U.PORTO

MESTRADO INTEGRADO EM MEDICINA
ARTIGO DE REVISÃO

The role of actigraphy in the assessment of central disorders of hypersomnolence: a systematic review and meta-analysis

Susana Rosa Valente Maia

M

2023

The role of actigraphy in the assessment of central disorders of hypersomnolence: a systematic review and meta-analysis

Susana Rosa Valente Maia
up201808340@icbas.up.pt
Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Orientadora
Mestre Marta Azevedo Gonçalves
Coordenadora do Centro de Medicina do Sono, Hospital Cuf Porto
Colaboradora externa da Faculdade de Medicina da Universidade do Porto

Co-Orientadora
Professora Doutora Ana Sofia Torres Baptista
ACeS Porto Ocidental
Medicina Geral e Familiar, Instituto Cuf Porto
Professora auxiliar convidada da Faculdade de Medicina da Universidade do Porto

Junho 2023

The role of actigraphy in the assessment of central disorders of hypersomnolence: a systematic review and meta-analysis

Autor

Susana Maia

Orientadora

Mestre Marta Gonçalves

Co-orientadora

Assinado por: Ana Sofia Torres Baptista
Identificação: BI13481269
Data: 2023-06-01 às 12:47:04

Professora Doutora Ana Baptista

Junho 2023

Acknowledgements

I would like to express my deepest gratitude to my supervisor Dr. Marta Gonçalves for her friendship and guidance throughout this thesis. Her knowledge and expertise in the sleep field inspired me during the last years.
I would like to extend my sincere thanks to my co-supervisor Prof. Dr. Ana Batista for her availability and support.
I am extremely grateful to my parents, my father, for being an example to follow, and my mother for her wise words when needed.
Finally, I cannot forget to thank my family and friends. Special thanks to Teo for his emotional support and for motivating me during my academic years and Joana and João for their unconditional support.

Resumo

Introdução: Narcolepsia tipo 1 (NT1), narcolepsia tipo 2, hipersónia idiopática (HI), síndrome de Kleine-Levin (SKL) e síndrome do sono insuficiente são distúrbios centrais da hipersonolência (DCH). Esta categoria também inclui a hipersónia associada a distúrbios médicos ou psiquiátricos e ao uso de medicamentos ou substâncias. A actigrafia é uma medida objetiva da sonolência que a Academia Americana de Medicina do Sono recomenda a sua realização durante 7 a 14 dias antes do teste de latências múltiplas do sono, sendo fundamental no diagnóstico diferencial da hipersonolência.

Objetivo: O objetivo desta revisão foi resumir os parâmetros actigráficos encontrados nos DCH.

Métodos: Foi realizada uma revisão sistemática recorrendo a seis bases de dados em março de 2023, tendo sido pesquisada a avaliação actigráfica dos DCH em adultos. A qualidade dos artigos incluídos foi analisada através da escala de Newcastle-Ottawa. Os modelos de efeitos fixos ou aleatórios foram usados na comparação da NT1 com os controlos e a heterogeneidade foi avaliada pelo I^2 e teste Q Cochrane.

Resultados: Das 1737 publicações encontradas na pesquisa, foram incluídos 8 estudos. O tamanho total da amostra foi de 473 participantes, distribuídos da seguinte forma: 106 NT1, 40 HI, 29 doentes com hipersonolência e valores de hipocretina 1 no líquido cefalorraquidiano dentro da normalidade, 20 SKL, 42 traumatismos cranioencefálicos (TCE), 19 depressões major, 12 distrofias miotónicas (DM), 13 insónias primárias e 192 controlos. Os actígrafos utilizados variaram entre os diferentes estudos. As diferenças significativas entre a NT1 e os controlos foram a diminuição no tempo total de sono (TTS), na eficiência do sono e na atividade motora diurna e um aumento na vigília após o início do sono, dos despertares, da atividade motora no sono e na duração da sesta. Na HI verificou-se uma duração da sesta superior aos controlos. Quanto ao SKL, o TTS encontrou-se aumentado nos episódios de hipersónia. Os doentes com TCE e depressão major apresentaram um TTS mais elevado que os controlos e os doentes com DM tiveram um TTS mais baixo do que os doentes com HI. Os actígrafos possuem algoritmos diferentes, não estando definida a programação da actigrafia a ser utilizada nos DCH.

Conclusão: A actigrafia é útil para objetivar o sono e distinguir os DCH. Porém, a falta de diretrizes limita o seu uso na prática clínica.

Palavras-chave: actigrafia, distúrbios centrais da hipersonolência, sonolência diurna excessiva.

Abstract

Introduction: Narcolepsy type 1 (NT1), narcolepsy type 2, idiopathic hypersomnia (IH), Kleine-Levin Syndrome (KLS), and insufficient sleep syndrome are central disorders of hypersomnolence (CDH). This category also includes hypersomnia associated with medical or psychiatric disorders, and medication or substance use. Actigraphy is an objective measure of sleepiness that the American Academy of Sleep Medicine recommends 7-14 days before multiple sleep latency test and is useful in the differential diagnosis of hypersomnolence.

Objective: We aimed to summarize the available actigraphy features of CDH.

Methods: Six bibliographic databases were used in March 2023. The quality assessment of the included articles was evaluated using the Newcastle-Ottawa scale. Fixed- or random-effects models were used to compare NT1 with controls, and heterogeneity was assessed using I^2 and the Cochrane Q test.

Results: From the 1737 publications yielded in our search, 8 studies were included. The total sample size was 473 participants, distributed between 106 NT1, 40 IH, 29 patients with hypersomnolence and hypocretin-1 levels in the cerebrospinal fluid within the normal range, 20 KLS, 42 traumatic brain injury (TBI), 19 major depressive disorder (MDD), 12 myotonic dystrophy (MD), 13 primary insomnia patients, and 192 controls. The actigraphy devices used varied among the studies. The most relevant differences between NT1 and controls were a decrease in total sleep time (TST), sleep efficiency, and daytime motor activity and an increase in wake after sleep onset, number of awakenings, sleep motor activity, and mean duration of the longest nap (LNAP). IH showed that LNAP were increased compared with controls. In terms of KLS, TST was higher during hypersomnia attacks than in asymptomatic patients. TBI and MDD patients showed a higher TST than controls, and MD patients had a lower TST than IH. Actigraphy devices have different analysis methodologies, and actigraphy settings for CDH have not yet been defined.

Conclusion: Actigraphy is a tool for objectively measuring sleep and can distinguish CDH. However, the lack of guidelines limits its use in clinical practice.

Keywords: actigraphy, central disorders of hypersomnolence, excessive daytime sleepiness.

List of abbreviations

AASM	American Academy of Sleep Medicine
CSF-Hcrt-1	Cerebrospinal fluid hypocretin-1
ESS	Epworth Sleepiness Scale
ICSD-3	International Classification of Sleep Disorders, 3rd Edition
MeSH	Medical Subject Headings
MSLT	Multiple Sleep Latency Test
PICOTS	Participants/Population, Interventions, Comparators/Controls, Outcomes, Timing and Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnography

Index

Introduction **1**
Methods **4**
Study design 4
Search strategy 4
Selection procedure 4
Data extraction 5
Assessment of study quality 6
Data synthesis 6
Results **7**
Study selection 7
Systematic review 7
Actigraphy 8
Narcolepsy and idiopathic hypersomnia 8
Kleine-Levin syndrome 10
Hypersomnia associated to medical disorder 10
Hypersomnia due to psychiatric disorder 10
Meta-analysis 11
Discussion **12**
Summary of the findings 12
Other considerations 13
Future directions 13
Limitations 14
Conclusion **15**
Tables **16**
Figures **27**
Bibliography **32**

List of tables

Table I: Eligibility criteria according to PICOTS framework **16**
Table II: Description of the queries used in the search **17**
Table III: Pathophysiologic subtypes of hypersomnia associated with medical or psychiatric disorders and due to medication according to International Classification of Sleep Disorders, 3rd Edition **18**
Table IV: Characteristics of the studies included in the review **19**
Table V: Newcastle - Ottawa quality assessment scale for case-control studies **21**
Table VI: Newcastle - Ottawa quality assessment scale for cohort study **21**
Table VII: Actigraphy outcomes of the studies included in the review **22**
Table VIII: Main results for comparison of actigraphy outcomes between patients with narcolepsy type 1 and healthy controls **26**

List of figures

Figure 1: Flow diagram of study selection according to PRISMA guidelines **27**
Figure 2: Forest-plot on absolute mean difference on sleep efficiency between patients with narcolepsy type 1 and healthy controls **28**
Figure 3: Forest-plot on absolute mean difference on sleep onset latency between patients with narcolepsy type 1 and healthy controls **28**
Figure 4: Forest-plot on absolute mean difference on wake after sleep onset between patients with narcolepsy type 1 and healthy controls **28**
Figure 5: Forest-plot on absolute mean difference on sleep motor activity between patients with narcolepsy type 1 and healthy controls **29**
Figure 6: Forest-plot on absolute mean difference on awakenings between patients with narcolepsy type 1 and healthy controls **29**
Figure 7: Publication bias funnel-plot for sleep efficiency between patients with narcolepsy type 1 and healthy controls **30**
Figure 8: Publication bias funnel-plot for sleep onset latency between patients with narcolepsy type 1 and healthy controls..... **30**
Figure 9: Publication bias funnel-plot for wake after sleep onset between patients with narcolepsy type 1 and healthy controls **30**
Figure 10: Publication bias funnel-plot for sleep motor activity between patients with narcolepsy type 1 and healthy controls **31**
Figure 11: Publication bias funnel-plot for awakenings between patients with narcolepsy type 1 and healthy controls **31**

Introduction

Sleep is an essential part of life and a behavioral state in which reactivity to internal and external stimuli is reduced. During sleep occur physiologic processes essential to the balance of the organism.[1]

Daytime sleepiness, according to the International Classification of Sleep Disorders, third edition (ICSD-3), corresponds to a difficulty in staying awake or alert during the day, which can lead to an individual to falling asleep involuntarily and is more common in monotonous environments.[2]

In addition to being a risk factor for cardiovascular and neurological disorders, excessive daytime sleepiness is a public health issue with significant socioeconomic consequences.[3] Drowsiness is a risk factor for domestic, occupational, and car accidents.[2,4] According to a study conducted in Europe in 2015, the prevalence of falling asleep on the wheel while driving was approximately 17%.[4] Despite the importance of its diagnosis and treatment, excessive daytime sleepiness remains undervalued.[3, 5]

