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RESEARCH ARTICLE

Daytime sleepiness and BMI exhibit gender and age differences in patients with central disorders of hypersomnolence

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Summary

The aim of the present study was to examine gender and age-specific effects on subjective daytime sleepiness (as measured by the Epworth Sleepiness Scale), body weight and eating behaviour in patients with central disorders of hypersomnolence. Based on the European Narcolepsy Network database, we compared 1035 patients with narcolepsy type I and 505 patients with other central disorders of hypersomnolence ("narcoleptic borderland"), including narcolepsy type II ($N = 308$) and idiopathic hypersomnia ($N = 174$), using logistic regression and general linear models. In the entire study population, the Epworth Sleepiness Scale was higher in women ($N = 735$, mean age = 30 years, mean Epworth Sleepiness Scale = 16.6 ± SD 3.9) than in men ($N = 805$, mean age = 32 years, mean Epworth Sleepiness Scale = 15.8 ± SD 4.4). In women with narcolepsy type I ($N = 475$), both Epworth Sleepiness Scale and body mass index increased in parallel with age. In women of the narcoleptic borderland ($N = 260$), the Epworth Sleepiness Scale markedly peaked in their early 30s, while body mass index only started to rise at that age. This rise in body mass index following the Epworth Sleepiness Scale peak cannot be explained by sleepiness-induced uncontrolled eating, as self-reported uncontrolled eating was negatively associated with the Epworth Sleepiness Scale in this group. We propose that the narcoleptic borderland harbours a unique

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cluster of women in their fertile years with an unexplored aetiology requiring further investigation towards tailored interventions.

KEYWORDS
excessive daytime sleepiness, hypersomnia, impulsive eating behaviour, obesity, sex

1 | INTRODUCTION

Excessive daytime sleepiness (EDS) and obesity are growing risk factors for life-threatening conditions like diabetes and cardiovascular disease, even in the absence of sleep disorders (Bock et al., 2022; Yusuf et al., 2022). Both EDS and obesity have been reported to be more prevalent in women than men (Kroll et al., 2020; Packard et al., 2021). However, reports on gender-specificity of EDS are controversial, and suggest that EDS is only higher in women until to their 4th decade of life (Boyes et al., 2017). Moreover, sleep quality and daytime sleepiness in women are not only modulated across life-periods, but also change with the oestrous cycle (Baker & Lee, 2018; Dorsey et al., 2020). Consistent with these findings, the Epworth Sleepiness Scale (EDS) was positively associated with the oestradiol level in women, which varies through the oestrus cycle and over life phases (Kische et al., 2016).

In the general population, EDS is associated with obesity (Bixler et al., 2005; Hayley et al., 2014; Panossian & Veasey, 2012; Slater et al., 2013). Potential mechanisms linking EDS and obesity are manifold, ranging from obstructive sleep apnea (OSA), alterations in hormones like ghrelin and leptin to the hypothalamic–pituitary–adrenal (HPA) axis and pro-inflammatory cytokines among others (Panossian & Veasey, 2012).

Narcolepsy type I (NT1) is a rare disorder characterized by EDS, enhanced rapid eye movement (REM) sleep pressure (two sleep-onset REM periods [SOREMPs] in a Multiple Sleep Latency Test [MSLT] and/or one SOREMP in a night-time polysomnography), cataplexy and hypocretin (also called orexin) deficiency. Hypocretin is a neuropeptide implicated in the maintenance of wakefulness, energy homeostasis, reward regulation and feeding behaviour (Tsujino & Sakurai, 2009). The loss of hypocretin is thought to directly cause narcoleptic key symptoms, and may also contribute to the weight gain and eating disorders in NT1 (Fortuyn et al., 2008). The body mass index (BMI) of patients with NT1 is 10%–20% higher than in the general population (Bassetti et al., 2019; Heier et al., 2011). Several mechanisms have been debated to be involved in weight gain of patients with NT1, including direct effects of hypocretin-mediated metabolic changes (Dauvilliers et al., 2022; Heier et al., 2011), impulsive eating behaviour (Dauvilliers et al., 2022; Fortuyn et al., 2008; van Holst et al., 2018) or reduced physical activity (Parmar et al., 2019), which are potentially further modulated by the high prevalence of psychiatric conditions in NT1.

While the European prevalence of NT1 of 0.05% is gender-independent (Ohayon et al., 2002), women exhibit an earlier symptom onset but longer delay of diagnosis (Luca et al., 2013; Zhang et al., 2022). Recent findings indicate that several key symptoms and diagnostic markers of NT1 are gender-specific (Gool et al., 2022; Luca et al., 2013; Nevsimalova et al., 2022; Schmidt & Bassetti, 2022). Also, experimental data in orexin knockout mice showed gender differences in cataplexy expression, which were further influenced by the oestrus cycle (Arthaud et al., 2022). Recently, a data-driven unsupervised clustering of the European Narcolepsy Network (EU-NN) database suggested a female-specific NT1 cluster with a characteristic configuration of signs and symptoms (Gool et al., 2022).

Narcolepsy type II (NT2) is even less prevalent than NT1 (Bassetti et al., 2019). Diagnosis criteria include EDS and enhanced REM sleep pressure in the absence of hypocretin deficiency and cataplexies. While it has been suggested that NT2 could be an early or mild form of NT1, it remains a controversial entity, because clear-cut disease markers are lacking (Bassetti et al., 2019).

