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CLINICAL REVIEW

Comparative polysomnography parameters between narcolepsy type 1/type 2 and idiopathic hypersomnia: A systematic review and meta-analysis

Ye Zhang [a], Rong Ren [a, **], Linghui Yang [a], Haipeng Zhang [a], Yuan Shi [a], Michael V. Vitiello [b], Xiangdong Tang [a, *], Larry D. Sanford [c]

[a] Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China
[b] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, 98195-6560, USA
[c] Sleep Research Laboratory, Center for Integrative Neuroscience and Inflammatory Diseases, Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

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SUMMARY

A meta-analysis exploring polysomnography (PSG) differences between narcolepsy type 1 (NT1)/type 2 (NT2) and idiopathic hypersomnia (IH), particularly one that stratifies the analysis by IH with and without long sleep time (LST), could provide information useful for appropriately re-classifying the central disorders of hypersomnolence. An electronic literature search was conducted in EMBASE, MEDLINE, All EBM databases, CINAHL, and PsycINFO inception to May 2021. Meta-analysis of 26 studies revealed that the effect sizes of differences in some PSG parameters between NT1 and IH were different from those between NT2 and IH. Specifically, there were significant increases in wake time after sleep onset (WASO), arousal index (AI), and N1 percentage, and significant decreases in sleep efficiency, sleep latency, and N2 percentage in NT1 compared with IH, but no differences for these sleep parameters between NT2 and IH. With the exception of rapid eye movement (REM) sleep percentage and REM latency, there were no significant differences in other PSG variables between NT2 and IH without LST. The findings suggest that, NT1, rather than NT2, showed shallower and more fragmented sleep compared with IH. Sleep macrostructure features are very similar between NT2 and IH without LST.

Introduction

The central disorders of hypersomnolence (CDH) are characterized by excessive daytime sleepiness (EDS), which can be debilitating and life-threatening [1]. Patients with CDH often show decreased school and work performance, substantial morbidity, and decreased quality of life [1,2].

Narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH) are the three main diseases of CDH. The diagnosis of and research on these diseases mainly depend on clinical symptoms (e.g., complaint of EDS, and cataplexy) combined with polysomnography (PSG) and a multiple sleep latency test (MSLT). The PSG not only allows for screening for other sleep disturbances such as obstructive sleep apnea (OSA) and rapid eye movement (REM) sleep behavior disorder [3,4], but also may reveal clinically relevant findings that are helpful for understanding the etiology and neurobiology of CDH. For instance, short (≤15 min) REM latency in nighttime PSGs has been suggested to have high predictive value for diagnosing NT1, even in the absence of a MSLT [5]. Diminished beta electroencephalogram (EEG) power during REM and non-REM (NREM) sleep in NT1 may reflect disturbances in sleep maintenance and decreased central arousal [6]. In contrast, although reporting sleep disruption, patients with NT2 seem to have the same number of awakenings on PSGs as controls, perhaps

* Corresponding author. Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Dian Xin Nan Jie 28#, Chengdu, 610041, China.
** Corresponding author. Sleep Medicine Center, Department of Respiratory and Critical Care Medicine, Mental Health Center, Translational Neuroscience Center, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Dian Xin Nan Jie 28#, Chengdu, 610041, China.
E-mail addresses: 498880651@qq.com (R. Ren), 2372564613@qq.com (X. Tang).

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Abbreviations

AASM	American Academy of Sleep Medicine
AHI	apnea hypopnea index
AI	arousal index
AWN	awakenings numbers
CAP	cyclic alternating pattern
CIs	confidence intervals
EDS	excessive daytime sleepiness
EEG	electroencephalogram
ESS	Epworth Sleepiness Scale
HLA	human leukocyte antigen
IH	idiopathic hypersomnia
LST	Long sleep time
MSLT	multiple sleep latency test
NICE	National Institute for Health and Care Excellence
NREM	non rapid eye movement
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OSA	obstructive sleep apnea
PLMI	periodic limb movement index
PSA	power spectral analysis
PSG	polysomnography
R&K	Rechtschaffen and Kales
REM	rapid eye movement
SE	sleep efficiency
SL	sleep latency
SMD	standardized mean difference
SOREM	sleep-onset REM period
SS	stage shift
SWS	slow wave sleep
TST	total sleep time
WASO	wake time after sleep onset

because they do not lack orexins [7–10]. For IH, the International Classification of Sleep Disorders (ICSD)-3 currently emphasizes a diagnosis based on total 24-h sleep time ≥660 min (typically 12–14 h) determined using 24-h PSG monitoring or by wrist actigraphy in association with a sleep log (averaged over at least seven days with unrestricted sleep), or MSLT measured mean sleep latency ≤8 min with 0–1 sleep-onset REM period (SOREM) [11]. In IH, decreased cyclic alternating pattern (CAP) A1 subtypes may indicate dysfunctions in thalamo-cortical processes that underlie problems in awakening from sleep and in the consolidation of slow wave sleep (SWS) [12–14], although the exact mechanisms underlying IH are still unclear.

There have been many studies exploring PSG changes in NT1/NT2 compared with healthy controls (HCs), or exploring PSG changes in IH compared with HCs [15,16], but studies comparing NT1/NT2 or IH patients only to HCs cannot distinguish whether the differences reflect a disease-specific effect. For instance, with the exception of SOREM, which is a typical feature of NT1, it is unclear whether the PSG changes are signatures of NT1/NT2 or IH, or are instead nonspecific markers of EDS. To fill this gap, conducting studies comparing PSG characteristics between NT1/NT2 and IH are needed as such are also useful for understanding pathological mechanisms common to these disorders [17]. To our knowledge, a number of studies have explored PSG differences between NT1/NT2 and IH, but the exact PSG differences of these diseases have not been fully established. Variations in findings across different studies may involve heterogeneity in demographic characteristics (e.g., sex and age), clinical variables (e.g., medication status), and study methodology (e.g., adaptation nights and PSG scoring methods). Meta-analysis of PSG data can be useful for understanding differences among studies and for assessing the roles of potential moderators, and has been used for these purposes in several neuropsychiatric diseases.

The classifications of CDH are still dynamic and debated with the goal to better understand their underlying neurobiological causes and improve treatment and prevention. In the ICSD-2, narcolepsy is classified into narcolepsy with and without cataplexy, while IH is classified as IH with and without long sleep time (LST) [18]. In ICSD-3, narcolepsy with and without cataplexy, was replaced by NT1 and NT2, while IH with and without LST was replaced by IH only [11]. In a recent position paper [19] and its discussion [4,20] regarding the re-classifications of the CDH, there was a fairly strong consensus that people who meet current NT1 criteria and people who are strongly suspected to be hypocretin deficient should be considered as a separate entity, which largely corresponds to the current diagnostic criteria for NT1 in the ICSD-3 [11]. However, how to deal with the original NT2 in the re-classifications of the CDH is still in debate. In the position paper, most of those with current NT2 would instead be diagnosed with idiopathic excessive sleepiness [19]. By comparison, Billiard suggested keeping the current NT1 and NT2 classifications [4], and Maski et al. [20] expressed concern that the re-classifications proposed by the position paper [19] may introduce many patients without hypocretin deficiency into an otherwise homogenous NT1 group. In addition, a recent review paper, raised the question as to "whether NT2 and IH without LST should be combined into one category [21]." This "back and forth" movement demonstrates the difficulty in definitely classifying CDH [22]. A meta-analysis designed to explore PSG differences between NT1/NT2 and IH, particularly one that stratifies the analysis by IH subgroups (IH with and without LST) may provide information useful for appropriately re-classifying the CDH. Therefore, we conducted this first systematic review and meta-analysis to identify the pooled effect sizes for the differences in PSG variables between NT1/NT2 and IH, and the potential moderators which could contribute to heterogeneity across studies. We also performed the meta-analysis with stratification by IH subgroups (IH with and without LST).

Methods

Protocol and registration

The protocol for this study was registered (PROSPERO ID: CRD42021256685) in accordance with the preferred reporting items for systematic reviews and meta-analyses statement [23].

Inclusion criteria and exclusion criteria

Included studies were selected to meet the following criteria: 1) patients met the diagnosis criteria for NT1/NT2 or IH according to the International Classification of Sleep Disorders [11,18,24], or when the diagnostic criteria for NT1/NT2 or IH was not specified, published methods enabled determining whether NT1/NT2 or IH was determined by clinical symptoms combined with PSG and MSLT findings. 2) The studies assessed differences in some PSG parameters (PSG parameters of interest are listed below in the section on "Data collection process") between NT1/NT2 and IH, or between NT1/NT2 and IH with/without LST. 3) The studies were

published in English in peer-reviewed journals. 4) If the same subjects participated in multiple studies, then only the most relevant dataset was included in our meta-analysis to avoid duplication of data.

