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Prevalence and incidence of narcolepsy symptoms in the US general population

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ABSTRACT

Objective: The objectives of this study are to evaluate the prevalence and incidence of Narcolepsy type 1 and type 2 and to determine the prevalence of narcolepsy diagnosis criteria in the US general population.
Methods: This longitudinal study was conducted in the adult US general population in two occasions. The initial interviews included 15 states (Arizona, California, Colorado, Florida, Idaho, Missouri, New York, North Carolina, North Dakota, Oregon, Pennsylvania, South Dakota, Texas, Washington, and Wyoming). The follow-up interviews, was done three years later in eight of these states. Of the 19,136 contacted individuals, 15,929 completed the initial interview and 10,931 completed the follow-up. Participants were interviewed using the Sleep-EVAL system, an artificial intelligence tool. Narcolepsy Type 1 (with cataplexy) and Narcolepsy Type 2 (without cataplexy) were defined according to the ICSD-3 classification. Symptoms of narcolepsy were assessed by frequency per week and duration. Medical visits and diagnoses were also collected.
Results: Participants were aged between 18 and 102 years of age (mean 45.8 ± 17.9 years), 51.3 % were women. The prevalence of narcolepsy with cataplexy was 12.6 per 100,000 individuals (95 % C.I., 0 to 30) and narcolepsy without cataplexy was 25.1 per 100,000. The incidence per year was 2.6 per 100,000 individuals (95 % C.I., 0 to 11).
Conclusions: Narcolepsy is a rare condition affecting 37.7/100,000 individuals (126,191 individuals in the current US population). Our US general population prevalence is in line with rates found in community-based studies but lower than what is reported in claim database studies.

1. Introduction

Narcolepsy, a chronic neurological sleep disorder first described in 1880 [1,2], is characterized by excessive hypersomnolence, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, automatic behaviors and sleep onset rapid-eye movement (REM) periods. The latest *International Classification of Sleep Disorders (ICSD3)* [3] described two subtypes of narcolepsy: Type 1 (with cataplexy - NT1) and Type 2 (without cataplexy – NT2). Narcolepsy is rare which makes assessing its prevalence and incidence very challenging [4].

The Silber et al. [5] study conducted in the Olmsted County, Minnesota, provides one of the oldest and best-known estimates of narcolepsy prevalence in the USA. The study utilized data from 1960 to 1989 and reported a prevalence of 56.3/100,000 individuals (35.8/100,000 with NT1) using Mayo clinic criteria for diagnosis and 46.1/100,000 using ICSD criteria. The incidence was estimated at 1.37/100.000 (0.74/100,000 individuals for NT1) using Mayo Clinic criteria and 1.09 using ICSD criteria. Another study conducted in King County, Washington, estimated the prevalence at 30.6/100,000 individuals (21.8/100,000 for NT1) [6] and the annual incidence at 0.39 to 0.62/100,000 individuals.

In the recent years, the use of US healthcare claim databases has led to varying estimates of narcolepsy prevalence. Scheer et al. [7] using the Truven Health MarketScan Commercial Dissertation Database, reported a prevalence of 79.4/100,000 in the US population during 2008–2010 (14.0/100,000 NT1). Another study [8], using the Symphony Health data from 2013 through 2016, reported a lower prevalence of 38.9/100,000 individuals in 2013, increasing to 44.3/100,000 in 2016. More recently, Abioye et al. [9], using the IBM MarketScan Commercial Claims and Encounters database from 2017 to 2019, reported an overall

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narcolepsy prevalence of 49.3/100,000 (9.7/100,000 NT1) for the US population in 2017 with an incidence at 7.6/100,000. The prevalence increased to 53.3/100,000 (10.7/100,000 NT1) in 2019 with an incidence at 5.5/100,000.

Although there is great appeal in using healthcare claim databases to determine prevalence for rare diseases such as narcolepsy, physicians may overuse certain diagnostic codes, such as those for NT2, to prescribe stimulants to patients who might benefit from them [10]. This makes it difficult to accurately analyze these databases and monitor this practice. The consequence is an artificially high prevalence of NT2 since this diagnosis does not require the presence of cataplexy. Therefore, any prevalence estimate based on claims data or clinical samples is likely to be an overestimate of the prevalence in the general population [11,12]. The accuracy of narcolepsy prevalence estimates can be affected not only by the type of sample used, but also by differences in diagnostic criteria, potentially resulting in overestimation. A meta-regression analysis by Wang et al. [13] revealed that having stringent diagnostic criteria are essential to determine the true prevalence of narcolepsy, while the use of non-specific criteria can lead to overestimates.