Similar to NT2, idiopathic hypersomnia (IH) is less prevalent than NT1 (Sowa, 2016) and a diagnosis of exclusion with high EDS. IH is frequently accompanied by prolonged nocturnal sleep and sleep drunkenness (Nevsimalova et al., 2021). The main criterion discriminating IH from NT2 is the absence of enhanced REM sleep pressure, a marker that has been criticized for having low sensitivity, specificity and consistency over time (Lammers et al., 2020). In IH, female gender is over-represented (Nevsimalova et al., 2021). Patients with IH have lower BMI and lower prevalence of obesity than patients with NT1 (Futenma et al., 2022) but, to our knowledge, BMI comparisons of patients with IH with matched healthy subjects have not been reported. Reports on BMI and obesity in IH and NT2 are sparse and controversial, some of them suggesting elevated BMI and obesity also in certain patient groups (Futenma et al., 2022; Nevsimalova et al., 2021; Šonka et al., 2010).

Taken together, EDS and obesity, both potential predictors for life-threatening conditions, are tightly connected in the overall population. Patients with NT1 characterized by high levels of EDS often suffer from obesity and eating disorders. Although literature suggests gender-specific differences of EDS, obesity, as well as NT1, these are still under-evaluated and usually neglected when it comes to individualized patient care (Schmidt & Bassetti, 2022; Tokatli et al., 2022). The EU-NN database presents a unique data set of patients with central disorders of hypersomnolence, representing extreme groups of the daytime sleepiness spectrum of the overall population. We therefore reasoned that this database offers a unique opportunity to disentangle gender- and age-dependent differences in subjective daytime sleepiness (ESS), BMI, and eating behaviour.

2 | METHODS

Our study population constitutes the EU-NN database, and entails data collected from 29 different European sleep centres between 2010 and 2020. Because two-thirds of our cohort was diagnosed as NT1 ($N = 1035$) and because other central disorders of hypersomnolence lack clear-cut diagnostic criteria, some of which have changed over time, often resulting in uncertain diagnoses (Lammers et al., 2020), patients with non-NT1 diagnoses were combined in the group "narcoleptic borderland (NBL)", as defined earlier (Bassetti et al., 2019). For historical reasons, most of the records were classified based on the International Classification of Sleep Disorders, second edition (ICSD-II), thus we report the composition of the NBL group according to the ICSD-II terminology as follows: narcolepsy without cataplexy ($N = 308$); IH without long sleep time ($N = 126$); IH with long sleep time ($N = 48$); physiological or unspecified hypersomnia ($N = 13$); and narcolepsy unspecified ($N = 10$). Other disorders encompassing less than 10 patients (as hypersomnia associated with psychiatric disorders) were excluded. For specific analyses, we distinguished within the NBL between narcolepsy without cataplexy ($N = 308$) and IH with or without long sleep time ($N = 174$), and labelled them NT2 and IH, respectively, in order to align with the ICSD-III classification. Subjective daytime sleepiness as defined by the ESS, BMI, age, apnea–hypopnea index (AHI), medication status as well as psychiatric diagnoses were recorded at the time of first diagnosis. Excessive weight gain/eating behaviour parameters were assessed by medical interview as follows: excessive weight gain: *the patient reports an increase of more than 10% of his/her weight within 6 months after the first symptoms of narcolepsy/hypersomnolence occurred*; uncontrolled eating behaviour: *the patient reports episodes of uncontrolled eating since the first symptoms of narcolepsy/hypersomnolence*; nocturnal eating: *the patient eats during awakenings of nocturnal sleep since the first symptoms of narcolepsy/hypersomnolence*. Obesity was defined as BMI ≥ 30 kg m^{-2}.

We used logistic regression models for categorical outcome measures and generalized linear models for numeric outcome measures. All models were fitted based on the independent factors "Gender", "Patient group" with levels "*Narcolepsy type I*" and "*Narcoleptic borderland*", "*Age*" referring to log2(Age), "AHI", "Medication" with levels "With Medication" and "Drug-Naïve", "Psychiatric diagnosis" with levels "With psychiatric diagnosis" and "Without psychiatric diagnosis". For the regression models, missing AHI values were imputed with the overall median AHI value, and log-transformed in order to reduce skewness of the data distribution (log2(AHI + 1)). The results of the regression models are reported in supporting information, and reported *p*-values are derived from these models if not stated otherwise. Age distributions of our study groups are illustrated in a histogram (Figure S1; 15 bins distributed equally over years for patients aged between 0 and 80 years at diagnosis). Age dependencies of sleepiness and BMI were illustrated using local regression fitting (locally estimated scatterplot smoothing [LOESS]; Figure 2). In order to avoid a bias through underpowered age groups, only patients between 16 and 50 years were included for direct comparisons of BMI and daytime sleepiness in women (Figure 2c–f). Significance levels of group differences for uncontrolled eating effects were obtained with post-hoc tests (Figure 3). Correlation between ESS and BMI was analysed with Spearman correlation (Figure S2). The level of significance was not corrected for multiple testing and established at $p < 0.05$. All statistical analyses were performed in R (v4.3.0).