By screening titles and abstracts, we excluded: 1) animal studies; 2) guidelines, case series, case reports, editorials, comments, statements, and review papers; 3) studies unrelated to NT1/NT2 and IH; and 4) studies in which it was clearly stated in the abstract that no PSG was conducted or no comparisons of PSG parameters were conducted between our target groups. By full text screening, we excluded: 1) guidelines, case series, case reports, editorials, comments, statements, and review papers which were not caught in the initial screen; 2) studies in which the diagnosis of NT1/NT2 or IH was not based on standardized diagnostic criteria (i.e., lacking MSLT data of narcolepsy); 3) studies which did not provide separate PSG data for NT1 and NT2; and 4) studies containing no information on the outcomes of interest.

Information sources, search, and study selection

We searched MEDLINE via OVID; EMBASE via OVID; PsycINFO via EBSCO; CINAHL via EBSCO; and all EBM databases (search strategies are provided in Tables S1–S5). The reference lists of all primary studies were also screened for additional references. We performed the literature search on May 30th, 2021. Two reviewers (Y.S. and Y.Z.) independently selected relevant published studies. We resolved disagreements by discussing with the senior author (X.D.T). If more than one narcolepsy group of interest (e.g., NT1 and NT2 patients) or more than one IH group of interest (e.g., IH with and without LST) were included in a study, we considered it more than once in different comparisons.

Data collection process and quality assessment of included studies

Two reviewers (Y.S. and Y.Z.) independently extracted the data from the original studies using a pre-designed form. The extracted data were entered by one reviewer and verified by the two reviewers. Disagreements were resolved by thorough discussion with X.D.T. The PSG variables examined in this review include sleep macrostructure variables including total sleep time (TST), wake time after sleep onset (WASO), awaking numbers (AWN) per hour, number of stage shifts (SS) per hour, sleep efficiency (SE), sleep latency (SL), and percentage of N1, N2, N3 and REM sleep, and REM latency. Other PSG variables include apnea hypopnea index (AHI), periodic limb movement index (PLMI), and arousal index (AI). In addition, we also extracted sleep microstructure parameters (i.e., CAP parameters), power spectral analysis (PSA), and sleep spindle data. Demographic, clinical, and methodological variables extracted include the number of participants and their mean age, sex (male percentage), body mass index (BMI), disease group (NT1/NT2 and IH with/without LST), including patients taking psychoactive medications (Yes vs. No), subjective daytime sleepiness (Epworth Sleepiness Scale (ESS) score), objective daytime sleepiness (mean SL determined by MSLT), adaptation night (Yes vs. No), and PSG scoring methods (Rechtschaffen and Kales (R&K) vs. American Academy Sleep Medicine (AASM)). Y.S. and Y.Z. independently assessed the risk of bias of the included studies by using the adapted version of the National Institute for Health and Care Excellence (NICE) checklist [25].

Statistical analysis

We conducted the meta-analyses for PSG differences between the combined NT1/NT2 patients and the IH patients, a necessary step to explore the effect sizes of PSG differences in comparisons between NT1 and IH and between NT2 and IH across a subgroup analysis. Following these analyses, we conducted subgroup analyses for comparisons between NT1/NT2 and IH with/without LST. A random effects model, accounting for random variations between studies by including both within-study and between-study variance in the calculated effect sizes, was used to obtain a relatively conservative effect size estimates [26]. The sample size, means, and standard deviations for NT1/NT2 and IH patients were used for estimating the standardized mean difference (SMD) for the PSG differences between groups [27]. For the global effect-size estimation, the Q statistic and I^2 were used to test the magnitude of heterogeneity and to inform on the degree of overlap across the 95% confidence intervals (CIs) of different studies [28]. To better judge the clinical relevance of the pooled effect sizes, differences in means between groups were also considered [27]. Egger's regression method was used to evaluate publication bias [29], with p values of <0.05 suggesting the presence of bias. The Duval and Tweedie's trim and fill test was used to adjust the effect sizes if publication bias was detected [30]. A subgroup analysis or meta-regression was conducted to examine the potential source of heterogeneity of pooled effect sizes [27]. All analyses were done using Comprehensive Meta-Analysis software [31].

Results

Study selection

Our search yielded 817 publications (Fig. 1). After removing the duplicates, the title/abstract of the remaining 626 articles were screened. A total of 69 studies were selected for full text review. Of these, 27 articles [8,10,14,17,32–54] met inclusion criteria for the systematic review (Table 1), and 26 of the 27 studies were included in our meta-analysis. The excluded studies with reasons for their exclusion are listed in Table S6.

Description of the included studies

As shown in Table 1, the sample sizes of the 27 studies ranged from 16 participants (3 NT1, 3 NT2, and 10 IH) [32] to 848 participants (453 narcolepsy patients and 395 IH) [45]. Mean age of NT1/NT2 and IH ranged from 12 to 49 y (reported in 26 studies). Males as percentages of NT1/NT2 patients and IH ranged from 0 to 100% (reported in 25 studies). Eleven studies [8,10,32,34–36,41,42,45,52,53] used AASM PSG criteria, six studies [14,17,33,44,46,51] used R&K PSG criteria and the remaining 10 studies did not report which PSG scoring rule they used. Six studies [35,38,40,50,51,54] did not report or specify whether they included an adaptation night, seven studies [8,14,33,41,43,44,48] included an adaptation night, and the other 14 studies did not include an adaptation night. Four studies [17,39,41,51] did not report or specify whether they excluded participants who used medication impacting sleep, three studies [32,40,50] did not exclude participants who used medication impacting sleep, and 20 studies clearly stated that their participants were drug naïve or had a washout period for medications impacting sleep before PSG examinations. The quality assessments of these studies are listed in Table S7.

Meta-analyses for comparisons between NT1 and IH, and between NT2 and IH

Our analyses revealed that the effect sizes for differences in some PSG parameters such as WASO, SE, SL, N1, N2, AI, and PLMI between NT1 and IH were significantly different from those

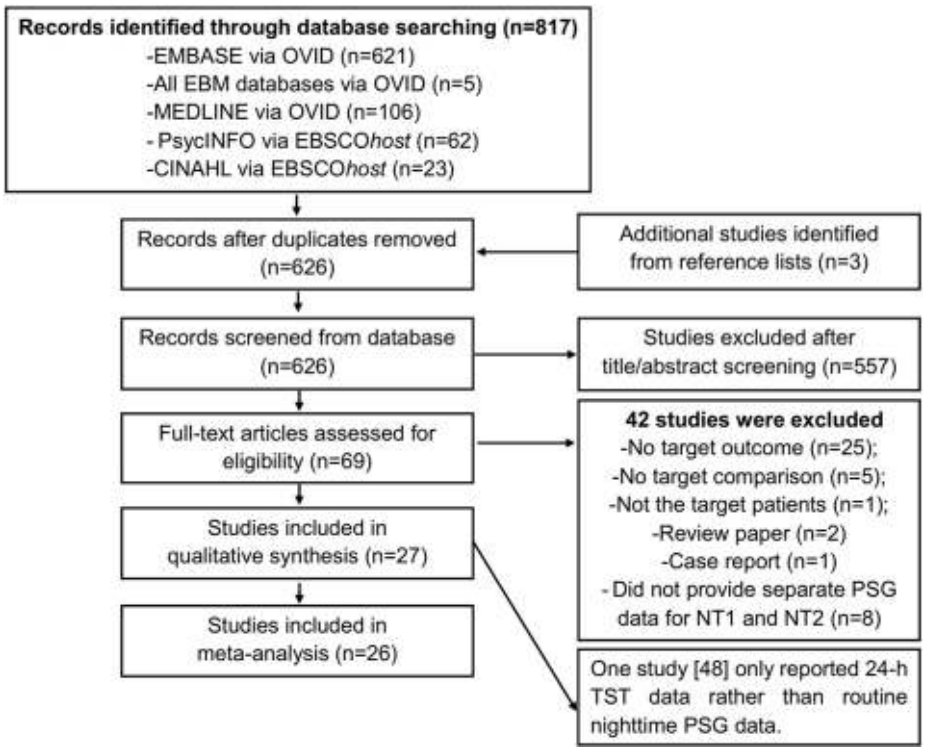

Fig. 1. Flow chart used for the identification of eligible studies. NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography; TST, total sleep time.

between NT2 and IH ($p < 0.05$). Specifically, there were statistically significant increases in WASO, AI, N1 percentage, and PLMI, and decreases in SE, SL, and N2 percentage in NT1 compared with IH ($p < 0.05$), while there were no differences for these sleep parameters between NT2 and IH ($p > 0.05$) with the exception that NT2 showed a statistically significant decreased N2 percentage compared with IH although its magnitude was less than that in comparisons between NT1 and IH ($p < 0.05$) (Table 2).

