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CLINICAL REVIEW

Sleep in posttraumatic stress disorder: A systematic review and meta-analysis of polysomnographic findings

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SUMMARY

Polysomnographic studies have been performed to examine sleep abnormalities in posttraumatic stress disorder (PTSD), but clear associations between PTSD and sleep disturbances have not been established. A systematic review of the evidence examining the polysomnographic changes in PTSD patients compared with controls was conducted using MEDLINE, EMBASE, All EBM databases, PsycINFO, and CINAHL databases. Meta-analysis was undertaken where possible. The searches identified 34 studies, 31 of which were appropriate for meta-analysis. Pooled results indicated decreased total sleep time, slow wave sleep and sleep efficiency, and increased wake time after sleep onset in PTSD patients compared with healthy controls. PTSD severity was associated with decreased sleep efficiency and slow wave sleep percentage. Rapid eye movement (REM) sleep percentage was significantly decreased in PTSD patients compared with controls in studies including participants with mean age below 30 y, but not in studies with other mean age groups (30–40 y and >40 y). Our study shows that polysomnographic abnormalities are present in PTSD. Sex, age, PTSD severity, type of controls, medication status, adaptation night, polysomnographic scoring rules and study location are several of the demographic, clinical and methodological factors that contribute to heterogeneity between studies.

Introduction

Posttraumatic stress disorder (PTSD) involves responses to a traumatic event that persist maladaptively. It is characterized by intrusive thoughts related to the event, avoidance of reminders of the event, negative mood and cognitions, and heightened arousal and reactivity [1]. Sleep disturbances are fundamental and enduring features of PTSD patients, and they have been considered the hallmark of the disorder [2–4]. The majority of PTSD patients have significant sleep disturbances [2,5], which independently contribute to poor daytime function, are often resistant to first-line treatment, and often require sleep-focused treatments [4]. Sleep disturbances are also predictive of the development of PTSD [6–8].

Assessments of sleep disturbances include sleep diary, self-report questionnaire, face-to-face interview, actigraphy, and polysomnography (PSG). Among these methods, PSG is required to distinguish rapid eye movement (REM) sleep, non-REM sleep, and stages 1–3 (N1-3) of non-REM sleep. PSG determined alterations in sleep are highly important for understanding the etiology and neurobiology of PTSD [4,9]. For instance, Ross et al. emphasized REM sleep disturbances and nightmares as hallmarks of PTSD [10]. Germain et al. [4] also emphasized a role for REM sleep, and proposed that it amplifies altered function of the amygdala and medial frontal cortex in PTSD patients whereby amplification of abnormal amygdala activation in combination with reduced activation of the medial prefrontal cortex could subserve nightmares. Other

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Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnea hypopnea index
CAPS	Clinician administered PTSD scale
CIs	confidence intervals
EEG	electroencephalogram
HC	Healthy controls
HPA	hypothalamic-pituitary-adrenal
MDD	major depressive disorder
NICE	National Institute for Health and Care Excellence
OR	odds ratio
OSA	obstructive sleep apnea
PSA	power spectral analysis
PSG	polysomnography
PTSD	posttraumatic stress disorder
R&K	Rechtschaffen and Kales
REM	rapid eye movement
REML	rapid eye movement sleep latency
REMD	rapid eye movement sleep density
SE	sleep efficiency
SL	sleep latency
SMD	standardized mean difference
SNS	sympathetic nervous system
SWS	slow wave sleep
TE	trauma exposed individuals
TST	total sleep time
WASO	wake time after sleep onset

investigators have noted significant alterations in NREM sleep, as both visually scored delta sleep and EEG delta amplitude may be reduced in individuals with PTSD [11].

Previous studies have examined PSG data in attempts to understand sleep changes in PTSD. However, the exact changes in PSG variables (i.e., total sleep time (TST) [12,13], N3 [14,15] and REM percentage [13,16]) in PTSD compared to either trauma exposed survivors without PTSD (TE) or healthy controls (HC) have not been fully established. Variations in results across studies could involve demographic heterogeneity (i.e., age and gender), clinical variables (i.e., PTSD severity, comorbidity and medication status), trauma-related factors (i.e., different trauma type, number of trauma exposures, and the time of sleep assessments since trauma) [17–21], and experimental methodology (i.e., adaptation night and PSG scoring rules). These factors can be considered with meta-analytic procedures and two prior meta-analysis studies examining PSG alterations in PTSD have been published.

In 2007, Kobayashi et al. [22] provided the first meta-analysis on PTSD and PSG determined sleep. This study included 20 studies and found that PTSD patients had more N1 sleep, less N3, and greater REM density compared with those without PTSD, and that studies with a high percentage of male participants or a low rate of comorbid depression were more likely to find PTSD-related sleep disturbances. Although this impressive work provided important insights, our preliminary literature search found more than 15 articles in this area published since 2007. Adding these newly published studies into a meta-analysis could provide substantial new data and insights regarding alterations in sleep in PTSD patients. It should also be noted that the limited number of included studies in Kobayashi study [22] prevented some potential sources of heterogeneity to be explored and that important questions remained unanswered. For instance, whether PSG changes in PTSD patients varied with trauma type (i.e., combat exposure, natural disaster, and sexual assault) has not been explored and whether PTSD severity impacted PSG determined sleep is still unclear. In addition, from a methodological perspective, previous studies used different types of controls (TE or HC) compared with PTSD patients. This could yield inconsistent findings regarding the PSG changes in PTSD since TE controls could also show sleep disturbances regardless of whether they meet the diagnostic criteria for PTSD [5,18]. Other methodological issues, such as different study locations, different PSG scoring rules and including or not including adaptation nights, which could contribute to inconsistent PSG findings between PTSD patients and controls has not been explored. These gaps may be filled by an updated meta-analysis which includes additional studies and data.

In 2016, Baglioni et al. [23] performed the second meta-analysis that examined PSG determined sleep in PTSD. However, this study was designed to explore PSG changes in all mental disorders and only included 13 PTSD studies. The limited number (less than half of the total number of available studies) of included PTSD studies and the lack of systematic assessments of potential sources of heterogeneity between studies in this contribution meant that many relevant questions remained unanswered. Furthermore, studies in PTSD patients [14,24] employing power spectral analysis (PSA), a method for quantifying EEG frequency components, including those reflecting general brain arousal level [25,26], were not summarized in either of the previous meta-analysis studies [22,23]. Thus, there is an urgent need to systematically review and summarize findings across studies.

The present review covers case-control studies, updates and extends previous findings, and uses a meta-analytic approach to identify the pooled effect size (and range of credible values) for PSG changes in patients with PTSD compared with controls. We also identify moderators that could explain heterogeneity across studies and we summarize existing PSA findings. This study should thereby provide information needed to enable a better understanding of the neurobiology of PTSD and its relationship to sleep.

Methods

Protocol and registration

The methodology for this study follows PROSPERO protocol CRD42018095700 registered May 29, 2018 in accordance with the preferred reporting items for systematic reviews and meta-analyses statement [27].

Information sources

We searched MEDLINE via OVID (up to Mar 2, 2019); EMBASE via OVID (up to Mar 2, 2019); All EBM databases via OVID (up to Mar 2, 2019); PsycINFO via EBSCO (up to Mar 2, 2019); and CINAHL via EBSCO (up to Mar 2, 2019).

Search

Our search strategy was formulated following the “PICOS principle” [28] to provide a structured search approach with the best capacity to capture all relevant studies. **Participants (*P*):** The participants were adult patients with PTSD according to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria/clinical

interview. **Intervention (*I*):** This element was not applicable as this is a systematic review and meta-analysis of observational studies. **Comparison (*C*):** The control groups were TE or HC. However, we did not indicate control type in the search strategy because some studies may not be indexed by this information in the literature databases. Thus, indicating control types in the search strategy could prevent some relevant studies from being captured. **Outcomes (*O*):** The primary outcomes were PSG changes in patients with PTSD compared with controls. The secondary outcomes were the potential contributions of demographic, clinical and methodological factors, such as sex, age, PTSD severity, type of controls, trauma type, exclusion of obstructive sleep apnea (OSA), medication status, duration of medication withdrawal, and study location, to heterogeneity between studies. **Study design (*S*):** We focused on case-control studies. However, we did not indicate the study design in the search strategy because some studies may not be indexed by study design in the literature databases which may also prevent some relevant studies from being captured.

The search strategies for each database are shown in Tables S1–S5. We initially conducted the search strategies on Jun 13–19, 2018. We used the same search strategies to re-run the literature search on Mar 2, 2019 to identify newly published studies. The reference lists of all primary studies and review articles were checked for additional references.

Inclusion criteria

We only included case-control studies that explored PSG changes in adult patients with PTSD compared with TE or HC. Furthermore, the reviewed studies were published in English and were obtained from peer-reviewed journals. If the same sample was used in more than one publication, then only the dataset with the largest sample was chosen to avoid data duplication.

Exclusion criteria

By title and abstract screening, we excluded: 1) animal studies; 2) case reports, case series, guidelines, statements, and comments; 3) reviews unrelated to sleep or psychiatry; 4) studies unrelated to PTSD; and 5) studies in which it was clearly stated in the abstract that no PSG was conducted and no control group was included. By full text screening, we excluded studies: 1) with diagnosis of PTSD not based on standardized diagnostic criteria (i.e., DSM criteria); 2) not using TE or HC as control; 3) not having a whole-night PSG record; and 4) containing no information on the outcomes of interest.

Study selection

Two investigators (Zhang, Y. and Ren, R.) selected relevant publications independently according to the eligibility criteria. Any disagreement was resolved by thorough discussion and consultation with the senior author (Tang, X. D.). When a study had more than one control group of interest (e.g., one group of controls was TE and another group was HC), we considered it twice for the two different comparisons.

Data collection process

Two investigators (Zhang, Y. and Ren, R.) extracted the data independently using a pre-designed form. Disagreements were resolved by thorough discussion and consultation with the senior author (Tang, X. D.). The data were entered by a single author (Zhang, Y.) and verified by both reviewers (Zhang, Y. and Ren, R.). Data were obtained from the original articles and by contacting the authors when necessary. The PSG variables examined in this review include TST, sleep latency (SL), wake after sleep onset (WASO), sleep efficiency (SE), REM latency (REML), percentage of stage N1, N2, SWS, and REM sleep. Additional PSG variables include REM density (REMD) and PSA data (delta, theta, alpha, sigma, and gamma frequency activity). Demographic and clinical variables extracted include the number of subjects and their age and sex (%), the type of controls, trauma type (combat exposure vs. non-combat exposure), PTSD severity scored by valid scales, diagnostic criteria of PTSD, psychiatric comorbidity (Yes vs. No), medication status (medication free vs. not excluding those who used sleep medication and those not including a washout period), and duration of medication withdrawal. For medication status, if the included studies excluded participants using psychotropic medications known to impact sleep (i.e., antidepressants, antipsychotics, and sedative medications) or arranged a washout period for these medications before the study began, we considered that the participants were medication free. In addition, we also extracted methodological variables from the included studies such as whether OSA was excluded (Yes vs. No), exclusion criteria of OSA (apnea hypopnea index (AHI) $\geq$10 vs. AHI$\geq$15), adaptation nights (Yes vs. No), study location (in sleep laboratory/at home) and PSG scoring criteria (American academy of sleep medicine (AASM) or Rechtschaffen and Kales (R&K)).