3 | RESULTS

3.1 | Demographics and main symptoms

We analysed 1540 patients at first diagnosis (1035 with NT1 and 505 from the NBL). Demographics and main symptoms are summarized in Table 1. With the exception of sleep drunkenness, symptoms associated with central disorders of hypersomnolence were more prevalent in patients with NT1 as compared with the NBL (Figure 1; Statistical details Tables S1 and S2: "ESS", "BMI", "Obesity", "Excessive weight gain", "Nocturnal eating", "Sleep drunkenness", "Hypnagogic/hypnopompic hallucinations" abbreviated as "Hypnagogic hallucinations", "Cataplexy" encompassing cataplexy-like events, "Disturbed night-time sleep" [all $p < 0.001$], "Uncontrolled eating" [$p = 0.004$]). The symptoms "Hypnagogic hallucinations" and "Sleep drunkenness" were more prevalent in women than in men ($p < 0.001$ and $p = 0.03$, respectively). When considering NT1 patients only, "Hypnagogic hallucinations" but not "Sleep drunkenness" were more prevalent in women than in men ($p = 0.005$ and $p = 0.5$, respectively; statistical details not shown). When considering NBL patients only, "Sleep drunkenness" but not "Hypnagogic hallucinations" were more prevalent in women than in men ($p = 0.007$ and $p = 0.08$, respectively; statistical details not shown). "Obesity", "Excessive weight gain" and "Disturbed night-time sleep" were positively associated with AHI ($p < 0.001$, $p = 0.008$ and $p = 0.04$, respectively), while "Sleep drunkenness" and "Hypnagogic hallucinations" were negatively associated with AHI ($p = 0.01$for both factors). "Excessive weight gain", "Uncontrolled eating", "Cataplexy" and "Sleep drunkenness" were negatively associated with "With medication" ($p = 0.03$, $p < 0.001$, $p = 0.004$, $p = 0.01$, respectively). "Uncontrolled eating", "Cataplexy", "Disturbed night-time sleep", "Sleep drunkenness" and "Hypnagogic hallucinations" were positively associated with "With psychiatric diagnosis" ($p = 0.005$, $p = 0.004$, $p < 0.001$, $p < 0.05$, $p < 0.05$, respectively, Table S1). Age at symptom onset did not differ between patient groups ($p = 0.4$; Table S3), but was lower in women than men ($p = 0.03$). This gender difference was driven by the NT1, but not by NBL patients ($p = 0.005$ and $p = 0.6$ for factor "Gender" for separate group analyses of NT1 and NBL patients, respectively; Table S3). Diagnostic delay was not associated with patient group or gender ($p = 0.4$ and $p = 0.5$ for factors "Patient group" and "Gender", respectively; Table S3). While diagnoses during childhood are mostly attributable to patients with NT1 of both genders, especially women of the NBL showed a peak in about 20 years for the age at diagnosis (Figure S1). Most of the demographic and symptom-related variables exhibit differences between the EU-NN centres (Table S4).

TABLE 1 EU-NN database demographics and symptoms.

Characteristic	*N*	NT1 Women, *N* = 475[a]	NT1 Men, *N* = 560[a]	NBL Women, *N* = 260[a]	NBL Men, *N* = 245[a]
Age	1540	29.5 (14.1)	32.0 (15.8)	29.7 (12.2)	31.2 (13.0)
ESS	1434	17.0 (3.9)	16.2 (4.3)	15.9 (3.8)	14.9 (4.5)
BMI	1540	26.2 (6.5)	27.5 (5.2)	24.5 (5.2)	26.1 (4.4)
Obesity	1540	127 (27%)	147 (26%)	36 (14%)	42 (17%)
Excessive weight gain	462	72 (51%)	88 (49%)	19 (24%)	8 (13%)
Nocturnal eating	464	37 (26%)	45 (25%)	7 (9.2%)	10 (15%)
Uncontrolled eating	451	50 (35%)	48 (28%)	20 (26%)	10 (16%)
Cataplexy-like events	1538	460 (97%)	539 (96%)	19 (7.3%)	10 (4.1%)
Sleep drunkenness	1479	123 (27%)	127 (23%)	140 (56%)	96 (41%)
Hypnagogic hallucinations	1532	281 (60%)	274 (49%)	87 (34%)	60 (24%)
Disturbed nighttime sleep	1496	309 (67%)	341 (62%)	78 (31%)	75 (32%)
AHI (value per hr)	1176	3.6 (7.1)	8.3 (15.4)	2.3 (4.0)	5.1 (7.4)
MSLT sleep latency	999	3.8 (3.2)	3.6 (2.8)	5.9 (3.7)	4.9 (3.0)
Psychiatric diagnosis	1540	29 (6.1%)	27 (4.8%)	21 (8.1%)	17 (6.9%)
With primary medication	1540	218 (46%)	278 (50%)	91 (35%)	89 (36%)
Modafinil		112 (24%)	148 (26%)	48 (18%)	47 (19%)
Methylphenidate-HCl		37 (7.8%)	42 (7.5%)	48 (18%)	22 (9.0%)
Sodium oxybate		20 (4.2%)	26 (4.6%)	17 (6.5%)	7 (2.9%)
Other		49 (10%)	62 (11%)	3 (1.2%)	13 (5.3%)
Drug-naive		257 (54%)	282 (50%)	23 (8.8%)	156 (64%)
Age category	1540				
< 16 years		73 (15%)	80 (14%)	11 (4.2%)	20 (8.2%)
16–25 years		150 (32%)	145 (26%)	110 (42%)	73 (30%)
26–40 years		149 (31%)	175 (31%)	85 (33%)	101 (41%)
41–65 years		95 (20%)	146 (26%)	53 (20%)	48 (20%)
> 65 years		8 (1.7%)	14 (2.5%)	1 (0.4%)	3 (1.2%)
Age at symptom onset	1495	20.2 (11.0)	23.1 (13.4)	21.2 (10.8)	22.1 (11.5)
Delay of diagnosis (years)	1321	10.1 (10.8)	10.3 (12.3)	9.8 (9.1)	10.9 (10.3)

[a]Mean (SD); *n* (%).
AHI, apnea–hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale; MSLT, Multiple Sleep Latency Test; NBL, narcoleptic borderland; NT1, narcolepsy type I.