For comparisons between NT1 and IH, publication bias was not detected by Egger's test between groups (Figs. S1–S13). For comparisons between NT2 and IH, publication bias was detected by Egger's test for the difference in N2 percentage between groups (Figs. S14–S25). Adjustment for publication bias with the trim-and-fill method failed to confirm the significantly decreased N2 percentage in NT2 compared with IH found in the original analysis (SMD = −0.122; 95% CI: −0.349 to 0.105).

Subgroup analysis according to IH with and without LST

As shown in Table 3, the effect sizes of differences in PSG parameters vary across the four possible comparisons among groups (NT1 and IH with LST, NT1 and IH without LST, NT2 and IH with LST, and NT2 and IH without LST). For example, increased N1 percentage was greater in subgroups comparing NT1 and IH with LST (compared with those in subgroups comparing NT2 and IH with/without LST) ($p < 0.001$). Decreased SL was found in subgroups comparing NT1 with IH with/without LST, but not in subgroups comparing NT2 with IH with/without LST ($p = 0.021$). Increased WASO was found in subgroups comparing NT1 with IH with/without LST, but not in subgroups comparing NT2 with IH with/without LST ($p = 0.009$). For the comparisons between NT2 and IH with LST, there were increased N1 percentages and decreased REM latency in NT2 compared with IH with LST. For comparisons between NT2 and IH without LST, with the exception of REM sleep percentage and REM latency, there were no significant differences in PSG parameters between groups ($p > 0.05$).

Other moderator analysis

As shown in Tables S8–S9, subgroup analysis and sensitivity analysis revealed that the presence of significant differences in male percentage, age, and BMI between narcolepsy and IH patients did not significantly alter the directions of changes in sleep continuity or sleep architecture in NT1/NT2 compared with IH.

Medication status was a significant source of heterogeneity for differences in TST and REM latency between NT1 and IH ($p < 0.05$). However, when limiting the analysis to studies excluding patients taking psychoactive medications, the directions of changes in TST and REM latency in NT1 compared with IH did not change.

Regarding daytime sleepiness, our meta-regression analysis revealed that the increased ESS score in NT1 compared with IH was significantly associated with increased WASO in NT1 patients ($p < 0.05$). Furthermore, the decreased SL assessed by the MSLT in NT1 compared with IH was significantly associated with increased WASO in NT1 compared with IH ($p < 0.05$).

Methodologically, a subgroup analysis and sensitivity analysis revealed that having an adaptation night (Yes vs. No) and scoring method (AASM vs. R&K) were not significantly associated with differences in PSG measured sleep continuity or sleep architecture between NT1/NT2 and IH ($p > 0.05$).

Sleep parameters not meta-analyzed

As shown in Table S10, 24-h TST [48], PSA data [14,46] and CAP parameters [14] were also explored for possible differences between NT1/NT2 and IH patients. However meta-analytic evaluation of these parameters was not possible because of the limited number of available studies and methodological differences across studies.

Table 1
Study characteristics.