Quality assessment

A risk of bias assessment was performed (Zhang, Y. and Ren, R.) using an adapted version of the National Institute for Health and Care Excellence (NICE) checklist [29]. This checklist assisted in reviewing studies for internal validity by methodically appraising the selection of case-control studies, confounding factors and statistical methods [29].

Statistical analysis

The meta-analysis was conducted using the Comprehensive Meta-Analysis software program. To estimate the aggregate effect-size (standardized mean difference (SMD)) for the differences in PSG variables (i.e., TST, SL, WASO, SE, REML, N1, N2, N3, and REM sleep) between patients with PTSD and controls, the mean and standard deviation and sample size for each group were entered for calculation. For studies which did not provide measures of N3 (slow wave sleep, SWS), but reported S3 and S4 data, the mean values of S3 and S4 effect sizes were used as the N3 effect size. For each global effect-size estimate, the Q statistic and I^2 were calculated to examine the presence and magnitude of heterogeneity, and to inform on the degree of overlap between the 95% confidence intervals (CIs) of different studies. I^2 values of 75%, 50%, and 25% are considered to indicate high, moderate, and low heterogeneity [30]. The random effects model was used if significant heterogeneity was found; otherwise, the fixed effects model was applied. Publication bias was tested using the Egger regression method [31], with p values of <0.05 suggesting the presence of bias. The Duval and Tweedie's trim and fill test method was used to adjust the effect size for publication bias [32].

An analysis was carried out to analyze potential factors that could moderate heterogeneity across studies. The following predefined moderators were investigated: age, sex, PTSD severity, type of controls (TE vs. HC), trauma type (combat exposure vs. non-combat exposure), exclusion of OSA (Yes vs. No), different exclusion criteria of OSA (AHI$\geq$10 vs. AHI$\geq$15), psychiatric comorbidity (Yes vs. No), medication status (medication free vs. not excluding those who used sleep medication or arranging a washout period for sleep medications), duration of medication withdrawal ($\geq$two weeks vs.

≥two months vs. ≥six months), adaptation (Yes vs. No), PSG scoring methods (R&K vs. AASM) and study location (at home vs. in lab). A subgroup analysis or meta-regression analysis was performed depending on whether the moderators were categorical or continuous variables.

Results

Study selection

Our search yielded 2130 publications (Fig. 1). After removing the duplicates, we screened the title and abstract of the remaining 1369 articles. A total of 77 articles were selected for full paper review. Of these, 34 articles [12–16,20,24,33–59] were found to meet inclusion criteria for the systematic review (Table 1), and 31 of the 34 studies were included in the meta-analysis (the excluded studies and reasons for their exclusion are provided in Table S6).

Description of the included studies

The sample sizes of the 34 included studies ranged from 14 participants (7 patients with PTSD and 7 controls) [51] to 509 participants (126 patients with PTSD and 383 controls) [57] (Table 1). Mean age (reported in 33 studies) ranged from 22.1 to 71.5 y for PTSD patients and from 22 to 77 y for the control group. Females as percentages of PTSD patients and controls ranged from 0 to 100% (reported in 30 studies). Only one [39] of the 34 included studies in the systematic review performed a home PSG. In one study [57], PSGs were performed in the sleep lab for 70 participants and PSGs were performed at home for four participants. With respect to comorbidity, eight studies [20,33,35,36,44,55,58,59] excluded patients with psychiatric comorbidity and five studies [12,41,50,51,53] did not specify or did not report whether or not they excluded the PTSD patients with psychiatric comorbidity. The tools used for evaluating PTSD severity varied and 18 studies used the Clinician Administered PTSD Scale (CAPS) [12–14,20,24,33–40,47,48,54,55,58].

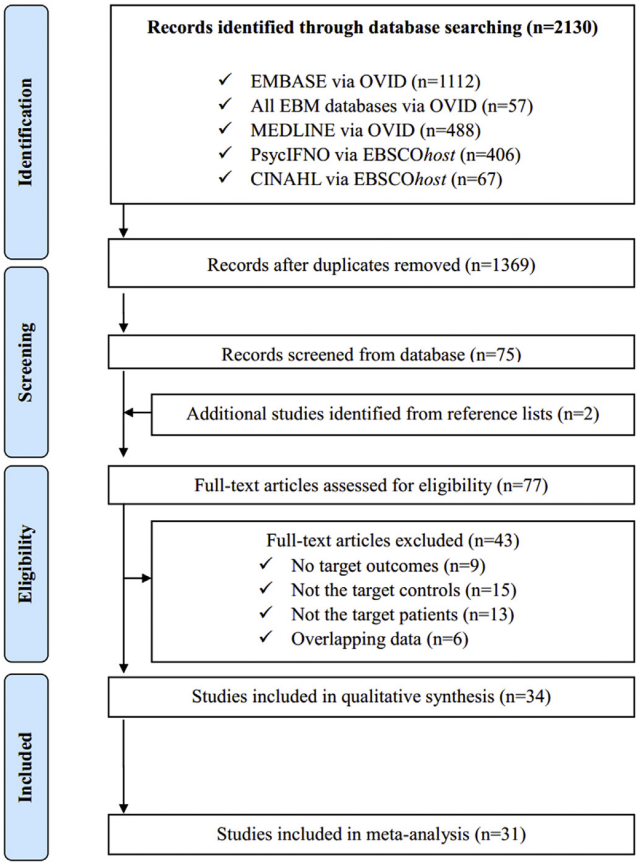

Fig. 1. Flow chart used for the identification of eligible studies.

Six studies [13,14,20,34,56,58] used AASM PSG criteria and most other studies used R&K criteria for scoring sleep (one study [57] did not report which scoring criteria was used). Seventeen studies [12,13,16,34,36,39,42,43,47,48,50,54–59] used TE as the control group, 11 studies [14,20,38,40,41,44–46,51–53] used HC as the control group, four studies [33,35,37,49] used both types of control groups, one study [15] used a mixed control group (TE + HC), and one study [24] did not specify the type of control group (The definition of HC across different included studies is provided in Table S7). Twenty-eight studies [12,15,16,20,24,33,34,36–51,53–55,58,59] included adaptation nights for PSG recordings, five studies [13,14,35,52,56] performed only one night of PSG without adaptation, and one study [57] did not report whether there was an adaptation night. The PSG in 27 studies [12–16,20,24,33–49,51,54,58] was performed in medication free PTSD patients, five studies [52,55–57,59] did not exclude PTSD patients who used sleep medications when performing the PSG, and two studies [50,53] did not report medication status when performing PSG.

Risk of bias of individual studies

Table 2 shows risk of bias assessment based on the NICE checklist. In eight studies [24,40,43,51–53,56,57], it was not clear whether the same exclusion criteria were used for cases and controls. Almost no studies reported participation rate or compared participants vs. non-participants. In one study [49], it was not clear whether the PTSD and control samples were drawn from comparable populations. In our included studies, five [12,41,50,51,53] did not specify/report whether or not they excluded patients with psychiatric comorbidity and two of these five [50,53] also did not report medication status. An additional 23 studies [13–16,24,34,37–40,42,43,45–49,52,54–57,59] provided information on psychiatric comorbidity and medication status, but did not take into account, or did not report, their potential effects on their findings. Therefore, the tenth item of the NICE checklist (*the main potential confounders are identified and taken into account in the design and analysis*) was scored "Not addressed/reported" for these 28 studies.

Comparison between PTSD patients and controls: the whole sample

In the whole sample, meta-analysis revealed significantly decreased SE (SMD = −0.317, 95% CI: −0.504 to −0.131), TST (SMD = −0.205, 95% CI: −0.352 to −0.059) and SWS percentage (SMD = −0.213, 95% CI: −0.386 to −0.039), and increased WASO (SMD = 0.251, 95% CI: 0.100 to 0.402) in patients with PTSD compared with controls ($p < 0.05$; Table 3). However, Egger's test indicated some publication bias in these results (for visualization, see forest plots of pooled effect sizes and funnel plots demonstrating precision by SMD for each PSG variable in Figs. S1–S20). After adjusting for publication bias with the trim-and-fill method, the direction of effect size for SE (SMD = −0.317, 95% CI: −0.504 to −0.131) did not change, and the group differences remained significant ($p < 0.05$). However, after adjusting for publication bias, the effect size for differences in SWS percentage (SMD = 0.043, 95% CI: −0.150 to 0.237) and TST (SMD = 0.039, 95% CI: −0.119 to 0.198), and WASO (SMD = 0.045, 95% CI: −0.110 to 0.201) between PTSD patients and controls did not reach a statistically significant level ($p > 0.05$).

Table 1
Study characteristics.