3.2 | BMI and daytime sleepiness

Approximately 50% of patients with NT1 reported an increase of more than 10% of their weight within 6 months after the first symptoms of NT1 occurred, in contrast to only 19% of patients of the NBL. Confirming earlier findings, BMI and ESS scores at the time of diagnosis were significantly higher in patients with NT1 than in the NBL (Figure 1; Statistical details Table S2: $p < 0.001$ for both variables). BMI and ESS were only weakly correlated in the NT1 population in both men and women, and not correlated in the NBL population in both men and women (Figure S1; Spearman correlation). While in our overall population, BMI was higher in men than in women ($p = 0.007$; mean 27.1 versus 25.6), the ESS was higher in women than in men ($p < 0.001$; mean 16.6 ± SD 3.9 versus 15.8 ± SD 4.4). MSLT sleep latencies, however, were similar in women and men in the NT1 population ($p = 0.4$; mean 3.8 ± SD 3.2 versus 3.6 ± SD 2.8; Table 1), and even showed a trend to be longer in women as compared with men in patients of the NBL ($p = 0.08$; mean 5.9 ± SD 3.7 versus 4.9 ± SD 3.0). BMI was positively associated with "With Medication" ($p < 0.03$), while ESS was negatively associated with "With medication" ($p < 0.001$). BMI was positively associated with "With psychiatric diagnosis" ($p = 0.03$). Because both ESS and BMI not only differed with respect to gender but were also age-dependent (both $p < 0.001$), we next wanted to better understand their dependency on age.

3.3 | Evolution of BMI and subjective daytime sleepiness as a function of age

The BMI rose with roughly a logarithmic dependency on age at first diagnosis (Figure 2a). In women of the NBL, the BMI seems to drop specifically in their early thirties. In contrast, their daytime sleepiness

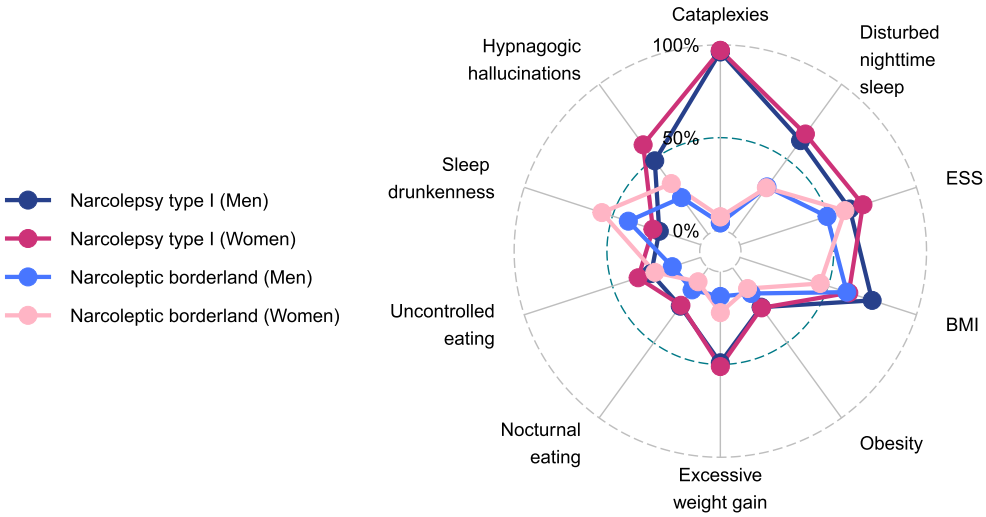

FIGURE 1 Prevalence of symptoms in narcolepsy type I (NT1) and the narcoleptic borderland (NBL) in women and men ($N = 1540$) as spider graph. The Epworth Sleepiness Scale (ESS) was scaled to values spanning from 10 (0%) to 20 (100%), body mass index (BMI) was scaled to values spanning from 20 (0%) to 30 (100%).

seems to peak in this life phase, equalizing with the ESS scores of women with NT1 at the same age, the group of patients with the overall highest ESS levels (Figure 2b).

To compare the association of sleepiness and BMI with age directly, we placed the two variables ESS and BMI for women in a single graph (Figure 2c–f). In women with NT1, ESS and BMI rose in a similar manner with age (Figure 2c). However, in women from the NBL (Figure 2d), the age dependency of ESS and BMI diverged markedly between 30 and 40 years. At the maximum ESS in the early 30s of the NBL group, the BMI was still very low, and at this time started to rise steeply until it reached its maximum about 10 years later. When comparing the age dependency of ESS and BMI between the two main groups of the NBL, the here-described pattern was less prominent in women with NT2 (Figure 2e) than in women with IH (Figure 2f), indicating that women with IH were driving the observed pattern.

3.4 | Daytime sleepiness and BMI – is impulsive eating behaviour the link?

To further test whether impulsive eating behaviour might mediate the increase of BMI after the peak of daytime sleepiness in women of the NBL, we next investigated the prevalence of impulsive eating behaviour in our patient groups. Not only excessive weight gain (50% versus 19%; $p < 0.001$; statistical details Table S1) and obesity (26% versus 15%; $p < 0.001$), but also uncontrolled (31% versus 22%; $p = 0.004$) and nocturnal (25% versus 12%; $p < 0.001$) eating were more prevalent in NT1 as compared with the NBL. While the prevalence of "Excessive weight gain" was negatively associated with age ($p = 0.002$), the prevalence of "Obesity" was positively associated with age ($p < 0.001$).