Study	Sample size	Percentage of male	Mean age	Mean BMI	Including patients taking psychoactive medications	MSLT	ESS	Adaptation	PSG scoring methods
Anderson et al., 2007 [51]	63 NT1	58.7%	44.0 ± 17.6	27 ± 6	NR	4.1 ± 2.6	18.6 ± 3.3	NR	R&K
	77 IH	49.4%	34.3 ± 12.0	25 ± 4	NR	8.3 ± 3.1	16.3 ± 3.3	NR	R&K
Bassetti et al., 2003 [54]	4 NT1	50%	NR	30 ± 6.93	No	3.38 ± 2.43	18 ± 2.45	NR	NR
	4 NT2	75%	NR	26.25 ± 2.22	No	2.75 ± 1.71	18.5 ± 2.08	NR	NR
	5 IH	40%	NR	26 ± 3	No	6 ± 3.74	17.4 ± 2.51	NR	NR
Bin-Hasan et al., 2018 [34]	11 NT1	54.6%	12.3 ± 2.6	25.5 ± 5.6	No	2.9 ± 2.2	17.8 ± 2.7	No	AASM
	6 NT2	83.3%	12.9 ± 3	23.9 ± 3.3	No	4.4 ± 2.8	15.4 ± 1.5	No	AASM
	12 IH	33.3%	15.3 ± 3.5	24.3 ± 4.7	No	8.5 ± 3	14.6 ± 4.8	No	AASM
Cairns et al., 2019 [35]	24 NT1	42%	35.2 ± 14.6	31.7 ± 6.1	No	NR	18.2 ± 4.5	NR	AASM
	30 NT2	40%	35.9 ± 12.1	30.2 ± 7.4	No	NR	17.5 ± 4.2	NR	AASM
	25 IH	40%	36.4 ± 13.4	24.9 ± 3.7	No	NR	15.1 ± 4.7	NR	AASM
Drakatos et al., 2013 [36]	24 NT1	29.2%	31 ± 12	29 ± 6	No	NR	NR	No	AASM
	38 NT2	65.8%	34 ± 9	27 ± 5	No	NR	NR	No	AASM
	21 IH	23.8%	34 ± 12	28 ± 8	No	NR	NR	No	AASM
Delrosso et al., 2013 [52]	8 narcolepsy (4NT1 and 4NT2)	50%	27.5 ± 12.73	33.69 ± 7.37	No	NR	19.75 ± 2.92	No	AASM
	8 IH	13%	32.62 ± 14.34	28.69 ± 5.35	No	NR	16.63 ± 3.62	No	AASM
Erdem et al., 2013 [37]	94 NT1	88.3%	25.10 ± 7.46	25.24 ± 3.89	No	2.4 ± 1.7	18.44 ± 2.93	No	Unspecified
	49 NT2	91.8%	24.92 ± 7.50	25.30 ± 4.20	No	4.1 ± 2.1	17.74 ± 3.65	No	Unspecified
	140 IH	80%	26.90 ± 6.84	24.21 ± 3.66	No	5.3 ± 2.6	18.20 ± 3.33	No	Unspecified
Holm et al., 2014 [38]	12 NT1	33.3%	27.8 ± 6.84	22.70 ± 2.27	No	NR	19.00 ± 2.09	NR	NR
	12 NT2	41.7%	29.8 ± 8.88	25.63 ± 4.96	No	NR	16.33 ± 2.93	NR	NR
	12 IH	25.0%	31.4 ± 13.13	25.13 ± 4.34	No	NR	16 ± 3.57	NR	NR
Hong et al., 2006 [39]	79 NT1	57%	31.1 ± 14.22	25.2 ± 3.56	NR	2.1 ± 1.78	14.9 ± 4.44	No	NR
	22 NT2	72.7%	24.8 ± 9.38	22.4 ± 2.81	NR	2.5 ± 1.41	15.0 ± 4.69	No	NR
	20 IH	55%	29.3 ± 12.97	21.6 ± 3.13	NR	5.7 ± 2.68	13.6 ± 4.92	No	NR
Kim et al., 2016 [40]	29 NT1	75.9%	29.4 ± 16.8	25.9 ± 4.0	Yes	2.2 ± 2.2	15.3 ± 5.4	NR	NR
	22 NT2	54.5%	21.6 ± 12.3	22.9 ± 4.10	Yes	3.7 ± 2.2	14.2 ± 3.8	NR	NR
	24 IH	29.2%	36.3 ± 17.9	24.9 ± 4.9	Yes	4.4 ± 2.3	15.5 ± 5.8	NR	NR
Kretzschmar et al., 2016 [49]	35 NT1	45%	40 ± 18	NR	No	1.9 ± 1.6	16.6 ± 4.1	No	Two both
	8 IH	17%	34 ± 17	NR	No	3.9 ± 3.5	16.3 ± 1.9	No	Two both
Lippert et al., 2019 [41]	12 NT1	58%	31.9	24.1 ± 3.3	NR	4.3 ± 2.5	17 ± 2.5	Yes	AASM
	7 NT2	43%	34.4	24.9 ± 4.5	NR	4.5 ± 1.6	14 ± 3.1	Yes	AASM
	24 IH	42%	39.2	28.2 ± 5.6	NR	5.6 ± 1.8	15 ± 2.6	Yes	AASM
Maski et al., 2020 [42]	150 NT1	55.4%	12 ± 3.6	24.5 ± 6.2	No	3.6 ± 2.9	15.1 ± 3.6	No	AASM
	22 NT2	59.1%	14.3 ± 2.6	23.5 ± 4.1	No	7.1 ± 4.7	13.3 ± 4.9	No	AASM
	27 IH	11.1%	15.6 ± 2.2	24.8 ± 2.9	No	9 ± 3.7	13.1 ± 5.4	No	AASM
Maski et al., 2021 [10]	46 NT1	54.3%	12.9 ± 3.7	26.3 ± 6.3	No	3.3 ± 3	17.5 ± 2.8	No	AASM
	12 NT2	58.3%	14 ± 2.9	22.7 ± 4.1	No	4.8 ± 2.5	16.3 ± 3.2	No	AASM
	18 IH	11.1%	16 ± 2	23.9 ± 4.6	No	8.8 ± 4.1	13.18 ± 5.1	No	AASM
Philip et al., 2013 [32]	3 NT1	33.3%	38.67	27.27	Yes	6.37	12.67	No	AASM
	3 NT2	0	32.33	22.4	Yes	5	13	No	AASM
	6 IH without LST	33.3%	39.5	22.8	Yes	5.8	12.5	No	AASM
	4 IH with LST	0%	41	20.35	No	11.28	9.75	No	AASM
Pizza et al., 2011 [43]	44 NT1	59.1%	29 ± 16	NR	No	3.9 ± 3	16 ± 4	Yes	NR
	7 NT2	57.1%	27 ± 10	NR	No	5.3 ± 2.2	11 ± 3	Yes	NR
	16 IH	62.5%	49 ± 12	NR	No	5.6 ± 1.3	16 ± 4	Yes	NR
Pizza et al., 2013 [44]	39 NT1	51.3%	31.79 ± 15.39	26.32 ± 4.72	No	3.59 ± 2.36	17.31 ± 3.18	Yes	R&K
	7 NT2	85.7%	26.29 ± 6.82	24.18 ± 2.20	No	7.40 ± 4.39	15.17 ± 3.55	Yes	R&K
	19 IH	57.9%	43.84 ± 14.10	25.20 ± 3.59	No	5.90 ± 1.11	16.50 ± 4.36	Yes	R&K
Pizza et al., 2013 [14]	17 NT1	76.5%	45.0 ± 12.94	NR	No	3.3 ± 2.5	17 ± 3	Yes	R&K
	19 IH	68.4%	46.0 ± 12.75	25.8 ± 3.51	No	5.6 ± 1.37	NR	Yes	R&K
Pizza et al., 2015 [8]	79 NT1	57%	32.77 ± 15.34	27.16 ± 5.62	No	3.23 ± 2.27	16.75 ± 3.16	Yes	AASM
	22 NT2	63.6%	30.32 ± 11.19	25.20 ± 3.49	No	6.36 ± 1.56	16.25 ± 4.49	Yes	AASM
	22 IH	63.6%	39.36 ± 12.46	24.50 ± 3.68	No	6.03 ± 0.96	15.33 ± 4.44	Yes	AASM
Poli et al., 2009 [48]	14 NT1	100%	38.21 ± 13.71	28 ± 4.4	No	4.30 ± 3.65	14.79 ± 4.63	Yes	NR
	14 IH	100%	33.29 ± 14.64	24.2 ± 2.8	No	6.35 ± 1.28	13.0 ± 3.06	Yes	NR
Ramm et al., 2019 [47]	10 NT1	70%	26.7	NR	No	2.5	18.4	No	NR
	14 IH	21.4%	33.6	NR	No	5.3	15.2	No	NR
Sasai-Sakuma et al., 2015 [45]	158 NT1	49.4%	28.2 ± 10.9	23.9 ± 4.1	No	2.0 ± 1.9	17.1 ± 4.4	No	AASM
	295 NT2	58.0%	25.7 ± 8.7	21.7 ± 2.9	No	3.2 ± 1.9	16.3 ± 4.4	No	AASM
	395 IH	48.6%	29.0 ± 9.4	21.9 ± 3.5	No	4.5 ± 2.0	16.1 ± 4.5	No	AASM
Sasai-Sakuma et al., 2015 [46]	28 NT1	35.7%	29.6 ± 4.2	NR	No	1.4 ± 1.4	15.4 ± 4.4	No	R&K
	16 NT2 with HLA+	50%	24.9 ± 3.8	NR	No	1.5 ± 1.1	15.8 ± 3.0	No	R&K
	22 NT2 with HLA-	54.5%	27.8 ± 7.2	NR	No	3.3 ± 2.0	14.6 ± 3.6	No	R&K
	22 IH	40.9%	28.9 ± 4.5	NR	No	4.1 ± 2.0	14.1 ± 5.2	No	R&K
Suzuki et al., 2015 [50]	68 NT1	45.6%	34.2 ± 13.1	NR	Yes	NR	15.2 ± 5.8	NR	NR
	35 IH	45.7%	31.4 ± 9.2	NR	Yes	NR	15.1 ± 5.1	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size	Percentage of male	Mean age	Mean BMI	Including patients taking psychoactive medications	MSLT	ESS	Adaptation	PSG scoring methods
Takei et al., 2012 [17]	52 NT1	46.2%	27.2 ± 8.9	NR	NR	1.4 ± 1.3	14.6 ± 3.7	No	R&K
	62 NT2	48.4%	26.7 ± 7.4	NR	NR	2.1 ± 1.6	14.9 ± 3.5	No	R&K
	50 IH	54%	29.5 ± 9.7	NR	NR	3.9 ± 1.9	14.1 ± 4.8	No	R&K
Thakrar et al., 2018 [53]	70 NT1	40%	38.3 ± 13.9	30.4 ± 7.5	No	3.5 ± 2.9	18.6 ± 3.5	No	AASM
	47 NT2	34%	38 ± 12.4	27.9 ± 7.1	No	4.2 ± 2.5	16.2 ± 4.4	No	AASM
	9 IH	33.3%	33.4 ± 9.1	26.0 ± 4.6	No	8.4 ± 4.7	16.2 ± 4.7	No	AASM
Vanková et al., 2001 [33]	28 NT1	25%	34 ± 11.2	NR	No	2 ± 1.2	NR	Yes	R&K
	10 IH	30%	37.5 ± 8.3	NR	No	6.2 ± 3	NR	Yes	R&K

+, positive; -, negative; AASM, American Academy of Sleep Medicine; BMI, body mass index; ESS, Epworth Sleepiness Scale; R&K, HLA, HLA, human leukocyte antigen; IH, idiopathic hypersomnia; MSLT, multiple sleep latency test; NR, not reported; NT1, narcolepsy type 1; NT2, narcolepsy type 2; R&K, Rechtschaffen and Kales; LST, long sleep time.

Discussion

Summary of findings

To our knowledge, this is the first meta-analysis to explore PSG differences between NT1/NT2 and IH. There were significant increases in WASO, AI, N1 percentage, and PLMI, and significant decreases in SE, SL, and N2 percentage in NT1 compared with IH, while there were no observed differences in these sleep parameters in comparisons between NT2 and IH. In comparisons of NT2 and IH without LST, we found that PSG parameters were similar. Microstructure methods (i.e., CAP) and sophisticated analyses (i.e., PSA) are likely to be useful in assessing differences in sleep profiles between NT1/NT2 and IH, but the exact differences across conditions have not been fully established due to limited available studies and methodological differences across studies.

Effect sizes for differences in PSG parameters between NT1 and IH, and between NT2 and IH

Our meta-analysis differentiated NT1 and NT2, and their potential relationship to IH. NT1 differs from NT2 in that it is characterized by cataplexy, different levels of orexin in the cerebrospinal fluid, and greater loss of orexin neurons [55,56]. NT1 and NT2 are now recognized as having clearly distinct pathophysiology [11] and potentially different brain metabolism [57]. It therefore should be asked whether the effect sizes for differences in PSG parameters between NT1 and IH, and between NT2 and IH, are different. Our analysis revealed a shallower and more fragmented sleep indicated by an increased amount of stage N1 and AI in NT1 compared with IH; this was not found in comparisons between NT2 and IH. This finding indirectly indicates that NT1 has more severely disturbed nighttime sleep, which is supported by our recent meta-analysis reporting significantly decreased TST, SL, SE, N2 percentage, REM percentage, REM latency, and increased WASO, AWN, SS, and N1 percentage in NT1 patients compared with NT2 patients [15]. There have been differing opinions regarding whether NT1 and NT2 should be reclassified. In a recent position paper, Lammers et al. proposed that people who meet current NT1 criteria and people who are strongly suspected to be hypocretin deficient should be considered as a separate entity, while most of those with current NT2 will instead have idiopathic excessive sleepiness [19]. By comparison, Maski et al. argued that this classification may introduce many non-hypocretin deficient patients to the otherwise homogenous NT1 group [20], and Billiard also suggested that the general frame of the ICSD-3 classification of CDH should be kept [4]. Regardless of how CDH may be re-classified, innovations are always hoped for that will improve our understandings on the nature of the disease and provide clinical benefits for patients. From the perspective of disturbed nighttime sleep which is a potential target of treatment for narcolepsy [58], considering NT1 and NT2 as different populations may be beneficial for management of the disease.