ICSD-3 classifies the central disorders of hypersomnolence in narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, and insufficient sleep syndrome. Hypersomnia associated with medical or psychiatric disorders and medication or substances is also included in this group, and each one can be subdivided into different pathophysiological subtypes. Hence, central disorders of hypersomnolence includes disorders in which excessive daytime sleepiness is of central origin, which requires the absence of other sleep disorders.[2]

Narcolepsy type 1 is characterized by excessive daytime sleepiness for at least three months associated with low cerebrospinal fluid hypocretin-1 (CSF-Hrct-1) concentration, and/or cataplexy and a mean sleep latency ≤ 8 minutes with at least two sleep onset rapid eye movement sleep periods on multiple sleep latency test (MSLT). Narcolepsy type 2 is a disorder similar to narcolepsy type 1. However, cataplexy is absent, and CSF-Hcrt-1 concentration is not measured or greater than 110 pg/mL. Excessive daytime sleepiness lasting longer than three months is a characteristic of idiopathic hypersomnia. Additionally, cataplexy must be absent and hypersomnolence must be objectified with a total 24-hour sleep time greater than 660 minutes or a mean sleep latency ≤ 8 minutes on MSLT to diagnose idiopathic hypersomnia. Kleine-Levin syndrome presents as recurrent hypersomnolence, occurring at least once every 18 months, and is associated with cognitive and behavioural dysfunction. Hypersomnia due to medical or psychiatric disorders is associated with the underlying disorder. If hypersomnia is related to the current use of a drug, it refers to hypersomnia due to medication or substance. Insufficient sleep syndrome diagnosis implies that

patients complain of excessive daytime sleepiness and their sleep time is shorter than expected for age.[2]

Currently, European sleep experts have identified limitations of ICSD-3 and are suggesting a new central disorders of hypersomnolence classification: “Narcolepsy”, “Idiopathic hypersomnia” and “Idiopathic excessive sleepiness”.[6]

The first step in approaching excessive daytime sleepiness is to recognize it as a problem.[7] When dealing with a patient with hypersomnolence, patient history is fundamental to ruling out different causes of sleepiness. Thus, sleep, medical, and psychiatric histories should be carefully assessed. Nighttime and daytime symptoms related to the causes of excessive sleepiness, as well as medication and substance use, should also be questioned. The differential diagnosis of excessive daytime sleepiness includes insufficient sleep, sleep disordered breathing, central disorders of hypersomnolence, and circadian rhythm sleep-wake disorders. Furthermore, hypersomnolence can be a symptom of medical or psychiatric disorders and a consequence of medication use. Scales and sleep logs are used to complement the clinical history. The Epworth Sleepiness Scale (ESS) is one of the most used scales to evaluate the likelihood of falling asleep in different situations. The score of this scale ranges from 0 to 24, and excessive sleepiness is defined as a score of ≥ 11.[5, 7]

Physical examination, which should include a general medical examination paying close attention to the upper airway, and a neurologic examination, can also reveal signs of an underlying sleep disorder.[5]

Regarding the objective assessment of hypersomnolence, testing such as actigraphy, polysomnography (PSG), MSLT, and maintenance of wakefulness test, will help confirm the diagnosis and guide the appropriate treatment.[5]

Actigraphy is a low-cost, non-invasive, and well-tolerated technique. Actigraphy devices can be used on the wrist of the non-dominant hand, and from the measurement of movement, they allow inference of the periods corresponding to sleep (absence of movement) and wakefulness (periods of activity). The actigraph can be used at home by the patient for several days or weeks, and the sleep log should also be filled. Actigraphy data is posteriorly downloaded and analysed using specific software, and information is collected.[8] The American Academy of Sleep Medicine (AASM) published a clinical practice guideline that recommends actigraphy 7 to 14 days before MSLT in patients with central disorders of hypersomnolence. The goals of actigraphy are to determine the total sleep time prior to MSLT and rule out insufficient sleep syndrome and circadian rhythm sleep-wake disorders.[9] Another indication for actigraphy is the measurement of the sleep duration for the diagnosis of idiopathic hypersomnia.[2]

Actigraphy has obvious advantages, such as recording activity/sleep over several days at the patient's home and is not dependent on the patient's memory. However, actigraphy has limitations

such as its limited use in assessing sleep onset latency and the need for patients to complete sleep logs to improve the quality of the recordings analysis.[10]

Actigraphy is a simple tool that should be used before MSLT. Thus, its data is important for understanding its role in the diagnosis of diseases that cause sleepiness with a central origin. Therefore, the goal of this systematic review was to summarize the available actigraphy features of central disorders of hypersomnolence.

Methods

Study design

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.[11] Eligibility criteria and search strategy were established based on a Participants / Population, Interventions, Comparators / Controls, Outcomes, Timing, and Study design (PICOTS) framework, as described in Table I.

Search strategy

PubMed, EMBASE, Web of Science, Scopus, Cochrane, and SciELO were the bibliographic databases searched for this review, which was conducted on March 2, 2023, and was last updated on March 9, 2023.

The search strategy resulted from the combination of the controlled terms Medical Subject Headings (MeSH) and Emtree with uncontrolled terms. Table II provides a detailed description of the queries used in each database during the search. Duplicate publications were excluded with the assistance of a reference manager.

Selection procedure

To reduce selection bias, the titles and abstracts were evaluated independently by two elements using Rayaan, a web-based tool for systematic reviews,[12] using the following inclusion criteria:

- Studies related to central disorders of hypersomnolence diagnosis;
- Central disorders of hypersomnolence should be classified according to ICSD-3. Regarding hypersomnia associated with medical or psychiatric disorders and hypersomnia due to medication or substance, the criteria for inclusion were the different pathophysiologic subtypes mentioned on ICSD-3. The subtypes included in this review are listed in Table III;
- Studies related to central disorders of hypersomnolence diagnosis must mention the acquisition of actigraphy data;
- Randomized controlled trials, cohort, and case-control observational studies;
- Adult participants;

- Studies published after January 2015. ICSD-3 was published in 2014. For this reason, this timescale was chosen to avoid publications in which the central disorders of hypersomnolence were classified according to a different version;
- Studies written in English, Portuguese or Spanish;
- If the same group of patients participated in different studies, only the most recent publication was included to avoid data duplication.

Studies that mentioned the following were excluded (Table I):

- Central disorders of hypersomnolence classification using criteria other than ICSD-3;
- Research without control or comparison groups;
- Studies related to central disorders of hypersomnolence therapeutics;
- Actigraphy data not available;
- Case reports, guidelines, comments, and review papers;
- Animal studies;
- Pediatric participants;
- Pregnancy;
- Full text not available;
- No information on the outcomes of interest.

Conflicting decisions on selection were resolved through consensus. Full text evaluation of the remaining records was also carried out by the same elements, fulfilling the pre-established criteria.

Data extraction

Data from the original studies were collected using a Microsoft® Excel pre-established spreadsheet. Author, year of publication, country, study design, sample size, number of participants for each diagnosis and healthy controls, sex, age, ESS, and sleep latency at MSLT were gathered. Regarding actigraphy, the following data were extracted (if available): device manufacturer and model, name and version of the software used for actigraphy data analysis, epoch length, actigraphy duration, sleep diary filling, bed time, get up time, time in bed, total sleep time, sleep efficiency, sleep onset latency, wake after sleep onset, sleep motor activity, number of awakenings, fragmentation index, daytime motor activity, mean duration of the longest sleep episodes during the day, interdaily stability, intradaily variability, relative amplitude, discriminant score, and new discriminant score.
Data extraction was conducted by one element and verified by another element. Disagreements were resolved through consensus.

Assessment of study quality

Case-control and cohort studies were evaluated using the Newcastle-Ottawa quality assessment scale. Each study was rated with stars regarding different items, including selection, comparability, and exposure or outcome for case-control or cohort studies, respectively. The scale ranges from 0 to 9, and the quality of the studies were classified as low (0-3 stars), moderate (4-6 stars), and high (7-9 stars). Two elements independently scored each included study, and different viewpoints regarding the quality of the articles were resolved by consensus.

Data synthesis

Meta-analyses were conducted using the open-source software jamovi, version 1.6.23, with the METAFOR package,[13-15] for all outcomes with at least three studies. Actigraphy outcomes were expressed as absolute mean differences and 95% confidence intervals. A fixed-effects model for comparing patients with narcolepsy type 1 with healthy controls was used when heterogeneity was considered low (I^2 < 50%); otherwise, a DerSimonian-Laird random-effects model was used. Heterogeneity was assessed using Higgins I^2 statistic and Cochrane Q test. Visual inspection of funnel plots was used to assess publication bias, and no statistical test was used because the number of publications was low. A p-value less than .05 was considered statistically significant.

Results

Study selection

The database search identified 1737 publications and after exclusion of duplicates, 1283 were analysed. In this step, titles and abstracts were screened, allowing the exclusion of 1248 studies. The remaining 35 studies were assessed for eligibility through full-text review. Of these, 27 studies did not meet the inclusion criteria: 20 did not have a control group, 5 had insufficient data, and 2 were case reports. Thus, 8 studies were included in this systematic review.[16-23] The study selection flow diagram is illustrated in Figure 1.

Systematic review

The selected studies were published between 2015 and 2021 and conducted in different countries: Italy, Switzerland, United States of America, France, Taiwan, Portugal, and Denmark. Concerning the study design, seven were case-control studies, and one was a cohort study.

The main characteristics of the studies included in this review are available in Table IV. The sample size ranged from 34 to 93, with a total sample size of 473 participants, consisting of 106 patients with narcolepsy type 1, 40 patients with idiopathic hypersomnia, 29 patients with hypersomnolence and normal CSF-Hrct-1, 20 patients with Kleine-Levin Syndrome, 42 patients with traumatic brain injury, 19 patients with major depressive disorder, 12 patients with myotonic dystrophy, 13 patients with primary insomnia, and 192 healthy controls. Considering the age and sex of all participants, only one study did not provide these data.[18] The mean age ranged from 20 to 44 years, and the percentage of males varied between 13% and 86%.

