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Prevalence and Incidence of Comorbidities in Individuals with Narcolepsy or Idiopathic Hypersomnia: A Systematic Literature Review

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Introduction

- Narcolepsy and idiopathic hypersomnia are central disorders of hypersomnolence characterized by excessive daytime sleepiness and nighttime sleep abnormalities (including disrupted nighttime sleep in narcolepsy and nonrestorative, often prolonged sleep in idiopathic hypersomnia)[1]
- Higher prevalence and/or risk of cardiovascular (CV) and cardiometabolic (CM) conditions have been observed in individuals with narcolepsy and idiopathic hypersomnia, compared with individuals without these conditions[2-4]
- Comorbidity prevalence and incidence estimates among people with narcolepsy vary widely across the literature

Objective

- A systematic literature review (SLR) was conducted to identify studies reporting the prevalence and/or incidence of comorbidities among individuals diagnosed with narcolepsy and idiopathic hypersomnia

Methods

- This gold-standard SLR was conducted following *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines to identify relevant studies
- Electronic database searches (Embase®, MEDLINE®, and EBM), supplemented by review of conference proceedings, trial registries (clinicaltrials.gov and World Health Organization International Clinical Trials Registry Platform), and reference lists of eligible studies, were conducted through 10 December 2024 based on prespecified *Population, Intervention, Comparison, Outcomes, and Study design* (PICOS) criteria
- Titles and abstracts of publications were screened by 2 independent reviewers; the full text of the included publications was reviewed by 2 independent reviewers, with discrepancies resolved by consensus
- Data extraction and risk of bias assessments were performed by a single analyst and checked by a second analyst, with discrepancies resolved by consensus
  - Quality assessment was conducted using relevant *Critical Appraisal Skills Programme* (CASP) checklist domains

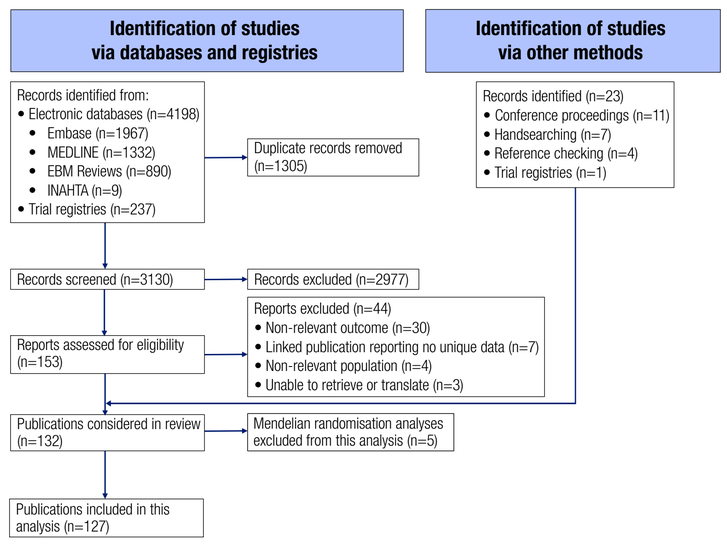
Table 1. Study Eligibility Criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	• Individuals with narcolepsy, including type 1 (ie, with cataplexy), type 2 (ie, without cataplexy), or mixed; or idiopathic hypersomnia, including those with and without long sleep time • Subgroups of interest: Age, gender, ethnicity, insurance type, and country (US vs ex-US)	• None
Intervention or exposure	• NA	• NA
Comparators or controls	• No restrictions; however, ideal comparisons were: – Narcolepsy vs non-narcolepsy – Idiopathic hypersomnia vs non-idiopathic hypersomnia	• None
Outcomes	• Studies with a comorbidity-related objective; no restrictions on comorbidities of interest, nor on the timepoint at which the data were collected (eg, lifetime, before diagnosis), other than those listed in the exclusion criteria column • Measures: – Prevalence of comorbidities (eg, proportions, excess prevalence) – Disease frequency incidence rates – Relative measures (eg, odds ratios, risk ratios)	• The following were not considered relevant comorbidities: Injury, burns, precocious puberty, vitamin deficiencies, pregnancy-related comorbidities, sleep symptoms (eg, periodic limb movements unless categorized as a disorder, sleep-onset rapid eye movements, sleep paralysis, excessive daytime sleepiness), comorbidities or outcomes without standardised diagnostic criteria or dichotomised using validated thresholds (eg, BMI, psychiatric scale scores,raw blood pressure values) • Studies in narcolepsy or idiopathic hypersomnia that did not have a comorbidity-related objective were flagged during screening
Study design	• Experimental clinical trials (including randomised controlled trials and single-arm trials) • Any observational study design (eg, cohort studies, case series, case-control studies, cross-sectional studies) • Systematic reviews/meta-analyses for reference checking	• Case studies • Animal/in vitro studies
Language	• No restriction	• None
Geography	• No restriction	• None
Publication date	• Full publications: 2009 onwards (last 15 years) • Conference abstracts: 2022 onwards (last 3 years)	• None