Comparisons between NT1 and IH

In comparisons between NT1 and IH, NT1 patients showed increased AI, N1, WASO, and decreased N2 percentage, SE, SL, and REM latency relative to IH patients. These comparisons suggest that the overall PSG patterns in NT1 and IH are very different. Recently, a [^{18}F]-fluorodeoxyglucose positron emission tomography study suggested differential regional brain metabolism between NT1 and IH patients. This study revealed several areas of hypermetabolism (i.e., left post−central gyrus, paracentral lobule, anterior cingulate gyrus, left parahippocampal gyrus, left superior temporal gyrus, inferior frontal gyrus, and claustrum) in NT1 patients compared with IH patients [59]. Some of these regions have been demonstrated to be involved in sleep-wake regulation [60−62], and these differences in regional brain metabolism may contribute to the different PSG patterns between NT1 and IH.

Comparisons between NT2 and IH

We found the PSG features of NT2 are very similar to those of IH with the exception of increased REM sleep percentage and decreased REM latency in NT2. Additionally, the MSLT is often unreliable for distinguishing NT2 from IH, raising concerns as to whether they are even distinct disorders [20,63−65]. However, the differences in REM sleep percentage and REM latency between NT2 and IH suggest that heterogeneity exists between the two diseases.

Previous studies have suggested that disturbed REM sleep is associated with hypocretin deficiency, and that hypocretin deficiency is linked to human leukocyte antigen (HLA)-DRB1*1501/DQB1*0602 [66−68]. Existing evidence suggests that some patients classified as NT2 that have an unrecognized hypocretin deficiency likely to resemble NT1, while those without hypocretin deficiency likely more closely resemble patients with IH without LST [21]. Fronczek et al. [21] therefore proposed that IH without LST and NT2 patients without hypocretin deficiency should be merged into a single disorder, “narcolepsy spectrum disorder,” while the NT2 patients with unrecognized hypocretin deficiency should be merged with the original NT1 patients as NT1. Additionally, Sasai et al. reported that NT2, HLA-DRB1*1501/DQB1*0602-negative patients showed similar clinical features, including similar severity of hypersomnia and treatment response, and similar rates of REM-related symptoms (i.e., sleep paralysis and hypnagogic hallucinations) compared with those in patients with IH without LST, while NT2, HLA-DRB1*1501/DQB1*0602-

Table 2
Polysomnographic differences between NT1/NT2 and IH.

	No. of Comparisons	No. of NT1/NT2 and IH	Means of NT1/NT2	Means of IH	Differences in means between NT1/NT2 and IH	SMD (95%CI)	Q	I^2	p for subgroup effects
TST min									0.241
NT1 vs. IH	23	1067/917	451.190	460.949	−9.759	−0.179 (−0.368 to 0.009)	60.243[c]	63.481	
NT2 vs. IH	18	632/831	450.278	460.180	−9.902	−0.020 (−0.208 to 0.167)	30.140[a]	43.596	
WASO min									<0.001
NT1 vs. IH	12	562/277	46.495	26.469	20.026	0.497 (0.344–0.650)[c]	9.579	0	
NT2 vs. IH	9	188/209	20.882	25.817	−4.935	−0.089 (−0.290 to 0.113)	7.243	0	
SE %									<0.001
NT1 vs. IH	24	1102/978	87.405	90.809	−3.404	−0.366 (−0.566 to −0.166)[c]	77.294[c]	70.244	
NT2 vs. IH	20	702/872	91.889	90.672	1.217	0.101 (−0.002 to 0.203)	16.392	0	
SL min									0.005
NT1 vs. IH	18	938/562	7.348	12.591	−5.243	−0.516 (−0.723 to −0.309)[c]	50.094[c]	66.064	
NT2 vs. IH	15	383/443	10.478	12.391	−1.913	−0.143 (−0.302 to 0.016)	15.859	11.724	
SS (events/h)									0.780
NT1 vs. IH	3	135/60	15.393	14.170	1.223	0.203 (−0.650 to 1.057)	13.581[b]	85.274	
NT2 vs. IH	2	29/41	14.409	14.280	0.129	0.063 (−0.425 to 0.552)	0.001	0	
N1%									0.001
NT1 vs. IH	18	921/832	9.748	6.062	3.686	0.565 (0.279–0.851)[c]	95.672[c]	82.231	
NT2 vs. IH	15	660/803	6.616	6.504	0.112	0.017 (−0.151 to 0.184)	22.038	36.474	
N2%									
NT1 vs. IH	18	921/832	43.163	51.758	−8.595	−0.822 (−1.102 to −0.542)[c]	89.366[c]	80.977	0.003
NT2 vs. IH	15	660/803	48.933	52.681	−3.748	−0.302 (−0.503 to −0.101)[b]	30.925[b]	54.729	
SWS%									0.494
NT1 vs. IH	20	996/933	18.144	17.729	0.415	0.026 (−0.166 to 0.218)	54.561[c]	65.177	
NT2 vs. IH	16	667/827	18.568	17.143	1.425	0.107 (−0.022 to 0.235)	16.855	11.055	
REM%									0.003
NT1 vs. IH	18	921/844	21.154	21.019	0.135	0.008 (−0.141 to 0.157)	26.071	34.794	
NT2 vs. IH	15	655/815	23.145	21.353	1.792	0.289 (0.182–0.396)[c]	11.311	0	
REM latency min									0.172
NT1 vs. IH	17	737/447	36.576	91.802	−55.226	−1.184 (−1.517 to −0.850)[c]	86.348[c]	81.470	
NT2 vs. IH	15	357/416	53.889	94.430	−40.541	−0.842 (−1.202 to −0.483)[c]	63.394[c]	77.916	
AHI (events/h)									0.657
NT1 vs. IH	17	643/691	3.024	2.139	0.885	0.197 (0.006–0.387)[a]	28.932[a]	44.697	
NT2 vs. IH	14	553/637	1.900	2.010	−0.110	0.126 (−0.124 to 0.375)	30.457[b]	57.317	
AI (events/h)									0.006
NT1 vs. IH	9	513/592	18.095	13.185	4.910	0.622 (0.411–0.914)[c]	20.733[b]	61.414	
NT2 vs. IH	9	535/579	13.166	12.602	0.564	0.149 (−0.113 to 0.411)	20.602[b]	61.169	
PLMI (events/h)									<0.001
NT1 vs. IH	11	532/591	4.746	1.651	3.095	0.322 (0.191–0.453)[c]	5.581	0	
NT2 vs. IH	9	503/556	0.972	1.305	−0.333	−0.086 (−0.210 to 0.037)	7.264	0	

%, percentage; Q, Cochran's Q statistic; AHI, apnea hypopnea index; AI, arousal index; IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PLMI, periodic limb movement index; PSG, polysomnographic; REM, rapid eye movement sleep; SWS, slow wave sleep; SE, sleep efficiency; SL, sleep latency; SMD, standardized mean difference; SS, stage shifts; TST, total sleep time; WASO, wake time after sleep onset.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

positive patients more closely resembled NT1 [69]. Thus, the Sasai et al. study may be viewed as supporting the proposed re-classifications by Fronczek et al. which merge NT2 patients without hypocretin deficiency and IH without LST into one category.