Only four studies mentioned the ESS score and sleep latency in MSLT.[16-17,21,23] Patients with narcolepsy type 1 had the highest mean ESS scores, and controls had the lowest scores (ranging from 4 to 6). Regarding sleep latency in MSLT, it was lower in patients with narcolepsy type 1.[16,23]

Two studies did not mention if the participants were using medication with impact on sleep.[17,22] Four studies specified that all patients were drug naïve or did a washout of medication impacting sleep.[16,18-19,23] Two studies included patients that were using medication (modafinil or sodium oxybate, and flumazenil).[20-21]

The Newcastle-Ottawa quality assessment scale for cohort and case-control studies was between 5 to 8 stars. The quality assessments of the studies included in this review are presented in Tables V and VI.

Actigraphy

The actigraphs used in the analysed studies included Micro Motionlogger (Ambulatory Monitoring, Inc. NY),[16] Actiwatch (Neurotechnology),[17] Motionlogger Watch (Ambulatory Monitoring, Inc. NY),[19] Actiwatch AW64 (Cambridge Neurotechnology Ltd., UK),[20] Motion Watch 8 (CamNtech Ltd., UK),[22] and Actiwatch Spectrum Pro (Philips Respironics, USA).[23] The device used in two studies was not specified.[18,21]

In terms of epoch length, three studies used 1-minute epochs,[16,19,22] while one study used 30-second epochs.[23] This topic was not mentioned in the other four studies.[17-18,20-21]

In four studies, the actigraphy recording lasted seven days,[16,18-20] and fourteen days in three studies.[17,21,23] In Lin *et al.*, controls used the actigraph for seven days, while patients with Kleine-Levin Syndrome used the device for fourteen days during the asymptomatic period and six months to monitor hypersomnia attacks. Only twelve out of twenty participants used the actigraph for six months.[22]

Participants in the majority of the studies included in this review completed a sleep log.[16-20,23] Two studies, however, did not specify the filling.[21-22]

The actigraphy outcomes of each study are presented in Table VII. Three studies recorded the time in bed in patients with narcolepsy type 1 and idiopathic hypersomnia.[16,20,23] Total sleep time was measured in seven studies, involving patients with narcolepsy type 1, idiopathic hypersomnia, traumatic brain injury, major depressive disorder, myotonic dystrophy, and Kleine-Levin syndrome.[16-18,20-23] Regarding sleep efficiency and sleep onset latency, five studies gathered these parameters, including patients with narcolepsy type 1, idiopathic hypersomnia, and Kleine-Levin syndrome.[16,19-20,22-23] Wake after sleep onset and awakenings during sleep were recorded in patients with narcolepsy type 1, idiopathic hypersomnia, and Kleine-Levin syndrome in four studies.[16,20,22-23] Sleep motor activity was collected in four studies, including patients with narcolepsy type 1, idiopathic hypersomnia, and Kleine-Levin syndrome.[16,19-20,22] Daytime motor activity was analysed in three studies with narcolepsy type 1, idiopathic hypersomnia, and Kleine-Levin syndrome patients.[16,22-23] Interdaily stability, intradaily variability, and relative amplitude were available in narcolepsy type 1 and Kleine-Levin syndrome patients in three studies.[20,22-23] Two studies analysed the mean duration of the longest sleep episodes during the day and the discriminant score in patients with narcolepsy type 1 and idiopathic hypersomnia.[16,20] Only one study collected bedtime, get-up time, fragmentation index, and new discriminant score in patients with narcolepsy type 1.[20]

Narcolepsy and idiopathic hypersomnia

Narcolepsy was the most investigated central disorder of hypersomnolence in the evaluated studies. The diagnostic value of actigraphy for narcolepsy was assessed in four studies.[16,19-20,23]

Filardi and co-authors investigated the role of actigraphy in distinguishing patients with narcolepsy type 1 from idiopathic hypersomnia and controls. According to their findings, patients with narcolepsy type 1 had lower total sleep time and sleep efficiency than those with idiopathic hypersomnia and controls. Wake after sleep onset, the number of awakenings, and sleep motor activity were higher in patients with narcolepsy type 1 than in the other two groups. During the daytime, patients with narcolepsy type 1 had diminished daytime motor activity and a mean duration of the longest sleep episodes during the day higher than those with idiopathic hypersomnia and controls. This study presented a discriminant score that incorporated sleep motor activity, number of awakenings, and duration of naps that had shown positive (95%) and negative (87%) predictive values in patients with narcolepsy type 1.[16]

Tonetti *et al.* demonstrated that simultaneous subjective and objective assessments, such as sleep logs and actigraphy, were more effective than separate assessments in screening patients with narcolepsy type 1, proving the value of actigraphy. In this study, sleep efficiency, sleep onset latency, and sleep motor activity were significantly different between patients with narcolepsy type 1 and controls. Regardless of diagnostic assessment, actigraphy correctly identified patients with narcolepsy type 1.[19]

To validate the findings of Filardi and colleagues, Leger *et al*. examined the discriminant score using a different actigraphy model and compared patients with narcolepsy type 1, primary insomnia, and controls. The fragmentation index and mean duration of the longest sleep episodes during the day were substantially higher in patients with narcolepsy type 1 than in those with primary insomnia and controls. The discriminant score was higher in patients with primary insomnia and narcolepsy type 1 than in controls. Thus, the discriminant score was not a strong differentiator for this group of patients. As a result, Leger *et al*. suggested a new discriminant score combining the mean duration of the longest sleep episodes during the day and the fragmentation index, which was higher in patients with narcolepsy type 1 than in the other two groups.[20]

One of the goals of Torstensen and co-authors investigation was to determine whether actigraphy could distinguish patients with narcolepsy type 1, hypersomnolence with normal CSF-Hcrt-1 and controls. Regarding the sample of this study, fourteen patients had narcolepsy type 1 and twenty-nine patients had complaints of hypersomnolence, without cataplexy, and with a CSF-Hcrt-1 > 200 pg/ml. These patients were subsequently diagnosed with narcolepsy type 2 (n=1), idiopathic hypersomnia (n=2), Kleine-Levin syndrome (n=1), insufficient sleep syndrome (n=4), and no sleep disorders (n=21). When patients with narcolepsy type 1 were compared with those with hypersomnolence normal CSF-Hcrt-1, the first group had a higher wake after sleep onset and intradaily variability and lower daytime motor activity, whereas the comparison between patients

with narcolepsy type 1 and controls showed higher time in bed, sleep onset latency, wake after sleep onset, awakenings, and lower sleep efficiency and daytime motor activity.[23]

Kleine-Levin syndrome

Concerning Kleine-Levin syndrome, only one study was included in this review, and its aim was to monitor the movements of patients with Kleine-Levin syndrome using actigraphy during an asymptomatic period and a hypersomnia attack. Lin *et al.* found no significant differences between this patient group and controls during the asymptomatic phase. Interdaily stability was lower in hypersomnia attacks than in the asymptomatic period and in controls. Another finding from *Lin et al.*, the daytime motor activity was significantly lower at the beginning of a hypersomnia attack. There were also other actigraphy variables, such as the mean rhythm - MESOR and the most active ten hours - M10, which were only obtained in this study. These parameters decrease at the beginning of the hypersomnia attack, demonstrating that there was a reduction in the activity level before this period, with full recovery after symptom resolution.[22]

Hypersomnia associated to medical disorder

Although hypersomnia associated with medical disorders includes several subgroups, our research yielded two studies that matched all the required inclusion criteria.[17,21]

Imbach and colleagues investigated sleep-wake disturbances in patients with traumatic brain injury. In this regard, the patients were assessed twice: immediately after the injury with clinical, imaging, and laboratory assessments, and six months later with actigraphy, PSG, MSLT, and laboratory assessment. Actigraphy demonstrated that the total sleep time was higher in these patients than in controls.[17]

Patients with myotonic dystrophy suffer from hypersomnolence. Therefore, Chen *et al.* investigated total sleep time comparing patients with myotonic dystrophy, idiopathic hypersomnia, and controls and found that patients with idiopathic hypersomnia slept longer than those with myotonic dystrophy and controls.[21]

Hypersomnia due to psychiatric disorder

In terms of hypersomnia due to psychiatric disorders, only one study on major depressive disorder was found. [18]

Cook et al. investigated sleep duration in patients with major depressive disorders and controls, finding that time in bed and total sleep time were considerably higher in the first group. [18]

Meta-analysis

Only studies comparing patients with narcolepsy type 1 and controls were included in the meta-analysis, since this was the only comparison between central disorders of hypersomnolence that encompassed the same actigraphy outcome in at least three studies. Table VIII summarises data from the meta-analysis on pooled absolute mean difference for the included outcomes. No significant differences between patients with narcolepsy type 1 and controls were obtained regarding time in bed and total sleep time. We found a significantly lower sleep efficiency for patients with narcolepsy type 1 compared to controls (absolute mean difference of -13.62; 95%CI -18.87 to -8.37; Figure 2); however, these patients showed significantly higher sleep onset latency (absolute mean difference of 4.36; 95%CI 2.57 to 6.14; Figure 3), wake after sleep onset (absolute mean difference of 44.88; 95%CI 8.83 to 80.92; Figure 4), sleep motor activity (absolute mean difference of 17.15; 95%CI 13.02 to 21.29; Figure 5), and awakenings (absolute mean difference of 13.01; 95%CI 10.98 to 15.17; Figure 6).

We found a significantly high heterogeneity between studies (I^2 ranging from 69% to 91%) for all assessed actigraphy outcomes, except for sleep onset latency (I^2 of 40%, Figure 3), sleep motor activity (I^2 of 52%, Figure 5), and awakenings (I^2 of 42%, Figure 6). Since no meta-analyses included 10 or more studies, publication bias was not assessed using statistical tests. Funnel plots for each meta-analysis are shown in Figures 7, 8, 9, 10, and 11.

Discussion

Summary of the findings

To the best of our knowledge, this is the first systematic review evaluating the role of actigraphy in different central disorders of hypersomnolence, and we summarized the yielded studies on the subject.