BMI, body mass index; NA, not applicable.

Results

Figure 1. PRISMA Diagram



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- 127 publications met the eligibility criteria; the majority were cohort or cross-sectional studies (n=106; 83.5%), and most were conducted among people with narcolepsy (n=117; 92.1%)
- Among studies conducted in individuals with narcolepsy, data were available in several forms: overall narcolepsy only (n=45), narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2) separately (n=34), NT1 only (n=36), and NT2 only (n=2)
  - Of these, 55 studies reported data for a comparator population
- Prevalence data, reported as measures of frequency (ie, percentage) or association (eg, odds ratio), were available for 114 (97.4%) publications assessing a population with narcolepsy across 310 comorbidities, and for all 23 publications assessing a population with idiopathic hypersomnia across 105 comorbidities
- Among publications assessing a population with narcolepsy, 5 reported incidence measures of frequency and 8 reported incidence measures of association; among publications assessing a population with idiopathic hypersomnia, 1 reported incidence measures of association

Table 2. Studies Reporting Comorbidity Prevalence Frequency Among Individuals with Narcolepsy

Category	Comorbidity	Publications, n
Cardiovascular	Arrhythmia	6
	Atrial fibrillation	1
	Cardiac arrest	1
	Arrhythmia/atrial fibrillation	1
	Cardiac disorders	1
	Cardiovascular disease	22
	Congenital heart defect	1
	Coronary heart disease	1
	Hypertension	26
	Long QT syndrome	1
	Low blood pressure	1
	Myocardial infarction	4
	Mitral valve disorder	1
	Nocturnal angina	1
	Peripheral vascular disease	1
	Postural orthostatic tachycardia syndrome	3
	Stroke (transient ischaemic attack)	6
	Tricuspid valve disorder	1
Cardiometabolic	Abdominal obesity	1
	Diabetes	29
	Dyslipidaemia	18
	Endocrine disorders	2
	Endocrine, nutritional and metabolic diseases, and immunity disorders	8
	Metabolic syndrome	5
	Obesity	44
	Obesity/overweight	6
	Overweight	14
	Type B insulin resistance syndrome	2

>10 publications; >1 publication

- Among the studies assessing a population with narcolepsy, comorbidity prevalence was most commonly reported as a frequency measure, with hypertension, cardiovascular disease (CVD), diabetes, dyslipidaemia, obesity, and overweight among the most commonly reported comorbidities

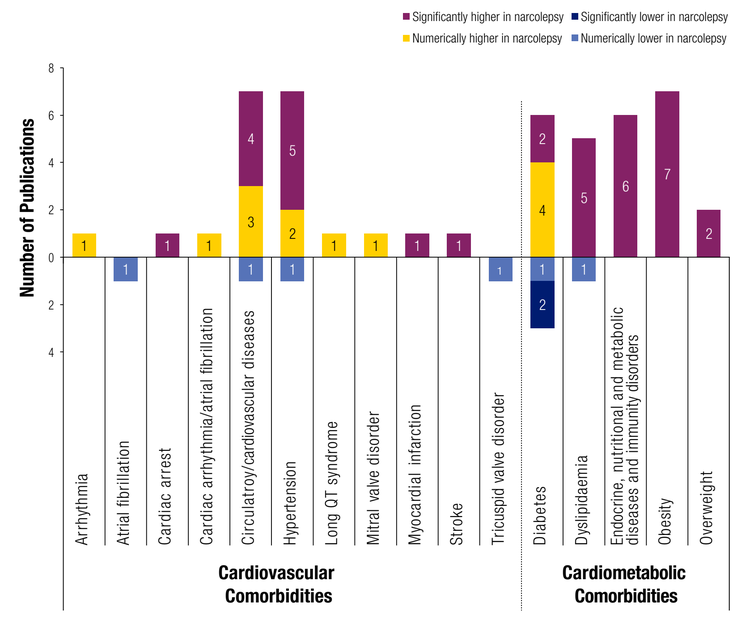
Table 3. Studies Reporting Comorbidity Prevalence Frequency Among Individuals with Idiopathic Hypersomnia