Study	Sample size	Female%	Age	Diagnostic	PTSD severity (Mean ± SD)	Comorbid mental illness	Medication status	Adaptation	PSG scoring methods	Study location
Lipinska et al., 2017 [33]	21 PTSD	100	P: 25.54 ± 4.35	DSM-IV	CAPS: 67.67 ± 14.12	Excluded	Medication free	Y	R&K	In-lab
	19 TE	100	TE: 24.42 ± 4.53		CAPS: 28.95 ± 11.69					
	20 HC	100	HC: 25.30 ± 4.62		NA					
Stocker et al., 2016 [12]	Blast Exposure 26 PTSD; 11 TE	Unspecified	P: 29.94 ± 5.71 TE: 29.13 ± 5.50	DSM-IV	CAPS: 53.58 ± 15.29 CAPS: 18.09 ± 11.10	Unspecified	Medication free	Y	R&K	In-lab
	No Blast Exposure 21 PTSD; 13 TE	Unspecified	P: 31.73 ± 6.50 TE: 28.55 ± 5.73	DSM-IV	CAPS: 52.52 ± 15.64 CAPS: 13.62 ± 10.53	Unspecified	Medication free	Y	R&K	In-lab
Kobayashi et al., 2016 [34]	38 PTSD	65.79	P: 22.5 ± 4.7	DSM-IV	CAPS: 41.5 ± 17.7	7 anxiety disorder; 5 MDD	Medication free	Y	AASM	In-lab
	33 TE	51.52	TE: 22.7 ± 3.8		CAPS: 8.2 ± 7.7	1 anxiety disorder; 1 MDD; 1 cannabis abuse				
Zhang et al., 2017 [13]	23 PTSD	82.6	P: 47.22 ± 7.22	DSM-IV	CAPS: 72.78 ± 15.69	3 MDD; 1 GAD	Medication free	N	AASM	In-lab
	13 TE	69.23	C: 44.38 ± 11.03		CAPS: 16.38 ± 10.79					
Mellman et al., 2014 [20]	19 PTSD	64.1	P: 22.4 ± 4.7	DSM-IV	CAPS: 41.9 ± 17.7	Excluded	Medication free	Y	AASM	In-lab
	24 HC	45.8	HC: 23.7 ± 5.8		NA					
Lipinska et al., 2014 [35]	16 PTSD	100	P: 26.71 ± 6.15	DSM-IV	CAPS: 73.04 ± 10.22	Excluded	Medication free	N	R&K	In-lab
	15 TE	100	TE: 25.76 ± 4.96		CAPS: 36.27 ± 15.79					
	14 HC	100	HC: 27.17 ± 5.83		NA					
Richards et al., 2013 [14]	21 PTSD	100	P: 30.10 ± 6.96	DSM-IV	CAPS: 58.86 ± 17.32	3 MDD	Medication free	N	AASM	In-lab
	21 HC	100	30.57 ± 7.67		NA					
	19 PTSD	0	P: 31.21 ± 6.39	DSM-IV	CAPS: 52.79 ± 13.81	5 MDD	Medication free	N	AASM	In-lab
	22 HC	0	30.23 ± 8.76		NA					
Cohen et al., 2013 [36]	16 PTSD	Unspecified	P: 27.9 ± 4.8	DSM-IV	CAPS: 62.4 ± 11.9	Excluded	Medication free	Y	R&K	In-lab
	13 TE	Unspecified	TE: 29.0 ± 3.8		CAPS: 27.1 ± 14.2					
van Liempt et al., 2013 [37]	12 PTSD	0	P: 37.69 ± 6.55	DSM-IV	CAPS: 64.11 ± 7.93	12 MDD	Medication free	Y	R&K	In-lab
	15 TE	0	TE: 37.18 ± 6.08		CAPS: 3.65 ± 4.31					
	15 HC	0	HC: 34.53 ± 8.18		CAPS: 0					
Yetkin et al., 2010 [38]	24 PTSD	0	P: 28.3 ± 6.3	DSM-IV	CAPS: 73.8	62.5% MDD; 33.3% alcohol abuse; 12.5% GAD; 8.3% social phobia	Medication free	Y	R&K	In-lab
	16 HC	0	HC: 27.5 ± 5.9		NA					
Herbst et al., 2010 [39]	34 PTSD	38.2	P: 42.2 ± 10.5	DSM-IV	CAPS: 62.7 ± 18.2	70.59% Dep 64.71% past SUD	Medication free	Y	R&K	At-home
	26 TE	50.0	TE: 39.8 ± 11.3		CAPS: 0.8 ± 1.5					
Habukawa et al., 2007 [40]	10 PTSD	50	P: 23.4 ± 6.1	DSM-IV	CAPS: 84.4 ± 17.1	8 Dep; 2 PD	Medication free	Y	R&K	In-lab
	10 HC	50	HC: 24.4 ± 9.7		NA					
Woodward et al., 2000 [15]	56 PTSD	0	P: 45.0 ± 2.8	DSM-IV	Unspecified	86% MDD; 21% PD; 7% Agoraphobia; 16% SP; 7% OCD; 71% alcohol abuse and/or dependence	Medication free	Y	R&K	In-lab
	14 controls (10 TE; 4HC)	0	C: 43.8 ± 6.2							

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size	Female%	Age	Diagnostic	PTSD severity (Mean ± SD)	Comorbid mental illness	Medication status	Adaptation	PSG scoring methods	Study location
Raboni et al., 2014 [41]	13 PTSD	76.9	P: 30.5 ± 5.2	DSM-IV	IES: 27.0 ± 5.9	Unspecified	Medication free	Y	R&K	In-lab
	11 HC	72.7	HC: 29.0 ± 4.4		IES: 15.4 ± 6.5					
Dow et al., 1996 [42]	14 PTSD	0	P: 45 ± 4	DSM−III−R	Mississippi: 140 ± 13	14 depression; 8 Alcohol abuse; 6 Drug abuse; 3 OCD; 4 PD; 2 SP; 3 ASPD or BPD	Medication free	Y	R&K	In-lab
	12 TE	0	HC: 45 ± 2		Mississippi: 61 ± 12					
Engdahl et al., 2000 [43]	30 PTSD	0	P: 71.5 ± 4.2	DSM−III−R	Unspecified	1 dysthymia; 6 GAD	Medication free	Y	R&K	In-lab
	29 TE	0	TE: 71.0 ± 4.2		Unspecified					
Germain et al., 2003 [44]	9 PTSD	55.6	P: 39.0 ± 12.1	DSM-III-R	PSS-SR: 34.31 ± 6.93	Excluded	Medication free	Y	R&K	In-lab
	13 HC	46.2	HC: 32.6 ± 11.2		PSS-SR: 2.50 ± 2.84					
Hurwitz et al., 1998 [45]	18 PTSD	N/R	P: 45.4 ± 5.6	DSM-III-R	IES: 43.2 ± 16.5	11% dysthymia; 22% MDD; 28% PD; 11% OCD; 11% SP; 6% alcohol abuse; 6% BD	Medication free	Y	R&K	In-lab
	10 HC	N/R	HC: 46.5 ± 3.2		NA					
Lavie et al., 1998 [59]	12 PTSD	N/R	P: 31 ± 4.4	DSM-III	IES intrusion: 14.08 ± 4.4; Avoidance: 12.16 ± 5.2	Excluded	1 patient used low doses of oxazepam throughout the study	Y	R&K	In-lab
	12 TE	N/R	TE: 32.8 ± 5.3		IES intrusion: 2.16 ± 3.1; Avoidance: 2.16 ± 2.7					
Mellman et al., 1995 [46]	20 PTSD	0	NR	DSM-III-R	Unspecified	2 MDD; 8 SUD	Medication free	Y	R&K	In-lab
	8 HC	0	NR		Unspecified					
Neylan et al., 2003 [47]	24 PTSD	0	P: 49.4 ± 5.7	DSM-IV	CAPS: 64 ± 17	At least four current depression	Medication free	Y	R&K	In-lab
	18 TE	0	TE: 47.8 ± 9.3		CAPS: 2 ± 4					
Otte et al., 2007 [48]	17 PTSD	100	P: 36 ± 10	DSM-IV	CAPS: 56 ± 16	3 MDD	Medication free	Y	R&K	In-lab
	16 TE	100	TE: 35 ± 9		CAPS: 0.5 ± 1					
Ross et al., 1994 [16]	11 PTSD	0	P: 41.1 ± 3.5	DSM-III-R	NR	5 MDD; 2 PD; 6 agoraphobia; 2 GAD; 1 hypomania	Medication free	Y	R&K	In-lab
	8 TE	0	TE: 43.9 ± 2.8		NR					
Woodward et al., 1996 [49]	80 PTSD inpatients	5	PI: 46	DSM-III-R	NR	Some patients comorbid MDD, SUD, PD or agoraphobia, the number of comorbid was unspecified	Medication free	Y	R&K	In-lab
	7 PTSD outpatients	0	PO: 45	DSM−III−R	NR					
	6 TE	0	TE: 48		NR					
	8 HC	25	HC: 44		NA					
Klein et al., 2002 [50]	8 PTSD	37.5	P: 22.1 ± 2.0	DSM-III-R	IES: 20.7 ± 7.5	NR	NR	Y	R&K	In-lab
	6 TE	50	TE: 22.0 ± 2.5		IES: 4.2 ± 5.2					
Glaubman et al., 1990 [51]	7 PTSD	0	P: 41.43 ± 10.98	DSM-III	NR	NR	Medication free	Y	R&K	In-lab
	7 HC	0	HC: 40.29 ± 12.43							

Fuller et al., 1994 [52]	10 PTSD	0	P: 46	Clinical interview	NR	3 MDD	2 used fluoxetine; 1 used triazolam	N	R&K	In-lab
	10 HC	0	HC: 43		NA					
Inslicht et al., 2018 [24]	33 PTSD	49	P: 29.6 ± 5.3	DSM-IV	CAPS: 52.5 ± 13.7	6 MDD	Medication free	Y	R&K	In-lab
	33 controls (unspecified TE or HC)	42	HC: 30.3 ± 8.4		CAPS: 0.0 ± 0.0					
Germain et al., 2006 [53]	10 PTSD	70	P:34.6 ± 6.3	DSM	NR	NR	NR	Y	R&K	In-lab
	10 HC	70	H:36.9 ± 11.1							
Otte et al., 2005 [54]	20 PTSD	0	P: 49 ± 7	DSM-IV	CAPS: 65 ± 18	4 current depression	Medication free	Y	R&K	In-lab
	17 TE	0	TE: 48 ± 10		CAPS: 2 ± (<1)					
Ulmer et al., 2018 [55]	29 PTSD	12.9	P: 31 ± 8.7	DSM-IV	CAPS: 58.8 ± 13.5	Excluded	6.5% used anti -depressant use, 4.8% used sedative-hypnotic medications of the participants	Y	R&K	In-lab
	33 TE	12.9	TE: 33 ± 7.4		CAPS: 19.7 ± 12.9					
Baird et al., 2018 [56]	40 PTSD	0	P: 70.9 ± 3.9	DSM-V	CAPS-5: 17.1 ± 8.5	8 MDD	32.5% used sedatives	N	AASM	70 participants in-lab and 4 at home
	34 TE	0	TE: 71.7 ± 2.9		CAPS-5: 2.1 ± 3.5					
Balba et al., 2018 [57]	126 PTSD	8.7	P: 52.3 ± 15.3	DSM-V	Unspecified	16.7% anxiety	42.5% sleep medication	Unspecified	Unspecified	In-lab
	383 TE	8.1	TE: 58.4 ± 14.6							
Cowdin et al., 2014 [58]	17 PTSD	64.7	P: 22.35 ± 4.62	DSM-IV	CAPS: 47.4 ± 17.1	Excluded	Medication free	Y	AASM	In-lab
	13 TE	61.5	TE: 20.77 ± 2.68							

PD, panic disorder; Dep, depression; CES, Combat Exposure Score; SP, social phobia; OCD; obsessive compulsive disorder; IES, Impact of Event Scale; Mississippi scale: a tool for screening PTSD; ASPD, antisocial personality disorder; BPD, borderline personality disorder; PSS-SR, Posttraumatic Symptom Scale, self-report version; BD, bipolar disorder; SUD, substance use disorders.

Table 2
Risk of bias assessment based on an adapted version of the NICE checklist.