The BMI was positively associated with uncontrolled and nocturnal eating (Figure 3a; data for nocturnal eating not shown; statistical details Table S4: $p < 0.001$ for both variables). This association was mostly driven by female patients (Figure 3a; statistical details Table S6: "Gender: uncontrolled eating" interaction: $p = 0.01$; "Gender: nocturnal eating" interaction: $p = 0.04$). In contrast to BMI, the ESS was not associated with either uncontrolled eating or nocturnal eating, when considering the overall study population (Figure 3b; data for nocturnal eating not shown; statistical details Table S5). In women from the NBL as opposed to women with NT1, the ESS was negatively associated with uncontrolled eating (Figure 3b; statistical details Table S7a: "Patient group: uncontrolled eating" interaction: $p < 0.02$). When analysing the female subpopulations of NT1, NBL, NT2 and IH separately, a negative association of uncontrolled eating with ESS was found in all but the NT1 subpopulations ($p = 0.8$, $p < 0.001$, $p = 0.004$, $p = 0.03$, respectively; statistical details Table S7b).

4 | DISCUSSION

The present study examined the effects of gender, age and eating behaviour on subjective daytime sleepiness and BMI in a large cohort of patients with central disorders of hypersomnolence, representing the population at the extreme end of the daytime sleepiness spectrum. Women showed overall higher subjective sleepiness, with a peak in the early 30s specifically in women of the NBL.

4.1 | Daytime sleepiness, weight gain and eating behaviour: A chicken-and-egg situation?

In our population, patients with NT1 had a higher BMI, and the prevalence of obesity and weight gain after hypersomnolence symptom onset was higher when compared with patients of the NBL in accordance with previous reports (Bassetti et al., 2019; Dauvilliers et al., 2022; Heier et al., 2011; Figure 1). Searching for possible reasons for the high prevalence of excessive weight gain in NT1, we investigated associations of BMI with subjective sleepiness and eating behaviour to examine the relationship between EDS, eating behaviour and/or physical activity, and body weight. Indeed, more patients with

NT1 reported episodes of uncontrolled or night-time eating since their first hypersomnolence symptoms as compared with patients of the NBL. While the underlying mechanisms are still unclear, these findings suggest that the hypocretin system may be involved in eating disturbances and weight gain, corroborating previous results (Bassetti et al., 2019; Dauvilliers et al., 2022; Fortuyn et al., 2008; Heier et al., 2011; van Holst et al., 2018). The loss of hypocretin might directly affect brown adipose tissue metabolism (Straat et al., 2020), and further affect eating behaviour by modulating the cortical reward and control circuits. In one study, the ventromedial prefrontal cortex (vmPFC) was activated during food-driven attention in patients with NT1, when compared with healthy controls or patients with IH who have normal hypocretin levels (van Holst et al., 2018). Moreover, vmPFC activation was correlated with spontaneous calorie intake (van

