.558, $p = 0.021$). These findings robustly intimate a causal linkage between Barrett's esophagus (BE) and the onset of OSAS. In stark contrast, outcomes from the MR-Egger method (OR: 1.485, 95% CI: 0.341–6.475, $p = 0.617$) and the simple mode (OR: 1.83, 95% CI: 1.105–3.016, $p = 0.051$) refrained from corroborating a causal relationship between BE and OSAS (Figure 2A). The IVW method presents a distinct merit, adeptly managing multiple SNPs concurrently and maintaining its efficacy even amidst tenuous correlations between SNPs (36). Significant heterogeneity was evident, as indicated by Cochran's *Q*-test ($Q = 9.989$, $p = 0.0292$). The MR-Egger intercept analysis underscored a lack of directional pleiotropy ($p = 0.893$; Table 2). Scatterplots detailing the outcomes of these evaluations are shown in Figure 3A. The leave-one-out assessment revealed that no singular SNP predominantly swayed the overarching influence of BE (as the exposure) on the incidence of OSAS (as the outcome), as depicted in Figure 3B.

3.3 The impact of BE on the occurrence of OSAS

Through our rigorous analysis, we discerned specific SNPs that exhibited genome-wide notable associations with BE, ensuring the inclusion of those not found in linkage disequilibrium. After meticulous screening to exclude pleiotropic SNPs linked with obesity, smoking, and other potential confounders, a concise set of 11 SNPs emerged as IVs, as detailed in Supplementary Table 2. The results derived from the IVW method offered compelling evidence, pointing to a reliable causal link between OSAS and BE, as underscored by an OR of 1.095 (95% CI: 1.040–1.153, $p = 0.00052$). In contrast, other analytical methods yielded disparate results. While the weighted median process suggested an OR of 1.066 (95% CI: 0.993–1.145, $p = 0.078$), the weighted mode method produced an OR of 1.054 (95% CI: 0.942–1.181, $p = 0.381$). Moreover, the MR-Egger approach showed an OR of 1.115 (95% CI: 0.753–1.653, $p = 0.6$), and the simple mode method indicated an OR of 1.054 (95% CI: 0.939–1.183, $p = 0.390$). These findings, encapsulated in Figure 2B, did not conclusively affirm a causal association between OSAS and BE. Significant heterogeneity across the involved studies emerged, as illuminated by Cochran's *Q*-test results ($Q = 8.893$, $p = 0.0442$), pinpointing variances in effect estimates across disparate datasets. However, the MR-Egger intercept analysis suggested a lack of directional pleiotropy ($p = 0.929$), implying minimal to no influence of horizontal pleiotropic effects on the MR results. These fundamental observations are illustrated in Figure 4A. The subsequent leave-one-out assessment consistently revealed that none of the individual SNPs significantly impacted the overall association between OSAS exposure and the incidence of BE, as depicted in Figure 4B.

4 Discussion

This is the first comprehensive study delving into the nuanced relationship between OSAS and BE through the two-sample Mendelian randomization approach. Our study, conducted among individuals of European ancestry, provides compelling evidence of a causal relationship between OSAS and BE, highlighting the interconnection between these seemingly unrelated conditions. Amidst rising healthcare challenges, our findings shed fresh light on the underlying mechanisms linking OSAS and BE, offering pivotal insights that could pave the way for enhanced diagnostic precision and therapeutic interventions.

The objective of our study was to investigate the causal association between OSAS and BE using multiple MR methods. We employed the IVW method as the primary approach, supplemented by weighted median and mode methods. Our findings indicated a causal link from OSAS to BE according to these methods. Interestingly, the IVW analysis also suggested that BE may causally influence the development of OSAS. However, it is important to note that the MR-Egger method did not provide support for a