Future directions

An appropriate re-classification of CDH which will be useful for further determination of its underlying neurobiological causes and that provides clearer directions for treatment or prevention and healing [19] will require more effort discerning the PSG differences between NT1/NT2 and IH. In addition to studies of sleep macro-structure, efforts should explore PSG differences between NT1/NT2 and IH using other promising metrics including PSA, sleep spindles, and CAP parameters. Regarding PSA, evidence suggests intermediate delta power in IH that is lower compared with HCs, but higher compared with NT1 [14]. Sleep spindle index has also found to be significantly increased in IH patients compared with that in a mixed sample of NT1 and NT2 [70]. Additionally, IH patients showed a higher CAP rate in light NREM sleep compared with NT1 but a lower rate compared with HCs in SWS, and a striking reduction of the CAP A1 subtype [14]. However, it should be noted that the number of studies focusing on these PSG metrics is currently limited, and the findings discussed above are limited, confined to comparisons between NT1 and IH [14], and between a mixed sample of different NT1 and NT2, and IH [70]. Studies specifically making comparisons between NT2 and IH on PSA, CAP and sleep spindle data are needed, which will be useful to further understand neurobiological difference between NT1/NT2 and IH, and to guide potential re-classification of CDH.

Other considerations

In our meta-analysis, a few of our included studies showed significant differences in sex (male percentage), age, and BMI between NT1/NT2 and IH patients. It therefore should be asked whether these differences could bias our meta-analysis findings. Our subgroup analysis revealed that differences in sex, age, and BMI between groups were not significant sources of heterogeneity for differences in sleep continuity and sleep architecture between NT1/NT2 and IH patients, suggesting that these factors did not produce an obvious impact on our meta-analysis findings.

Table 3
Subgroup analysis across IH with and without LST.

	No of comparison	No. of NT1/NT2 and IH with/without LST	Means of NT1/NT2	Means of IH	Differences in means between NT1/NT2 and IH with/without LST	SMD (95%CI)	Q	I^2	p for subgroup effects
TST min									0.670
NT1 vs. IH with LST	2	49/22	513.971	535.140	−21.169	−0.317 (−1.272 to 0.638)	1.735	42.350	
NT1 vs. IH without LST	8	486/665	463.330	457.645	5.685	0.004 (−0.184 to 0.193)	11.313	38.126	
NT2 vs. IH with LST	2	15/22	475.352	535.140	−59.788	−4.818 (−14.340 to 4.705)	11.891[b]	91.590	
NT2 vs. IH without LST	7	445/646	454.071	461.258	−7.187	0.043 (−0.142 to 0.227)	7.918	24.222	
WASO min									0.009
NT1 vs. IH with LST	1	46/18	56.500	26.600	29.90	0.814 (0.251−1.377)[b]	0.000	0	
NT1 vs. IH without LST	4	152/104	20.166	11.808	8.358	0.419 (0.161−0.678)[b]	1.975	0	
NT2 vs. IH with LST	1	12/18	21.000	26.600	−5.600	−0.252 (−0.985 to 0.481)	0	0	
NT2 vs. IH without LST	3	76/85	4.820	11.598	−6.778	−0.091 (−0.411 to 0.228)	0.618	0	
SE%									0.069
NT1 vs. IH with LST	3	73/43	88.332	90.062	−1.730	−0.304 (−0.693 to 0.084)	0.974	0	
NT1 vs. IH without LST	9	514/687	88.580	89.513	−0.933	−0.125 (−0.331 to 0.082)	15.985[a]	49.954	
NT2 vs. IH with LST	3	53/43	90.315	90.062	0.253	0.092 (−0.322 to 0.506)	0.319	0	
NT2 vs. IH without LST	9	484/690	92.502	90.255	2.247	0.116 (−0.002 to 0.234)	6.880	0	
SL min									0.021
NT1 vs. IH with LST	2	70/39	7.629	18.314	−10.685	−0.874 (−1.289 to −0.458)[c]	0.236	0	
NT1 vs. IH without LST	7	353/286	5.855	9.919	−4.064	−0.375 (−0.590 to −0.159)[b]	8.909	32.654	
NT2 vs. IH with LST	2	50/39	13.195	18.314	−5.119	−0.400 (−0.835 to 0.035)	0.156	0	
NT2 vs. IH without LST	7	186/289	7.416	10.170	−2.754	−0.120 (−0.358 to 0.118)	8.085	25.791	
SS (events/h)									0.786
NT1 vs. IH without LST	2	56/38	14.283	14.354	−0.071	−0.140 (−1.233 to 0.952)	6.272[a]	84.056	
NT2 vs. IH without LST	1	7/19	15.100	14.910	0.190	0.053 (−0.814 to 0.920)	0.000	0.000	
N1%									<0.001
NT1 vs. IH with LST	2	70/39	10.532	4.874	5.658	1.040 (0.616−1.464)[c]	0.667	0	
NT1 vs. IH without LST	6	428/646	10.651	7.530	3.121	0.261 (−0.232 to 0.753)	53.755[c]	90.699	
NT2 vs. IH with LST	2	50/39	6.880	4.874	2.006	0.463 (0.027−0.899)[a]	0.003	0	
NT2 vs. IH without LST	6	467/649	7.773	7.914	−0.141	−0.107 (−0.307 to 0.094)	8.325	39.940	
N2%									0.028
NT1 vs. IH with LST	2	70/39	42.339	50.467	−8.128	−0.905 (−1.946 to 0.136)	6.124[a]	83.671	
NT1 vs. IH without LST	6	428/646	45.664	53.299	−7.635	−0.698 (−1.218 to −0.178)[b]	58.991[c]	91.524	
NT2 vs. IH with LST	2	50/39	43.195	50.467	−7.272	−0.943 (−2.241 to 0.355)	6.798[b]	85.291	
NT2 vs. IH without LST	6	467/649	54.136	55.278	−1.142	−0.073 (−0.194 to 0.048)	4.424	0	
SWS%									0.625
NT1 vs. IH with LST	2	70/39	24.480	21.626	2.854	0.320 (−0.825 to 1.465)	7.859[b]	87.276	
NT1 vs. IH without LST	6	428/646	12.962	12.970	−0.008	−0.009 (−0.187 to 0.170)	7.396	32.394	
NT2 vs. IH with LST	2	50/39	25.951	21.626	4.325	0.458 (−0.305 to 1.222)	2.725	63.298	
NT2 vs. IH without LST	6	467/649	11.0477	11.617	−0.569	0.060 (−0.060 to 0.181)	4.102	0	
REM%									0.023
NT1 vs. IH with LST	2	70/39	22.492	23.271	−0.779	−0.117 (−0.517 to 0.282)	0.088	0	
NT1 vs. IH without LST	6	428/646	20.607	19.724	0.883	0.029 (−0.125 to 0.182)	6.008	16.774	
NT2 vs. IH with LST	2	50/39	24.169	23.271	0.898	0.154 (−0.278 to 0.586)	0.938	0	
NT2 vs. IH without LST	6	467/649	22.056	19.693	2.363	0.299 (0.177−0.420)[c]	4.272	0	
REM latency min									0.776
NT1 vs. IH with LST	2	70/39	40.528	122.569	−82.041	−1.554 (−2.918 to −0.190)[a]	8.433[b]	88.142	
NT1 vs. IH without LST	6	336/267	33.803	89.733	−55.930	−1.130 (−1.518 to −0.742)[c]	19.636[b]	74.536	
NT2 vs. IH with LST	2	50/39	60.399	122.569	−62.170	−1.265 (−2.391 to −0.139)[a]	5.319[a]	81.199	
NT2 vs. IH without LST	7	186/289	48.855	90.235	−41.380	−0.873 (−1.458 to −0.288)[b]	42.536[c]	85.891	
AHI (events/h)									0.168
NT1 vs. IH with LST	1	3/4	1.500	4.130	−2.630	−0.871 (−2.435 to 0.694)	0	0	
NT1 vs. IH without LST	7	376/531	3.228	2.412	0.816	0.234 (−0.018to 0.487)	11.702	48.726	
NT2 vs. IH with LST	1	3/4	0.630	4.130	−3.500	−1.299 (−2.944 to 0.345)	0	0	
NT2 vs. IH without LST	7	428/534	2.093	2.226	−0.133	0.130 (−0.180 to 0.441)	15.357[a]	60.929	
AI (events/h)									0.094
NT1 vs. IH with LST	2	70/39	16.356	11.364	4.992	0.875 (0.459−1.290)[c]	0.610	0	
NT1 vs. IH without LST	3	238/467	17.242	9.907	7.335	0.896 (0.390−1.401)[b]	10.299[b]	80.581	
NT2 vs. IH with LST	2	50/39	12.339	11.364	0.975	0.270 (−0.358 to 0.897)	1.922	47.961	
NT2 vs. IH without LST	4	396/489	10.864	9.354	1.510	0.274 (−0.144 to 0.693)	13.227[b]	77.319	
PLMI (events/h)									<0.001
NT1 vs. IH without LST	4	317/487	2.662	1.484	1.178	0.296 (0.143−0.448)[c]	1.227	0	
NT2 vs. IH without LST	5	418/509	1.059	1.263	−0.204	−0.125 (−0.255 to 0.006)	3.701	0	

%, percentage; Q, Cochran's Q statistic; AHI, apnea hypopnea index; AI, arousal index; IH, idiopathic hypersomnia; LST, long sleep time; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PLMI, periodic limb movement index; PSG, polysomnographic; REM, rapid eye movement sleep; SWS, slow wave sleep; SE, sleep efficiency; SL, sleep latency; SMD, standardized mean difference; SS, stage shifts; TST, total sleep time; WASO, wake time after sleep onset.