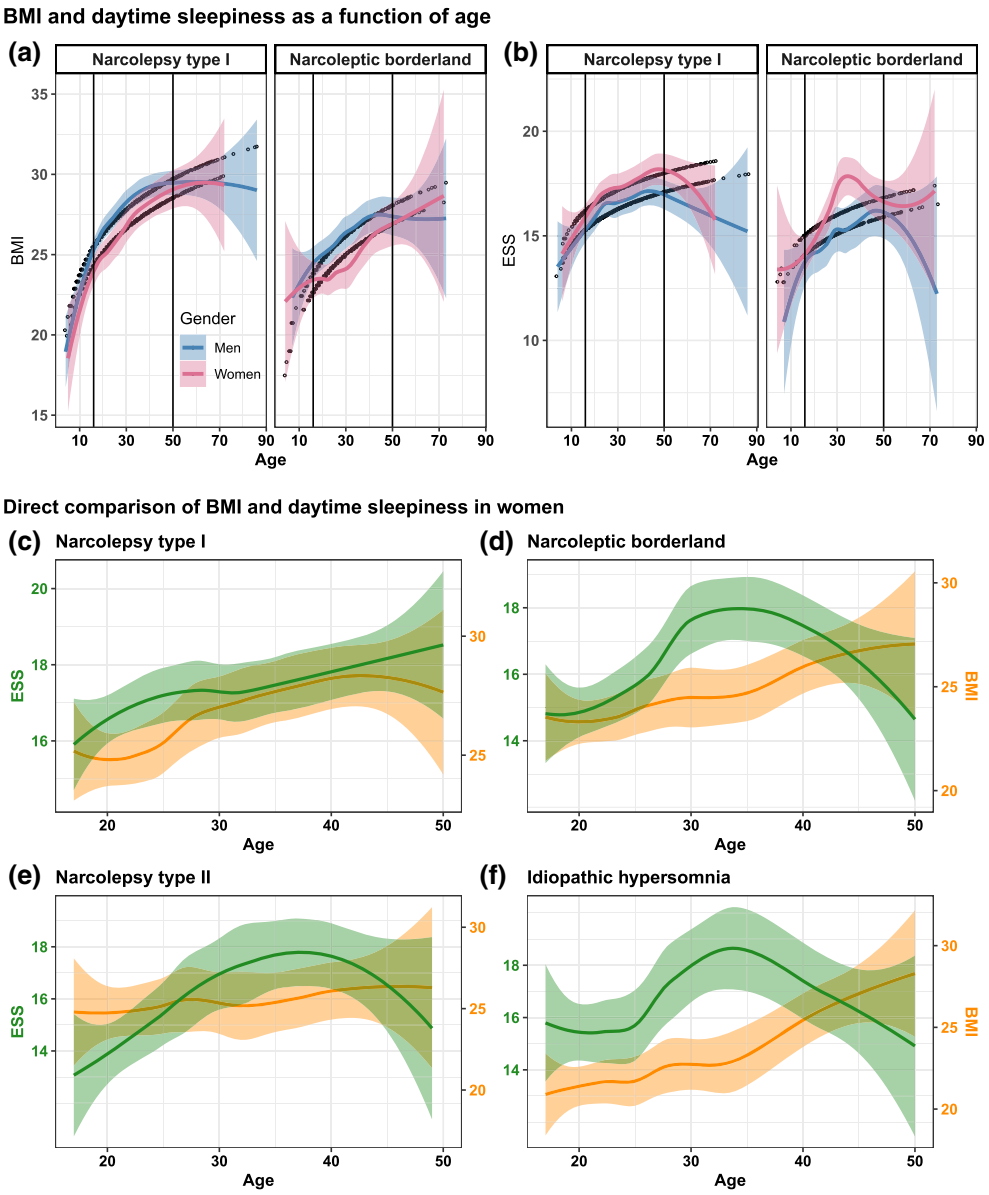

FIGURE 2 Body mass index (BMI) and daytime sleepiness as a function of age at diagnosis. Overall, BMI (a) and sleepiness (b) increase dependent on time of diagnosis. Red and blue lines and shadows show non-linear local regression fitting (LOESS) and respective confidence intervals. Black circles show predicted values per patient by linear regression (glm with factors *Gender* and *log2*(*Age*), all factors $p < 0.001$). Confidence intervals of local regression fitting (red and blue lines and shadows) are always overlapping with the linear regression model (black circles), with the exception of Epworth Sleepiness Scale (ESS) in women of the narcoleptic borderland (NBL). Black vertical lines show cut-offs for low abundant age ranges (16 and 50 years, respectively). (c and d) Daytime sleepiness and BMI in women with narcolepsy type I (NT1) and of the NBL, respectively. Due to low numbers of patients below 16 and above 50 years at diagnosis, only data between 16 and 50 years are shown. (e and f) Within the NBL, daytime sleepiness and BMI diverge in women with idiopathic hypersomnia (IH), with a peak about 30–40 years, but not in women with narcolepsy type II (NT2). Green and orange lines and shadows show ESS and BMI, respectively (shadows indicate confidence intervals of local smoothing).

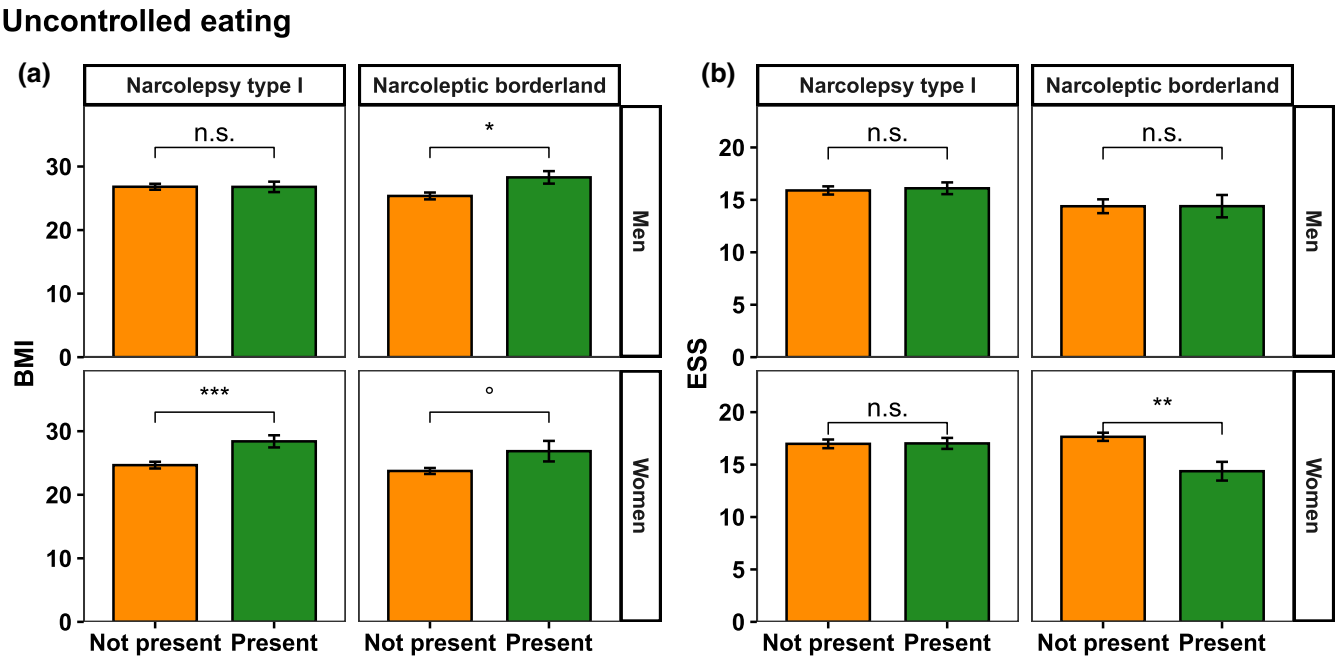

FIGURE 3 Associations of uncontrolled eating with body mass index (BMI) (a) and Epworth Sleepiness Scale (ESS) (b). Shown are bar charts with standard error bars for men and women with narcolepsy type I (NT1) and from the narcoleptic borderland (NBL). Significances are indicated for the respective post-hoc *t*-tests (***$p < 0.001$; **$p < 0.01$; *$p < 0.05$; °$p < 0.1$).

Holst et al., 2018), while EDS was similar for the NT1 and IH groups. These findings suggest that in NT1, hypocretinergic control or reward circuits may affect eating behaviour when compared with individuals without hypocretin deficiency.