The actigraphy device used varied among studies. The equipment and analysis software used are crucial because their data collection, calculation, and integration methodologies differ, resulting in different actigraphy results.[24] Cook *et al*. support this claim by stating that estimations of sleep-wake parameters in actigraphy may fluctuate between different scoring algorithms.[25] Leger and co-authors raised this issue in their study, and obtained different results from Filardi *et al*., with the actigraphy model being one of the causes for the results achieved.[20]

In all studies included in the review, total sleep time was the most researched actigraphy outcome, and found to be useful in distinguishing central disorders of hypersomnolence.[16-18,20-23] Alakuijala *et al*. concluded that actigraphy is reliable in excluding insufficient sleep in patients with narcolepsy, enabling a more precise total sleep time assessment than PSG.[26] Regarding actigraphy outcomes, total sleep time, sleep efficiency, and wake after sleep onset were consistent when PSG was compared with actigraphy. However, the sleep onset latency result was not concordant.[24]

Actigraphy showed to be useful in differentiating central disorders of hypersomnolence when compared to healthy controls.[16,23] The notable differences between narcolepsy type 1 and controls were a decrease in total sleep time, sleep efficiency, and daytime motor activity, and an increase in wake after sleep onset, awakenings, sleep motor activity, and mean duration of the longest sleep episodes during the day.[16,19-20,23] These results are similar to those of a recent systematic review evaluating the role of quantitative actigraphy in clinical sleep medicine.[27] In their new index discriminant score, Filardi *et al*. combined actigraphy parameters from nighttime and daytime. This index demonstrated to be effective in diagnosing narcolepsy type 1 because it reflects the disrupted nocturnal sleep and hypersomnolence that characterise this disorder.[16] Posteriorly, Leger and colleagues computed a new discriminant score that included the mean duration of the longest sleep episodes during the day and the fragmentation index, which discriminated patients with narcolepsy type 1 from controls and patients with primary insomnia. However, the patients were not drug naïve at the time of the actigraphy recording.[20]

The most relevant finding regarding idiopathic hypersomnia was increased mean duration of the longest sleep episodes during the day compared with controls.[16] This result is consistent with the literature: one criteria included in idiopathic hypersomnia diagnosis is a total 24-hour sleep time ≥

660 minutes, measured by 24-hour PSG or actigraphy. Here, actigraphy can be a useful tool because of its simple technique and recording.[2]

In terms of Kleine-Levin syndrome, the study included in this review found no differences in actigraphy findings between these patients controls during the asymptomatic period. However, at the start of the hypersomnia attack, the daytime motor activity decreased and then increased during the late phase of the attack and recovered thereafter. Lin *et al*. stated that lower interdaily stability can be explained by a loss of stability of the daily circadian profile and may be a sign of incomplete recovery.[22]

The most significant observation in patients with traumatic brain injury was an elevated total sleep time.[17] Regarding myotonic dystrophy, patients had lower total sleep time than patients with idiopathic hypersomnia.[21]

Increased total sleep time was also observed in patients with major depressive disorder.[18]

Other considerations

Actigraphy may also be used as a confirmatory tool to evaluate patients with hypersomnolence. Kretzschmara *et al*. demonstrated that actigraphy plays a more important role in the diagnosis of insufficient sleep, as these patients tend to overestimate their sleep in their clinical history and sleep diaries. In the case of idiopathic hypersomnia, the authors discovered that these patients described their sleep habits more accurately, with actigraphy serving as a confirmatory tool. Although no study on insufficient sleep syndrome was included in this review, it is very prevalent, and actigraphy helps distinguish it from other central disorders of hypersomnolence.[28]

There is a lack of knowledge regarding the best actigraphy parameters for use in central disorders of hypersomnolence. To fill this gap, Leger *et al*. found that seven days of actigraphy monitoring was sufficient for patients with narcolepsy type 1.[29] Cook *et al*. also investigated the setting configuration for total sleep time estimation in idiopathic hypersomnia patients. Their findings demonstrated that a 25-epoch parameter configuration was superior to 30-seconds for estimating total sleep time.[30]

Future directions

As Filardi *et al*. and Leger *et al*. presented discriminant and new discriminant scores, functions of this type are likely to be developed in the future. These scores must be further investigated to determine their diagnostic capabilities in central disorders of hypersomnolence, and whether the results can be generalised to all actigraphy models. New discriminant score testing on drug naïve patients with narcolepsy type 1 should also be performed.

According to an actigraphy review published by the AASM, actigraphy settings are fundamental for accurately collecting data.[31] Future studies should focus on filling this gap for all central disorders of hypersomnolence.

Currently, there are various gadgets on the market that should be used with extreme caution because they may not have an algorithm for sleep scoring and may not allow precise data acquisition. Therefore, these devices have not been validated and are not recommended for clinical use. With digital progress, it is predicted that many of these devices will be approved and usable for central disorders of hypersomnolence assessment in the future.[32]

According to Lammers *et al*., a new classification is required for the central disorders of hypersomnolence. In fact, this group of disorders encompasses a wide range of disorders for which there is neither a central cause nor a known causative or comorbid link.[6] Actigraphy would play a more significant role if there were only three categories as suggested by the investigation already available for patients with narcolepsy and idiopathic hypersomnia.

Limitations

In terms of limitations, we found no studies on narcolepsy type 2, insufficient sleep syndrome, and hypersomnia due to medication or substance abuse, and few publications regarding the included central disorders of hypersomnolence. Our review also showed great variability among these studies.

Registered actigraphy data varied between the included studies, which limited their inclusion for quantitative synthesis. It was only possible to analyse comparisons between patients with narcolepsy type 1 and healthy controls, and only for a limited number of parameters. In addition, most results of our meta-analyses showed significant heterogeneity, which might be related to the type of actigraph used, as well as to the different acquisition procedures in the included studies. Guidelines on actigraphy acquisition might be helpful in ensuring that the results are consistent in the future regarding these topics.

Conclusion

This review emphasizes the importance of actigraphy as a tool for objectively measuring sleep in patients with central disorders of hypersomnolence. Actigraphy, together with clinical evaluation, can distinguish between narcolepsy type 1, idiopathic hypersomnia, and insufficient sleep syndrome. However, the absence of standards for the collection and interpretation of actigraphy data does not allow for a more organized application of this simple technique in clinical practice.

Tables

Table I: Eligibility criteria according to PICOTS framework.

PICOTS	Inclusion criteria	Exclusion criteria
Participants / Population	Studies encompassing adult patients with the diagnosis of CDH according to the ICSD-3	Studies including pediatric or pregnant patients or not performed in humans
Interventions	Studies that evaluated sleep characteristics using actigraphy	Studies evaluating therapeutic interventions
Comparators / Control	Studies comprising healthy controls and/or comparing different types of CDH	Studies with no comparators
Outcomes	Studies that reported actigraphy data outcomes, namely TIB, TST, SE, SOL, WASO, SMA, Awk, DMA, LNAP, IS, IV, RA and/or DS	Studies with no available actigraphy data
Time frame	Studies published after January 2015	Studies published previously to 2015
Study design	Randomized controlled trials, cohort and case-control studies	All other study designs

Awk: number of awakenings, CDH: central disorders of hypersomnolence, DMA: daytime motor activity, DS: discriminant score, ICSD-3: International Classification of Sleep Disorders - 3rd Edition, IS: interdaily stability, IV: Intradaily variability, LNAP: mean duration of longest sleep episodes during day, PICOTS: Participants/Population, Interventions, Comparators/Controls, Outcomes, Timing, and Study design, RA: relative amplitude, SE: sleep efficiency, SMA: sleep motor activity, SOL: sleep onset latency, TIB: time in bed, TST: total sleep time, WASO: wake after sleep onset.

Table II: Description of the queries used in the search.

Database	Query
PubMed	("Disorders of Excessive Somnolence"[Mesh] OR "Narcolepsy"[Mesh] OR "Idiopathic Hypersomnia"[Mesh] OR "Kleine-Levin Syndrome"[Mesh] OR "Sleep Deprivation"[Mesh] OR "Central Disorders of Hypersomnolence" OR "Narcolepsy type 1" OR "Narcolepsy type 2" OR "Idiopathic Hypersomnia" OR "Kleine-Levin Syndrome" OR "Hypersomnia due to a Medical Disorder" OR "Hypersomnia due to a Medication or Substance" OR "Hypersomnia associated with a Psychiatric Disorder" OR "Insufficient Sleep Syndrome") AND ("Actigraphy"[Mesh] OR Actigraph*)
EMBASE	('narcolepsy'/exp OR narcolepsy OR 'narcolepsy type 1'/exp OR 'narcolepsy type 1' OR 'narcolepsy type 2'/exp OR 'narcolepsy type 2' OR 'idiopathic hypersomnia'/exp OR 'idiopathic hypersomnia' OR (idiopathic AND ('hypersomnia'/exp OR hypersomnia)) OR 'kleine levin syndrome'/exp OR 'kleine levin syndrome' OR 'central disorders of hypersomnolence' OR (('central'/exp OR central) AND ('disorders'/exp OR disorders) AND of AND ('hypersomnolence'/exp OR hypersomnolence)) OR 'insufficient sleep syndrome'/exp OR 'insufficient sleep syndrome') AND ('actimetry'/exp OR actimetry OR 'actigraph'/exp OR actigraph*)
Web of Science	(“narcolepsy” OR “narcolepsy type 1” OR “narcolepsy type 2” OR “idiopathic hypersomnia” OR (idiopathic AND hypersomnia) OR “kleine levin” OR “central disorders of hypersomnolence” OR (central AND hypersomnolence) OR “insufficient sleep syndrome” OR (insufficient AND sleep AND syndrome)) AND (actimetry OR actigraph*)
Scopus	(“narcolepsy” OR “narcolepsy type 1” OR “narcolepsy type 2” OR “idiopathic hypersomnia” OR (idiopathic AND hypersomnia) OR “kleine levin” OR “central disorders of hypersomnolence” OR (central AND hypersomnolence) OR “insufficient sleep syndrome” OR (insufficient AND sleep AND syndrome)) AND (actimetry OR actigraph*)
Cochrane	(“narcolepsy” OR “narcolepsy type 1” OR “narcolepsy type 2” OR “idiopathic hypersomnia” OR (idiopathic AND hypersomnia) OR “kleine levin” OR “central disorders of hypersomnolence” OR (central AND hypersomnolence) OR “insufficient sleep syndrome” OR (insufficient AND sleep AND syndrome)) AND (actimetry OR actigraph*)
SciELO	(“narcolepsy” OR “narcolepsy type 1” OR “narcolepsy type 2” OR “idiopathic hypersomnia” OR (idiopathic AND hypersomnia) OR “kleine levin” OR “central disorders of hypersomnolence” OR (central AND hypersomnolence) OR “insufficient sleep syndrome” OR (insufficient AND sleep AND syndrome) OR narcolepsia OR ((hipersónia OR hipersonolência) AND idiopática) OR (central AND (hipersónia OR hipersonolência))) AND (actimetry OR actigraph* OR actigrafia)

Table III: Pathophysiologic subtypes of hypersomnia associated with medical or psychiatric disorders and due to medication according to International Classification of Sleep Disorders, 3rd Edition.[2]

Pathophysiologic subtypes of hypersomnia
Hypersomnia associated with medical disorders
Hypersomnia secondary to Parkinson disease
Posttraumatic hypersomnia
Genetic disorders with primary central nervous system somnolence
Hypersomnia secondary to brain tumors, infections, or other central nervous system lesions Hypersomnia secondary to endocrine disorder
Hypersomnia secondary to metabolic encephalopathy
Residual hypersomnia in patients with adequately treated obstructive sleep apnea
Hypersomnia associated with a psychiatric disorder
Hypersomnia associated with mood disorder
Hypersomnia associated with a conversion disorder or somatic symptom disorder
Hypersomnia due to medication or substance
Hypersomnia due to sedating medications
Hypersomnia due to substance abuse
Hypersomnia due to stimulant withdrawal

Table IV: Characteristics of the studies included in the review.