Author(s), date	Study addresses an appropriate and clearly focused question	The cases and controls are taken from comparable populations	The same exclusion criteria are used for both cases and controls	What was the participation rate for cases and controls?	Participants and non-participants are compared to establish their similarities or differences	Cases are clearly defined and differentiated from controls	It is clearly established that controls are not cases	Measures were taken to prevent knowledge of primary exposure from influencing case ascertainment.	Exposure status is measured in a standard, valid, and reliable way.	The main potential confounders are identified and taken into account in the design and analysis.
Lipinska et al., 2017 [33]	√	√	√	?	?	√	√	?	√	√
Stocker et al., 2016 [12]	√	√	√	?	?	√	√	?	√	?
Kobayashi et al., 2016 [34]	√	√	√	?	?	√	√	?	√	?
Zhang et al., 2017 [13]	√	√	√	?	?	√	√	?	√	?
Mellman et al., 2014 [20]	√	√	√	?	?	√	√	?	√	√
Lipinska et al., 2014 [35]	√	√	√	?	?	√	√	?	√	√
Richards et al., 2013 [14]	√	√	×	?	?	√	√	?	√	?
Cohen et al., 2013 [36]	√	√	√	?	?	√	√	?	√	√
van Liempt et al., 2013 [37]	√	√	√	?	?	√	√	?	√	?
Yetkin et al., 2010 [38]	√	√	√	?	?	√	√	?	√	?
Herbst et al., 2010 [39]	√	√	√	?	?	√	√	?	√	?
Habukawa et al., 2007 [40]	√	√	?	?	?	√	√	?	√	?
Woodward et al., 2000 [15]	√	√	√	?	?	√	√	?	√	?
Raboni et al., 2014 [41]	√	√	√	√	√	√	√	?	√	?
Dow et al., 1996 [42]	√	√	√	?	?	√	√	?	√	?
Engdahl et al., 2000 [43]	√	√	?	?	?	√	√	?	√	?
Germain et al., 2003[44]	√	√	√	?	?	√	√	?	√	√
Hurwitz et al., 1998 [45]	√	√	√	?	?	√	√	?	√	?
Lavie et al., 1998[59]	√	√	√	?	?	√	√	?	√	?
Mellman et al., 1995 [46]	√	√	√	?	?	√	√	?	√	?
Neylan et al., 2003 [47]	√	√	√	?	?	√	√	?	√	?
Otte et al., 2007 [48]	√	√	√	?	?	√	√	?	√	?
Ross et al., 1994 [16]	√	√	√	?	?	√	√	?	√	?
Woodward et al., 1996[49]	√	×	√	?	?	√	√	?	√	?
Klein et al., 2002 [50]	√	√	√	√	?	√	√	?	√	?
Glaubman et al., 1990 [51]	√	√	?	?	?	√	√	?	√	?
Fuller et al., 1994 [52]	√	√	?	?	?	√	√	?	√	?
Inslicht et al., 2018 [24]	√	√	?	?	?	√	√	?	√	?
Germain et al., 2006 [53]	√	√	?	?	?	√	√	?	√	?
Otte et al., 2005 [54]	√	√	√	?	?	√	√	?	√	?
Cowdin et al., 2014 [58]	√	√	√	?	?	√	√	?	√	√
Ulmer et al., 2018 [55]	√	√	√	?	?	√	√	?	√	?
Baird et al., 2018 [56]	√	√	?	√	?	√	√	?	√	?
Balba et al., 2018 [57]	√	√	?	?	?	√	√	?	√	?

√ Well Addressed
√ Adequately Addressed
× Poorly Addressed
? Not Addressed/Reported

Moderator analysis (Table 4)

Sex

A meta-regression analysis revealed that an increased percentage of female PTSD patients across different studies was significantly associated with increased WASO in PTSD patients compared with controls (Point estimate = 0.410, $p = 0.044$).

Age

A meta-regression analysis revealed that differences in REM percentage between PTSD patients and controls were significantly associated with the mean age of PTSD patients. Furthermore, significantly decreased REM percentage compared with controls was found in studies in which PTSD patients had a mean age <30 y (SMD = −0.235, 95% CI: −0.439 to −0.030), but not in studies with

Table 3
Summary of meta-analysis.

	No. of comparison	No. of P/C	Means of P	Means of C	SMD	Q	I^2
TST min	40	1111/948	355.466	371.763	−0.205**	71.881**	45.744
SL min	36	960/865	17.117	16.094	0.087	45.031	22.276
WASO min	24	664/826	33.720	28.933	0.251**	36.480*	36.952
SE %	38	1036/887	80.154	83.490	−0.317**	100.361***	63.133
N1%	38	1073/924	8.952	6.581	0.147	86.960***	57.452
N2%	39	1085/936	52.882	52.083	0.041	71.149**	46.591
SWS%	40	1099/948	10.731	13.300	−0.213*	101.042***	61.402
REM%	40	1137/973	20.897	21.021	0.012	107.429***	63.697
REML min	33	834/446	57.988	67.668	−0.061	43.103	25.759
REMD	14	288/224	–	–	0.192	17.574	26.025

*p < 0.05, **p < 0.01, ***p < 0.001.
%, percentage; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance [30]; Q, Cochran's Q statistic; REM, rapid eye movement sleep, REMD, rapid eye movement sleep density; REML, rapid eye movement sleep latency; P/C, PTSD/controls; SMD, standardized mean difference; SWS, slow wave sleep; SE, sleep efficiency; SL, sleep latency; TST, total sleep time. Means for REMD were not calculated because definitions and algorithms of REMD varied across studies.

Table 4
Moderator analyses across subgroup analysis and meta-regression analysis.

Moderators		TST	SL	WASO	SE	N1%	N2%	SWS%	REM%	REML	REMD
Trauma Type											
Combat exposure	No. of comparison	22	18	11	20	20	21	22	21	15	8
	No. of P/C	814/682	697/626	382/578	773/648	788/658	800/670	814/682	797/666	551/198	169/114
	SMD	−0.076	0.019	0.013	−0.030	0.143	−0.013	−0.103	0.140	−0.060	0.290*
	Q	35.849*	15.722	10.913	26.193	31.329*	22.039	40.265**	57.455***	23.694	4.655
	I^2	41.421	0	8.364	27.462	39.354	9.250	47.846	65.190	40.912	0
Non-combat exposure	No. of comparison	7	11	8	11	9	9	9	9	9	3
	No. of P/C	117/109	191/177	151/142	191/177	173/161	173/161	173/161	173/161	143/134	38/47
	SMD	−0.172	0.022	0.432**	−0.544**	0.221	0.058	−0.211	−0.246*	−0.019	0.109
	Q	5.280	12.132	8.612	32.106***	15.255	6.171	14.945	5.683	9.171	3.293
	I^2	0	17.571	18.720	68.853	47.558	0	46.470	0	12.769	39.268
Between group difference	Q	0.343	0.001	7.104	5.437	0.186	0.297	0.346	5.574	0.052	0.326
	P	0.558	0.979	0.008	0.020	0.666	0.586	0.556	0.018	0.819	0.568
Sex (female%)	No. of comparison	35	31	21	33	34	34	35	35	28	10
	No. of P/C	1018/889	867/806	601/789	943/828	992/877	992/877	1006/889	1044/914	841/387	207/177
	Point estimate	0.003	−0.204	0.410	−0.223	0.168	−0.237	0.211	−0.205	0.200	−0.137
	SE	0.250	0.192	0.203	0.275	0.226	0.204	0.245	0.265	0.202	0.559
	P	0.990	0.289	0.044	0.417	0.455	0.246	0.389	0.440	0.320	0.807
Mean age of PTSD patients	No. of comparison	39	36	24	37	37	38	39	39	32	13
(Continuous variable)	No. of P/C	1091/940	960/865	664/826	1016/879	1053/916	1065/928	1079/940	1117/965	814/438	268/216
	Point estimate	0.006	0.001	−0.012	0.010	−0.005	0.002	−0.003	0.014	−0.003	−0.004
	SE	0.006	0.005	0.004	0.007	0.007	0.006	0.007	0.007	0.006	0.008
	P	0.347	0.896	0.008	0.159	0.472	0.767	0.657	0.049	0.623	0.601
Mean age of PTSD patients (Categorical variable)											
<30 y	No. of comparison	7	11	7	11	10	10	10	10	10	4
	No. of P/C	141/113	215/181	151/130	215/181	207/175	207/175	207/175	207/175	177/148	71/58
	SMD	−0.211	0.079	0.359**	−0.471*	0.127	0.015	−0.131	−0.235*	0.037	0.149
	Q	11.079	21.196*	7.234	46.057***	22.343**	7.645	21.433*	4.564	13.011	3.756
	I^2	45.841	52.821	17.055	78.288	59.719	0	58.008	0	30.825	20.117
30–40 y	No. of comparison	11	8	9	8	9	10	10	8	4	3
	No. of P/C	175/181	118/122	146/153	118/122	153/159	165/171	165/171	135/144	55/49	43/37
	SMD	−0.257*	0.082	0.408**	−0.373*	0.256*	0.025	−0.101	−0.161	−0.224	0.453
	Q	7.499	6.318	5.378	8.913	3.169	12.851	14.140	15.418*	3.712	2.525
	I^2	0	0	0	21.467	0	29.969	36.352	54.599	19.187	20.781
>40 y	No. of comparison	21	17	8	18	18	18	19	21	18	6
	No. of P/C	775/646	627/562	367/543	683/576	693/582	693/582	707/594	775/646	582/241	154/121
	SMD	−0.183	0.070	0.027	−0.139	0.064	0.114	−0.330*	0.231	−0.067	0.041
	Q	47.558***	17.459	9.582	31.312*	55.134***	48.078***	64.917***	71.832***	24.363	5.752
	I^2	57.946	8.356	26.946	45.708	69.166	64.641	72.272	72.157	30.222	13.076
Between group difference	Q	0.229	0.006	7.511	2.483	1.130	0.341	1.337	7.244	1.021	1.980
	P	0.892	0.997	0.023	0.289	0.568	0.843	0.512	0.027	0.600	0.372
CAPS score	No. of comparison	17	15	17	15	19	19	19	20	14	8
	No. of P/C	379/325	304/264	380/332	304/264	385/341	385/341	385/341	436/377	305/238	184/141
	Point estimate	−0.014	0.012	0.010	−0.042	0.003	0.004	−0.021	−0.002	−0.013	0.013
	SE	0.008	0.009	0.008	0.012	0.009	0.007	0.010	0.008	0.010	0.012
	P	0.077	0.198	0.186	<0.001	0.737	0.558	0.037	0.782	0.196	0.247
Control type											
HC	No. of comparison	17	16	9	17	18	18	18	17	15	6
	No. of P/C	366/209	343/192	134/146	363/200	393/233	393/233	393/233	380/222	341/175	89/76
	SMD	−0.359**	0.152	0.496**	−0.604**	0.282	0.120	−0.536**	−0.096	−0.068	0.438
	Q	26.232	28.530*	11.008	58.814***	58.029***	45.883***	47.364***	55.694***	22.463	9.219
	I^2	39.007	47.424	27.324	72.796	70.704	62.949	64.108	71.272	37.675	45.763
TE	No. of comparison	22	20	14	20	19	20	21	22	18	8
	No. of P/C	689/725	617/673	474/666	617/673	624/677	636/689	650/701	701/737	493/271	199/148
	SMD	−0.113	0.030	0.130	−0.110	0.070	0.001	0.039	0.035	−0.053	0.058
	Q	36.801*	15.824	16.109	25.280	20.941	24.687	25.813	46.795**	20.598	5.779
	I^2	42.936	0	19.302	24.842	14.045	23.036	22.519	55.123	17.469	0
Between group difference	Q	2.527	0.624	4.857	5.352	1.219	0.462	10.322	0.396	0.010	2.290
	P	0.112	0.430	0.028	0.021	0.269	0.497	0.001	0.529	0.921	0.130
Whether excluding OSA											
No	No. of comparison	12	14	11	14	13	14	14	13	12	4
	No. of P/C	305/558	339/583	320/572	339/583	349/598	361/610	361/610	348/599	203/190	62/63
	SMD	−0.013	0.099	0.338*	−0.542**	0.259	0.013	−0.283	−0.043	−0.046	0.394
	Q	12.972	16.961	30.084**	57.041***	45.204***	39.960***	57.439***	56.661***	13.833	4.689
	I^2	15.202	23.354	66.760	77.209	73.454	67.468	77.367	78.821	20.480	36.023
Yes	No. of comparison	28	22	13	24	25	25	26	27	21	10
	No. of P/C	806/390	621/282	344/252	697/304	724/326	724/326	738/338	789/374	631/256	226/161
	SMD	−0.263**	0.079	0.248**	−0.203	0.089	0.055	−0.173	0.031	−0.070	0.128
	Q	50.673**	28.067	3.357	43.027**	41.719*	31.185	43.039*	50.730**	29.232	11.755
	I^2	46.717	25.180	0	46.545	42.472	23.040	41.913	48.748	31.581	23.439
Between group difference	Q	3.463	0.022	0.266	2.522	0.764	0.060	0.303	0.122	0.025	0.977
	P	0.063	0.881	0.606	0.112	0.382	0.806	0.582	0.727	0.874	0.323