In this study, we investigated the prevalence and incidence of narcolepsy type 1 and type 2, as well as the prevalence of the symptoms underlying the narcolepsy diagnosis in a representative sample of the US general population.

2. Methods

2.1. Study population

The target population was non-institutionalized individuals aged 18 or over living in the USA. During the first wave, 15 states were selected to represent the U.S. population based on the number of inhabitants of each state, and the geographical area (US census data: www.census.gov): Arizona, California, Colorado, Florida, Idaho, Missouri, New York, North Carolina, North Dakota, Oregon, Pennsylvania, South Dakota, Texas, Washington, and Wyoming. The final sample included 19,136 individuals representative of the general population of these states (138 million); 15,929 of them completed the interview. The CASRO (Council of American Survey Research Organizations) cooperation rate [14] was 83.2 %. The second wave took place about 3 years later: 10,931 participants (of 12,218 from wave 1), living in 8 states (Arizona, California, Colorado, Idaho, New York, Oregon, Pennsylvania and Texas) were interviewed for a second time going through the same interview they completed three years before. Data were collected between 2002 and 2015 (wave 1: 2002–2012; wave 2: 2006–2015).

2.2. Procedures

Randomly selected telephone numbers using a computerized residential telephone directory in each state were drawn in proportion to the population of each county in each state. Using the Kish's method [15], one respondent per household was selected based on age and gender while maintain a representative sample. If the selected household member refused to participate, the household was removed and replaced with another number from the same area, and the process was repeated. Informed verbal consent was obtained from all potential participants before the interviews were conducted. Individuals who refused to participate or who dropped out before completing half of the interview were classified as refusers. The final sample included 21.4 % unregistered phone numbers. The interviews lasted an average of 74.5 (±37.8) minutes. The interviews lasting more than 45 min were conducted through two or three phone calls. Calls were made at various times of the day, including evenings and weekends. The project manager or team leaders called participants who completed the interview and ensured consistency of answers with random questions related to the interview during the 6–8 min phone call. The study was reviewed and approved by the Stanford University Institutional Review Board (IRB).

Individuals who were not fluent in English or Spanish, had a hearing or speech impairment, or had a medical condition that prevented a telephone interview were excluded from the study.

2.3. Instrument

Interviewers used Sleep-EVAL, a hybrid artificial intelligence (AI) neural network and knowledge-based expert system for the evaluation and diagnosis and of sleep, mental disorders, and medical conditions [16,17], to conduct the interviews. During the interview, the system formulated an initial diagnostic hypothesis that it then attempted to confirm or reject by asking supplemental questions or by deductions. Concurrent diagnoses were allowed in accordance with the *DSM-IV-TR* [18] and the *ICSD-2* [19]. The system terminated the interview once all diagnostic possibilities were exhausted.

The system has been tested and validated in various contexts [20]. For narcolepsy, the agreement between the Sleep-EVAL system and three sleep specialists was tested on 60 randomly selected participants. The kappa on the diagnosis of narcolepsy was very high: 0.96; with a sensitivity of 94.7 % and a specificity of 100 % [21]. A sub-sample of 284 participants in the pilot study answered also to the Stanford Sleep Inventory [22]. Correlations between the two instruments, administered within a six-month interval, were good: $r = 0.77$ on cataplexy; $r = 0.80$ on sleep paralysis; $r = 0.62$ on hypnagogic and/or hypnopompic hallucinations and 0.62 on automatic behaviors. A Kappa of 0.84 was obtained between the two instruments on the narcolepsy diagnosis. Sleep-EVAL has a sensitivity of 82.7 % and a specificity of 98.4 % [23].

Since the DSM-IV-TR [18] and the *ICSD*-2[19] classification systems were used at the time of the interviews, to achieve a DSM-5 [24] and *ICSD-3* [3] diagnosis, participants' answers were run again through the Sleep-EVAL System that built new diagnostic trees according to the updated guidelines for Narcolepsy diagnoses. New diagnostic trees were tested on a clinical sample of subjects with narcolepsy ($n = 362$) and their family members ($n = 3755$). Concordance with the clinical diagnosis and the new trees was at 92 %.