Notwithstanding these prior findings, obesity and EDS often co-occur in the general population with a presumably normal hypocretin system even when controlling for OSA, a common cause of EDS (Bixler et al., 2005; Hayley et al., 2014; Panossian & Veasey, 2012; Slater et al., 2013). Therefore, we were surprised to find no correlation between BMI and sleepiness in our NBL population, even when accounting for gender differences. We decided to have a deeper look into the dimension of age. Consistent with previous reports, we found a roughly logarithmic rise of BMI until the age of 50 years in all groups (Yang et al., 2021). With respect to subjective daytime sleepiness, women from the NBL showed a marked increase in the early 30s, while the BMI only started to rise at the peak time of sleepiness (Figure 2d). Indeed, an increase of sleepiness in this age period in women when compared with men has previously been described in the healthy population (Boyes et al., 2017). Could the high daytime sleepiness in women from the NBL affect the control of their eating behaviour? Several studies suggested an involvement of control and reward circuits of the frontal brain in food choices, and their high sensitivity to sleep deprivation and sleepiness (Horstmann et al., 2011; Killgore et al., 2013; Libedinsky et al., 2011). More specifically, the vmPFC shows enhanced activity upon high- versus low-caloric food cues, especially in obese people (Martin et al., 2010), and reduced blood-oxygen-level-dependent (BOLD) response in the vmPFC predicts future weight gain in healthy adolescents (Stice et al., 2015). Prefrontal neural responses to food and control of eating behaviour in obese persons are modulated in a gender-specific manner (Horstmann et al., 2011). Food-related vmPFC activation has been negatively correlated with sleepiness and, only in women, with overeating (Killgore et al., 2013), suggesting a gender-specific sensitivity of food-control mechanisms to sleepiness. In today's societies where food is abundantly available, the role of food regimens monitored by the prefrontal cortex may increase. However, we found that uncontrolled eating behaviour was negatively associated with daytime sleepiness in women from the NBL, and could therefore not corroborate our hypothesis that uncontrolled eating behaviour might be the causal link between EDS and weight gain.

4.2 | EDS: Gender and age are two major contributing factors

Objective sleep parameters, subjective and objective sleep quality, and daytime sleepiness are age- and gender-dependent (Dorsey et al., 2020; Pierling et al., 2021; Svetnik et al., 2017), and additionally modulated in women during their fertile life phase over the oestrus cycle (Baker & Lee, 2018; Dorsey et al., 2020). We found higher levels of subjective daytime sleepiness in women than in men in both NT1 and in the NBL. MSLT sleep latencies, an objective measure for daytime sleepiness, were similar in women and men in the NT1 patient group, and even showed a trend to be longer in women compared with men in the NBL patient group. Is it surprising that our findings on subjective daytime sleepiness were not mirrored by objective measures? While MSLT sleep latencies have been reported to be shorter in women than men in patients with NT1 (Won et al., 2014), a study

in hypersomnolent patients found no gender differences for MSLT sleep latencies, and moreover demonstrated a discordance of objective and subjective measures of daytime sleepiness (Evangelista et al., 2021).

Corroborating earlier reports, women had an earlier age of symptom onset in the NT1 group (Luca et al., 2013), but not in the NBL group. Delay of diagnosis was independent of patient group and gender, while more sophisticated analysis methods revealed a trend to longer delay of diagnosis in women as compared with men, based on the EU-NN database (Zhang et al., 2022). Apart from gender differences, several studies investigated the evolution of daytime sleepiness over time. In the healthy population, specifically in the 3rd and 4th lifetime decades, the ESS was higher in women as compared with men (Boyes et al., 2017), and a recent study in patients that underwent hypersomnia evaluation found that ESS scores better predicted MSLT sleep latencies in older men than in younger women (Carvalho et al., 2024). Dauvilliers et al. reported a relatively stable MSLT sleep latency in patients with NT1 between 21 and 65 years (Dauvilliers et al., 2004). In our population, patients with NT1 exhibit a slight increase of subjective daytime sleepiness as measured with the ESS up to the age of 50 years. To our knowledge, the age dependency of subjective daytime sleepiness has not been investigated in the NBL. Thus, our data are the first to indicate that subjective daytime sleepiness in the NBL is modulated in a gender- and age-dependent manner, consistent with findings in the healthy population (Boyes et al., 2017). More specifically, we found that women from the NBL, unlike patients with NT1 or men from the NBL, show a distinct subjective daytime sleepiness peak in their early 30s. This life period coincides with female fertility and potentially with childbirth and caring for small children, which is a common cause of disturbed night sleep and in our society still more often experienced by women than men. Supporting this reasoning, oestradiol levels were positively associated with the ESS (Kische et al., 2016), and severe sleep debt has been associated with younger women living in a couple with kids (Leger et al., 2020). One possible explanation why EDS did not similarly increase in narcoleptic women is a possible ceiling effect: subjective sleepiness already reaches very high levels a decade earlier. Unfortunately, the EU-NN database does not contain any information regarding the parental status, and further studies are needed to explore external factors for daytime sleepiness such as sleep disturbances resulting from parental care of young children. However, many additional age- and gender-dependent factors, for example hormonal and metabolic changes, as well as subjective sleep quality and mood disorders like depression might contribute to the EDS peak in the early 30s in women of the NBL (Mong & Cusmano, 2016). Based on our findings, we suggest that the NBL contains a unique cluster of women in their fertile life period with a yet to be explored symptom configuration and aetiology. Because the cross-sectional design prevented us to explore the evolution of sleepiness and body weight across ages in central disorders of hypersomnolence, further longitudinal studies are needed to understand these complex changes.