(*continued on next page*)

Table 4 (*continued*)

Moderators		TST	SL	WASO	SE	N1%	N2%	SWS%	REM%	REML	REMD
Different exclusion criteria of OSA											
AHI≥15	No. of comparison	5	5	5	5	5	5	5	5	3	3
	No. of P/C	87/67	87/67	87/67	87/67	87/67	87/67	87/67	87/67	63/37	63/37
	SMD	−0.049	0.093	0.354*	0.028	0.267	0.109	0.163	−0.180	0.228	0.251
	Q	3.423	3.114	0.460	3.590	1.267	4.132	2.907	5.885	3.946	0.084
	I^2	0	0	0	0	0	3.199	0	32.027	49.313	0
AHI≥10	No. of comparison	7	2	6	3	5	5	5	6	4	4
	No. of P/C	222/157	57/57	205/141	113/71	154/105	154/105	154/105	205/141	111/94	111/94
	SMD	−0.181	−0.174	0.187	0.083	0.055	−0.065	−0.091	0.041	−0.053	−0.168
	Q	7.196	0.147	1.875	0.265	10.151*	5.825	11.814*	12.227*	3.737	1.327
	I^2	16.617	0	0	0	60.596	31.334	66.141	59.107	19.725	0
Between group difference	Q	0.420	1.126	0.684	0.058	0.609	0.547	0.787	0.663	0.693	2.748
	P	0.517	0.289	0.408	0.810	0.435	0.460	0.375	0.415	0.405	0.097
Psychiatric comorbidities											
No	No. of comparison	4	8	5	8	7	8	8	8	8	3
	No. of P/C	56/62	130/130	86/89	118/118	118/118	130/130	130/130	130/130	130/130	44/50
	SMD	−0.204	−0.062	0.366*	−0.337**	0.307	−0.139	−0.083	−0.139	0.027	−0.020
	Q	1.741	7.757	1.740	5.313	8.485	4.989	9.033	3.304	9.575	1.725
	I^2	0	9.757	0	0	29.289	0	22.503	0	26.892	0
Yes	No. of comparison	29	21	14	23	26	26	27	28	19	8
	No. of P/C	930/794	705/643	468/658	793/677	848/730	848/730	862/742	913/778	589/234	184/139
	SMD	−0.244*	0.095	0.187	−0.330*	0.099	0.099	−0.299**	0.069	−0.187*	0.183
	Q	64.993***	27.614	24.537*	76.336***	46.260**	32.278	61.168***	70.524***	20.318	10.816
	I^2	56.919	27.574	47.018	71.180	45.957	22.574	57.494	61.715	11.407	35.282
Between group difference	Q	0.037	0.966	0.941	0.001	1.299	2.654	1.508	1.670	1.514	0.631
	P	0.848	0.326	0.332	0.972	0.254	0.103	0.220	0.196	0.218	0.427
Medication status											
Medication free	No. of comparison	33	29	20	31	34	34	35	35	29	–
	No. of P/C	876/460	725/377	459/366	801/399	868/464	868/464	882/476	920/501	764/384	–
	SMD	−0.252**	0.101	0.300***	−0.376**	0.164	0.052	−0.257*	0.054	−0.099	–
	Q	56.411**	39.309	18.470	78.029***	81.238***	69.409***	81.397***	97.818***	39.150	–
	I^2	43.273	28.769	0	61.553	59.379	52.456	58.230	65.242	28.480	–
Not excluded patients taking sleep medications	No. of comparison	5	5	3	5	4	4	5	5	3	–
	No. of P/C	217/472	217/472	195/450	217/472	205/460	217/472	217/472	217/472	62/56	–
	SMD	0.060	−0.001	−0.035	0.055	−0.022	0.078	0.104	−0.200	0.268	–
	Q	4.892	2.630	3.824	5.030	3.262	1.658	5.839	8.140	0.308	–
	I^2	18.226	0	47.704	20.484	8.020	0	31.499	50.863	0	–
Between group difference	Q	4.946	0.717	4.005	7.179	1.703	0.040	4.885	1.741	3.262	–
	P	0.026	0.397	0.045	0.007	0.192	0.841	0.027	0.187	0.071	–
Duration of medication withdrawal											
≥2 wk	No. of comparison	8	7	3	8	8	8	8	8	7	5
	No. of P/C	137/83	171/75	57/34	137/83	137/83	137/83	137/83	137/83	126/75	95/52
	SMD	−0.451*	0.652***	0.710	−0.926*	0.437	−0.110	−0.399	−0.041	0.077	0.461**
	Q	11.549	4.513	5.441	45.007***	49.641***	38.086***	39.161***	39.656***	15.049*	1.875
	I^2	39.391	0	63.241	84.447	85.899	81.620	82.125	82.348	60.129	0
≥2 mo	No. of comparison	5	–	4	1	3	3	3	4	3	3
	No. of P/C	165/100	–	148/84	56/14	97/48	97/48	97/48	148/84	92/70	92/70
	SMD	−0.243	–	0.165	0.211	0.148	−0.084	−0.312	0.168	−0.180	−0.128
	Q	3.708	–	1.779	0	9.710**	4.093	8.102*	5.643	0.793	1.025
	I^2	0	–	0	0	79.403	51.138	75.313	46.838	0	0
≥6 mo	No. of comparison	3	3	3	3	3	3	3	3	1	1
	No. of P/C	54/59	54/59	54/59	54/59	54/59	54/59	54/59	54/59	30/29	30/29
	SMD	−0.039	0.049	0.118	−0.115	0.166	0.041	−0.150	−0.044	−0.381	0
	Q	2.437	0.435	1.750	1.475	0.984	2.925	2.342	20.468***	0	0
	I^2	17.915	0	0	0	0	31.623	14.608	90.229	0	0
Between group difference	Q	2.131	6.114	1.981	5.317	0.349	0.178	0.389	0.304	1.681	6.358
	P	0.345	0.013	0.371	0.070	0.840	0.915	0.823	0.859	0.432	0.042
Adaptation night											
No	No. of comparison	10	9	5	9	11	11	11	12	10	1
	No. of P/C	321/154	279/114	137/116	279/114	319/157	319/157	319/157	353/183	313/140	34/26
	SMD	−0.240	−0.062	0.238	−0.236	0.010	0.141	−0.354**	0.047	0.154	−0.219
	Q	23.010**	11.437	0.679	14.444	6.148	8.211	13.522	21.848*	4.619	0
	I^2	60.887	30.054	0	44.612	0	0	26.046	49.653	0	0
Yes	No. of comparison	29	26	18	28	26	27	28	27	23	13
	No. of P/C	654/411	555/368	401/327	631/390	628/384	640/396	654/408	658/407	521/306	254/198
	SMD	−0.230**	0.156	0.306***	−0.379**	0.225	−0.004	−0.183	−0.006	−0.161	0.236*
	Q	35.041	30.722	18.336	68.957***	76.297***	61.023***	73.822***	84.952***	32.821	15.219
	I^2	20.095	18.624	7.287	60.845	67.233	57.393	63.426	69.395	32.969	21.150
Between group difference	Q	0.003	1.577	0.204	0.462	1.663	0.891	0.960	0.075	4.571	2.574
	P	0.958	0.209	0.652	0.497	0.197	0.345	0.327	0.785	0.033	0.109
PSG scoring methods											
AASM	No. of comparison	6	4	6	4	6	6	6	6	3	1
	No. of P/C	160/147	120/104	160/147	120/104	160/147	160/147	160/147	160/147	82/71	19/24

Table 4 (*continued*)

Moderators		TST	SL	WASO	SE	N1%	N2%	SWS%	REM%	REML	REMD
	SMD	−0.164	−0.016	0.239*	−0.094	−0.029	0.162	−0.171	−0.050	0.280	−0.318
	Q	5.762	2.160	0.698	1.539	2.323	7.086	10.622	12.055*	0.298	0
	I^2	13.226	0	0	0	0	29.440	53.105	58.523	0	0
R&K	No. of comparison	33	31	17	33	31	32	33	33	30	13
	No. of P/C	825/418	714/378	378/296	790/400	787/394	799/406	813/418	851/443	752/375	269/200
	SMD	−0.242**	0.136	0.315***	−0.388**	0.214	0.004	−0.246*	0.019	−0.113	0.231*
	Q	52.277*	40.921	18.276	80.150***	79.356***	62.092**	78.413***	93.961***	37.690	14.987
	I^2	38.787	26.688	12.451	60.075	62.196	50.074	59.190	65.943	23.057	19.923
Between group difference	Q	0.263	0.910	0.278	2.810	2.229	0.855	0.138	0.102	4.620	2.820
	P	0.608	0.340	0.598	0.094	0.135	0.355	0.711	0.750	0.032	0.093
Study location											
At home	No. of comparison	2	–	2	–	–	–	–	2	2	2
	No. of P/C	68/52	–	68/52	–	–	–	–	68/52	68/52	68/52
	SMD	−0.139	–	0.303	–	–	–	–	−0.017	−0.133	−0.223
	Q	0.711	–	0.265	–	–	–	–	2.097	0.537	0
	I^2	0	–	0	–	–	–	–	52.323	0	0
In lab	No. of comparison	37	–	21	–	–	–	–	37	30	12
	No. of P/C	1003/862	–	556/740	–	–	–	–	1029/887	726/360	220/172
	SMD	−0.224**	–	0.268**	–	–	–	–	0.026	−0.068	0.287**
	Q	71.074***	–	35.313*	–	–	–	–	102.929***	41.044	12.004
	I^2	49.349	–	43.364	–	–	–	–	65.024	29.344	8.363
Between group difference	Q	0.177	–	0.029	–	–	–	–	0.023	0.100	5.635
	P	0.674	–	0.865	–	–	–	–	0.879	0.752	0.018