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

Another concern is whether using medications impacting sleep (i.e., antidepressants and gamma-hydroxybutyrate) could moderate our meta-analysis findings. It is well known that antidepressants may reduce REM sleep [55], and that sodium oxybate is beneficial for decreasing SS, AWN, WASO, and N1 percentage, and increasing SWS and SE in NT1 [71,72]. Our subgroup analysis revealed that medication status was a significant source of heterogeneity for differences in TST and REM latency between NT1 and IH. When we reran the meta-analysis only in studies excluding patients who used psychoactive medications, we found that the directions (decrease) of changes in TST and REM latency did not change. This finding suggests that taking psychoactive medications also did not produce an obvious bias in our findings.

Limitations

This review has limitations. First, some factors, such as variations in bedtime schedule across sleep labs and discomfort from wearing PSG devices, which may potentially impact sleep changes, could not be accounted for in our meta-analysis, due to the lack of data. Second, although we explored whether taking psychoactive medications when performing PSG impacted our findings, we could not specifically explore the effects of different medications (e.g., modafinil, methylphenidate, sodium oxybate, antidepressants, etc.). Third, it should be noted that different included studies used different exclusion criteria (AHI>5, 10 or 15 events/h, etc.) to exclude OSA patients from participants, which may also potentially impact our findings. Unfortunately, we were unable to find sufficient data to enable clarifying their effects on our findings. Fourth, the data concerning the 24-h PSG data are limited and all our meta-analysis findings were derived from nighttime PSG data. These limitations suggest that our findings should be interpreted cautiously.

Conclusions

The current meta-analysis demonstrates that NT1, but not NT2, shows shallower and more fragmented sleep compared with IH. With the exception of REM sleep and REM latency, sleep macrostructure features are very similar between NT2 and IH without LST. Furthermore, exploring differences in electroencephalogram frequency components and CAP parameters between NT1/NT2 and IH may be useful for assessing the neuropathological differences underlying the three diseases. Our findings highlight the need to give greater considerations to PSG differences between NT1/NT2 and IH, and between NT1/NT2 and IH with/without LST to aid in understanding the neuropathology of CDH and for its potential reclassification in the future.

Practice points

1) Peoples with narcolepsy type 1 exhibit decreased sleep continuity (i.e., decreased sleep efficiency, and increased arousal index and wake time after sleep onset) and more light sleep (increased N1) compared with those with idiopathic hypersomnia. By comparison, there are no significant differences in majority of sleep parameters in narcolepsy type 2 compared with idiopathic hypersomnia.
2) The polysomnography parameters are similar between narcolepsy type 2 and idiopathic hypersomnia without long sleep time.

Research agenda

1) Investigate the 24-h polysomnography differences, including sleep macrostructure, electroencephalographic frequency components, cyclic alternating pattern, and sleep spindles between narcolepsy type 1/type 2 and idiopathic hypersomnia with/without long sleep time.
2) Investigate the re-classifications of central disorders of hypersomnolence with nuanced consideration of clinical/individual factors, and further application of neuroimaging and other research tools.

Conflicts of interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2022.101610.

References

[1] Khan Z, Trotti LM. Central disorders of hypersomnolence: focus on the narcolepsies and idiopathic hypersomnia. Chest 2015;148:262–73.
[2] Roth T, Roehrs TA. Etiologies and sequelae of excessive daytime sleepiness. Clin Therapeut 1996;18:562–76.
*[3] Billiard M, Dauvilliers Y. Idiopathic hypersomnia. Sleep Med Rev 2001;5:349–58.
*[4] Billiard M. Diagnosing hypersomnolence. Sleep Med Rev 2020;52:101343.
[5] Andlauer O, Moore H, Jouhier L, Drake C, Peppard PE, Han F, et al. Nocturnal rapid eye movement sleep latency for identifying patients with narcolepsy/hypocretin deficiency. JAMA Neurol 2013;70:891–902.
[6] Mukai J, Uchida S, Miyazaki S, Nishihara K, Honda Y. Spectral analysis of all-night human sleep EEG in narcoleptic patients and normal subjects. J Sleep Res 2003;12:63–71.
[7] Baumann CR, Mignot E, Lammers GJ, Overeem S, Arnulf I, Rye D, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. Sleep 2014;37:1035–42.
[8] Pizza F, Vandi S, Iloti M, Franceschini C, Liguori R, Mignot E, et al. Nocturnal sleep dynamics identify narcolepsy type 1. Sleep 2015;38:1277–84.
[9] Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, et al. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 2002;59:1553–62.
[10] Maski KP, Colclasure A, Little E, Steinhart E, Scammell TE, Navidi W, et al. Stability of nocturnal wake and sleep stages defines central nervous system disorders of hypersomnolence. Sleep 2021:44.
[11] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[12] Ferri R, Bruni O, Miano S, Terzano MG. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). Sleep Med 2005;6:29–36.
[13] Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev 2012;16:27–45.
[14] Pizza F, Ferri R, Poli F, Vandi S, Cosentino FII, Plazzi G. Polysomnographic study of nocturnal sleep in idiopathic hypersomnia without long sleep time. J Sleep Res 2013;22:185–96.
[15] Zhang Y, Ren R, Yang L, Zhang H, Shi Y, Sanford LD, et al. Polysomnographic nighttime features of narcolepsy: a systematic review and meta-analysis. Sleep Med Rev 2021;58:101488.

* The most important references are denoted by an asterisk.