Authors, year	Country	Study design	Sample size	Age (years), mean ± SD	Males (%)	ESS (score), mean ± SD	SL-MSLT (minutes), mean ± SD	Actigraphy device	Actigraphy outcomes
Filardi *et al.*,[16] 2015	Italy	Case-control	93 39 NT1 24 IH 30 HC	NT1 34.21 ± 15.58 IH 31.96 ± 15.20 HC 29.37 ± 9.47	NT1 58,97% IH 45,83% HC 50,00%	NT1 16.41 ± 3.42 IH 14.50 ± 3.57 HC 4.47 ± 2.63	NT1 3.14 ± 1.77 IH 6.14 ± 1.09	Micro Motionlogger®, Ambulatory Monitoring, Inc. Ardsley, NY	7-day actigraphy: TIB, TST, SE, SOL, WASO, SMA, Awk, DMA, LNAP, DS
Imbach *et al.*,[17] 2015	Switzerland	Cohort	84 42 TBI 42 HC	TBI 35.50 ± 14.40 HC 36.50 ± 13.20	TBI 73.81% HC 73.81%	TBI 6.10 ± 3.10 HC 5.60 ± 3.30	TBI 8.70 ± 4.60 HC 12.10 ± 4.70	Actiwatch, Neurotechnology	14-day actigraphy: TST
Cook *et al.*,[18] 2015	USA	Case-control	38 19 MDD 19HC	N/R	N/R	N/R	N/R	N/R	7-day actigraphy: TST
Tonetti *et al.*,[19] 2017	Italy	Case-control	80 40 NT1 40 HC	NT1 33.23 ± 14.20 HC 28.98 ± 6.12	NT1 61,76% HC 38.24%	N/R	N/R	Motionlogger Watch, Ambulatory Monitoring, Inc. Ardsley, NY	7-day actigraphy: SE, SOL, SMA
Leger *et al.*,[20] 2018	France Italy	Case-control	39 13 NT1 13 PI 13 HC	NT1 39.38 ± 11.48 PI 38.69 ± 10.72 HC 38.00 ± 10.77	NT1 30,77% PI 30,77% HC 30,77%	N/R	N/R	Actiwatch AW64, Cambridge Neurotechnology Ltd, Cambridge, UK	7-day actigraphy: bed time, get up time, TIB, TST, SE, SOL, WASO, SMA, Awk, FI, LNAP, IS, IV, RA, DS, NDS

(continues on the next page)

Table IV (continued)

Authors, year	Country	Study design	Sample size	Age (years), mean ± SD	Males (%)	ESS (score), mean ± SD	SL-MSLT (minutes), mean ± SD	Actigraphy device	Actigraphy outcomes
Chen *et al.*,[21] 2020	USA	Case-control	47 12 MD 16 IH 19 HC	MD 32.00 ± 12.30 IH 29.00 ± 11.80 HC 27.50 ± 6.80	MD 58.33% IH 12.50% HC 36.84%	MD 14.20 ± 3.50 IH 15.10 ± 3.60 HC 6.40 ± 3.60	MD 8.00 ± 5.00 IH 9.70 ± 5.60 HC 11.30 ± 5.20	N/R	14-day actigraphy: TST
Lin *et al.*,[22] 2021	Taiwan Portugal USA	Case-control	34 20 KLS 14 HC	KLS 20.10 ± 4.80 HC 20.20 ± 4.60	KLS 85.00% HC 86.00%	N/R	N/R	Motion Watch 8, CamNtech Ltd, Cambridge, UK	KLS: 14-day actigraphy during asymptomatic period and 6 months to monitor hypersomnia attacks. HC: 7-day actigraphy. TST, SE, SOL, WASO, SMA, Awk, DMA, IS, IV, RA
Torstensen *et al.*,[23] 2021	Denmark	Case-control	58 14 NT1 29 Normal CSF-Hcrt-1 hypersomnolence 15 HC	NT1 39.60 ± 17.50 Normal CSF-Hcrt-1 hypersomnolence 35.50 ± 12.80 HC 43.80 ± 18.60	NT1 36.00% Normal CSF-Hcrt-1 hypersomnolence 28.00% HC 57.00%	NT1 15.00 ± 4.00 Normal CSF-Hcrt-1 hypersomnolence 15.00 ± 5.00 HC 6.00 ± 3.00	NT1 6.30 ± 4.50 Normal CSF-Hcrt-1 hypersomnolence 11.10 ± 5.00 HC 12.20 ± 5.10	Actiwatch Spectrum Pro, Philips Respironics, USA	14-day actigraphy: TIB, TST, SE, SOL, WASO, Awk, DMA, IS, IV, RA

Awk: number of awake episodes, CSF-Hcrt-1: Cerebrospinal fluid hypocretin-1, DMA: daytime motor activity, DS: discriminant score, ESS: Epworth Sleepiness Scale, FI: fragmentation index, HC: healthy control, IH: idiopathic hypersomnia, IS: interdaily stability, IV: Intradaily variability, KLS: Kleine-Levin syndrome, LNAP: mean duration of longest sleep episodes during day, MD: myotonic dystrophy, MDD: major depressive disorder, MSLT: Multiple Sleep Latency Test, NDS: new discriminant score, N/R: not reported, NT1: narcolepsy type 1, NY: New York, PI: primary insomnia, RA: relative amplitude, SD: standard deviation, SE: sleep efficiency, SL: sleep latency, SMA: sleep motor activity, SOL: sleep onset latency, TBI: traumatic brain injury, TIB: time in bed, TST: total sleep time, UK: United Kingdom, USA: Unites States of America, WASO: wake after sleep onset.

Table V: Newcastle - Ottawa quality assessment scale for case-control studies.

Author	Adequate definition of case	Representativeness of cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total quality scores
Filardi *et al.*[16]	*	*	*	*	*	*	*	*	8
Cook *et al.*[18]		*	*		*	*	*	*	6
Tonetti *et al.*[19]	*	*	*	*	*	*	*	*	8
Leger *et al.*[20]		*	*		*	*	*	*	6
Chen *et al.*[21]		*			*	*	*	*	5
Lin *et al.*[22]	*	*	*	*	*	*	*		7
Torstensen *et al.*[23]	*	*	*	*	*	*	*	*	8

Table VI: Newcastle - Ottawa quality assessment scale for cohort study.

Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up length	Adequacy of follow up of cohorts	Total quality scores
Imbach *et al.*[17]	*	*	*		**	*	*	*	8

Table VII: Actigraphy outcomes of the studies included in the review.

Outcome	Mean ± SD	Comparisons
TIB (min)		
Filardi *et al*.	NT1 471.04 ± 65.13; IH 465.07 ± 85.59; HC 478.82 ± 59.69	ns
Leger *et al*.	NT1 474.57 ± 58.18; PI 508.18 ± 47.72; HC 455.62 ± 51.38	N/R
.Torstensen *et al.*	NT1 588.00 ± 60.00; Normal CSF-Hcrt-1 hypersomnolence 570.00 ± 96.00; HC 528.00 ± 60.00	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.48; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.10; HC vs NT1: p=.02
TST (min)		
Filardi *et al*.	NT1 362.57 ± 83.49; IH 417.41 ± 74.73; HC 457.97 ± 53.04	NT1 vs HC: p=.0001; NT1 vs IH: p=.01; IH vs HC ns
Imbach *et al.*	TBI 498.00 ± 66.00; HC 426.00 ± 48.00	p<.00001
Cook *et al.*	MDD 441.00 ± 37.80; HC 411.00 ± 31.80	p=.015
Leger *et al*.	NT1 404.69 ± 50.75; PI 436.46 ± 37.36; HC 423.54 ± 46.06	N/R
Chen *et al*.	MD 429.00 ± 38.00; IH 456.00 ± 65.00; HC 393.00 ± 64.00	p=.02
Lin *et al.*	No KLS attack 467.00 ± 82.50; KLS attack 583.10 ± 110.30; HC 463.70 ± 71.30	N/R
Torstensen *et al.*	NT1 426.00 ± 84.00; Normal CSF-Hcrt-1 hypersomnolence 438.00 ± 66.00; HC 444.00 ± 60.00	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.54; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.87; HC vs NT1: p=.47
SE (%)		
Filardi *et al*.	NT1 76.97 ± 13.97; IH 89.65 ± 5.34; HC 95.70 ± 1.99	NT1 vs HC: p=.0001; NT1 vs IH: p=.0001; IH vs HC ns
Tonetti *et al*.	NT1 78.78 ± 10.77; HC 95.13 ± 1.96	NT1 vs HC: p<.001
Leger *et al*.	NT1 86.00 ± 8.78; PI 87.03 ± 3.60; HC 93.01 ± 2.96	N/R
Lin *et al*.	No KLS attack 82.20 ± 5.30; KLS attack 79.50 ± 4.20; HC 84.40 ± 9.50	N/R
Torstensen *et al*.	NT1 73.00 ± 15.00; Normal CSF-Hcrt-1 hypersomnolence 79.00 ± 5.00; HC 84.00 ± 4.00	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.08; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.001; HC vs NT1: p=.02

(continues on the next page)

Table VII (continued)