*p < 0.05, **p < 0.01, ***p < 0.001.
AASM, American academy of sleep medicine; AHI, apnea hypopnea index; %, percentage; I^2, the percentage of total variation across studies that is due to heterogeneity rather than chance [30]; Q, Cochran's Q statistic; OSA, obstructive sleep apnea; REM, rapid eye movement sleep, REMD, rapid eye movement sleep density; REML, rapid eye movement sleep latency; R&K, Rechtschaffen and Kales; P/C, PTSD/control; SMD, standardized mean difference; SWS, slow wave sleep; SE, sleep efficiency; SL, sleep latency; TST, total sleep time.

mean ages of 30–40 y (SMD = −0.161, 95% CI: −0.524 to 0.203) or >40 y (SMD = 0.231, 95% CI: −0.046 to 0.508). There also were significant between group differences (p = 0.027). Egger's tests found no publication bias in these findings for any age subgroup (p > 0.05). Forest plots of pooled effect sizes for REM percentage across age subgroups and funnel plots of precision by SMD to visualize possible publication bias across age subgroups are shown in Figs. S21–S26.

A meta-regression analysis also revealed that differences in WASO between PTSD patients and controls were significantly associated with mean patient age. Furthermore, significantly increased WASO compared with controls was found in studies in which PTSD patients had a mean age <30 y (SMD = 0.359, 95% CI: 0.092 to 0.627) and in studies with mean ages of 30–40 y (SMD = 0.408, 95% CI: 0.176 to 0.640), but not in the studies with mean ages of >40 y (SMD = 0.027, 95% CI: −0.164 to 0.218). There were significant between group differences (p = 0.023); however, Egger's test indicated some publication bias in these results. After adjusting for publication bias with the trim-and-fill method, increased WASO in PTSD patients was still detected in studies in which PTSD patients had a mean age <30 y (SMD = 0.466, 95% CI: 0.234 to 0.698) and in those with mean ages of 30–40 y (SMD = 0.408, 95% CI: 0.176 to 0.640), but not in studies with mean ages of >40 y (SMD = −0.188, 95% CI: −0.396 to 0.019). Forest plots of pooled effect sizes for WASO across age subgroups and funnel plots of precision by SMD to visualize possible publication bias across age subgroups are shown in Figs. S27–S32.

Type of controls

A subgroup analysis revealed that type of control (TE vs. HC) was a statistically significant source of heterogeneity for differences in SWS percentage, WASO, and SE between PTSD patients and controls (Figs. S33–S44). Significantly decreased SWS percentage was found in PTSD patients compared with HC (SMD = −0.536, 95% CI: −0.851 to −0.221), but not compared with TE (SMD = 0.039, 95% CI: −0.115 to 0.192). Significantly increased WASO was found in PTSD patients compared with HC (SMD = 0.496, 95% CI: 0.209 to 0.782), but not compared with TE (SMD = 0.130, 95% CI: −0.022 to 0.283). Significantly decreased SE was found in PTSD patients compared with HC (SMD = −0.604, 95% CI: −0.990 to −0.218), but not compared with TE (SMD = −0.110, 95% CI: −0.273 to 0.053). Egger's test indicated some publication bias in these results. However, after adjusting for publication bias with the trim-and-fill method, decreased SWS percentage (SMD = −0.463, 95% CI: −0.834 to −0.091) and SE (SMD = −0.773, 95% CI: −1.189 to −0.358), and increased WASO (SMD = 0.496, 95% CI: 0.209 to 0.783) were still detected in PTSD patients compared with HC, and these differences each reached a statistically significant level (p < 0.05).

Type of control was not a source of heterogeneity for differences in TST between PTSD patients and controls; however, significantly decreased TST was only found in PTSD patients compared with HC (SMD = −0.359, 95% CI: −0.605 to −0.112), but not compared with TE (SMD = −0.133, 95% CI: −0.289 to 0.064). No publication bias was detected when comparing PTSD patients with HC (p > 0.05) (Figs. S45–S48).

Trauma type

A subgroup analysis revealed that trauma type (combat exposure vs. non-combat exposure) was a statistically significant source of heterogeneity for differences in WASO, SE, and REM percentage between PTSD patients and controls. Significantly increased WASO (SMD = 0.432, 95% CI: 0.166 to 0.698), decreased SE (SMD = −0.544, 95% CI: −0.941 to −0.146), and decreased REM sleep percentage (SMD = −0.246, 95% CI: −0.464 to −0.028) were found in PTSD patients compared with controls in studies in which trauma type was non-combat exposure. WASO (SMD = 0.013, 95% CI: −0.143 to 0.168), SE (SMD = −0.030, 95% CI: −0.197 to 0.137), and REM percentage (SMD = 0.140, 95% CI: −0.095 to 0.375) did not significantly differ between PTSD patients and controls in studies in which trauma type was combat exposure. Egger's test indicated some

publication bias in these results. However, after adjusting for publication bias with the trim-and-fill method, the direction of effect size for WASO, SE, and REM sleep percentage did not change, and the group differences remained significant in studies in which trauma type was non-combat exposure ($p < 0.05$) (Figs. S49–S60).

PTSD severity

The increased severity of PTSD (mean CAPS score) was significantly associated with decreased percentage of SWS in patients with PTSD compared with controls (Point estimate = −0.021, p = 0.037). When we explored this association separately in studies using TE and HC as the control groups, the association of PTSD severity with decreased SWS percentage was found in studies using HC as the control group (Point estimate = −0.023, $p = 0.027$), but not in studies using TE as the control group (Point estimate = −0.012, $p = 0.421$).

Increased PTSD severity was also significantly associated with decreased SE in patients with PTSD compared with controls (Point estimate = −0.042, $p < 0.001$). When we explored this association separately in studies using TE and HC as the control groups, the association of PTSD severity with decreased SE was found in studies using HC as the control group (Point estimate = −0.067, $p = 0.015$), but not in studies using TE as the control group (Point estimate = −0.019, $p = 0.053$).

Exclusion of OSA and different exclusion criteria of OSA

A subgroup analysis did not reveal any significant associations between whether the included studies used an exclusion criterion to exclude OSA and differences in PSG variables between PTSD patients and controls. In the studies that did use different exclusion criteria of OSA (AHI≥10 vs. AHI≥15), there was no association between the criteria and differences in PSG variables between PTSD patients and controls ($p > 0.05$).

Medication status

Medication status was a significant source of heterogeneity for differences between PTSD patients and controls in SE, TST, SWS percentage and WASO. We found decreased SE (SMD = −0.376, 95% CI: −0.597 to −0.154), TST (SMD = −0.252, 95% CI: −0.421 to −0.084) and SWS percentage (SMD = −0.257, 95% CI: −0.453 to −0.062), and increased WASO (SMD = 0.300, 95% CI: 0.158 to 0.442) in comparisons between groups in studies whose patients were medication free, but not in studies that did not exclude patients taking sleep medications.

Duration of medication withdrawal

A subgroup analysis revealed that duration of medication withdrawal was a significant source of heterogeneity for differences between PTSD patients and controls in SL and REMD. Increased SL (SMD = 0.652, 95% CI: 0.350 to 0.953) and REMD (SMD = 0.461, 95% CI: 0.115 to 0.808) in PTSD patients compared with controls was found in the studies whose participants did not take medication impacting sleep at least two weeks prior to evaluation, but not in those studies whose participants did not take medication impacting sleep at least two months or six months prior to evaluation.

Psychiatric comorbidity

A meta-regression analysis did not reveal any significant associations between whether the included studies excluded patients with psychiatric comorbidity (Yes vs. No) and differences in PSG variables between PTSD patients and controls ($p > 0.05$).

Study location

Due to limited data, subgroup analysis was not performed for SL, SE, and percentages of N1, N2 and SWS. Study location (in lab vs. at home) was a significant source of heterogeneity for differences in REMD between PTSD patients and controls. When excluding the home PSG studies, REMD was significantly increased (SMD = 0.287, 95% CI: 0.072 to 0.503) in patients with PTSD compared with controls.

Adaptation night

Based on within study comparisons, PTSD patients showed an apparent decrease in REML compared with controls in studies having an adaptation night (SMD = −0.161, 95% CI: −0.351 to 0.028), and an apparent increase in REML compared with controls in studies not having an adaptation night (SMD = 0.154, 95% CI: −0.064 to 0.372). Neither effect size reached statistical significance ($p > 0.05$). However, a comparison across studies, revealed that the difference in effect sizes of the two subgroups (*decreased REML in PTSD in studies with adaptation* vs. *increased REML in PTSD in studies without adaptation*) was statistically significant ($p = 0.033$), and therefore whether included studies had an adaptation night (Yes vs. No) was a significant source of heterogeneity between PTSD patients and controls for differences in REML.

PSG scoring methods

A subgroup analysis revealed that PSG scoring methods (AASM vs. R&K) was a significant source of heterogeneity between PTSD patients and controls for differences in REML. However, after excluding studies using AASM criteria, we did not find any significant difference in REML between PTSD patients and controls in the studies using R&K criteria (SMD = −0.113, 95% CI: −0.270 to 0.044).

PSA findings

We could not perform a meta-analytic assessment for PSA as the published studies were methodologically too different to be compared. In total, eight studies [14,15,24,36,48,53,54,58] conducted PSA with different methodological approaches and different findings. The results are summarized in Table 5.

Discussion

Summary of findings

The major findings of the present review were that: 1) TST, SWS and SE were decreased and WASO increased in patients with PTSD compared with healthy controls; 2) PTSD severity was associated with decreased SE and SWS percentage; 3) although REM sleep percentage did not significantly differ between PTSD patients and controls across the whole sample, it was significantly decreased in PTSD patients in studies where the mean age of participants was below 30 y, but not in studies with greater mean ages (30–40 y and >40 y); and 4) WASO was significantly increased in PTSD patients compared with controls in studies where the mean age of participants was below 30 y and between 30 and 40 y, but not in studies where the mean age of participants was above 40 y. We also found that some clinical (i.e., type of controls, medication status and duration of medication withdrawal) and methodological (i.e., adaptation night, PSG scoring methods, study location) factors were sources of heterogeneity in findings of PSG changes in comparisons between PTSD patients and controls across studies.

PSG abnormalities in PTSD

Our systematic review showed that sleep continuity and sleep architecture are disturbed in patients with PTSD. It is therefore

Table 5
Power spectral analysis.