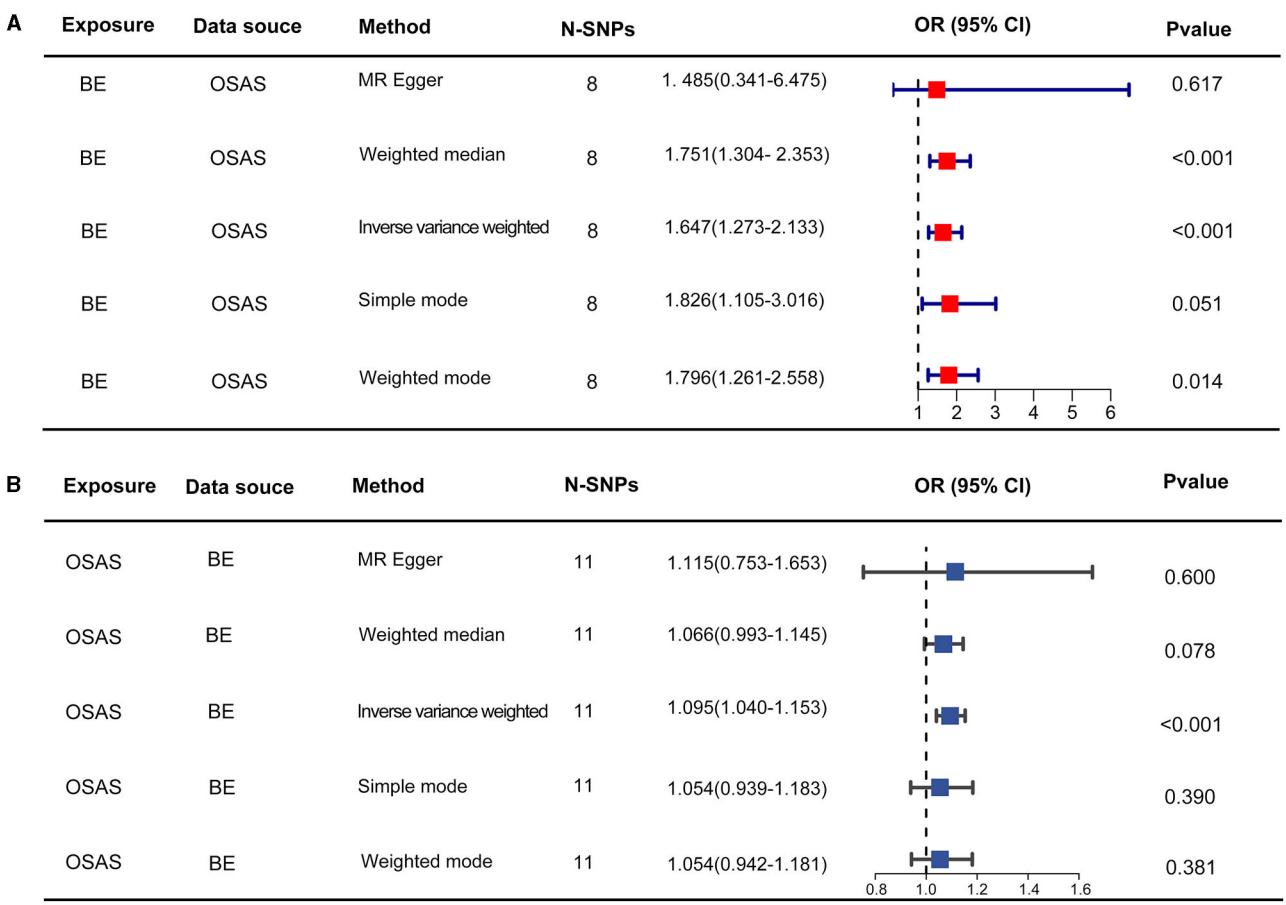

FIGURE 2
The results of two-sample MR assessing causal relationships between OSAS and BE. **(A)** Represents the causal estimates of OSAS influencing BE. **(B)** Illustrates the causal estimates of BE affecting OSAS. MR, Mendelian randomization; OSAS, obstructive sleep apnea syndrome; BE, Barrett's esophagus; OR, odds ratio.

TABLE 2 OSAS and BE: pleiotropy and heterogeneity analysis.

Exposure	Outcome	Heterogeneity		MR-egger intercept	
		Cochrane's *Q*	Heterogeneity (pval)	Egger-intercept	Pleiotropy (pval)
OSAS	BE	9.989	0.0292	0.0064	0.893
BE	OSAS	8.893	0.0442	−0.0017	0.929

OSAS, obstructive sleep apnea syndrome; BE, Barrett's esophagus; MR, Mendelian randomization.

causal relationship in either direction. This discrepancy highlights the complexity inherent in MR research. The IVW method, commonly used in two-sample MR studies, generates an overall estimate of the causal effect when instrumental variables are robust and unaffected by pleiotropy (37). MR-Egger is specifically designed to address biases arising from pleiotropy but can be overly cautious, potentially leading to an underestimation of true effects. To account for potential pleiotropy, we incorporated the MR-Egger intercept in our analysis, following established methodologies. Based on our analysis, and following the methodology adopted in various literature sources, we considered the IVW as the primary approach for our research (38–40).