5 | LIMITATIONS

Due to the cross-sectional retrospective study design, our results should be interpreted with caution on the level of causal relationships. With respect to the statistical power of our analyses, data from more than 1400 patients were available for the analysis of BMI and subjective daytime sleepiness. However, for the analysis of impulsive eating behaviour, only patient-reported data of 450 patients but no clinical diagnoses were available. Thus, we cannot exclude a bias towards more frequent data entry when symptoms were present, although we expect this bias to be similar in the different patient groups. Due to the limited sample size, we refrained from looking into the age-dependency of eating behaviour. Usually, the effect of age on dependent variables is modelled as a linear or logarithmic relationship, which is appropriate for many biological measures. Also, in our models for the dependent variables ESS and BMI, we assumed a logarithmic relationship of age, which proved to be appropriate for most patient groups. However, in some cases (here daytime sleepiness in women of the NBL), the concept of life periods would be beneficial for data interpretation. We therefore suggest to include the concept of life periods for future investigations on daytime sleepiness in women from the NBL (e.g. age as factor with levels [1] < 16 years "childhood/adolescence"; [2] 16–25 years "young adulthood/education"; [3] 26–40 years "adulthood/fertile"; [4] 41–65 years "middle adulthood/perimenopause"; [5] > 65 years "elderly/retirement"). Age at diagnosis peaked in early adulthood, with a low sample size for patients below 16 and above 50 years (Figure S1), therefore we acknowledge that our data are underpowered in these age ranges. In addition to the parameters addressed in our study, we are aware that many more important factors, including medication, mood disorders, fatigue, other sleep disorders like sleep-disordered breathing and lifestyle may contribute to the EDS and weight gain in NT1 and the NBL. With respect to medication, mood disorders and AHI, we added those as additional factors in our regression models. Due to the complexity and variety of treatment regimens and mood disorder diagnoses, we limited the analysis to the levels "With medication" versus "Drug-naïve" and "With psychiatric diagnosis" versus "Without psychiatric diagnosis", respectively, being aware that different treatments and mood disorders might have divergent effects. More specifically, sodium oxybate in NT1 is associated with weight loss (Schinkelshoek et al., 2019), some antidepressants may result in weight gain, and psychostimulants like methylphenidate may decrease appetite. In addition, most of the investigated variables exhibit differences between the EU-NN centres (Table S1). Reasons could be differences in diagnostic approaches and clinical practice of the clinicians, or regional differences in lifestyle and predisposing factors of the patients. These centre differences, together with the unbalanced contributions of different countries, indicate that our results are not representative for the European population and need to be validated in independent patient groups. In order to better characterize the NBL, the multi-centre "Swiss Primary Hypersomnolence and Narcolepsy Cohort study" (SPHYNCS; Dietmann et al., 2021) was launched at the University hospital,

Inselspital, Bern in 2020, and was extended to other European sleep centres in 2023. Clinical, biological (immunological, microbiome, peptidome), electrophysiological, long-term activity tracking, as well as information about life circumstances including eating behaviour, psychosocial and lifestyle factors are collected. The SPHYNCS is also collecting detailed data from healthy controls, which are missing in the EU-NN database so far. The data of the SPHYNCS will enable us to follow-up open questions and new hypotheses arising from this work.

6 | CONCLUSION AND CLINICAL IMPLICATION

In a large cohort of patients with central disorders of hypersomnolence, in comparison with the NBL, patients with NT1 had a higher BMI and daytime sleepiness, as well as a higher prevalence of impulsive eating and excessive weight gain shortly after symptoms onset. Specifically, in women from the NBL (but not in the other invested groups, namely NT1 women, NT1 men and men of the NBL), we found a marked subjective daytime sleepiness peak in the early 30s, while the BMI only started to rise at that age. This pattern seems to be mostly driven by women with IH. We suggest that the NBL contains a unique cluster of women in their fertile life period with a yet unexplored aetiology. Further research is needed to explore the underlying causes and mechanisms that contribute to the observed patterns. A better understanding of the factors contributing to EDS in this particular patient group will help to tailor interventions such as pharmacological treatments or lifestyle modifications.

AUTHOR CONTRIBUTIONS

Laura Ferrazzini: Writing – original draft; data curation; formal analysis; visualization. **Markus Schmidt:** Conceptualization; investigation; writing – review and editing; supervision. **Zhongxing Zhang:** Data curation; resources; writing – review and editing. **Ramin Khatami:** Data curation; writing – review and editing; resources; investigation. **Yves Dauvilliers:** Investigation. **Lucie Barateau:** Writing – review and editing. **Geert Mayer:** Investigation. **Fabio Pizza:** Investigation; writing – review and editing. **Giuseppe Plazzi:** Investigation. **Jari K. Gool:** Writing – review and editing; investigation. **Rolf Fronczek:** Investigation; writing – review and editing. **Gert Jan Lammers:** Investigation. **Rafael del Rio-Villegas:** Investigation. **Rosa Peraita-Adrados:** Investigation. **Markku Partinen:** Investigation. **Sebastiaan Overeem:** Investigation. **Karel Sonka:** Investigation; writing – review and editing. **Joan Santamaria:** Investigation. **Raphael Heinzer:** Investigation. **Francesca Canellas:** Investigation. **Antonio Martins da Silva:** Investigation. **Birgit Högl:** Investigation. **Christian Veauthier:** Investigation. **Aleksandra Wierzbicka:** Investigation. **Eva Feketeova:** Investigation. **Jitka Buskova:** Investigation. **Michel Lecendreux:** Investigation. **Silvia Miano:** Investigation. **Ulf Kallweit:** Investigation. **Anna Heidbreder:** Investigation. **Claudio L. A. Bassetti:** Investigation; funding acquisition; writing – review and editing; conceptualization; supervision. **Julia van der Meer:** Conceptualization; writing – original draft; writing – review and editing; visualization; validation; methodology; formal analysis; project administration; supervision; data curation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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