Study	Quantitative measures	Sample size (P/C)	Patients	Controls	p value
Richards et al., 2013 [14]	Power spectra for Delta (1−4 Hz), theta (4 −8 Hz), alpha (8 −12 Hz), sigma (12 −15 Hz), beta1 (15 −23 Hz), beta2 (23 −30 Hz) and gamma (30−50 Hz) bands were analyzed.	21/21(Female); 19/22 (Male)	there was a significant effect of PTSD on NREM delta activity (i.e. delta energy). There were no other significant main effects of PTSD on NREM energy in the higher frequency bands.		
Cohen et al., 2013 [36]	Quantify the frequency content of the sleep EEG from 0.50 to 50 Hz. The frequency bands of interest were defined as: delta (0.5−4 Hz), theta (4−8 Hz), alpha (8−12 Hz), sigma (12−16 Hz), beta (16−32 Hz) and gamma (32−50 Hz).	16/13	No statistically significant differences in whole-night REM or NREM spectral power between the PTSD and non-PTSD groups in any frequency band; PTSD group had less REM beta activity, less REM sigma, less NREM sigma and more NREM gamma compared to the non-PTSD group		
Otte et al., 2007 [48]	Delta Integrated Amplitude-Total	17/16	193,152.9 (51,684.6)	217,788.4 (70,785.4)	
	Delta Time in Band	17/16	10,967.7 (2225.5)	12,385.7 (2919.3)	
	Delta Baseline Crossings	17/16	48,319.8 (9052.7)	53,161.4 (11,446.9)	
Inslicht et al., 2018 [24]	Delta spectral power (ln (μV^2))	33/33	2.15 ± 0.36	2.25 ± 0.39	
Cowdin et al., 2014 [58]	REM 1 relative theta (right frontal)	17/13	16.8 ± 3.4	18.6 ± 4.7	0.244
	REM 1 relative theta (left frontal)	17/13	15.5 ± 4.0	18.9 ± 4.2	0.026
	REM last relative theta (right frontal)	17/13	16.6 ± 4.1	19.7 ± 4.4	Group main effect: 0.015
	REM last relative theta (left frontal)	17/13	14.7 ± 4.1	18.3 ± 3.4	
Germain et al., 2006 [53]	Delta activity (0.5 −4 Hz)	10/5	0.844 ± 0.061	0.078 ± 0.038 (home)	
	Delta activity (0.5 −4 Hz)	10/10	0.844 ± 0.061	0.786 ± 0.054 (lab)	
	Beta activity (20 −32 Hz)	10/5	0.004 ± 0.004	0.005 ± 0.002 (home)	
	Beta activity (20 −32 Hz)	10/10	0.004 ± 0.004	0.005 ± 0.002 (lab)	
Otte et al., 2005 [54]	Delta integrated amplitude	20/16	127,441 ± 40259	156,557 ± 42763	0.04
Woodward et al., 2000 [15]	Power estimation of alpha, sigma, and beta	56/14	PTSD patients exhibited a significantly different multivariate profile of alpha, sigma, and beta EEG power values over NREM and REM sleep than did controls		<0.05

REM, rapid eye movement sleep; NREM, non rapid eye movement sleep.

important to ask whether the PSG abnormalities in PTSD are unique in comparison to primary insomnia and major depressive disorder (MDD), which are often associated with PSG changes. Although all these diseases show disrupted sleep, they appear to differ in terms of REM sleep. In primary insomnia, REM sleep is decreased, but there is no change in REML [60]. Comparisons of PTSD and MDD have provided no definite conclusions regarding whether there were differences in PSG data between the two disorders [42,61−63]; however, a recent hypothesis is that PTSD patients have significantly increased REM interruption and increased REMD compared with MDD patients [64]. We found no change in REM sleep percentage in PTSD patients when the whole sample was considered, but age was a statistically significant source of heterogeneity across the meta-regression analysis. This led us to examine age subgroups which revealed significantly decreased REM sleep percentage in PTSD patients in studies including participants with mean age below 30 y, but not studies with groups that had greater mean ages (30−40 y and >40 y).

Various studies suggest that REM sleep is important for mediating adaptive emotional processing [21,65,66], and that it may be important for regulating, or is at least a biomarker of [67], subsequent appropriate or inappropriate engagement of fear. REM-rich sleep is thought to benefit non-declarative types of memory (emotional and procedural aspects of memory) [68−70], and under experimental conditions, REM sleep deprivation can specifically impair extinction memory consolidation, and an intervening REM period can facilitate successful fear extinction [71,72]. REM sleep can be fragmented and disrupted soon after trauma [16,20,73] and in acutely symptomatic patients within several years of PTSD onset [40,74], but can be increased later in the progression of the disorder [43]. The findings of Mellman et al. also indicated that disruptions in REM sleep in the aftermath of trauma may be linked to the development and symptoms of PTSD, whereas increases in REM sleep later in its progression may reflect an attempt at adaptive changes within the fear system [20]. Unfortunately, due to a lack of data, we were unable to directly examine the association of PTSD

duration with REM sleep percentage. However, the significant relationship between younger age and decreased REM sleep percentage in PTSD patients could indirectly support a role for disturbed REM in PTSD as differences across age cohorts could also reflect time since the precipitating trauma.

Compared with REM sleep, previous studies have indicated that SWS-rich, early sleep consistently benefits the consolidation of declarative memories [68,70,75]. Although our findings suggest patients with PTSD have reduced SWS compared with HC groups, similar findings have been observed in insomnia [60] and depression [76]. However, compared with previous meta-analytic studies [22,23], we further found that the decrease of SWS percentage in PTSD patients was significantly associated with increased PTSD severity as evaluated by CAPS. This suggests that developing "sleep therapies" which improve SWS may be therapeutic in patients with PTSD.

Moderator analysis

Age

In addition to the association between younger age and decreased REM sleep percentage in PTSD patients mentioned above, our findings also indicated that WASO could be increased in younger groups of PTSD patients, and then with aging, decrease to a level comparative to that in controls. Previous studies have shown that healthy older adults have higher wakefulness and less REM sleep compared with younger adults [77–79]. Thus, our findings that patterns of changes in sleep parameters vary with age in PTSD patients are likely not simply attributable to the effects of aging. This led us to consider whether our findings regarding the associations of advancing age of PTSD patients with the change of PSG variables could be related to the time since trauma. Stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis, one of the major stress response systems, resulting in increased levels of cortisol and adrenocorticotropin hormone; however, as time passes, HPA activity decreases and cortisol rebounds to below normal levels [80]. The HPA axis plays important roles in modulating sleep and maintaining alertness, and increased HPA activation could result in more nocturnal awakenings and lighter sleep [81]. Furthermore, orexin function, which is also involved in the regulation of REM sleep, may have a similar pattern with the changes of HPA activation after stress begins [82–84]. Thus, we speculate that the associations of age with changes in REM and WASO may be associated with changes in HPA and orexin function over time since trauma.

Sex

Our meta-regression analysis indicated that the included studies with a greater percentage of female patients with PTSD tended to report increased WASO in PTSD patients compared with controls. The sex differences in WASO may involve sex differences in the orexin system and its responses to stress [85,86]. The orexin system is involved in the regulation of wakefulness and sleep [82,87,88], and its association with the development of PTSD has been demonstrated [89]. Greater activation of the orexin system in females has also been suggested to play a role in sex differences in the response to stress (e.g., exaggerated startle response, hypervigilance, and sleep disturbances related to increased arousability in females compared to males) [86].

Medication status

Our findings indicated that medication status was a significant source of heterogeneity for differences in TST, WASO, SE, and SWS percentage. In our review, only a few of the included studies did not exclude patients who had undergone pharmacological therapies (i.e., sedative hypnotics and antidepressants) which may impact sleep measures. This may be due to the fact that serious PTSD and depression symptoms, and sleep disturbances, in some PTSD patients did not allow the withdrawal of treatment. This may potentially bias the pooled effect size for comparisons in PSG variables between PTSD patients and controls. However, we still found decreased TST, SE, and SWS, and increased WASO in patients with PTSD compared with controls after excluding studies which contained patients who had used antidepressant or sedative hypnotics. To our knowledge, there are very few studies to specifically evaluate the effects of pharmacological treatments on PSG findings in patients with PTSD. For antidepressants, Zhang et al. found that a 12-wk paroxetine therapy protocol could decrease WASO, but did not change other PSG variables in PTSD patients [13]; Gillin et al. reported that nefazodone did not change any PSG variable after a 12-wk therapy period [90]; however, Neylan et al. found that TST and delta sleep were increased after 12-wk of nefazodone therapy in PTSD patients [91]. No study that we are aware of has explored the effects of sedative hypnotics on PSG parameters in PTSD patients. This indicates that more prospective studies are needed concerning the effects of pharmacological treatments on PSG parameters in PTSD. Most studies included in the current meta-analysis work also did not report specifics regarding pharmacological treatment, which prevented us from specifically analyzing the effects of different medications on our pooled effect sizes.

Duration of medication withdrawal

Another concern is that although the PTSD patients in the majority of our included studies were medication free, they may have undergone pharmacological treatments in the past. Most of these patients had durations of medication withdrawal ranging from $\geq$2 wk, $\geq$ 2 mo or $\geq$6 mo before a PSG was performed. Our subgroup analysis revealed that, with the exception of SL and REMD, different durations of medication withdrawal across different studies were not associated with differences in PSG variables between PTSD patients and controls. This suggests that our findings of differences in sleep architecture between PTSD patients and controls were not be biased by amount of time since discontinuation of medication in PTSD patients.

Psychiatric comorbidity

Clinically, PTSD frequently occurs with psychiatric comorbidities, such as depression, anxiety, and substance use disorders, which are also associated with PSG changes [23,92]. It is thus plausible that these comorbidities may interact and produce either over- or under-estimations of PSG changes in PTSD patients in our meta-analysis. However, our meta-regression analysis revealed that whether or not psychiatric comorbidity was excluded was not associated with differences in PSG variables between PTSD patients and controls in the included studies. Although influences of comorbidity were not statistically significant in our meta-analysis, their potential effects cannot definitively rule out. Indeed, only very limited studies (n = 7) in our meta-analysis stated that they excluded PTSD patients with psychiatric comorbidity, which may not provide sufficient statistical power to detect the effects of psychiatric comorbidity. Thus, more studies with careful design and data analyses for the effects of psychiatric comorbidity are needed before unequivocal statements can be made.

Type of controls

Our findings indicated that type of controls (TE vs. HC) used for comparisons was a statistically significant moderator for the association between some PSG variables (i.e., WASO, SE and SWS) and PTSD. This was not reported in previous meta-analysis studies [22,23]. Sleep disturbances are commonly seen in trauma survivors

without PTSD [5], and greater dysfunction in brain areas (i.e., amygdala, hippocampus, and prefrontal cortex) [93,94] associated with fear extinction and sleep regulation [95] has also been demonstrated in TE compared with HC. These differences may contribute to factors underlying why type of control was a source of heterogeneity.

