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# Narcolepsy: Comorbidities, complexities and future directions

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ABSTRACT

Patients with narcolepsy live with a lifelong sleep-wake disorder, impairing their quality of life, productivity, educational and employment outcomes. Clinicians are becoming aware that a significant aspect of the burden of this disease relates to frequent comorbid conditions, including aspects of the patient's emotional, metabolic, sleep and immune health. This review explores the literature describing the comorbidities seen in patients with narcolepsy, to enhance understanding of these often complex presentations. It hopes to encourage a multidisciplinary approach, to collaborate with patients and a broad clinical team, and to maximise clinical and quality of life outcomes, for those living with narcolepsy.


## 1. Introduction

Narcolepsy is a chronic neurological sleep-wake disorder that is characterised by excessive daytime sleepiness and, in narcolepsy type 1 (NT1), cataplexy. Many patients with narcolepsy have difficulties with concentration, memory retention and daytime fatigue [1]. The first symptoms of narcolepsy typically present between the ages of 10–25 years with significant variation in its presentation [2] and delayed diagnosis has been consistently reported in the literature [3,4]. Narcolepsy is diagnosed using overnight polysomnography (PSG), followed by a multiple sleep latency test (MSLT), cerebrospinal fluid hypocretin levels and a range of symptoms-based assessments, applying either the International Classification of Disease (ICD), International Classification of Sleep Disorders (ICSD-3) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria [2,5,6].

A diagnosis of narcolepsy type 1 is confirmed by daily excessive daytime sleepiness for ≥3 months, a mean sleep latency ≤8 min and ≥2 sleep-onset rapid eye movement periods (SOREMP) on the MSLT, the presence of cataplexy and reduced levels (≤110 pg/ml) of the cerebrospinal fluid neuropeptide hypocretin 1 [2]. Narcolepsy type 2 (NT2) is defined by excessive daytime sleepiness and the same MSLT criteria as for NT1, but cataplexy is absent and, if measured, normal hypocretin 1 levels (i.e., >110 pg/ml) support the diagnosis [2]. Idiopathic hypersomnia (IH) is characterised by excessive daytime sleepiness with a mean sleep latency of ≤8 min

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**Abbreviations**

| | |
|---|---|
| ADHD | attention deficit hyperactivity disorder |
| aOR | adjusted odds ratio |
| BMI | body mass index |
| CI | confidence interval |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders – fifth edition |
| ICD-10 | International Classifications of Diseases – 10th revision |
| ICSD-2 | International Classifications of Sleep Disorders - second edition |
| ICSD-3 | International Classifications of Sleep Disorders - third edition |
| IH | idiopathic hypersomnia |
| MSLT | multiple sleep latency test |
| NT1 | narcolepsy type 1 |
| NT2 | narcolepsy type 2 |
| PSG | polysomnography |
| REM | rapid eye movement |
| SOREMP | sleep-onset rapid eye movement period |
| WHO | World Health Organization |

and <2 SOREMP, or a total sleep time of >660 min across a 24 h period [7].

Based on international databases, it is estimated that the global prevalence of narcolepsy ranges from 25 to 50 cases per 100 000 population in Europe, North America and Japan [8]. Since the condition may often go undiagnosed, and detailed registry data is lacking in many countries, the true prevalence of narcolepsy may be higher [9]. Whether diagnosed or undiagnosed, narcolepsy has a profound impact on patients' quality of life, livelihood, income, work productivity and personal safety [1,10]. People with narcolepsy experience significantly higher rates of health-related contact such as hospital admissions, outpatient visits, diagnostic testing, specialist medical visits and medication use [11,12]. Timely, effective and appropriate treatment results in improved clinical outcomes, education and employment opportunities and enhanced quality of life [1]. There are considerable challenges which influence treatment decisions and outcomes. These relate to both the higher incidence of certain comorbid conditions in patients with narcolepsy, and limited pharmacological treatment options, some being either contraindicated or having the potential to exacerbate comorbidities, further decreasing quality of life [13]. In some countries, including those with high quality healthcare systems, accessibility to pharmacological treatments is restricted [9].

Several studies describe the complex associations between narcolepsy, chronic comorbidities and treatment challenges. In a recent review, neuropsychiatric symptoms, such as depression, anxiety, psychosis and cognitive impairment, were demonstrated to be common amongst patients with narcolepsy [14]. This was supported in the meta-analysis, by Li et al. which reported that depression or depressive symptoms were highly prevalent in patients with narcolepsy [15]. Jennum et al. examined the data on autonomic effects of hypocretin deficiency and inferred that NT1 was associated with multiple cardiovascular risk factors, comorbidities and cardiovascular disease [16]. Mohammadi et al. concluded that patients with narcolepsy had a higher prevalence of obesity, diabetes mellitus, hypertension and dyslipidemia compared to healthy controls [17].

These studies highlight the complex and multifaceted burden of comorbidities in patients with narcolepsy. No studies, to date, have collated all the reported comorbidities, across the peer-reviewed literature, to present an overview of the spectrum of comorbid diseases in patients with narcolepsy.

This study represents a systematic review of the literature adopting the ontological, non-hierarchical assertion that patients with narcolepsy could face many and multiple comorbidities. The objective was to review and document the comorbidities, reported as being prevalent in patients with a confirmed diagnosis of narcolepsy. This included all individuals with a confirmed diagnosis of NT1, NT2 and IH, and encompassed all genders and age groups, globally.

## 2. Methods

All steps in the review protocol were conducted in accordance with the preferred reporting items for systematic review and meta-analysis statement [18], commencing with articulating the review questions, defining the search strategy, developing the selection criteria and synthesising the results.

### 2.1. Search strategy

The search strategy was developed collaboratively by the co-authors. The databases PUBMED, SCOPUS, PsychINFO, Web of Science, Embase, CINAHL, International Prospective Register of Systematic Reviews, and The Cochrane Database of Systematic Reviews, were searched, up to and including 5th April 2021, using the combination of two concepts, corresponding subject headings and key terms as shown in supplementary text 1 and Table S1. Search limits were set to include all peer-reviewed journal articles from 1st January 2000, all languages, all methodologies, and involving human participants. The article references were uploaded into the bibliographical management software EndNote® and duplicates were deleted. The remaining references were exported to Rayyan®; a web and mobile app for processing systematic reviews.