2.4. Variables

Excessive sleepiness was assessed through a series of 24 questions. Epworth Sleepiness Scale (ESS) [25] was also administered. Other questions allowed to assess cataplexy, sleep paralysis, and hypnagogic and hypnopompic hallucinations (see Table 1 for the list of questions that were asked during the interview to assess narcolepsy-related symptoms and guide diagnostic decision).

2.5. Statistical analysis

A weighting procedure was applied to compensate for disparities between the initial sample (W1) and the standard population with respect of age, gender and geographic distributions. The concordance of the sample with the general population according to the census data served as the standard population. When significant deviations were found between the sample and the reference population distribution, data were weighted to adjust for sample design. The standard population and the sample were distributed within various cells (number of counties (x) 6 age groups (x) gender (x) ethnic origin). For each cell, a weight was derived from the following equation: $W_i = n_{expected}/n_{observed}$, where the $n_{expected}$ represented the number of subjects expected in the sample for a given county, age group, gender and ethnic origin, and the $n_{observed}$ represented the number obtained in the sample for this cell. Results are presented with weighted percentages and 95 % confidence intervals when appropriate. Yearly incidence was calculated using the following formula: incidence = (# of new cases)/(sample size * timeframe). Bivariate analyses (Chi-square test or Fisher's exact test) were employed to compare outcomes in participants as applicable and Z-tests for independent proportions were calculated for pairwise comparisons

Table 1
Variables assessed during the interview.

Symptoms	Questions/Scale
Excessive Sleepiness	Situations when the excessive sleepiness arose
	Intensity of excessive sleepiness
	Frequency in the same day and within a week
	Frequency of periods of sudden and irresistible sleep
	Frequency of naps per week and per day
	Duration of excessive sleepiness and naps
	Daytime consequences associated with sleepiness
	Periods in the day where the sleepiness was more likely to occur
	Consultations and treatment for excessive sleepiness
	Epworth Sleepiness Scale (ESS)
Cataplexy	Limbs affected by muscle weakness (legs, knees, arms, shoulders; bilaterally or unilaterally), and other parts of the body affected by muscle weakness (head, slurred speech, sagging or dropping of the jaw, or a paralysis)
	Emotional situations when muscle weakness was more likely to occur
	Duration of an episode
	Frequency
	Occurrence of the most recent episode
	Age when the first episode occurred
	Who witnessed an episode
Sleep Paralysis	Moment it occurred (at sleep onset or upon awakening)
	Frequency
	Occurrence of the most recent episode
	Age of the subject when the first episode occurred
Hypnagogic and Hypnopompic Hallucinations	10 descriptions of hallucinatory phenomena that may occur at sleep onset or upon awakening
	Frequency
	Occurrence of the most recent hallucination
	If the subject was frightened by these hallucinations
	Age of the subject when the first hallucinations occurred

between categories with Bonferroni corrections. All analyses were performed using the statistical package for the social sciences (SPSS, version 27; SPSS, Inc.).

3. Results

A total of 19,136 individuals were contacted to participate in the study, 15,929 completed the interview and were included in the analyses. Participants were on average 45.8 years old (SD 17.9 years; range: 18–102 years) and 51.3 % of them were women. More than half (53.5 %) of the sample was married or living with someone. Almost 40 % of the sample was working on a daytime schedule; shift work made up about 20 % of the sample. Fifty-nine percent lived in areas with a population density >200 inhabitants per square mile.

Prevalence of hypersomnolence symptoms.

Daily episodes of irrepressible need to sleep or lapses into sleep lasting three months or longer are among the cardinal symptoms of narcolepsy. Prevalence of hypersomnolence ranged from 0.9 % to 9.1 % percent depending on the symptoms (Table 2). Men and women as well as the different age groups experienced similar rates of daily episodes of sudden and irresistible sleep. Daily tendency to fall asleep easily anywhere was more frequent in men than in women ($p < 0.0001$) but comparable between age groups. Finally, a daily feeling of moderate to severe daytime sleepiness was more frequent in women than in men ($p < 0.0001$) and significantly decreased with age ($p < 0.0001$) (Table 2b).