Outcome	Mean ± SD	Comparisons
SOL (min)		
Filardi *et al*.	NT1 13.29 ± 13.34; IH 11.53 ± 9.73; HC 8.32 ± 4.68	ns
Tonetti *et al.*	NT1 11.65 ± 5.95; HC 7.94 ± 2.72	NT1 vs HC: p<.005
Leger *et al*.	NT1 12.38 ± 13.74; PI 11.23 ± 7.38; HC 4.38 ± 4.52	N/R
Lin *et al.*	No KLS attack 25.80 ± 21.40; KLS attack 17.50 ± 9.20; HC 23.40 ± 24.70	N/R
Torstensen *et al.*	NT1 36.70 ± 25.00; Normal CSF-Hcrt-1 hypersomnolence 34.80 ± 16.80; HC 18.10 ± 12.30	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.80; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.001; HC vs NT1: p=.02
WASO (min)		
Filardi *et al*.	NT1 92.50 ± 55.17; IH 36.46 ± 26.68; HC 12.49 ± 8.80	NT1 vs HC: p=.0001; NT1 vs IH: p=.0001; IH vs HC ns
Leger *et al*.	NT1 51.00 ± 39.29; PI 51.54 ± 15.77; HC 23.00 ± 9.08	N/R
Lin *et al*.	No KLS attack 52.30 ± 20.20; KLS attack 104.20 ± 31.50; HC 68.90 ± 71.00	N/R
Torstensen *et al*.	NT1 69.00 ± 30.00; Normal CSF-Hcrt-1 hypersomnolence 50.00 ± 18.00; HC 43.00 ± 13.00	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.04; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.15; HC vs NT1: p=.01
SMA (counts)		
Filardi *et al*.	NT1 29.80 ± 14.25; IH 16.12 ± 6.21; HC 9.98 ± 3.27	NT1 vs HC: p=.0001; NT1 vs IH: p=.0001; IH vs HC ns
Tonetti *et al*.	NT1 28.14 ± 10.88; HC 10.16 ± 3.03	NT1 vs HC: p<.001
Leger *et al*.	NT1 21.32 ± 13.60; PI 21.77 ± 8.28; HC 10.83 ± 4.21	N/R
Lin *et al*.	No KLS attack 38.00 ± 15.80; KLS attack 21.60 ± 12.40; HC 44.30 ± 9.90	N/R

(continues on the next page)

Table VII (continued)

Outcome	Mean ± SD	Comparisons
Awk (number)		
Filardi *et al*.	NT1 17.13 ± 6.90; IH 11.95 ± 6.63; HC 3.47 ± 2.13	NT1 vs HC: p=.0001; NT1 vs IH: p=.005; IH vs HC: p=.0001
Leger *et al*.	NT1 22.65 ± 11.76; PI 29.54 ± 6.83; HC 15.97 ± 5.52	NT1 vs PI: p=.11; NT1 vs HC: p=.12; PI vs HC: p=<.001
Lin *et al.*	No KLS attack 44.70 ± 9.40; KLS attack 86.70 ± 35.10; HC 44.40 ± 21.70	N/R
Torstensen *et al.*	NT1 49.00 ± 12.00; Normal CSF-Hcrt-1 hypersomnolence 41.00 ± 11.00; HC 35.00 ± 7.80	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.06; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.04; HC vs NT1: p=.001
DMA (counts)		
Filardi *et al*.	NT1 192.41 ± 30.26; IH 199.14 ± 45.11; HC 222.88 ± 15.94	NT1 vs HC: p=.0001; NT1 vs IH: ns; IH vs HC: p=.05
Lin *et al*.	No KLS attack 111.50 ± 57.60; KLS attack 53.00 ± 32.90; HC 98.50 ± 25.40	N/R
Torstensen *et al*.	NT1 72.00 ± 25.00; Normal CSF-Hcrt-1 hypersomnolence 89.00 ± 19.00; HC 93.00 ± 23.00	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.03; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.65; HC vs NT1: p=.03
LNAP (min)		
Filardi *et al*.	NT1 35.46 ± 15.50; IH 19.83 ± 17.38; HC 6.40 ± 11.46	NT1 vs HC: p=.0001; NT1 vs IH: p=.0001; IH vs HC: p=.005
Leger *et al*.	NT1 34.85 ± 10.97; PI 21.46 ± 7.55; HC 15.69 ± 7.25	NT1 vs PI: p=<.005; NT1 vs HC: p=<.001; PI vs HC: p=.23
IS		
Leger *et al*.	NT1 0.65 ± 0.15; PI 0.73 ± 0.14; HC 0.71 ± 0.11	N/R
Lin *et al*.	No KLS attack 0.49 ± 0.07; KLS attack 0.41 ± 0.15; HC 0.51 ± 0.09	KLS attack vs no KLS attack: p=.02; KLS attack vs HC: p=.02
Torstensen *et al*.	NT1 0.30 ± 0.10; Normal CSF-Hcrt-1 hypersomnolence 0.40 ± 0.10; HC 0.50 ± 0.10	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.11; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.04; HC vs NT1: p=.003

(continues on the next page)

Table VII (continued)

Outcome	Mean ± SD	Comparisons
IV		
Leger *et al*.	NT1 0.84 ± 0.28; PI 0.83 ± 0.27; HC 0.72 ± 0.14	N/R
Torstensen *et al.*	NT1 1.10 ± 0.30; Normal CSF-Hcrt-1 hypersomnolence 0.80 ± 0.10; HC 0.80 ± 0.20	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.01; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.07; HC vs NT1: p=.003
RA		
Leger *et al*.	NT1 0.85 ± 0.11; PI 0.90 ± 0.06; HC 0.94 ± 0.02	N/R
Lin *et al.*	No KLS attack 0.88 ± 0.07; KLS attack 0.74 ± 0.14; HC 0.85 ± 0.10	N/R
Torstensen *et al.*	NT1 0.80 ± 0.10; Normal CSF-Hcrt-1 hypersomnolence 0.80 ± 0.10; HC 0.90 ± 0.10	NT1 vs Normal CSF-Hcrt-1 hypersomnolence: p=.13; Normal CSF-Hcrt-1 hypersomnolence vs HC: p=.40; HC vs NT1: p=.01
DS		
Filardi *et al*.	NT1 1.57 ± 1.17; IH -0.22 ± 1.17; HC -1.80 ± -0.46	NT1 vs HC: p=.0001; NT1 vs IH: p=.0001 IH vs HC: p=.0001
Leger *et al*.	NT1 1.66 ± 1.68; PI 1.80 ± 0.82; HC -0.26 ± 0.68	NT1 vs PI: p=.95; NT1 vs HC: p=<.001; PI vs HC: p=<.001

Awk: number of awake episodes, CSF-Hcrt-1: cerebrospinal fluid hypocretin-1, DMA: daytime motor activity, DS: discriminant score, HC: healthy control, IH: idiopathic hypersomnia, IS: interdaily stability, IV: Intradaily variability, KLS: Kleine-Levin syndrome, LNAP: mean duration of longest sleep episodes during day, MD: myotonic dystrophy, MDD: major depressive disorder, Min: minutes, N/R: not reported, ns: non-significant, NT1: narcolepsy type 1, PI: primary insomnia, RA: relative amplitude, SD: standard deviation, SE: sleep efficiency, SMA: sleep motor activity, SOL: sleep onset latency, TBI: traumatic brain injury, TIB: time in bed, TST: total sleep time, WASO: wake after sleep onset.

Table VIII: Pooled main results for comparison of actigraphy outcomes between patients with narcolepsy type 1 and healthy controls.

Outcome	*k*, *n*	I^2, *p*-value	Model	Mean difference [95%CI], *p*-value
TIB	3, 124	**69%, *p* = .041**	DSL-REM	21.20 [-18.20; 60.60], *p* = 29
TST	3, 124	**79%, *p* = .003**	DSL-REM	-46.50 [-96.90; 4.00], *p* = .071
SE	4, 204	**78%, *p* = .003**	DSL-REM	**-13.62 [-18.88; -8.35], *p* < .001**
SOL	4, 204	40%, *p* = .17	FEM	**4.36 [2.57; 6.14], *p* < .001**
WASO	3, 124	**91%, *p* < .001**	DSL-REM	**44.88 [8.83; 80.92], *p* = .015**
SMA	3, 175	52%, *p* = .13	DSL-REM	**17.15 [13.02; 21.29], *p* < .001**
Awk	3, 124	42%, *p* = .17	FEM	**13.07 [11.0; 15.17], *p* < .001**

Values in bold are statistically significant. Difference expressed as the outcome for narcolepsy type 1 patients minus the outcome for healthy controls.
k: number of studies included in the analysis; *n*: total number of participants included in the analysis; 95%CI: confidence interval at 95%; I^2: heterogeneity.
Awk: number of awake episodes, DSL-REM: DeSimonian-Laird Random-effects model; FEM: fixed-effects model, SE: sleep efficiency, SMA: sleep motor activity, SOL: sleep onset latency, TIB: time in bed, TST: total sleep time, WASO: wake after sleep onset.