Earlier investigations have highlighted a pronounced augmentation in the likelihood of OSAS onset in individuals diagnosed with BE (41). Despite prior indications, the effects of OSAS on BE have been sparingly explored. Delving deeper into this association's genomic intricacies and clinical implications is paramount, especially when considering potential confounders such as obesity, smoking, and reflux. In this context, our study harnessed the power of a two-sample Mendelian randomization approach to probe the nexus between OSAS and BE. By deploying MR analysis, we adeptly sidestepped the pitfalls of confounding elements and the perils of reverse causation that often plague observational studies. Furthermore, this method alleviates the burdens of exorbitant expenses and logistical challenges typically affiliated with randomized controlled trials. The prevailing guidelines advocate for screening individuals deemed high-risk for BE, an antecedent to esophageal cancer (42). While both BE and

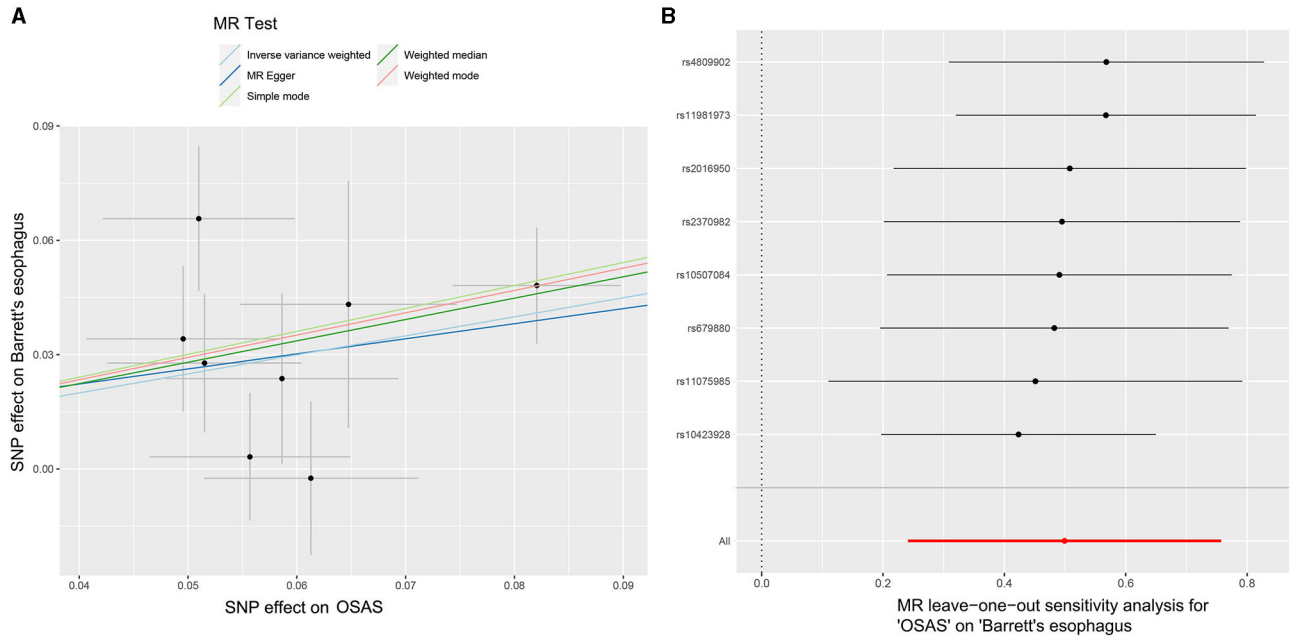

FIGURE 3
MR analyses illustrating the causal relationship between OSAS as the exposure and BE as the outcome. **(A)** Scatter plot illustrating individual SNP analyses investigating the impact of OSAS on BE incidence. **(B)** Leave-one-out plot showing the collective influence of SNPs on the relationship between OSAS and BE. MR, Mendelian randomization; OSAS, obstructive sleep apnea syndrome; BE, Barrett's esophagus; SNP, single nucleotide polymorphism.