### 2.2. Screening process

Two levels of screening were undertaken. At the first level, two reviewers, SG and EH, working independently, screened all the articles, by titles and abstracts, to extract eligible studies that reported on the incidence and/or prevalence of chronic comorbidities in patients with a confirmed diagnosis of narcolepsy, NT1, NT2 and IH. All terminologies that referred to an individual with narcolepsy having a chronic and/or multimorbidity condition were accepted, which included prevalence rates, incidence rates and odds ratios. Studies were excluded if they: 1) did not reflect the review objective; 2) reported data from animal or in vivo studies; 3) were case studies or case reports involving less than 20 patients with narcolepsy; 4) did not contain original research; 5) were expert opinions, book chapters, letters or conference abstracts; or 6) an English translation of the articles was not available. At the second level of screening, full texts of all the titles marked as "included" and "maybe" in Rayyan® were obtained and read and a final list of studies, for the review, was created. Reference lists of the most relevant studies were also screened.

### 2.3. Data extraction

The results were synthesised using Microsoft Excel®. For each included study, two authors independently extracted the following data: author; year of publication; country; study design number of cases with narcolepsy (NT1, NT2, IH where identified) vs. control; gender distribution (% males); type and prevalence of comorbidity (%); diagnostic method to confirm narcolepsy and other chronic

conditions; and age groups (adults and under 18 years). If the prevalence/incidence of comorbidity, in patients with narcolepsy vs. control, was statistically significant, the study reported the prevalence as % with associated p-values and excluded conditions that were not statistically significant. Where available, the odds ratio (adjusted or crude), with the corresponding 95% confidence intervals (CI), were also extracted. If there were multiple publications from the same cohort, repetitive comorbidity data was not included. All inter-reviewer differences in the data extraction, reporting and synthesis of results were resolved through discussion between the authors.

### 2.4. Synthesis and reporting of results

There was a wide range in reporting styles of narcolepsy subtype diagnosis NT1, NT2 and IH in the studies, possibly in part because the sub-type terminology has evolved over time. For consistency, if the study referred to narcolepsy patients with cataplexy, the category of NT1 was allocated to it, as per the ICSD-3 diagnostic criteria [2]. If the study referred to their population as narcolepsy without cataplexy, the category of NT2 was allocated. In studies where the authors had not clarified nor distinguished the study sample, as having NT1, NT2 or IH, either due to diagnostic and/or methodological limitations, the category of 'narcolepsy [type unspecified]' was assigned.

Due to the high level of heterogeneity, either statistically or in terms of methodology, in the reporting of comorbidity outcomes, the participants and the settings - a sub-group analysis or meta-analysis was not conducted. Subsequently, the study findings were categorised by study methodology, age groups (adults, and under 18 years of age) and World Health Organization (WHO) regions, these being Africa, Americas, Southeast Asia, Europe, Eastern Mediterranean, and Western Pacific.

While most authors reported crude prevalence and/or odds ratio of a singular comorbidity, in patients with narcolepsy (and controls), some authors reported diagnosis-related grouped data. They either grouped their data into WHO disease groups, or they used multilevel Clinical Classification Software for ICD data. To explore the complex burden of comorbidities, in patients of all ages with narcolepsy, one-way frequency tables were developed by counting every instance a particular chronic comorbidity was reported by the author. By team consensus, the data in the one-way frequency tables were thematically organised into broad medical categories and sub-categories. The categories, sub-categories and frequency counts were illustrated in an orbital tree chart. In situations where authors had grouped their data into the WHO or ICD multilevel classification codes, they were included in the relevant medical category, or sub-category, and labelled them as 'multiple categories'.

## 3. Results

### 3.1. Study selection

The study selection process is summarised in Fig. 1. The literature search retrieved 2938 results and 347 duplicate references were removed. After applying the two levels of screening to the remaining 2591 records, 29 studies were considered relevant to the review objectives and one study was manually added through reference chaining [19].

### 3.2. Characteristics of included studies

The characteristics of the 30 observational studies, included in the review, are provided in Tables 1a and 1b. The studies dated from

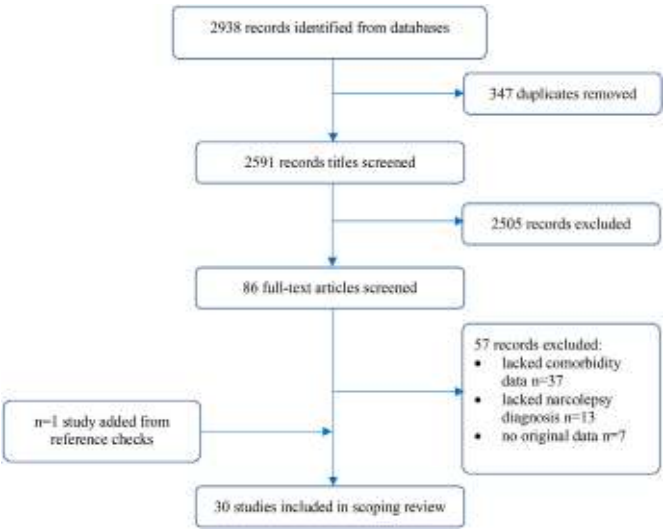


**Fig. 1.** Flowchart of the study selection process
See attached.pdf file titled: Fig. 1Flowchart of the study selection process.

2003 to 2020 and designs ranged from longitudinal cross-sectional studies [19–23], to prospective [24–28] and retrospective case-control studies [3,10–12,29–44]. In the cross-sectional and prospective cohort studies, patients with narcolepsy were recruited from either hospital and/or private sleep specialist centres [19–28] or with the help of narcolepsy patient organisations [21]. In the retrospective case-control studies, they were recruited from medical and sleep specialist centres [30,33–36,40,42], health insurance databases [3,12,31,32,41,43,44] or national registries [10,11,29,37–39]. Most case-control studies used a nested method, where authors recruited the control group from either the general population, health insurance - or other medical and hospital - databases and matched them for age and gender to narcolepsy cases. Twenty-five of the studies reported co-occurrence of chronic conditions, with any type of narcolepsy in adults aged 18 years and above [3,10,11,21–30,32–37,39–44], while only 4 studies focused on children and adolescents under age 18 years [12,19,20,38]. Only one study, which was a retrospective nested case-control study reported on comorbidities in both age groups [31].

Within the WHO regions, two studies were of multi-centre design [20,33]. In 2009, Dauvilliers et al. reported on a case-control study which included 67 narcolepsy patients from France, Germany, Spain and the UK, and 67 age-and sex-matched controls from France and the UK [22]. Aydinoz et al. also conducted a multi-centre design by retrospectively reviewing 468 patient charts from three major paediatric sleep centres in France, Taiwan and the USA [20]. The remaining studies were single-site, of which seven were conducted in the Americas [3,10–12,26,32,42]; 14 in Europe [21–23,27–30,34–40]; five in the Western Pacific region [19,31,41,43,44]; and two in the Eastern Mediterranean region [24,25], as shown in Fig. 2. No studies were conducted in Africa or Southeast Asia or Australia.