Trauma type

Exploring the associations between specific trauma categories (i.e., natural disaster, combat, and traffic accidents) and sleep disturbances has important clinical implications for preventing or treating sleep disturbances following traumatic events [19]. Hall Brown et al. reported that exposure to different trauma types produces different odds for insomnia [19]. To our knowledge, no studies have explored the associations between different trauma types and PSG changes in clinical and non-clinical samples. Our findings indicate that non-combat exposure is more likely to be detrimental to sleep continuity and REM sleep compared with combat exposure. The effects of trauma type we observed may relate to the fact that studies including PTSD patients with non-combat trauma exposure provided data on younger age (22.4–47.2 y) patients than those with combat exposure (27.9–71.5 y) (Table 1), and, as indicated above, age may be a significant factor in the effects of traumatic stress on sleep. It also should be noted that we only conducted a preliminary exploration of the effects of trauma type (combat exposure vs. non-combat exposure) on pooled effect sizes in our meta-analysis, and we did not explore the effects of different trauma types (i.e., sexual assault, traffic accident, and natural disasters) on PSG changes in PTSD patients. This was due to the limited number of studies.

OSA

Previous studies investigating PSG changes in patients with PTSD screened OSA using different criteria (i.e., AHI$\geq$15 or AHI$\geq$10) or did not assess OSA. Our findings did not reveal any effects arising from whether or not OSA was used as an exclusion factor on the pooled effect size for differences in PSG variables between PTSD patients and controls. However, the comorbidity of OSA and PTSD has been given great attention in recent years [96,97], and our previous meta-analysis indicated that the pooled prevalence rates of OSA based on different AHI criteria in PTSD patients was 43.6% for AHI$\geq$10 [98], thereby indicating that OSA is very common in PTSD patients. Future studies should consider the effects of OSA, and the AHI value in PTSD patients should be reported to facilitate evaluations of the impacts of OSA on PSG findings in PTSD.

PSA

Studies using sophisticated analyses such as PSA which might be useful for better defining the psychobiological profile of PTSD are rare. Some have found that PTSD is associated with a decline in delta sleep [15,47,48]. By comparison, Germain et al. found increased delta sleep in PTSD [53]. Unfortunately, we were not able to draw conclusions or suggest new hypotheses from existing PSA data as methodology differed too much across studies. However, a variety of functional roles in memory processing have been attributed to different EEG spectra, which could include potential involvement in abnormal processing of memory in PTSD. For instance, delta sleep is driven by thalamocortical oscillations and is thought to both represent the bioenergetic recovery process of cortical wake activity and to be involved in the replay phenomenon in procedural memory consolidation [99]. Theta frequency activity is suggested to have a role in encoding information during wakefulness and to coordinate communication in limbic and cortical structures during sleep-dependent memory consolidation processes [100]. Other EEG sleep phenomena such as sleep spindles (12–14 Hz oscillations during NREM that last a few seconds) also have been associated with memory processing, including both consolidation and integration [101,102]. Thus, determining potential changes in EEG spectral elements in PTSD could provide important neurobiological insight into altered memory processing associated with the disorder. To better explore these possible changes in PTSD, it would be valuable to perform PSA on larger samples, perhaps by sharing data between sleep laboratories as suggested by Baglioni et al. [60]. In addition, given the age differences we found for altered REM sleep, it would also likely be useful to stratify the subject populations by time since trauma or by age. This could aid in drawing conclusions regarding associations between PTSD and EEG spectra across time and within age groups.

Comparisons with previous meta-analyses

Our findings differed for some variables compared to those of previous meta-analyses. For instance, Kobayashi et al. reported that, compared to controls, a greater percentage of male PTSD patients showed increased SL and reduced TST [22] whereas we found that female patients with PTSD tended to report increased WASO. Kobayashi et al. [22] also reported decreased TST in younger but not older PTSD patients, and decreased SWS and increased REM sleep in older, but not younger PTSD patients. By comparison, we found that REM sleep percentage was decreased in PTSD patients in studies where the mean age of participants was below 30 y, but not in studies with greater mean ages (30–40 y and >40 y). Additionally, WASO was increased in PTSD patients in studies where the mean age of participants was below 30 y and between 30 and 40 y, but not in studies where the mean age of participants was above 40 y.

Additionally, using comparisons with the Kobayashi (2007) [22] and Baglioni (2016) [23] studies, we examined the potential effects of specific clinical and methodological factors (i.e., PTSD severity, trauma type, type of controls, medication status, duration of medication withdrawal, whether excluding OSA, whether excluding psychiatric comorbidity, adaptation night, PSG scoring rules) on the pooled effect size of our meta-analytic findings. On the other hand, compared with Kobayashi et al. [22], our included studies were very different; we excluded five of 20 their included studies due to our strict inclusion criteria and we included 16 more recent studies they did not have available. Compared with the Baglioni (2016) study, which explored PSG changes in all mental disorders [23], we excluded two of their 13 included PTSD and included an additional 18 studies. The increased number of included studies in our meta-analysis adds a substantial number of additional participants, provides new data and increases statistical power. This allowed us to make a more comprehensive assessment of possible sources of heterogeneity between studies, and results in different findings compared with previous meta-analysis [22,23]. Furthermore, we also summarize PSA findings in PTSD which are different from the Kobayashi (2007) and Baglioni (2016) studies, although performing a meta-analysis for these data was not possible.

Clinical implications for practice and research

Our study shows that sleep continuity and sleep architecture exhibit abnormalities in PTSD. PSG studies are not routinely performed in patients with PTSD, but our findings provide information that PSG may be useful for helping clinicians understand behavioral sleep problems and the effects of age and PTSD severity on sleep in their patients. The assessments of PTSD severity mainly depend on the use of valid questionnaires. Our findings of an association

between PTSD severity and changes in SWS percentage suggest that decreased SWS percentage in PTSD could be a useful neurophysiological parameter for assessing the severity of PTSD symptoms. The significant relationship between PTSD duration and changes in REM sleep percentage in PTSD patients could reflect an attempt at adaptive changes within the fear system [20,21,65,66]. It could be speculated that therapeutic intervention for SWS and REM deficits in PTSD may help ameliorate illness progression and improve PTSD symptoms. Unfortunately, there currently is insufficient evidence to conclude that power spectral alterations have specific roles in PTSD or its progression. Thus, additional work using PSA is needed to assess its importance for research and its potential clinical implications.

Limitations

The present study has limitations. First, as mentioned above, the effects of psychiatric comorbidity on our meta-analytic findings could not be definitively ruled out, indicating that our findings should be interpreted with caution. Second, we could not fully explore the possible effects of duration of medication withdrawal on our meta-analytic findings due to the limited number of included studies that reported relevant data. Third, our findings were mainly derived from studies which used R&K scoring rules. Although differences between AASM and R&K scoring rules are minor, they could skew findings. For example, parameters for N1, N2, and SWS derived from the same participants may vary based on which scoring rule is used [103]. Thus, it is possible that the addition of more new studies using AASM scoring rules may alter values for some sleep parameters in future meta-analysis studies. Fourth, differences in HC criteria used across studies may impact differences in PSG data in comparisons to PTSD patients. However, inconsistencies in descriptions of HC across different studies could not be easily formulated as a categorical variable that would have enabled an examination of effects on PSG changes in PTSD. Fifth, other methodological differences (i.e., different bedtime schedule and different definition of PSG parameters in different study location) may also contribute to heterogeneity between studies. Sixth, given that data on the number of trauma exposures and the time passed between trauma and sleep assessments were rarely reported in the included studies, their effects on PSG changes in PTSD could not be explored. The effects of trauma-related factors on PSG changes in PTSD are thus important topics for future studies.

In addition, given that there were multiple outcomes (i.e., TST, SL, SE and percentage of sleep stages) in our review, another point that should be acknowledged is that pooled analyses were done for each outcome and several subgroup analyses were also performed for each outcome, resulting in multiple statistical tests being conducted. Conducting multiple statistical analyses on the same participants increases the likelihood of spuriously finding significance in comparisons. This increases the risk of type 1 error (the null hypothesis is incorrectly rejected resulting in a false positive finding) [104,105], and indicates that our results should be interpreted with caution.

Conclusions

The present study conducted an in depth examination of the existing literature on PSG changes in PTSD compared with those in TE and HC controls. Although the included studies were methodologically diverse, they clearly identified sleep as a problem in patients with PTSD. Our findings highlight the need to give greater consideration to PSG changes in PTSD care and in efforts to understand its etiology and neurobiology. Our findings also demonstrate that SWS and REM deficits are indicative of illness progression and are potential targets for therapeutic intervention. Importantly, the significant relationship between younger age and decreased REM sleep percentage in PTSD patients could indirectly support a role for disturbed REM in the etiology of PTSD as differences across age cohorts could reflect time since the precipitating trauma. Our work also suggests that methodological considerations in future studies should include assessing the effects of potential heterogeneous factors (i.e., psychiatric comorbidity, medication status, sleep apnea and type of controls) on PSG changes in PTSD.

Practice points

- Patients with posttraumatic stress disorder exhibit disturbances in sleep architecture and sleep continuity compared to healthy controls.
- Female patients with posttraumatic stress disorder are more likely to have longer wake time after sleep onset compared with male patients, but the patterns of changes in different sleep stages are similar in female and male patients with posttraumatic stress disorder.
- Decreased slow wave sleep and sleep efficiency is associated with severity of posttraumatic stress symptoms.
- The relationship between younger age and decreased rapid eye movement sleep percentage in patients with posttraumatic stress disorder indirectly supports a role for disturbed rapid eye movement sleep in the etiology of posttraumatic stress disorder as differences across age cohorts could reflect time since the precipitating trauma. Furthermore, younger patients with posttraumatic stress disorder are more likely to show longer wake time after sleep onset compared with those of older age.

Research agenda

- Investigate sex differences in polysomnographic changes in patients with posttraumatic stress disorder.
- Investigate the effects of time free from sedative hypnotics or antidepressants and the comorbidity of mental illnesses on polysomnographic variables in patients with posttraumatic stress disorder.
- Investigate the associations between duration of posttraumatic stress symptoms/time since traumatic stress and changes in rapid eye movement sleep in patients with posttraumatic stress disorder.
- Investigate the associations of the changes of rapid eye movement sleep with fear emotional processing, activation of the hypothalamic-pituitary-adrenocortical axis and function of the orexin system, and changes in brain networks at different time points after traumatic stress in patients with posttraumatic stress disorder.
- Consider slow wave sleep and/or rapid eye movement sleep as potential therapeutic targets to develop effective strategies for treating posttraumatic stress disorder, and its underlying mechanisms.
- Further studies quantifying electroencephalographic changes and their associations with symptomology of posttraumatic stress disorder are needed.

Conflicts of interest

The authors do not have any conflicts of interest to disclose.

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Appendix A. Supplementary data

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