Daily naps were frequently reported with a prevalence of 5.0 % (95% C.I.:4.7%–5.3 %); taking 2 naps per day concerned 1.0 % (95%C.I.:0.8%–1.5 %) of the sample and 3 naps or more 0.4 % (95%C.I.:0.3%–0.5 %). Prevalence of daily naps was comparable between men and women but higher among older subjects ($p < 0.0001$) (Table 2b).

Table 2a
Prevalence of hypersomnolence symptoms.

	N	%	s.e.	N	%	(95 % C.I.)
Frequency	**During the day:**					
	Sudden and irresistible sleep			**Fall asleep easily anywhere**		
Daily	136	0.9	(0.8–1.0)	265	1.7	(1.5–1.9)
5-6 times/week	54	0.3	(0.2–0.4)	70	0.4	(0.3–0.5)
3-4 times/week	69	0.4	(0.3–0.5)	185	1.2	(1.0–1.4)
1-2 times/week	163	1.0	(0.8–1.2)	364	2.3	(2.1–2.5)
2-3 times/ month	139	0.9	(0.8–1.0)	307	1.9	(1.7–2.1)
<1 time/month	180	1.1	(0.9–1.3)	260	1.6	(1.4–1.8)
Never or rarely	15186	95.3	(95.0–95.6)	14478	90.9	(90.5–91.3)
	Moderate to severe sleepiness			**Naps**		
Daily	1443	9.1	(8.7–9.5)	801	5.0	(4.7–5.3)
5-6 times/week	405	2.5	(2.3–2.7)	392	2.5	(2.3–2.7)
3-4 times/week	934	5.9	(5.5–6.3)	1105	6.9	(6.5–7.3)
1-2 times/week	829	5.2	(4.9–5.5)	3184	20.0	(19.4–20.6)
<1 time/week	226	1.4	(1.2–1.6)	2794	17.5	(16.9–18.1)
Never/rarely	12091	76.0	(75.3–76.7)	7651	48.1	(47.3–48.9)

Duration of hypersomnolence symptoms was less than 3 months in 8.5 % of the cases.

A total of 13.8 % (95%C.I.:13.3%–14.3 %) of the sample had an ESS score greater or equal to 10. It was more frequent in women than in men ($p = 0.008$) and significantly decreased with age ($p < 0.0001$) (Table 2b). The ESS score was significantly correlated with the frequency of being sleepy ($r = 0.527$; $p < 0.0001$), tendency to fall asleep easily anywhere ($r = 0.348$; $p < 0.0001$), and episodes of sudden and irresistible sleep ($r = 0.188$; $p < 0.0001$).

3.1. Prevalence of symptoms associated with narcolepsy

Narcolepsy is frequently associated with symptoms of REM sleep intrusion into wakefulness. Taken individually, these symptoms were frequent in our sample (Table 3a). Although episodic events may not be clinically significant, it is epidemiologically important to assess their progression.

Prevalence of hypnagogic hallucinations occurring more than once a week was comparable in men and women and decreased significantly with age ($p < 0.0001$) (Table 3b). The last episode occurred in the last week in 22 % of them and in the last month in 23.5 %. These episodes began in childhood in 49.5 % of cases and in adolescence in 21.8 %. Prevalence of hypnopompic hallucinations occurring more than once a week was comparable in men and women and decreased with age ($p < 0.0001$). The last episode occurred in the last week in 17.2 % of them and in the last month in 21.8 %. These episodes began in childhood in 44.4 % and in adolescence in 24.2 % of cases. These hallucinations were frightening for 4.5 % of respondents when they occurred at sleep onset (hypnagogic) and for 3.9 % when they arise on awakening (hypnopompic).

For automatic behaviors in daily activities occurring at least several times a week or while driving, prevalence was similar in men and women and lower in the older subjects (Table 3b). Automatic behaviors began in adolescence in 37 % of them or between 18 and 24 years in 32.9 %.

Episodes of sleep paralysis at least once a week were as frequent in men as in women and in all age groups (Table 3b). In 18.9 % of them, sleep paralysis began in childhood; another 24.1 % reported it began in adolescence and another 17.1 % of cases said it started between the ages of 18 and 24. The last episode occurred in 38.8 % of them in the past week and 19.8 % in the past month. Episodes were more frequent upon awakening in the morning (62.9 %); 39.0 % said it happened while falling asleep and 34.0 % reported it happened while waking up from a

Table 2b
Prevalence of daily hypersomnolence symptoms by sex and age.