### 3.3. Diagnostic criteria for narcolepsy

The most common diagnostic criteria used, to confirm diagnosis of narcolepsy in the included studies, was either the ICSD criteria (n = 18) or the ICD criteria (n = 11). Self-reporting of a narcolepsy diagnosis was another method for subject selection. In the retrospective case-matched control study conducted by Flores et al., all the 437 subjects self-reported in the US National Health and

**Table 1a**
Characteristics of the n = 25 case control studies (for adults and under 18 years of age).

| Age Group | Authors, reference number | Narcolepsy n (% male); subtype n | Controls n (% male) | Comorbidity assessed | Prevalence narcolepsy % vs control % | p value | Odds ratio [95% CI] |
|---|---|---|---|---|---|---|---|
| Adults | Alasim et al., 2020 [24], | 74 (81.0%) NT1 = 44, NT2 = 30 | 265 (NR) | Psychiatric disorders | 45.0% vs 16.0% | p < 0.001 | |
| | | | | Major depressive disorders | 30.0% vs 9.0% | p < 0.001 | |
| | | | | Suicidality | 9.5% vs 0.4% | p = 0.002 | |
| | | | | Generalised anxiety disorder | 7.0% vs 1.0% | p = 0.008 | |
| | Alomar et al., 2019 [25], | 80 (84.0%) NT1 = 56, NT2 = 24 | 222 (71.2%) | Autoimmune disorder | 21.4% vs 12.2% | p < 0.05 | |
| | | | | Allergic disorders | 55.4% vs 27.5% | p < 0.05 | |
| | Barateau et al., 2017 [29], | 450 (39.6%) NT1 = 206, NT2 = 106, IH = 138 | 700 (30.1%) | Autoimmune disorder | 6.6% vs 3.4% | NR | |
| | | | | Autoinflammatory disease | 4.0% vs 1.4% | NR | |
| | | | | Allergic disorders | 6.9% vs 3.7% | NR | |
| | Black et al., 2017 [11], | 9312 (40.8%) NT [type unspecified] | 46559 (40.8%) | Anxiety disorders | 25.1% vs 11.9% | p < 0.001 | 2.5 [2.4–2.7] |
| | | | | Diabetes | 28.3% vs 19.0% | p < 0.001 | 1.8 [1.7–1.8] |
| | | | | Headache/migraine | 38.1% vs 18.1% | p < 0.001 | 2.9 [2.8–3.1] |
| | | | | Mood disorders | 37.9% vs 13.8% | p < 0.001 | 4.0 [3.8–4.2] |
| | | | | Obesity | 17.3% vs 8.4% | p < 0.001 | 2.3 [2.2–2.5] |
| | | | | Neoplasms | 55.7% vs 45.4% | p < 0.0001 | 1.6 [1.5–1.6] |
| | | | | Endocrine, nutritional, metabolic and immunity disorders | 81.7% vs 63.8% | p < 0.0001 | 2.8 [2.6–2.9] |
| | | | | Mental illness | 62.3% vs 31.2% | p < 0.0001 | 3.8 [3.6–4.0] |
| | | | | Nervous system | 87.6% vs 66.8% | p < 0.0001 | 3.7 [3.4–3.9] |
| | | | | Circulatory system | 80.9% vs 64.3% | p < 0.0001 | 2.6 [2.5–2.8] |
| | | | | Respiratory system | 90.9% vs 73.5% | p < 0.0001 | 3.7 [3.4–3.9] |
| | | | | Digestive system | 73.9% vs 52.9% | p < 0.0001 | 2.7 [2.5–2.8] |
| | | | | Genitourinary system | 77.5% vs 64.3% | p < 0.0001 | 2.2 [2.1–2.3] |
| | | | | Musculoskeletal | 89.5% vs 72.0% | p < 0.0001 | 3.5 [3.2–3.7] |
| | | | | Skin and subcutaneous tissue | 63.7% vs 49.3% | p < 0.0001 | 1.8 [1.8–1.9] |
| | Byrne et al., 2019 [30], | 20 (37.3%) NT [type unspecified] | 200 (37.3%) | Major depressive disorders | 0.03% vs 0.02% | NR | 2.0 [1.3–3.2] |
| | Chen et al., 2020 [31], | N = 478 (12 yr+) (59.2%) NT [type unspecified] | N = 1912 (59.2%) | Anxiety disorders | 6.8% vs 3.2% | p < 0.001 | aOR 2.7 [1.7, 4.3] |
| | | | | Ischemic stroke | 4.6% vs 2.5.% | p = 0.022 | |
| | | | | Obesity | 1.3% vs 0.2% | p = 0.003 | |
| | | | | Epilepsy | 2.9% vs 0.9% | p = 0.003 | |
| | Cohen et al., 2018 [32], | 68 (41.2%) NT1 = 28, NT2 = 40 | 272 (41.2%) | Psychiatric disorders | 45.6% vs 17.3% | p < 0.0001 | 4.7 [2.4–9.0] |
| | | | | Anxiety disorder | 20.6% vs 5.9% | p = 0.003 | 4.5 [2.0–10.4] |
| | | | | Thyroid disease | 13.2% vs 5.1% | p = 0.02 | 3.1 [1.2–7.9] |
| | | | | Hypertension | 20.6% vs 10.3% | p = 0.014 | 2.7 [1.2–5.9] |
| | | | | Hyperlipidaemia | 17.6% vs 9.6% | p = 0.039 | 2.5 [1.1–5.9] |
| | | | | Peripheral neuropathy | 4.4% vs 0.4% | p = 0.037 | 11.2 [0.2 –108.1] |
| | | | | Diabetes/glucose intolerance | 14.7% vs 6.6% | p = 0.039 | 2.4 [1.1–5.5] |
| | | | | Chronic low back pain | 25.0% vs 6.3% | p < 0.0001 | 5.5 [2.5–12.1] |
| | | | | Depression | 39.7% vs 14.7% | p < 0.0001 | 4.9 [2.5–9.7] |
| | | | | Obesity | 20.3% vs 9.9% | p = 0.021 | 2.3 [1.1–4.6] |
| | Cremaschi et al., 2019 [26], | 66 (30.0%) NT1 = 33, NT2 = 33 | 33 (30.3%) | Pain | 80.3% vs 21.2% | p < 0.001 | |
| | Dauvilliers et al., 2009 [22], | 67 (46.3%) NT [type unspecified] | 67 (46.3%) | Pain | 32.8% vs 17.9% | p < 0.001 | |
| | | | | Depression/mood disorder | 61.2% vs 13.5% | p < 0.001 | |
| | Evers et al., 2003 [34], | 96 (NR) NT [type unspecified] | 96 (NR) | Migraine | 21.9% vs 19.8% | NR | |
| | Feketeova et al., 2020 [35], | 61 (57.0%) NTI = 51, NT2 = 11 | 244 (57.0%) | Dyslipidaemia | 18.0% vs 19.0% | p = 0.043 | 2.2 [1.0–4.9] |
| | | | | Mental disorders | 20.0% vs 10.0% | p = 0.044 | 2.2 [1.0–4.6] |
| | Flores et al., 2016 [10], | 437 (49.9%) NT [type unspecified] | 874 (47.0%) | Depression | 48.3% vs 25.9% | p < 0.001 | |
| | | | | Bipolar disorder | 14.2% vs 4.6% | p < 0.001 | |
| | | | | Anxiety disorders | 51.0% vs 22.2% | p < 0.001 | |
| | | | | Post traumatic stress disorder | 14.9% vs 3.5% | p < 0.001 | |
| | | | | Panic disorder | 16.0% vs 4.1% | p < 0.001 | |
| | | | | Phobia disorder | 10.1% vs 1.7% | p < 0.001 | |
| | | | | Obsessive compulsive disorder | 12.8% vs 3.3% | p < 0.001 | |
| | Fortuyn et al., 2010 [36], | 60 (47.0%) | 120 (47.0%) | Anxiety disorders | 35.0% vs 3.0% | NR | 15.6 [3.6 –68.6] |
| | | | | Mood disorders | 13.0% vs 5.0% | NR | 2.9 [0.7–12.5] |
| | Jennum et al., 2013 [37], | 757 (45.6%) NT [type unspecified] | 3013 (45.6%) | Diabetes | NR | NR | 2.4 [1.2–4.7] |
| | | | | Obesity | NR | NR | 13.4 [3.1 –57.6] |
| | | | | Chronic obstructive pulmonary disease | NR | NR | 2.8 [1.4–5.8] |
| | | | | Lower back pain | NR | NR | 2.5 [1.4–4.2] |
| | | | | Arthritis | NR | NR | 2.5 [1.3–4.8] |
| | | | | Nervous system | NR | NR | 3.5 [1.9–6.5] |
| | Jennum et al., 2017 [39], | 1513 (45.0%) NT [type unspecified] | 6069 (44.9%) | Endocrine, nutritional and metabolic diseases | 13.8% vs 6.0% | p < 0.001 | 2.6 [2.0–3.3] |
| | | | | Mental and psychiatric disorders | 7.2% vs 3.4% | p < 0.001 | 2.2 [1.6–3.1] |
| | | | | Nervous system disorders | 57.9% vs 3.8% | p < 0.001 | 37.0 [27.3 –50.2] |