[16] Plante DT. Nocturnal sleep architecture in idiopathic hypersomnia: a systematic review and meta-analysis. Sleep Med 2018;45:17–24.
[17] Takei Y, Komada Y, Namba K, Sasai T, Nakamura M, Sugiura T, et al. Differences in findings of nocturnal polysomnography and multiple sleep latency test between narcolepsy and idiopathic hypersomnia. Clin Neurophysiol 2012;123:137–41.
[18] American Academy of Sleep Medicine. International classification of sleep disorders. In: Diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
*[19] Lammers GJ, Bassetti CLA, Dolenc-Groselj L, Jennum PJ, Kallweit U, Khatami R, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal by European experts. Sleep Med Rev 2020;52:101306.
*[20] Maski K, Mignot E, Scammell TE. COMMENTARY on Lammers et al, Diagnosis of central disorders of hypersomnolence: challenges in defining central disorders of hypersomnolence. Sleep Med Rev 2020;52:101327.
*[21] Fronczek R, Arnulf I, Baumann CR, Maski K, Pizza F, Trotti LM. To split or to lump? Classifying the central disorders of hypersomnolence. Sleep 2020;43(8):zsaa044.
*[22] Arnulf I, Leu-Semenescu S, Dodet P. Precision medicine for idiopathic hypersomnia. Sleep Med Clin 2019;14:333–50.
[23] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[24] Diagnostic Classification Steering Committee, Thorpy MJ. Chairman of the International classification of sleep disorders: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association; 1990.
[25] ExcellenceNIfHaC. Appendix E: methodology checklist: case econtrol studies. 2012. NICE article [PMG6B].
[26] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.
[27] Higgins J. Cochrane Handbook for systematic reviews of interventions (updated March 2011). The Cochrane Collaboration; 2011. Available from:, version 5.1.0. handbook,cochrane.org.
[28] Higgins J, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[29] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[30] Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Publication bias. In: Borenstein M, Hedges LV, Higgins JPT, Rothstein HR, editors. Introduction to meta-analysis. 1st ed. New Jersey, USA: John Wiley & Sons; 2009.
[31] Borenstein M, Hedges L, Higgins J. Comprehensive meta-analysis: a computer program for research synthesis. Englewood, New Jersey: Biostat; 2014.
[32] Philip P, Chaufton C, Taillard J, Sagaspe P, Leger D, Raimondi M, et al. Maintenance of Wakefulness Test scores and driving performance in sleep disorder patients and controls. Int J Psychophysiol 2013;89:195–202.
[33] Vanková J, Nevšímalová S, Šonka K, Špacková N, Švejdová-Blaejová K. Increased REM density in narcolepsy-cataplexy and the polysymtomatic form of idiopathic hypersomnia. Sleep 2001;24:707–11.
[34] Bin-Hasan S, Videnovic A, Maski K. Nocturnal REM Sleep without atonia is a diagnostic biomarker of pediatric narcolepsy. J Clin Sleep Med 2018;14:245–52.
[35] Cairns A, Bogan R. Comparison of the macro and microstructure of sleep in a sample of sleep clinic hypersomnia cases. Neurobiol Sleep Circadian Rhythms 2019;6:62–9.
[36] Drakatos P, Kosky CA, Higgins SE, Muza RT, Williams AJ, Leschziner GD. First rapid eye movement sleep periods and sleep-onset rapid eye movement periods in sleep-stage sequencing of hypersomnias. Sleep Med 2013;14:897–901.
[37] Erdem M, Bolu A, Ünlü AG, Alper M, Yetkin S. Comparison of polysomnography and multiple sleep latency test findings in subjects with narcolepsy and idiopathic hypersomnia. Noro psikiyatri arsivi 2013;50:252–5.
[38] Holm A, Bang-Berthelsen CH, Knudsen S, Kornum BR, Modvig S, Jennum P, et al. miRNA profiles in plasma from patients with sleep disorders reveal dysregulation of miRNAs in narcolepsy and other central hypersomnias. Sleep 2014;37:1525–33.
[39] Hong S-C, Lin L, Jeong J-H, Shin Y-K, Han J-H, Lee J-H, et al. A study of the diagnostic utility of HLA typing, CSF hypocretin-1 measurements, and MSLT testing for the diagnosis of narcolepsy in 163 Korean patients with unexplained excessive daytime sleepiness. Sleep 2006;29:1429–38.
[40] Kim T, Lee JH, Lee CS, Yoon IY. Different fates of excessive daytime sleepiness: survival analysis for remission. Acta Neurol Scand 2016;134:35–41.
[41] Lippert J, Young P, Gross C, Meuth SG, Dräger B, Schirmacher A, et al. Specific T-cell activation in peripheral blood and cerebrospinal fluid in central disorders of hypersomnolence. Sleep 2019;42(2). https://doi.org/10.1093/sleep/zsy223.
[42] Maski K, Pizza F, Liu S, Steinhart E, Little E, Colclasure A, et al. Defining disrupted nighttime sleep and assessing its diagnostic utility for pediatric narcolepsy type 1. Sleep 2020;43(10):zsaa066.
[43] Pizza F, Vandi S, Detto S, Poli F, Franceschini C, Mintagna P, et al. Different sleep onset criteria at the multiple sleep latency test (MSLT): an additional marker to differentiate central nervous system (CNS) hypersomnias. J Sleep Res 2011;20:250–6.
[44] Pizza F, Moghadam KK, Vandi S, Detto S, Poli F, Mignot E, et al. Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin. J Sleep Res 2013;22:32–40.
[45] Sasai-Sakuma T, Kinoshita A, Inoue Y. Polysomnographic assessment of sleep comorbidities in drug-naïve narcolepsy-spectrum disorders–A Japanese cross-sectional study. PLoS One 2015;10:e0136988–.
[46] Sasai-Sakuma T, Inoue Y. Differences in electroencephalographic findings among categories of narcolepsy-spectrum disorders. Sleep Med 2015;16:999–1005.
[47] Ramm M, Boentert M, Lojewsky N, Jafarpour A, Young P, Heidbreder A. Disease-specific attention impairment in disorders of chronic excessive daytime sleepiness. Sleep Med 2019;53:133–40.
[48] Poli F, Plazzi G, Di Dalmazi G, Ribichini D, Vicennati V, Pizza F, et al. Body mass index-independent metabolic alterations in narcolepsy with cataplexy. Sleep 2009;32:1491–7.
[49] Kretzschmar U, Werth E, Sturzenegger C, Khatami R, Bassetti CL, Baumann CR. Which diagnostic findings in disorders with excessive daytime sleepiness are really helpful? A retrospective study. J Sleep Res 2016;25:307–13.
[50] Suzuki K, Miyamoto M, Miyamoto T, Inoue Y, Matsui K, Nishida S, et al. The Prevalence and characteristics of primary headache and dream-enacting behaviour in Japanese patients with narcolepsy or idiopathic hypersomnia: a multi-centre cross-sectional study. PLoS One 2015;10:e0139229.
[51] Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. Sleep 2007;30:1274–81.
[52] Delrosso LM, Chesson Jr AL, Hoque R. Characterization of REM sleep without atonia in patients with narcolepsy and idiopathic hypersomnia using AASM scoring manual criteria. J Clin Sleep Med 2013;9:675–80.
[53] Thakrar C, Patel K, D'Ancona G, Kent BD, Nesbitt A, Selsick H, et al. Effectiveness and side-effect profile of stimulant therapy as monotherapy and in combination in the central hypersomnias in clinical practice. J Sleep Res 2018;27:e12627.
[54] Bassetti C, Gugger M, Bischof M, Mathis J, Sturzenegger C, Werth E, et al. The narcoleptic borderland: a multimodal diagnostic approach including cerebrospinal fluid levels of hypocretin-1 (orexin A). Sleep Med 2003;4:7–12.
[55] Scammell TE. Narcolepsy. N Engl J Med. 2015;373:2654–62.
[56] Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. Sleep 2009;32:993–8.
[57] Huang YS, Hsiao IT, Liu FY, Hwang FM, Lin KL, Huang WC, et al. Neurocognition, sleep, and PET findings in type 2 vs type 1 narcolepsy. Neurology 2018;90:e1478–87.
[58] Roth T, Dauvilliers Y, Mignot E, Montplaisir J, Paul J, Swick T, et al. Disrupted nighttime sleep in narcolepsy. J Clin Sleep Med 2013;9:955–65.
*[59] Trotti LM, Saini P, Crosson B, Meltzer CC, Rye DB, Nye JA. Regional brain metabolism differentiates narcolepsy type 1 and idiopathic hypersomnia. Sleep 2021;44(8):zsab050.
[60] Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. Sleep Med Rev 2007;11:113–33.
[61] Weng HH, Chen CF, Tsai YH, Wu CY, Lee M, Lin YC, et al. Gray matter atrophy in narcolepsy: an activation likelihood estimation meta-analysis. Neurosci Biobehav Rev 2015;59:53–63.
[62] Berridge CW, Schmeichel BE, Espana RA. Noradrenergic modulation of wakefulness/arousal. Sleep Med Rev 2012;16:187–97.
[63] Lopez R, Doukkali A, Barateau L, Evangelista E, Chenini S, Jaussent I, et al. Test-retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. Sleep 2017;40(12). https://doi.org/10.1093/sleep/zsx164.
*[64] Trotti LM, Staab BA, Rye DB. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. J Clin Sleep Med 2013;9:789–95.
*[65] Ruoff C, Pizza F, Trotti LM, Sonka K, Vandi S, Cheung J, et al. The MSLT is repeatable in narcolepsy type 1 but not narcolepsy type 2: a retrospective patient study. J Clin Sleep Med 2018;14:65–74.
[66] Mignot E, Young T, Lin L, Finn L, Palta M. Reduction of REM sleep latency associated with HLA-DQB1*0602 in normal adults. Lancet 1998;351:727.
[67] Overeem S, Black 3rd JL, Lammers GJ. Narcolepsy: immunological aspects. Sleep Med Rev 2008;12:95–107.
[68] Nishino S, Okura M, Mignot E. Narcolepsy: genetic predisposition and neuropharmacological mechanisms. REVIEW ARTICLE. Sleep Med Rev 2000;4:57–99.
*[69] Sasai T, Inoue Y, Komada Y, Sugiura T, Matsushima E. Comparison of clinical characteristics among narcolepsy with and without cataplexy and idiopathic hypersomnia without long sleep time, focusing on HLA-DRB1(*)1501/DQB1(*)0602 finding. Sleep Med 2009;10:961–6.
[70] Delrosso LM, Chesson AL, Hoque R. Manual characterization of sleep spindle index in patients with narcolepsy and idiopathic hypersomnia. Sleep Disord 2014:271802.
[71] Plazzi G, Pizza F, Vandi S, Arico D, Bruni O, Dauvilliers Y, et al. Impact of acute administration of sodium oxybate on nocturnal sleep polysomnography and on multiple sleep latency test in narcolepsy with cataplexy. Sleep Med 2014;15:1046–54.
[72] Boscolo-Berto R, Viel G, Montagnese S, Raduazzo DI, Ferrara SD, Dauvilliers Y. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431–43.