	Gender		p-value	Age Groups			p-value[c]
	Males (n = 7754)	Females (n = 8174)		<35 (n = 4978)	35-54[b] (n = 6259)	≥55 (n = 4692)	
	% (95 % C.I.)	% (95 % C.I.)		% (95 % C.I.)	% (95 % C.I.)	% (95 % C.I.)	
Hypersomnolence symptoms							
Sudden and irresistible sleep	1.0 (0.8–1.2)	0.7 (0.5–0.9)	n.s.	0.7 (0.5–0.9)	0.8 (0.6–1.0)	1.2 (0.9–1.5)	n.s.
Falls asleep easily anywhere	2.1 (1.8–2.4)	1.3 (1.1–1.5)	<0.0001	2.0 (1.6–2.4)	1.4 (1.1–1.7)	1.7 (1.3–2.1)	n.s.
Moderate to severe sleepiness	7.6 (7.0–11.1)	10.4 (9.7–11.1)	<0.0001	11.3 (10.4–12.2)	8.6 (7.9–9.3)[a]	7.2 (6.5–7.9)[a,b]	<0.0001
Naps	5.3 (4.8–5.8)	4.8 (4.3–5.3)	n.s	3.2 (2.7–3.7)	3.6 (3.1–4.1)	8.9 (8.1–9.7)[a,b]	<0.0001
Epworth Sleepiness Scale							
Score ≥10	13.1 (12.3–13.9)	14.6 (12.8–15.4)	0.008	18.4 (17.3–19.5)	13.8 (12.9–14.7)[a]	9.1 (8.3–9.9)[a,b]	<0.0001

[a] Pairwise Z-test post hoc comparisons with <35 y.o. group.
[b] Pairwise Z-test post hoc comparisons with 35–54 y.o. group.
[c] Adjusted for all pairwise comparisons using the Bonferroni correction.

Table 3a
Prevalence of REM intrusion symptoms and cataplexy-like symptoms.

	N	%	(95 % C.I.)	N	%	(95 % C.I.)
Frequency	**Hallucinations**					
	Hypnagogic			**Hypnopompic**		
>1 time/week	295	1.9	(1.7–2.1)	389	2.4	(2.2–2.6)
2-5 times/ month	189	1.2	(1.0–1.4)	317	2.0	(1.8–2.2)
1 time a month	199	1.3	(1.1–1.5)	350	2.2	(2.0–2.4)
<1 time a month	302	1.9	(1.7–2.1)	530	3.3	(3.0–3.6)
Rarely	812	5.1	(4.8–5.4)	1564	9.8	(9.3–10.3)
Never	14130	88.7	(88.2–89.2)	12780	80.2	(79.6–80.8)
	Automatic behaviors					
	Daily activities			**During driving**[a]		
Daily	84	0.5	(0.4–0.6)	49	0.3	0.2–0.4)
Several times/ week	164	1.0	(0.8–1.2)	149	0.9	(0.8–1.0)
Once per week	429	2.7	(2.4–3.0)	333	2.1	(1.9–2.3)
Once per month	710	4.5	(4.2–4.8)	713	4.5	(4.2–4.8)
≤ Once per year	879	5.5	(5.1–5.9)	1878	11.8	(11.3–12.3)
Never	13662	85.7	(85.2–86.2)	9478	59.5	(58.7–60.3)
	Sleep Paralysis			**Cataplexy-like symptoms**		
Daily	21	0.1	(0.05–0.15)	29	0.2	(0.1–0.3)
Several times/ week	45	0.3	(0.2–0.4)	32	0.2	(0.1–0.3)
Once per week	206	1.3	(1.1–1.5)	44	0.3	(0.2–0.4)
Once per month	330	2.1	(1.9–2.3)	95	0.6	(0.5–0.7)
≤ Once per year	1057	6.6	(6.2–7.0)	51	0.3	(0.2–0.4)
Never	14270	89.6	(89.1–90.1)	15678	98.4	(98.2–98.6)

[a] 20.9 % (n = 3326) of the sample do not drive.

nap.

Overall, 12.9 % (95%C.I.:12.4%–13.4 %) of the sample reported at least 1 REM intrusion symptoms occurring several times per week, 2 % (95%C.I.:2.7%–3.3 %) had 2 symptoms and 0.3 % (95%C.I.:0.2%–0.4 %) had 3 or 4 symptoms. At least one daily hypersomnolence symptoms was observed in 17.5 % of those with one REM intrusion symptom, in 26.1 % of those reporting 2 symptoms and 24.4 % of those with 3 or 4 symptoms.