**Table 1a** (*continued*)

| Age Group | Authors, reference number | Narcolepsy n (% male); subtype n | Controls n (% male) | Comorbidity assessed | Prevalence narcolepsy % vs control % | p value | Odds ratio [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | Circulatory/cardiovascular diseases | 12.1% vs 6.0% | p < 0.001 | 2.3 [1.6–3.1] |
| | | | | Respiratory diseases | 9.2% vs 3.9% | p < 0.001 | 2.5 [1.9–3.4] |
| | | | | Gastrointestinal diseases | 14.1% vs 6.9% | p < 0.001 | 2.2 [1.8–2.9] |
| | | | | Skin and subcutaneous tissue diseases | 5.6% vs 2.6% | p < 0.001 | 2.2 [1.5–3.2] |
| | | | | Musculoskeletal system and connective tissue diseases | 20.3% vs 11.7% | p < 0.001 | 1.9 [1.6–2.4] |
| | | | | Genitourinary system | 12.5% vs 7.9% | p < 0.001 | 1.7 [1.3–2.2] |
| | Kok et al., 2003 [40], | 171 (52.0%) NT1 = 138, IH = 33 | 10696 (43.0%) | Obesity | 33.0% vs 12.5% | p < 0.05 | |
| | | | | Overweight | 43.0% vs 36.0% | p < 0.05 | |
| | Kovalska et al., 2016 [27], | 42 (42.9%) NT [type unspecified] | 46 (41.3%) | Hypertension | 78.6% vs 56.6% | p = 0.041 | |
| | | | | Diabetes type 2 | 35.7% vs 15.2% | p = 0.047 | |
| | Lee et al., 2017 [41], | 258 (54.3%) NT [type unspecified] | 2580 (56.5%) | ADHD | 8.8% vs 0.9% | p < 0.001 | |
| | | | | Obesity | 3.1% vs 1.5% | p < 0.05 | |
| | | | | Epilepsy | 8.9% vs 1.5% | p < 0.0001 | |
| | | | | Intellectual disability | 2.3% vs 0.7% | p < 0.01 | |
| | | | | Depressive disorder (any) | 32.7% vs 6.3% | p < 0.001 | aOR 6.8 [4.9–9.4] |
| | | | | Dysthymic disorder | 24.8% vs 4.4% | p < 0.001 | aOR 6.6 [4.6–9.6] |
| | | | | Major depressive disorder | 10.9% vs 1.6% | p < 0.001 | aOR 6.8 [4.1–11.5] |
| | Ohayon et al., 2013 [42], | 320 (34.1%) NT [type unspecified] | 1464 (32.3%) | Hypercholesterolemia | 10.3% vs 6.8% | p < 0.05 | aOR 1.0 [1.1–2.2] |
| | | | | Heart diseases | 5.9% vs 2.9% | p < 0.01 | aOR 2.1 [1.2–3.5] |
| | | | | Upper respiratory tract disease | 27.5% vs 10.9% | p < 0.001 | aOR 2.5 [2.0–3.2] |
| | | | | Digestive system diseases | 16.3% vs 5.0% | p < 0.001 | aOR 3.3 [2.4–4.6] |
| | | | | Hypertension | 19.2% vs 14.7% | p < 0.05 | aOR 1.3 [1.0–1.7] |
| | | | | Major depressive disorder | 17.1% vs 6.4% | p < 0.001 | aOR 2.7 [2.0–3.7] |
| | | | | Bipolar disorders | 8.5% vs 1.9% | p < 0.001 | aOR 4.6 [2.7–7.6] |
| | | | | Post traumatic stress disorder | 11.3% vs 5.3% | p < 0.001 | aOR 2.1 [1.5–3.1] |
| | | | | Agoraphobia | 8.5% vs 1.3% | p < 0.001 | aOR 6.5 [3.7–11.4] |
| | | | | Panic disorder | 12.5% vs 3.9% | p < 0.001 | aOR 3.2 [2.2–4.7] |
| | | | | Social anxiety disorder | 21.1% vs 8.7% | p < 0.001 | aOR 2.4 [1.9–3.2] |
| | | | | Obsessive compulsive disorder | 3.7% vs 1.0% | p < 0.001 | aOR 3.8 [1.8–8.1] |
| | | | | Generalised anxiety disorder | 5.5% vs 1.7% | p < 0.001 | aOR 3.3 [1.8–6.0] |
| | | | | Simple phobia | 5.2% vs 1.3% | p < 0.001 | aOR 4.1 [2.2–7.9] |
| | | | | ADHD in childhood | 5.4% vs 2.5% | p < 0.01 | aOR 2.1 [1.2–3.9] |
| | Ruoff et al., 2017 [3], | 9312 (41.0%) NT [type unspecified] | 46559 (41.0%) | Adjustment disorders | 11.2% vs 5.4% | p < 0.0001 | 2.3 [2.1–2.4] |
| | | | | Anxiety disorders | 25.1% vs 11.9% | p < 0.0001 | 2.5 [2.4–2.7] |
| | | | | Attention deficit, conduct and disruptive behaviour disorders | 7.3% vs 1.3% | p < 0.0001 | 6.2 [5.6–7.0] |
| | | | | Cognitive disorders (delirium, dementia, amnestic and other) | 4.6% vs 1.5% | p < 0.0001 | 3.8 [3.3–4.3] |
| | | | | Mood disorders | 37.9% vs 13.8% | p < 0.0001 | 4.0 [3.8–4.2] |
| | | | | Bipolar disorders | 8.3% vs 2.1% | p < 0.0001 | 4.4 [3.9–4.8] |
| | | | | Depressive disorders | 35.8% vs 13.0% | p < 0.0001 | 3.9 [3.7–4.1] |
| | | | | Personality disorders | 1.1% vs 0.2% | p < 0.0001 | 5.8 [4.0–7.7] |
| | | | | Schizophrenia and other psychotic disorders | 3.4% vs 0.9% | p < 0.0001 | 3.8 [3.3–4.4] |
| | | | | Alcohol-related disorders | 1.9% vs 1.3% | p < 0.00021 | 1.4 [1.2–1.7] |
| | | | | Substance-related disorders | 4.0% vs 1.2% | p < 0.0001 | 3.5 [3.0–4.0] |
| | Sonka et al., 2010 [28], | 101 (47.0%) NT1 = 82, NT2 = 9 | 215 (47.9%) | Obesity (BMI >30) | 39.0% (NT1), 13.8% (NT2) vs 13.0% | p < 0.001 | |
| | Tseng et al., 2015 [43], | 2833 (54.9%) NT [type unspecified] | 15913 (53.7%) | Cancer | SIR = 1.32 [1.0–1.7] | p = 0.0248 | |
| | Yeh et al., 2020 [44], | 258 (54.3%) NT [type unspecified] | 2580 (56.5%) | Autism spectrum disorder | 2.3% vs 0.2% | p < 0.001 | |
| Under 18 yrs | Carls et al., 2020 [12], | 1427 (51.9%) NT1 = 515, NT2 = 914 | 4281 (51.9%) | Endocrine, nutritional and metabolic diseases | 27.5% vs. 5.2% | NR | |