Category	Comorbidity	Publications, n
Cardiovascular	Atrial fibrillation	2
	Coronary revascularisation	2
	Cardiovascular disease	3
	Cardiac arrest	1
	Hypertension	4
	Low blood pressure	1
	Major adverse cardiovascular events	2
	Myocardial infarction	2
	Nocturnal angina	1
	Orthostatic hypotension	1
	Postural orthostatic tachycardia syndrome	1
	Raynaud's-type phenomena	1
	Stroke	2
Cardiometabolic	Diabetes	4
	Dyslipidaemia	2
	Endocrine, nutritional and metabolic diseases, and immunity disorders	1
	Metabolic syndrome/ Metabolic syndrome-related disorder	2
	Obesity	2
	Overweight and obesity	1

>1 publication

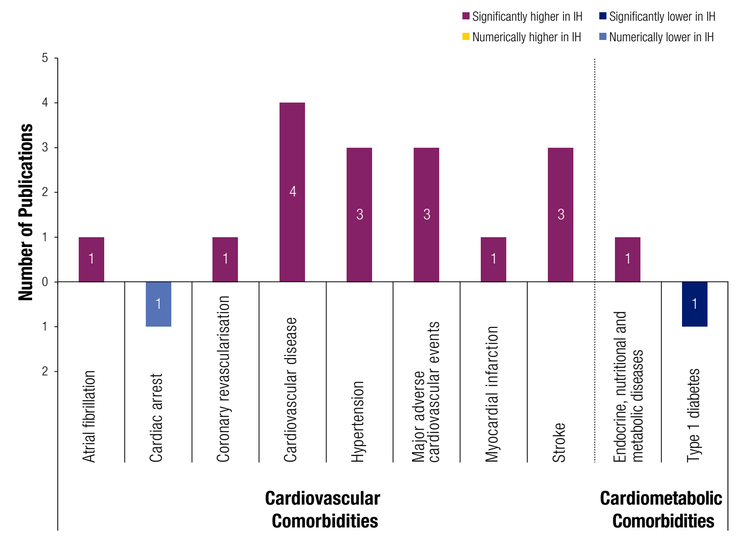
- The most commonly reported CV/CM comorbidity prevalence frequency estimates in individuals with idiopathic hypersomnia were for CVD, hypertension, and diabetes

Figure 2. Studies (n=27) Reporting Comorbidity Prevalence Measures of Association Among Individuals with Narcolepsy



- The majority of studies found a higher prevalence of cardiovascular and cardiometabolic comorbidities in individuals with narcolepsy relative to a comparator group

Figure 3. Studies (n=7) Reporting Comorbidity Prevalence Measures of Association Among Individuals with Idiopathic Hypersomnia



IH, idiopathic hypersomnia.

- The majority of studies found a higher prevalence of cardiovascular comorbidities in individuals with idiopathic hypersomnia relative to a comparator group

Conclusions

- Studies identified in this SLR demonstrate a growing body of literature evaluating the prevalence and incidence of comorbidities among individuals with narcolepsy or idiopathic hypersomnia, although evidence in idiopathic hypersomnia remains notably scarce compared with that in narcolepsy
- The majority of studies observed a higher prevalence of CV (eg, hypertension, CVD) and CM (eg, obesity) comorbidities among individuals with narcolepsy or idiopathic hypersomnia relative to those without, although estimates of prevalence varied across studies
  - Incidence data were more limited, especially in idiopathic hypersomnia
- This systematic literature review relies on published studies, which may overrepresent positive or significant findings[5]
- Future meta-analyses will be conducted to quantitatively synthesize findings from this SLR

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition, Text Revision*. Darien, IL: American Academy of Sleep Medicine; 2023. **2.** Black J, et al. *Sleep Med.* 2017; 33:13-18. **3.** Saad R, et al. *Sleep Med.* 2025;133:106587. **4.** Ben-Joseph RH, et al. *Sleep.* 2023;46(10):zsad161. **5.** Järvholm B, Bohlin I. *Scand J Public Health.* 2014;42(13 Suppl):3-10.

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