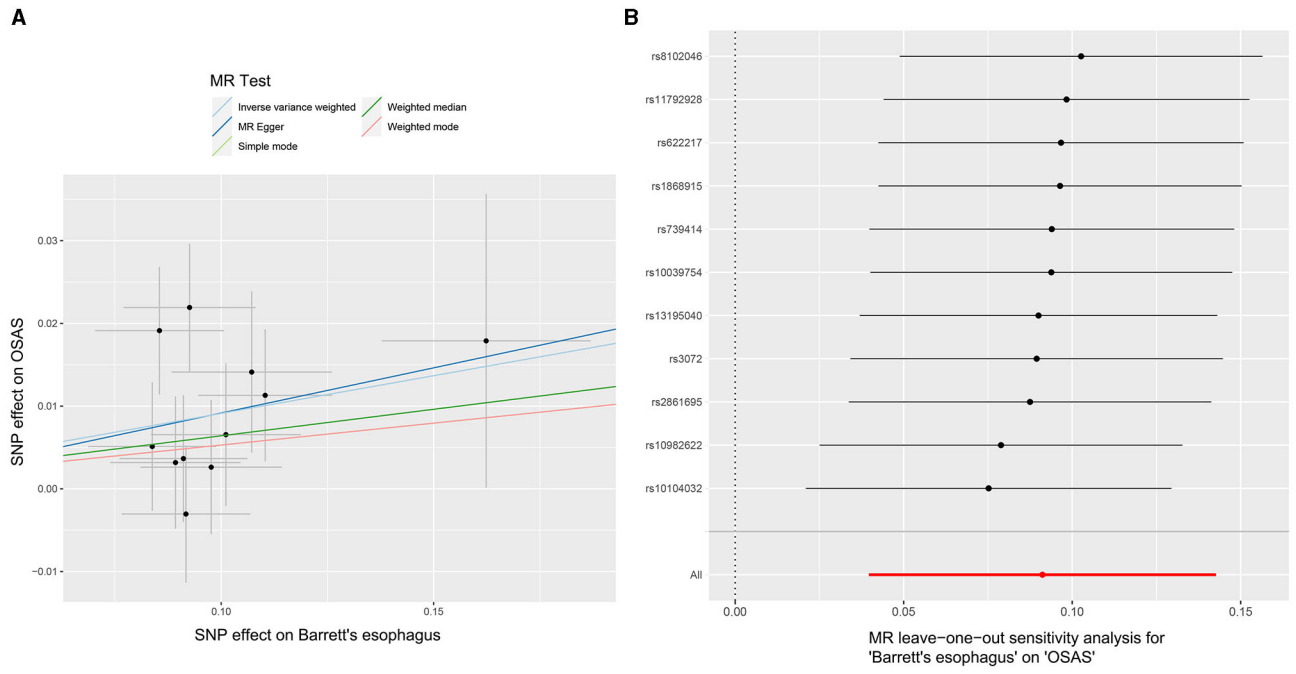

FIGURE 4
MR analyses demonstrating the causal relationship with BE as the exposure and OSAS as the outcome. **(A)** Scatter plot illustrating individual SNP analyses investigating the influence of BE on the prevalence of OSAS. **(B)** Leave-one-out plot demonstrating the combined impact of SNPs on the relationship between BE and OSAS. MR, Mendelian randomization; BE, Barrett's esophagus; OSAS, obstructive sleep apnea syndrome; SNP, Single Nucleotide Polymorphism.

OSAS exhibit similarities in common risk factors, such as elevated body mass index (BMI) and GERD, the exact correlation between these conditions still requires further investigation and conclusive determination (17, 43).

In comparison to individuals without OSAS, patients afflicted with OSAS exhibited a heightened risk of developing Barrett's esophagus ($p < 0.001$, OR:3.26,95% CI: 1.72–6.85) (44). With the severity of OSAS, there is a heightened risk of BE, setting the AHI of 10 as the critical marker. In a distinct multivariable regression analysis, where OSAS was delineated based on 10-point increments in the AHI, a notable increase in BE risk was discerned with every 10-point rise in AHI (OR 1.10, 95% CI: 1.02–1.19). While GERD plays a pivotal role in the onset of BE among OSAS sufferers, the observed correlations could also be amplified by other underlying factors, such as pronounced central obesity (marked rise in visceral abdominal fat) and a prevailing systemic inflammatory condition (45). Hence, an intricate interplay of factors could underpin the heightened prevalence of BE in OSAS patients.

A meta-analysis of six studies, including 2,333 patients who met the inclusion criteria, demonstrated a significant elevation in the risk of OSAS, a high risk of OSAS, and the presence of patient-reported OSAS symptoms in individuals with Barrett's esophagus compared to those without this condition. The combined OR was 2.19 (95% CI: 1.53–3.15), indicating a significant association between BE and OSAS. Additionally, a subgroup analysis comprising two studies focusing on cases with confirmed OSA through polysomnography and Barrett's esophagus demonstrated a significant association, with an OR of 2.59 (95% CI: 1.39–4.84) (41). In previous notions, it was postulated that BE escalates the prevalence of OSAS, potentially due to its association with obesity. However, a recent study has reported that the correlation between BE and OSAS remains unaltered, even in the presence of obesity-related factors (46).