(*continued on next page*)

**Table 1a** (*continued*)

| Age Group | Authors, reference number | Narcolepsy n (% male); subtype n | Controls n (% male) | Comorbidity assessed | Prevalence narcolepsy % vs control % | p value | Odds ratio [95% CI] |
|---|---|---|---|---|---|---|---|
| | | | | Mood disorders | 55.6% vs 13.9% | NR | |
| | | | | Circulatory system | 11.4% vs 2.1% | NR | |
| | | | | Nervous system disorders | 70.8% vs 18.9% | NR | |
| | | | | Respiratory | 57.2% vs 32.2% | NR | |
| | | | | Musculoskeletal | 38.5% vs 18.7% | NR | |
| | | | | Skin and subcutaneous tissue disorder | 33.3% vs 17.6% | NR | |
| | Chen et al., 2020 [31], | 65 (NR) NT [type unspecified]) | 260 (NR) | Anxiety disorders | 9.2% vs 0.4% | $p < 0.001$ | aOR 25.9 [15.2−42.9] |
| | Jennum et al., 2017 [38], | 243 (52.7%) NT [type unspecified] | 970 (52.8%) | Endocrine, nutritional and metabolic diseases | 8.2% vs 2.5% | $p = 0.001$ | 3.8 [1.7−8.4] |
| | | | | Mental and psychiatric disorders | 11.4% vs 2.1% | $p < 0.001$ | 5.8 [2.8−12.1] |
| | | | | Nervous system disorders | 65.2% vs 1.3% | $p < 0.001$ | 198.6 [49.0−804.9] |
| | | | | Musculoskeletal system and connective tissue diseases | 14.6% vs 7.6% | $p = 0.007$ | 2.1 [1.2−3.5] |
| | | | | Neoplasms | 3.2% vs 0.5% | $p = 0.009$ | 6.7 [1.6−27.9] |

ADHD, attention deficit hyperactive disorder; aOR, adjusted odds ratio; BMI, body mass index; IH, idiopathic hypersomnia; NR, not reported; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation; SIR, standardised incidence ratio.

Wellness Survey that their physician had diagnosed them with narcolepsy [10].

While many of the authors did not, or could not, differentiate the narcolepsy sub-types (NT1, NT2 and/or IH), two authors identified that they had specifically recruited individuals with a confirmed diagnosis of NT1 in their studies [19,36]. Fortuyn et al. recruited 60 patients with narcolepsy with cataplexy from the outpatient department of a sleep and neurological centre in the Netherlands [36], while Huang et al. recruited 102 children with a confirmed diagnosed of narcolepsy with cataplexy from a paediatric sleep centre in Taiwan [19]. Two authors included patients with a diagnosis of IH in their studies [22,40]. The 2009 study published by Dauvilliers et al. included NT1, NT2 and IH in their analysis as per ICSD-2 criteria [22]. Kok et al. described the prevalence of obesity among patients with a confirmed diagnosis on NT1 and IH [40].

### 3.4. Comorbidities in people with narcolepsy

To determine the type and prevalence of chronic conditions in their study samples, the authors conducted a combination of patient surveys, semi-structured interviews, medical examinations and reviews of medical notes for patients with narcolepsy in cross-sectional studies, and with both the patients with narcolepsy and corresponding age- and sex-matched controls in prospective cohort studies [19−29,33−36,40]. In the retrospective case-control studies, the authors linked and analysed narcolepsy and chronic disease diagnosis codes in patients with narcolepsy and in the control population [11,12,32,38,39,42,45]. In one of the largest retrospective case-control studies, Black et al. reviewed a medical claims database for the narcolepsy ICD diagnosis codes and compared narcolepsy and control subjects for frequency of co-morbid conditions as identified by multilevel clinical classification ICD codes [11].