Figures

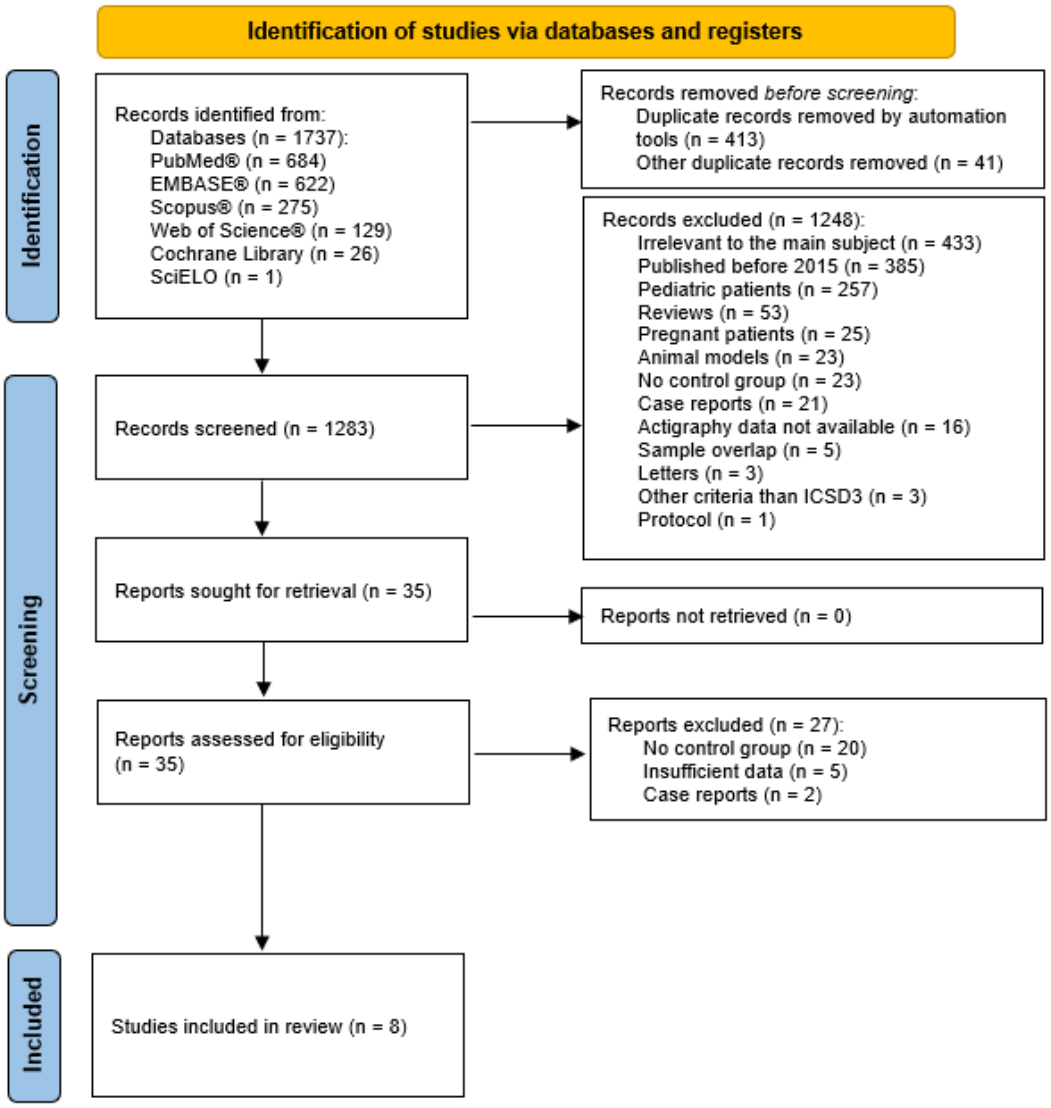

Figure 1: Flow diagram of study selection according to PRISMA guidelines.[11]

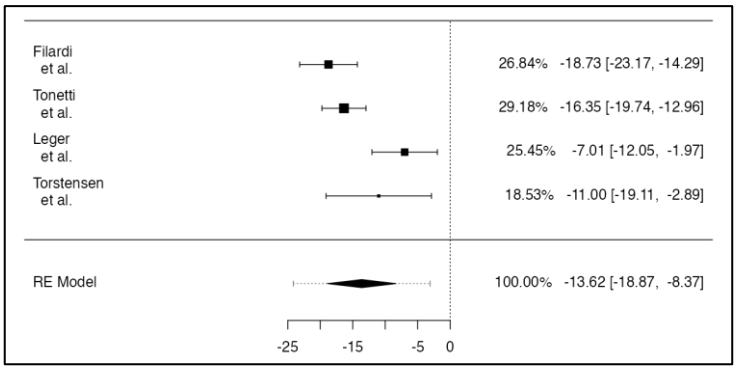

Figure 2: Forest-plot on absolute mean difference on sleep efficiency between patients with narcolepsy type 1 and healthy controls. A pooled absolute mean difference of -13.62 (95%CI of [-18.87, -8.37], $p < .001$) was observed, with significantly high heterogeneity between studies ($I^2 = 78\%$, $p = .003$).

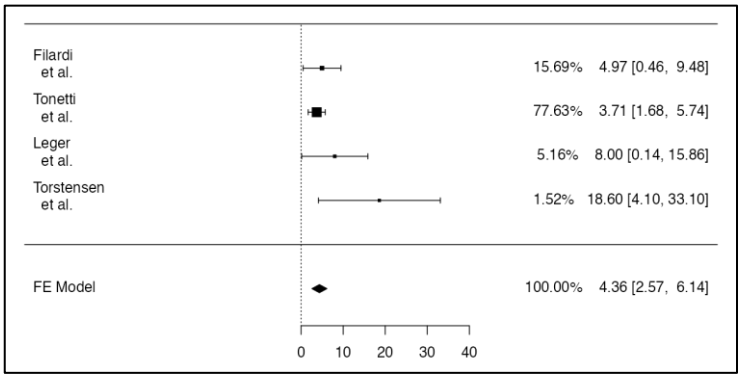

Figure 3: Forest-plot on absolute mean difference on sleep onset latency between patients with narcolepsy type 1 and healthy controls. A pooled absolute mean difference of 4.36 (95%CI of [2.57, 6.14], $p < .001$) was observed. No significant high heterogeneity between studies was obtained ($I^2 = 40\%$, $p = .17$).

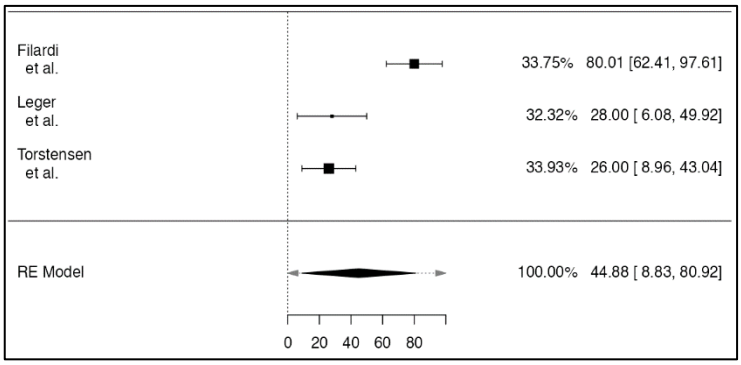

Figure 4: Forest-plot on absolute mean difference on wake after sleep onset between patients with narcolepsy type 1 and healthy controls.A pooled absolute mean difference of 44.88 (95%CI of [8.83, 80.92], $p = .015$) was observed, with significantly high heterogeneity between studies ($I^2 = 91\%$, $p < .001$).

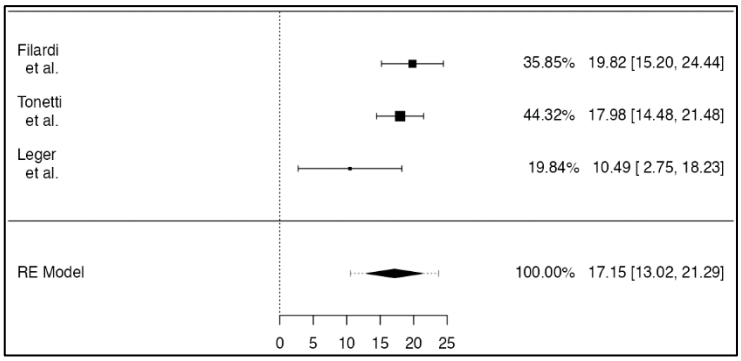

Figure 5: Forest-plot on absolute mean difference on sleep motor activity between patients with narcolepsy type 1 and healthy controls. A pooled absolute mean difference of 17.15 (95%CI of [13.02, 21.29], $p < .001$) was observed. No significant high heterogeneity between studies was obtained ($I^2 = 52\%$, $p = .13$).

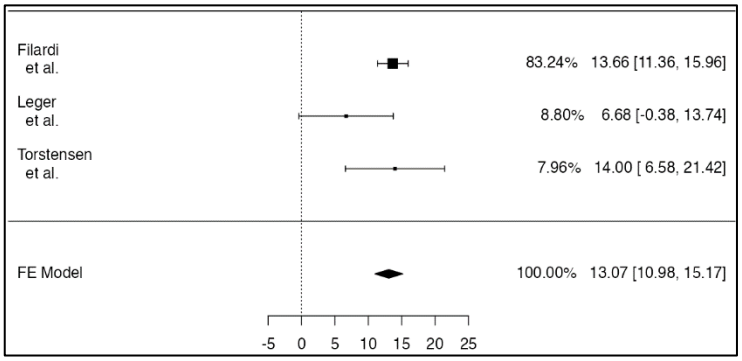

Figure 6: Forest-plot on absolute mean difference on awakenings between patients with narcolepsy type 1 and healthy controls. A pooled absolute mean difference of 13.07 (95%CI of [10.98, 15.17], p < .001) was observed, with no significantly heterogeneity between studies ($I^2 = 42\%$, p = .17).

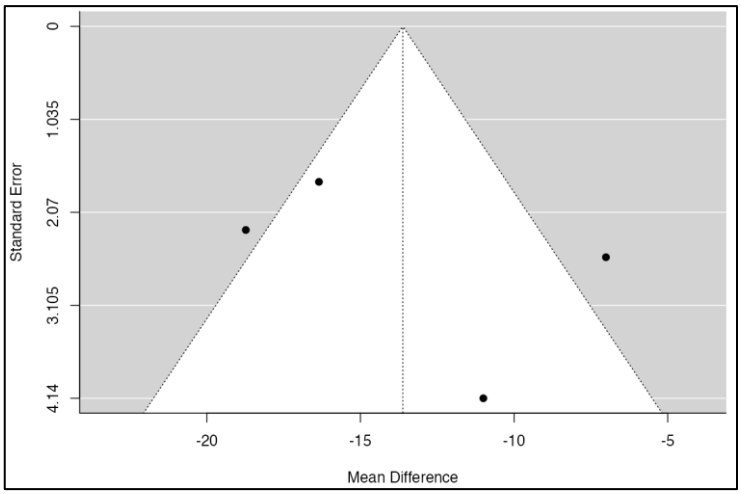

Figure 7: Publication bias funnel-plot for sleep efficiency between patients with narcolepsy type 1 and healthy controls.