Cataplexy-like symptoms occurring at least once a month were found in 1.3 % (95%C.I.:1.1%–1.5 %) of the sample (Table 3a) and more frequently in women than in men ($p < 0.0001$) and significantly decreased with age ($p < 0.0001$). In rare cases (3.6 % of cataplexy-like symptoms), it was associated with daily episodes of hypersomnolence. These symptoms began in childhood in 16.5 % of cases, in adolescence in 25.3 % or between 18 and 24 y.o. in 25.2 %. According to the subjects, the episodes peaked in frequency and intensity in adolescence for 14.7 % of cases and in early adulthood (18–24 y.o.) for 33.5 % of cases. The most recent episode occurred within the past 24 h in 39.6 % or within the past week in 49.9 % of cases. Cataplexy-like episodes were witnessed by a family member in 50.4 % of cases, a friend (38.2 %), an acquaintance (23.8 %), a stranger (21.9 %) or a physician (17.6 %).

3.2. Prevalence of interrupted sleep

The sleep of individuals with narcolepsy is often punctuated with multiple awakenings and/or an inability to resume sleep once awaken leading to early morning awakenings. Both of these symptoms are extremely prevalent in our sample (Table 4a). Multiple awakenings within the same night are less common (8.9 % of the sample awaken 3 or more times within the same night) and 6 % had difficulties resuming sleep after an awakening. Women were more likely than men to report waking up every night ($p < 0.0001$). Prevalence also linearly increased with age ($p < 0.0001$) (Table 4b). Waking up too early in the morning every day was less frequent but still affected a sizable part of the sample (Table 4). It was more prevalent in women than in men ($p < 0.0001$) and lower among the younger subjects compared to the 2 other age groups ($p < 0.01$).

3.3. Prevalence of NT1 and NT2

NT1 was identified in 0.0126 % (95%C.I.:0.000%–0.03 %) of the whole sample. Prevalence was similar between men and women (Table 5). NT1 did not differ significantly by age groups although it was slightly higher in individuals younger than 35 y.o. NT2 was observed in 0.0251 % (95%C.I.:0.0005%–0.0497 %) of the sample. NT2 prevalence was comparable between men and women and among age groups, although also slightly higher in individuals younger than 35 y.o. The combined prevalence for NT1 and NT2 was 0.0377 % (95%C.I.:0.008%–0.069 %).

Overall, 66.7 % of narcolepsy individuals in the sample identified by Sleep-EVAL were already diagnosed as such by a physician. If the prevalence of narcolepsy is calculated using only previously diagnosed cases, NT1 and NT2 combined are observed in 0.0251 % (95%C.I.:0.0005%–0.0497 %) of the sample. The incidence was also very low at 0.0026 % per year (95%C.I.:0.000%–0.0105 %).

4. Discussion

This study, based on a large representative sample of the U.S. general population, reports a current prevalence of narcolepsy at 37.7/100,000 individuals (12.6/100,000 for NT1, 25.1/100,000 for NT2), and a yearly incidence of 2.6/100,000.

Table 3b
Prevalence of symptoms associated with narcolepsy by sex and age.

	Gender		p-value	Age Groups			p-value[c]
	Males (n = 7754)	Females (n = 8174)		<35[a] (n = 4978)	35-54[b] (n = 6259)	≥55 (n = 4692)	
	% (95 % C.I.)	% (95 % C.I.)		% (95 % C.I.)	% (95 % C.I.)	% (95 % C.I.)	
Hypnagogic hallucinations ≥1 time/week	1.6 (1.3–1.9)	2.1 (1.8–2.4)	n.s.	3.4 (2.9–3.9)	1.4 (1.1–1.7)[a]	0.8 (0.5–1.1)[a]	<0.0001
Hypnopompic hallucinations ≥1 time/week	1.3 (1.3–2.1)	1.6 (1.3–2.1)	n.s.	2.1 (1.7–2.5)	1.3 (1.0–1.6)[a]	1.0 (0.7–1.3)[a]	<0.0001
Automatic behaviors in daily activities >1 time/week	1.4 (1.1–1.7)	1.7 (1.4–2.0)	n.s.	2.4 (2.0–2.8)	1.5 (1.2–1.8)[a]	0.8 (0.5–1.1)[a,b]	<0.0001
Automatic behaviors in driving >1 time/week	1.5 (1.2–1.8)	1.1 (0.9–1.3)	n.s.	1.7 (1.3–2.1)	1.4 (1.1–1.7)	0.5 (0.3–0.7)[a,b]	<0.0001
Sleep paralysis episodes ≥1 time/week	1.6 (1.3–1.9)	1.9 (1.6–2.2)	n.s.	1.8 (1.4–2.2)	1.7 (1.4–2.0)	1.7 (1.4–2.1)	n.s.
Cataplexy-like symptoms ≥1 time/month	0.9 (0.7–1.1)	1.6 (1.3–1.9)	<0.0001	2.0 (2.0–3.0)	1.2 (1.1–1.7)[a]	0.5 (0.4–0.8)[a,b]	<0.0001