There was wide variation in the reporting of comorbidities between the studies. Most authors reported crude prevalence figures of proportions of those with narcolepsy (and controls) with other diagnosed chronic condition(s). However, some grouped the chronic conditions into either WHO disease groups [38,39] or multilevel ICD classifications [11,12,42]. In addition, three studies reported on further exploratory analysis in addition to the crude prevalence rates. In these three studies, the authors conducted logistic regression analysis to explore predictors of age, gender and/or comorbidity types, in patients with narcolepsy, and reported their results as adjusted odds ratio (aOR) [31,41,42]. Chen et al. conducted a multivariate logistic regression and demonstrated a higher incidence of previously diagnosed anxiety disorders in patients with narcolepsy aged 12−17 years when compared to the adult group, and in female patients (aOR: 25.9; 95% CI: 15.194−42.896; aOR: 3.6; 95% CI: 1.818−7.062), respectively [31]. Lee et al. highlighted that female patients with narcolepsy, an older recruitment age and subjects diagnosed with attention deficit hyperactivity disorder (ADHD) were factors collectively associated with comorbidity of any depressive or dysthymic disorder [41]. Ohayon et al. reported that hypercholesterolemia (aOR: 1.93; 95% CI: 1.09−3.43) and heart diseases (aOR: 2.90; 95% CI: 1.38−6.07) were significantly more common in men with narcolepsy while, compared to the matched general population, diseases of the urinary system (aOR: 4.04; 95% CI: 1.48−11.01) were more common among women with narcolepsy [42].

**Table 1b**
Characteristics of the n = 5 cross-sectional studies (for adults and under 18 years of age).

| Age Group | Authors, reference number | Narcolepsy n (% male); Narcolepsy subtype n | Comorbidity assessed | Prevalence narcolepsy % |
|---|---|---|---|---|
| Adults | Dahmen et al., 2003 [21], | 100 (46.0%) NT [type unspecified] | Migraine | 37.0% |
| | Dauvilliers et al., 2009 [22], | 517 (47.6%) NT1 = 424, NT2 = 68, IH = 25 | Depressive symptoms | 55.1% |
| | Martinez-Orozco et al., 2014 [23], | 156 (NR) NT [type unspecified] | Autoimmune disorder | 16.6% |
| | | | Allergic disorders | 10.3% |
| Under 18 yrs | Aydinoz et al., 2015 [20], | 468 (55.5%) NT1 = 275, NT2 = 193 | Asthma | 11.1% |
| | | | Allergic rhinitis | 22.7% |
| | Huang et al., 2014 [19], | 102 (50.0%) NT1 = 102 | Schizophrenia | 9.8% |

IH, idiopathic hypersomnia; NT1, narcolepsy type 1; NT2, narcolepsy type 2.

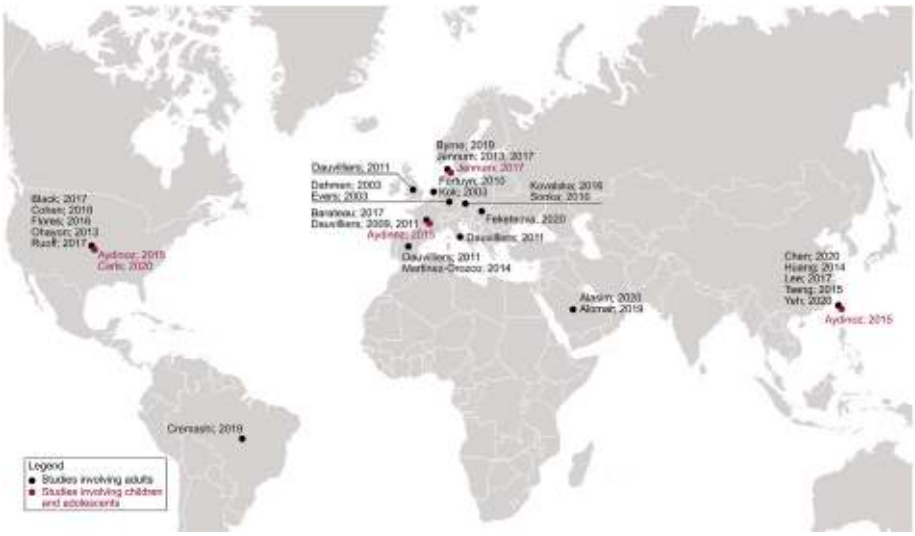


**Fig. 2.** Global distribution of patients with narcolepsy included in this review. See Table 1 for all the references.
See attached.eps file title: Fig. 2 Global distribution of patients with narcolepsy included in this review.

A total of 141 instances of any identified comorbidities were thematically organised into nine broad categories and 34 sub-categories (Fig. 3). Through this exercise, the results showed that the largest category of chronic conditions, in patients with narcolepsy, was mental and behavioural conditions (56/141). Within this subpopulation, the most frequent sub-categories were mood (20/56) and anxiety disorders (17/56). The mood disorder sub-category included five specific conditions: adjustment disorder, bipolar disorders, depressive disorders, dysthymic disorders, and suicidality. Anxiety disorders, obsessive-compulsive disorder, panic disorder and phobia disorder were grouped to form the sub-category of anxiety disorders. The second largest comorbidity category, reported in people with narcolepsy, was endocrine, nutritional, and metabolic conditions (21/141); within this category, obesity (9/21) and diabetes (4/21) were the most frequently reported. Other instances of reported comorbidities were grouped into categories related to the nervous system (10/141); sleep-wake disorders other than narcolepsy (9/141); musculoskeletal (9/141); immune disorders (9/141); circulatory (8/141) and respiratory (7/141) conditions.

### 3.5. Difference in prevalence of comorbidities by narcolepsy subtype NT1, NT2 and IH

Eleven of the 30 reviewed studies included a mix of narcolepsy NT1, NT2 and IH population subtypes. Of these, only six reported statistically significant variations in prevalence of comorbidities by sub-type [12,20,26,28,29,40], as highlighted in Table 2. Multiple authors focussed on differentials within narcolepsy subtypes of two key comorbidities: 1) obesity, and 2) immune dysregulation. In the category of obesity, all four authors reported statistically significant ($p > 0.00.5$) higher body mass index (BMI) in narcolepsy patients with cataplexy (NT1) compared to patients without cataplexy (NT2 and IH) [12,20,28,40]. In the category of immune dysregulation, Aydinoz et al. and Carls et al. studied both children and adolescents with narcolepsy and found that the frequency of immune disorders and allergic conditions, which included asthma and allergic rhinitis, were significantly higher ($p < 0.05$) in NT2, compared with NT1 patients [12,20]. Barateau et al. conducted their study across all ages and demonstrated that the frequency of auto-immune disease was higher in adults with NT2, whereas allergies and auto-inflammatory disorders were common in adults with IH [29].