In this MR investigation, we harnessed genetic datasets spanning various European nations to delve into the interrelation between OSAS and BE. By leveraging large case-control samples and rigorous statistical analysis, our findings confirm a significant association between these two conditions and unveil a bidirectional causal relationship. This outcome reinforces that OSAS could be instrumental in BE onset and vice versa, underscoring a multifaceted dynamic between these medical conditions. The intricacies of the BE and OSAS connection remain elusive, yet prevailing theories posit the involvement of mechanical stressors, neural reflex arcs, and inflammation-induced pathways (11). BE may impose pressure on adjacent tissues, potentially inducing airway blockage and heightening OSAS susceptibility. Furthermore, it might interfere with respiratory regulation through neural feedback loops bridging the esophageal and respiratory channels. Inflammatory cascades activated by BE-induced damage could unleash agents detrimental to respiratory and muscular structures, thereby facilitating OSAS. The Cochran Q test ($p < 0.05$) suggests the presence of heterogeneity. However, it does not invalidate the validity of the IVW estimates under the random-effects model, even in the presence of heterogeneity. Additionally, the MR-Egger intercept analysis indicated no directional pleiotropy, indicating minimal potential for measurement error or bias in the selected instrumental variables. These factors collectively support the robustness and credibility of the MR findings.

Nonetheless, it should be noted that our study does have certain limitations. Not all Mendelian Randomization methods support a causal relationship between OSA and BE. We may consider conducting clinical randomized controlled trials (RCTs) in future studies to further investigate this relationship. Due to the reliance on publicly accessible summary statistics, we could not access detailed demographic data, such as age and gender, which represents a limitation in our study. However, the essence of Mendelian randomization is to leverage genetic instrumental variables to discern potential causal relationships between exposures and outcomes, even without specific demographic details. Despite these limitations, our study contributes to the field by using genetic information to explore causal associations.

5 Conclusion

The relationship between OSA and BE is complex and not fully understood, as the current MR analysis indicates. However, research suggests a potential role of OSA in BE pathogenesis and vice versa, implying a bidirectional influence. This has implications for mitigating the risk of both conditions. When managing OSA, consider gastrointestinal symptoms and conduct pH monitoring or endoscopy if BE is suspected. Non-pharmacological interventions such as diet control, weight loss, and reducing alcohol consumption may be effective for BE patients. Screening for undiagnosed OSA in BE patients is essential.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

WT: Investigation, Methodology, Writing – original draft. YC: Resources, Software, Writing – original draft. LG: Data curation, Resources, Software, Writing – review & editing. GL: Investigation, Supervision, Writing – review & editing. PL: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1269514/full#supplementary-material

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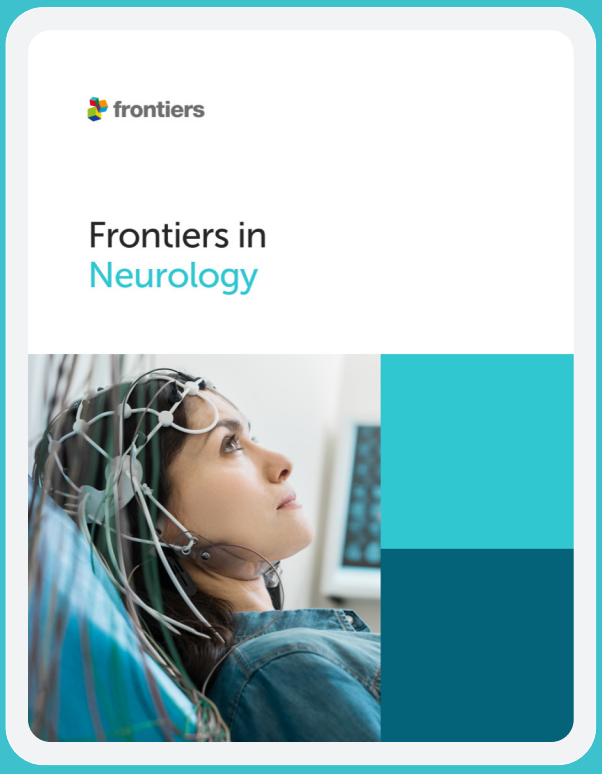

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