[a] Pairwise Z-test post hoc comparisons with <35 y.o. group.
[b] Pairwise Z-test post hoc comparisons with 35–54 y.o. group.
[c] Adjusted for all pairwise comparisons using the Bonferroni correction.

Table 4a
Prevalence of nocturnal awakenings and early morning awakenings.

	N	%	(95 % C.I.)
Nocturnal awakenings			
Every night	3672	23.1	(22.5–23.8)
5-6 nights/week	667	4.2	(3.9–4.5)
3-4 nights/week	1114	7.0	(6.6–7.4)
1-2 nights/week	1886	11.8	(11.3–12.3)
1 to 3 nights/month	1709	10.7	(10.2–11.2)
Never	6881	43.2	(42.4–44.0)
Number of awakenings per night			
0	10535	66.1	(65.4–66.8)
1	2258	14.2	(13.7–14.7)
2	1717	10.8	(10.3–11.3)
3	848	5.3	(5.0–5.6)
4 or more	571	3.6	(3.3–3.9)
Early morning awakenings			
Every night	554	3.5	(3.2–3.8)
5-6 nights/week	224	1.4	(1.2–1.6)
3-4 nights/week	561	3.5	(3.2–3.8)
1-2 nights/week	1474	9.3	(8.8–9.8)
1 to 3 nights/month	1326	8.3	(7.9–8.7)
Never	11791	74.0	(73.3–74.7)

The comparison of our results with prevalence estimates from claim databases is challenging, primarily due to the divergence in methodologies and the uncertainty surrounding the representativeness of these databases. While our findings align with recent studies that have used claim databases to estimate the prevalence of NT1 [7,9], we report a much lower prevalence of NT2.

One possible explanation is that clinicians use NT2 as a catch-all diagnosis for individuals with excessive daytime sleepiness who may benefit from newer treatments typically reserved for individuals diagnosed narcolepsy. Furthermore, the claim database studies used only ICD-10 codes to determine the presence of narcolepsy without further validation which is in sharp contrast to other studies [5,6] where confirmation was performed by interviews and/or examination of medical records.

It should be noted that certain symptoms commonly seen in narcolepsy are relatively frequent and may even occur daily in the general population. However, a diagnosis of narcolepsy according to DSM-5 [24] or ICSD-3 [3] requires a combination of these symptoms that is much rarer. To our knowledge, cataplexy-like symptoms have never been studied outside of narcolepsy. Our findings suggest that, although infrequent, cataplexy still affects many people who do not have narcolepsy. It has been previously shown that certain diseases (eg, viral encephalopathy) [26] and/or medication use (eg, lamotrigine, clozapine, modafinil) can cause cataplexy [27–30]. Interestingly, hypersomnolence symptoms that resemble an on/off switch, such as sudden and

Table 4b
Prevalence of nightly nocturnal awakenings and early morning awakenings by sex and age.

	Gender		p-value	Age Groups			p-value[c]
	Males (n = 7754)	Females (n = 8174)		<35[a] (n = 4978)	35-54[b] (n = 6259)	≥55 (n = 4692)	
	% (95 % C.I.)	% (95 % C.I.)		% (95 % C.I.)	% (95 % C.I.)	% (95 % C.I.)	
Multiple awakenings	19.6 (18.7–20.5)	26.5 (25.5–27.5)	<0.0001	15.8 (14.8–16.8)	21.4 (20.4–22.4)[a]	33.0 (31.7–34.3)[a,b]	<0.0001
Early mornings awakenings	3.0 (2.6–3.4)	4.0 (3.6–4.4)	<0.0001	2.7 (2.2–3.2)	4.1[a] (3.6–4.6)	3.5 (3.0–4.0)	<0.001

[a] Pairwise Z-test post hoc comparisons with <35 y.o. group.
[b] Pairwise Z-test post hoc comparisons with 35–54 y.o. group.
[c] Adjusted for all pairwise comparisons using the Bonferroni correction.