## 4. Discussion

This is the first systematic review to describe the burden of comorbidities experienced by patients with a diagnosis of narcolepsy. The comorbidities extend across multiple organ systems, including mental and behavioural conditions, endocrine, nutritional and metabolic conditions, circulatory, musculoskeletal, respiratory, nervous system, and immune system, amongst others. The most frequently reported co-morbidities were mood disorders and anxiety, followed by obesity and metabolic disorders. Identifying and improving awareness of comorbidities associated with narcolepsy is important to facilitate early diagnosis, as well as to offer appropriate management and preventative strategies in this cohort of patients.

Mental and behavioural conditions were commonly comorbid with narcolepsy, across all age groups in the reviewed studies, with anxiety most common in younger individuals and depression more notable in female patients diagnosed with narcolepsy at an older age [31]. Whilst hypersomnolence is a key component of narcolepsy, it may also be a concurrent feature in a range of mental and behavioural conditions, including major depression [46]. These confounding features result in challenges when making a diagnosis of narcolepsy. The withdrawal of REM-suppressing antidepressants, prior to an MSLT, may not be possible, confounding the ability to detect SOREMPs on the MSLT. In addition, hypersomnia associated with a psychiatric disorder is a distinct diagnosis as per the ICSD-3. Narcolepsy can have a major impact on quality of life and mood and a delay in diagnosis can further compound the situation for patients and their support network [47]. Therefore, a multidisciplinary approach to diagnosis and management of narcolepsy is needed to overcome these challenges [48].

Obesity and metabolic disorders, including diabetes and dyslipidaemia, were also more commonly reported comorbidities. There is a growing body to evidence showing that both children and adults with NT1 are more likely to be obese when compared to normal populations and patients with NT2 and IH [12,20,28,40]. Many researchers have inferred that alteration of hypocretin may impact food-seeking behaviour and appetite control [17], making it

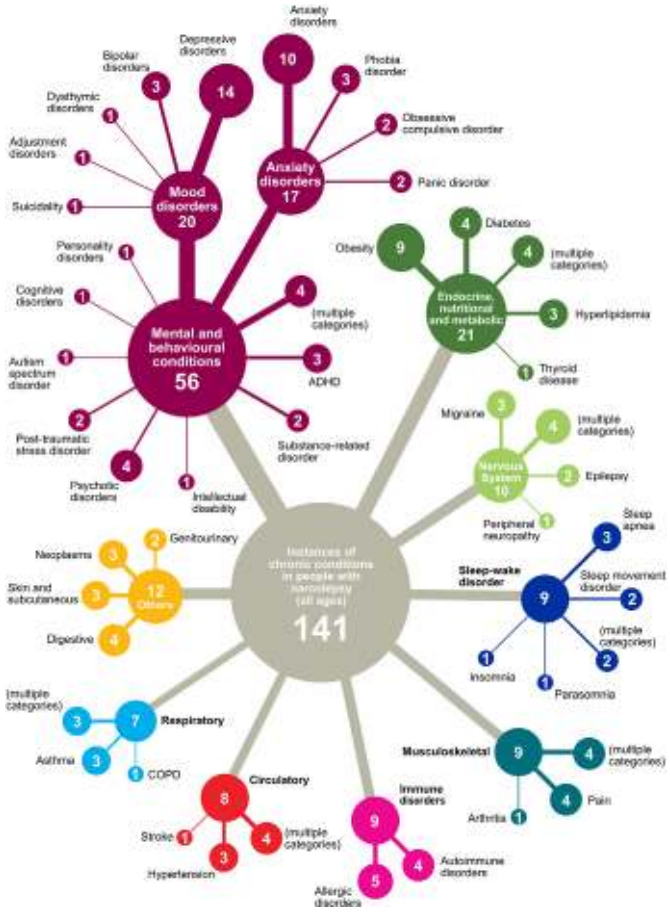


**Fig. 3.** Orbital tree of instances of chronic comorbidities in narcolepsy
See attached.eps file titled Fig. 3 Orbital tree of instances of chronic comorbidities in narcolepsy
Abbreviations: ADHD, attention deficit hyperactive disorder; COPD, chronic obstructive pulmonary disease
*The terminology "multiple categories" refers to cases where the authors had grouped their data into the WHO or ICD multilevel classification codes.

was not surprising that obesity, diabetes, hypertension and hyperlipidaemia were also identified as comorbidities. While recent research demonstrates no differences in fat mass, resting metabolic rate or central visceral adiposity, in narcolepsy versus matched controls, the long-term metabolic impact of obesity, in this population, needs to be further investigated [49,50]. In addition to obesity, patients with narcolepsy may also have increased overall risk for heart disease when compared to matched controls, possibly due to non-dipping blood pressure and REM sleep dysregulation [51]. In a population of 50 drug free narcolepsy patients, a high proportion of nocturnal non-dippers were observed with 24-h ambulatory blood pressure monitoring – a recognised adverse cardiovascular indicator - and those with narcolepsy were also noted to have higher rates of hyperlipidaemia and smoking [51]. Improved understanding of the pathophysiology of diabetes and obesity in narcolepsy may also help tailor more targeted future treatments, including hypocretin receptor antagonists [52]. Treatment of narcolepsy, with sodium oxybate, was shown to contribute to weight loss in nine hypocretin deficient patients with NT1, in addition to improving insulin sensitivity, in a hyperinsulinemic-euglycemic clamp study [53]. Regular and ongoing cardiometabolic assessments, of patients with narcolepsy, may be necessary, although longer term studies will be instructive in guiding future standards of care and practice parameters.

The presence of other diseases, including concurrent sleep, neurological, musculoskeletal and immune disorders, also raise the importance of multi-disciplinary consultation and awareness of narcolepsy. Immune-based disorders, including allergies, were more prevalent in patients with NT2 and IH, compared to NT1 [25,29], which, in itself, is described as an immune disorder. Alomar et al. and Barateau et al. concur that these findings may be due to the activation of the immune system and autoimmune process in NT2, and concluded that further research is required [25,29]. Large co-occurrence rates of sleep movement disorders, such as periodic limb movement and restless leg syndrome, and musculoskeletal issues, such as chronic pain with narcolepsy, were also identified [26,54].