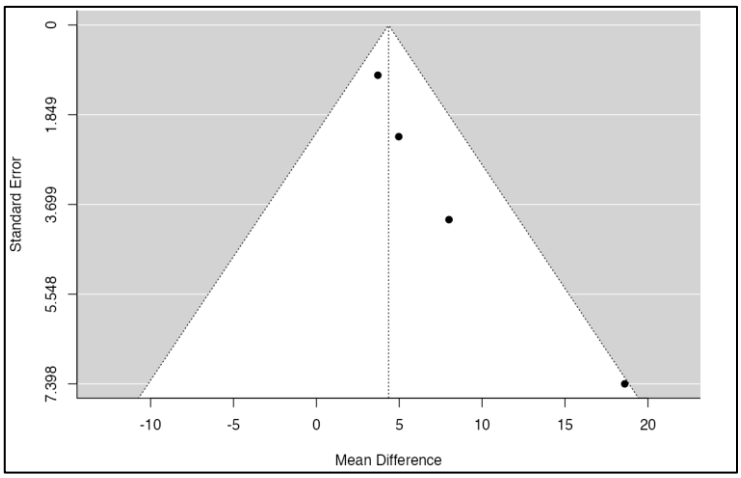

Figure 8: Publication bias funnel-plot for sleep onset latency between patients with narcolepsy type 1 and healthy controls.

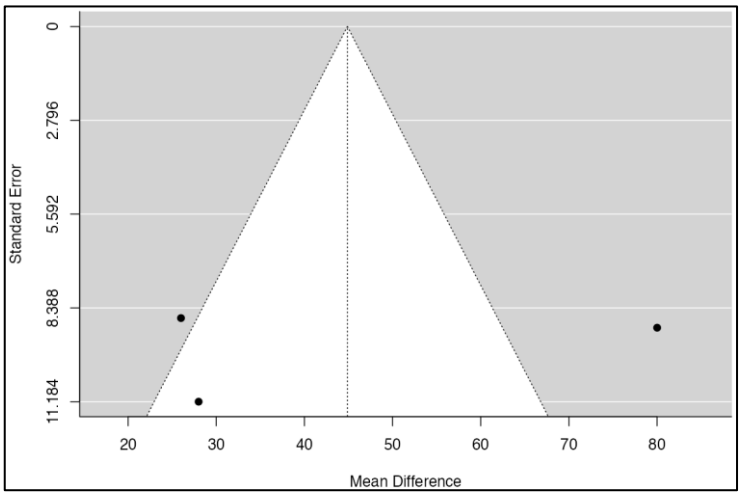

Figure 9: Publication bias funnel-plot for wake after sleep onset latency between patients with narcolepsy type 1 and healthy controls.

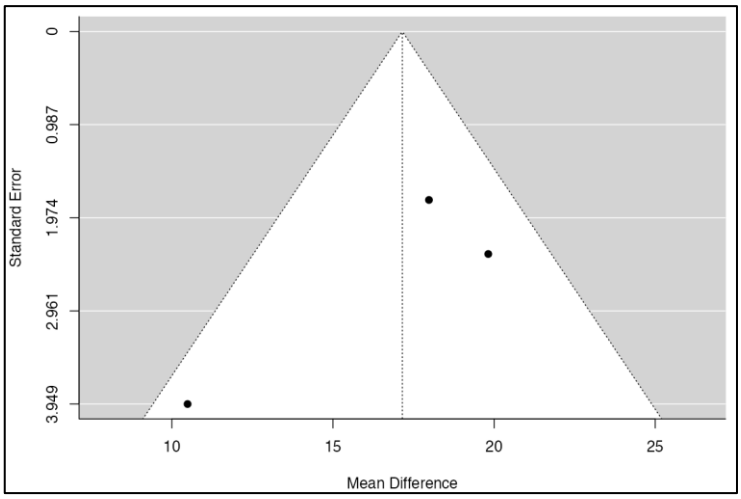

Figure 10: Publication bias funnel-plot for sleep motor activity between patients with narcolepsy type 1 and healthy controls.

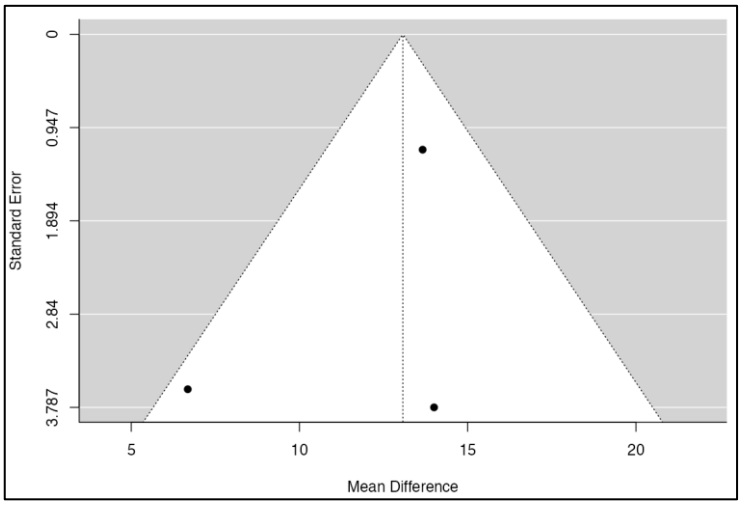

Figure 11: Publication bias funnel-plot for awakenings between narcolepsy type 1 patients and healthy controls.

Bibliography

1. Kryger M, Roth T, Dement W. Principles and Practice of Sleep Medicine. 6 ed. Philadelphia: Elsevier; 2017.
2. American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
3. Pérez-Carbonell L, Mignot E, Leschziner G, Dauvilliers Y. Understanding and approaching excessive daytime sleepiness. Lancet 2022;400(10357):1033-46.
4. Gonçalves M, Amici R, Lucas R, *et al*. Sleepiness at the wheel across Europe: a survey of 19 countries. J Sleep Res. 2015;24(3):242-53.
5. Gandhi KD, Mansukhani MP, Silber MH, Kolla BP. Excessive Daytime Sleepiness: A Clinical Review. Mayo Clin Proc. 2021;96(5):1288-301.
6. Lammers G, Bassetti C, Dolenc-Groselj L. Diagnosis of central disorders of hypersomnolence: A reappraisal by European experts. Sleep Med Rev. 2020;52(101306).
7. Murray BJ. Subjective and Objective Assessment of Hypersomnolence. Sleep Medicine Clinics. 2020;15(2):167-76.
8. Bassetti C, McNicholas W, Paunio T, Peigneux P. Sleep Medicine Textbook. 2nd ed: European Sleep Research Society; 2021.
9. Smith MT, McCrae CS, Cheung J, *et al*. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2018;14(7):1231-7.
10. Martin JL, Hakim AD. Wrist actigraphy. Chest. 2011;139(6):1514-27.
11. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372 (n71).
12. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan — a web and mobile app for systematic reviews. Systematic Reviews. 2016; 5:210.
13. The jamovi project. jamovi (version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org. 2021. https://www.jamovi.org.
14. R Core Team. R: A Language and environment for statistical computing. (Version 4.0). Retrieved from https://cran.r-project.org. 2020. https://cran.r-project.org.
15. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw. 2010;36(3):48.
16. Filardi M, Pizza F, Martoni M, Vandi S, Plazzi G, Natale V. Actigraphic assessment of sleep/wake behavior in central disorders of hypersomnolence. Sleep Med. 2015;16(1):126-30.
17. Imbach LL, Valko PO, Li T, et al. Increased sleep need and daytime sleepiness 6 months after traumatic brain injury: a prospective controlled clinical trial. Brain. 2015;138(Pt 3):726-35.
18. Cook JD, Goldstein MR, Plante DT. Subjective and objective measures of sleep duration and quality in major depressive disorder with comorbid hypersomnolence. Sleep. 2015;38:A329-A30.
19. Tonetti L, Filardi M, Plazzi G, Natale V. Advantages of single step over step-by-step screening for sleep disorders. Biological Rhythm Research. 2018;49(4):610-21.
20. Leger D, Gauriau C, Tonetti L, et al. Using actigraphy to assess sleep and wake rhythms of narcolepsy type 1 patients: a comparison with primary insomniacs and healthy controls. Sleep Med. 2018;52:88-91.
21. Chen ZY, Trotti LM, Rye DB. Myotonic dystrophy phenocopies sleep features of idiopathic hypersomnia. Annals of Neurology. 2020;88(SUPPL 25):S229-S30.
22. Lin C, Chin WC, Huang YS, et al. Different circadian rest-active rhythms in Kleine-Levin syndrome: a prospective and case-control study. Sleep. 2021;44(9).
23. Torstensen EW, Pickering L, Kornum BR, Wanscher B, Baandrup L, Jennum PJ. Diagnostic value of actigraphy in hypersomnolence disorders. Sleep Med. 2021;85:1-7.
24. Walia HK, Mehra R. Practical aspects of actigraphy and approaches in clinical and research domains. Handb Clin Neurol. 2019;160:371-379.

25. Cook JD, Plante DT. Wearable Technology as a Tool for Sleep-Wake Estimation in Central Disorders of Hypersomnolence. Current Sleep Medicine Reports. 2019;5(4):193-200.
26. Alakuijala A, Sarkanen T, Jokela T, Partinen M. Accuracy of Actigraphy Compared to Concomitant Ambulatory Polysomnography in Narcolepsy and Other Sleep Disorders. Front Neurol. 2021;12:629709.
27. Liguori C, Fernandes M, Zucconi M, et al. The evolving role of quantitative actigraphy in clinical sleep medicine. Sleep Medicine Reviews. 2023;68(101762).
28. Kretzschmar U, Werth E, Sturzenegger C, et al. Which diagnostic findings in disorders with excessive daytime sleepiness are really helpful? A retrospective study. J Sleep Res. 2016;25(3):307-13.
29. Leger D, Gauriau C, Faraut B, Elbaz M, Sauvet F, Natale V. A study on the optimal length of actigraphic recording in narcolepsy type 1. Clinical Neurophysiology Practice. 2019.
30. Cook JD, Eftekari SC, Leavitt LA, Prairie ML, Plante DT. Optimizing Actigraphic Estimation of Sleep Duration in Suspected Idiopathic Hypersomnia. J Clin Sleep Med. 2019;15(4):597-602.
31. Smith M, Heald J, Carden K. Use of Actigraphy for the Evaluation of Sleep Disorders and Circadian Rhythm Sleep-Wake Disorders: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med 2018;14(7):1209-30.
32. Ancoli-Israel S, Blackwell T, Buenaver L, et al. The SBSM Guide to Actigraphy Monitoring: Clinical and Research Applications. Behavioral Sleep Medicine. 2015;13:S4-S3

INSTITUTO DE **CIÊNCIAS BIOMÉDICAS ABEL SALAZAR**