Table 5
Prevalence of narcolepsy Type 1 and Type 2 by sex and age.

	Gender		p-value	Age Groups			p-value
	Males (n = 7754)	Females (n = 8174)		<34 (n = 4978)	35-54 (n = 6259)	≥55 (n = 4692)	
	% (95 % C.I.)	% (95 % C.I.)		% (95 % C.I.)	% (95 % C.I.)	% (95 % C.I.)	
Narcolepsy Type 1	0.0129 (0.000–0.038)	0.012 (0.000–0.036)	n.s.	0.0201 (0.000–0.06)	0.016 (0.000–0.047)	0	n.s.
Narcolepsy Type 2	0.026 (0.000–0.062)	0.024 (0.000–0.058)	n.s.	0.040 (0.000–0.096)	0.016 (0.000–0.047)	0.021 (0.000–0.063)	n.s.
Narcolepsy Type 1 or Type 2	0.039 0.000–0.083)	0.036 0.000–0.077)	n.s.	0.060 (0.000–0.128)	0.032 (0.000–0.076)	0.021 (0.000–0.063)	n.s.
Already diagnosed by a physician	0.026 (0.000–0.062)	0.024 (0.000–0.058)	n.s.	0.0201 (0.000–0.06)	0.032 (0.000–0.076)	0.021 (0.000–0.063)	n.s.

irresistible sleep during the day or easily falling asleep anywhere, reflect other aspects of hypersomnolence with low (albeit significant) correlations with the ESS. Limitations of the ESS in adequately assessing sleepiness have been repeatedly reported, especially in clinical populations or the elderly [31–33].

Noteworthy, the prevalence of associated narcolepsy symptoms in the general population, such as moderate to severe sleepiness, hypnagogic and hypnopompic hallucinations, automatic behaviors, and cataplexy-like symptoms, decreases with age. This is consistent with existing literature showing that the severity and frequency of cataplexy decreases with age [34,35]. The prevalence of narcolepsy diagnoses also decreased with age, although this was not significant in our study.

The nature of our study entailed several limitations. First, we did not confirm narcolepsy cases with additional clinical evaluation, as this would significantly increase the cost of the study. Additionally, although two-thirds of the identified cases of narcolepsy were already diagnosed according to participants, we did not request their medical records for confidentiality and ethical reasons. However, Sleep-EVAL has demonstrated good validity for the diagnosis of narcolepsy compared to sleep specialists [21]. Second, while we took great care to reach all segments of the community, we could not interview individuals who were not fluent in English or Spanish. The study also excluded individuals who were homeless, living in long-term care facilities, or did not have a phone. Third, the data were collected over an extended period of time. It could be argued that the prevalence of narcolepsy in the population has increased since the study began. However, there is no conclusive evidence that this is the case. The most recent studies have been conducted with claim databases. As previously mentioned, the prevalence of NT1 has remained stable over the past decades, while NT2 prevalence has skyrocketed. This raises many unanswered questions, since to date no study using claim databases has confirmed, even in subsamples, that NT2 people actually have the disorder, rather than a convenient diagnosis for patients with excessive sleepiness.

Importantly, this study is one of the few studies that provides the prevalence and incidence of narcolepsy based on a representative sample of US adults. Our results confirm that narcolepsy is a rare disease.

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CRediT authorship contribution statement

Maurice M. Ohayon: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. **Stéphanie Duhoux:** Methodology, Writing – original draft, Writing – review & editing. **Joseph Grieco:** Writing – original draft, Writing – review & editing. **Marie-Lise Côté:** Conceptualization, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

SD and JG are current employees of Tris Pharma. MMO is consultant for Tris Pharma and Takeda Pharmaceuticals. MMO has received grant from Novartis. MLC has received grants from Jazz Pharmaceuticals, Takeda Pharmaceuticals and Novartis.

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