There were several limitations in this review. A substantial number of studies were retrospective or longitudinal analyses of medical records, and the individual authors did not, or could not, imply causality and temporal sequencing, as per the Bradford Hill criteria [55]. It may be possible that instances of mental and behavioural conditions, reported in these studies, were either true comorbidities or misdiagnoses. Secondly, two of the review studies retrospectively analysed the same medical claims database in the

**Table 2**
Difference in prevalence/incidence of comorbidities in NT1 vs. NT2 vs. IH

| Authors, reference number | Narcolepsy cases | Comorbidity assessed | NT1 n (%) | NT2 n (%) | IH n (%) | p value |
|---|---|---|---|---|---|---|
| Aydinoz et al., 2015 [20] | NT1 n = 275 | BMI | **24.7 (SD=0.9)** | 21.3 (SD = 0.7) | NR | p < 0.01 |
| | NT2 n = 193 | Asthma | 13 (4.7%) | **39 (20.2%)** | NR | p < 0.0001 |
| | | Allergic rhinitis | 37 (13.5%) | **68 (35.2%)** | NR | p < 0.0001 |
| Barateau et al., 2017 [29] | NT1 n = 206 | Autoimmune disease | 10 (4.9%) | **14 (13.2%)** | 6 (4.3%) | p = 0.01 |
| | NT2 n = 106 | Autoinflammatory disorders | 7 (3.4%) | 2 (1.9%) | **9 (6.5%)** | p = 0.0002 |
| | IH n = 138 | Allergic disorders | 11 (5.3%) | 6 (5.7%) | **16 (11.6%)** | p = 0.003 |
| Carls et al., 2020 [12] | NT1 n = 515 | ADHD | 21 (4.1%) | **61 (6.7%)** | NR | p = 0.002 |
| | NT2 n = 914 | Allergic disorders | 98 (19.0%) | **222 (24.3%)** | NR | p = 0.022 |
| | | Epilepsy/seizures | **37 (7.2%)** | 41 (4.5%) | NR | p = 0.015 |
| | | Movement disorders | **14 (2.7%)** | 13 (1.4%) | NR | p = 0.011 |
| | | Obesity | **66 (12.8%)** | 84 (9.2%) | NR | p = 0.032 |
| | | Sleep related movement disorders | **73 (14.2%)** | 94 (10.3%) | NR | p = 0.028 |
| Cremaschi et al., 2019 [26] | NT1 n = 33 | Pain | **30 (84.8%)** | 25 (75.8%) | NR | p < 0.000 |
| | NT2 n = 33 | Depression | 1 (3.0%) | **8 (24.2%)** | NR | p = 0.004 |
| Kok et al., 2003 [40] | NTI n = 138 | BMI (male) | **28.7 (20.5 to 44.8)** | NR | 25.1 (21.5–30.0) | p = 0.004 |
| | IH n = 33 | BMI (female) | **28.3 (19.9 to 47.8)** | NR | 26.4 (18.5–35.4) | p = 0.004 |
| Sonka et al., 2010 [28] | NT1 n = 82 | BMI | **29.1 (SD=5.8)** | 25.4 (SD = 4.4) | NR | p < 0.0001 |
| | NT2 n = 29 | | | | | |

ADHD, attention deficit hyperactive disorder; BMI, body mass index; IH, idiopathic hypersomnia; NR, not reported; NT1, narcolepsy type 1; NT2, narcolepsy type 2; SD, standard deviation.

USA [3,11]. Black et al. defined the comorbid conditions, in people with narcolepsy study, using the ICD diagnosis codes and grouped their results into multilevel classification codes [11]. As per the methodology in the current study, we counted each multilevel classification category as one instance in Fig. 3 e.g., circulatory (multiple categories) even though that grouping would have had a range of individual conditions, such as hypertension and stroke, within it. On the other hand, Ruoff et al. analysed the same database and reported on a range of single-level and multilevel psychiatric categories only, which we also reported as individual instances [3], for it reflected what was reported in the literature. Therefore, whilst we infer that the mental and behavioural comorbidities are more prevalent in people with narcolepsy, there may also be a degree of reporting bias. Conversely, a lack of reporting on certain conditions, does not mean that those comorbidities are not prevalent in people with narcolepsy. In addition, due to evolving understanding, diagnostic technology, and sub-classification of narcolepsy over the past two decades, many of the authors did not, or could not, differentiate the narcolepsy sub-types (NT1, NT2 and/or IH) in their studies. Therefore, instead of conducting narcolepsy sub-type analysis, we illustrated the complex burden of all comorbidities in all narcolepsy patients of all ages. Lastly, there were no publications from Africa, Southeast Asia and Australia included in this review.

Patients with narcolepsy experience significant impairment of cognitive function and professional efficiency, increased error rates and reduced safety at work or when driving and higher direct and indirect health costs [1,10]. They report feeling socially isolated and inferior to others and are often hesitant to seek medical attention [13]. This review clearly demonstrates that their burden of comorbidities extends across multiple organ systems. Improved general, subspecialist and allied health clinician education and awareness of narcolepsy may help facilitate earlier diagnosis and improve multidisciplinary and preventative care, including regular assessments of comorbidities in this patient group. Optimising health across multiple physical and psychological domains will enable patients with narcolepsy to attain their highest level of functioning, health and wellbeing. Future research studies, including the incorporation of multi-national patient registries, are also necessary to gain better insight into the long-term effects of therapeutics used to manage narcolepsy in the setting of a wide range of comorbidities [56]. These studies should be conducted in different regions and all age groups, using structured methodology, clear phenotype characterisation of narcolepsy subtypes and standardised reporting of epidemiological comorbidity data.

### 4.1. Practice points

The burden of comorbidities in patients with narcolepsy extend across multiple organ systems. Future clinical practice should aim to provide individualised, responsive and responsible care, to narcolepsy patients, and may be based on:

- Incorporating multidisciplinary education and collaboration between general, subspecialist and allied health clinicians when managing patients with narcolepsy and their comorbid conditions.
- Conducting regular proactive assessments for concurrent mental and behavioural conditions, endocrine, nutritional, metabolic and circulatory disorders.
- Expanding access to narcolepsy diagnostic technology, including biomarker hypocretin testing, to identify and phenotype narcolepsy more readily.
- Using standard diagnostic criteria, either ICD or ISCD, to improve data sharing of narcolepsy comorbidities and associated complexities.

### 4.2. Research agenda

- Future research to inform narcolepsy comorbidities and complexities should be conducted in different regions and all age groups, using structured methodology, clear phenotype characterisation of narcolepsy subtypes and standardised reporting of epidemiological comorbidity data.
- Develop national and multi-national web-based narcolepsy registries to collect, store and disseminate data, for all ages, on narcolepsy in a comprehensive and systematic way. This could guide the study of the long-term impacts of therapeutics for narcolepsy on comorbidities, as well as overall patient outcomes.

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## Conflicts of interest

The authors have no additional conflicts of interest to declare.

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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.2022.101669.

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