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Original Article

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Psychiatric comorbidity in Danish patients with narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia: a case–control study

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Abstract

***Study Objectives*:** To examine the difference in psychiatric comorbidity of Danish patients with Narcolepsy type 1 (NT1), Narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH).

***Methods*:** Polysomnography (PSG), Multiple Sleep Latency Test (MSLT), and lumbar puncture were performed on 505 patients referred to a sleep clinic for diagnostic evaluation of hypersomnia. Diagnosis, clinical characteristics, electrophysiologic data, and cerebrospinal fluid hypocretin-1 (Csf-Hcrt-1) results were retrieved. Subsequently, the patients were identified in the Danish national health registers to collect information on psychiatric diagnoses and psychotropic medication use 10 years before the sleep disorder diagnosis. The prevalence of psychiatric comorbidities per hypersomnia group was compared to a 1:4 general population control group matched on age, gender, and educational level.

***Results*:** A diagnosis of NT2 and IH was significantly associated with total psychiatric comorbidity compared to the matched controls but not NT1 (NT1: OR = 1.5; NT2: OR = 6.1; IH: OR = 5.2). NT1 was not significantly associated with any psychiatric disorder. NT2 was significantly associated with schizophrenia spectrum disorders (OR = 8.5), mood disorders (OR = 6.7), neurotic disorders (OR = 3.8), personality disorders (OR = 3.1), and behavioral and emotional disorders (OR = 4.3). IH was significantly associated with schizophrenia spectrum disorders (OR = 3.3), mood disorders (OR = 5.9), neurotic disorders (OR = 3.0), and behavioral and emotional disorders (OR = 4.0).

Conclusions: NT2 and IH had a close relationship to psychiatric disorders before diagnosis of their sleep disorder, while NT1 did not. This supports previous studies finding higher rates of psychiatric illness in patients with hypersomnia; however, it highlights the similarity between NT2 and IH. We believe this link to psychiatric disorders could play a role in the pathophysiology. Future studies evaluating the relation between hypersomnias of central origin and psychiatric diseases should include hypersomnia subclassifications to further the understanding of the differences in these disorders.

Key words: narcolepsy; psychiatric disorders; electrophysiology; clinical neurophysiology

Statement of Significance

The research holds significant importance due to the large cohort of patients, subgrouping of Narcolepsy type 1, Narcolepsy type 2, and idiopathic hypersomnia, and lastly reporting the specific cerebrospinal hypocretin-1 levels for each of these included patients. This novel approach enables us to explore the differences in these sleep disorders, concerning their psychiatric disorders before their sleep diagnosis. Consequently, our investigation seeks to reveal insights into the largely unexamined domain of psychiatric disorders in specific hypersomnia disorders.

Narcolepsy is a chronic neurologic sleep disorder characterized by excessive daytime sleepiness (EDS), disrupted nighttime sleep, sleep paralysis, hypnagogic hallucinations, and cataplexy [1, 2]. The diagnosis is based on the clinical presentation combined with electrophysiological examinations consisting of polysomnography (PSG) one night before a Multiple Sleep Latency Test (MSLT)

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[1–4]. The determination of low cerebrospinal fluid hypocretin-1/orexin-1 (Csf-Hcrt-1/OX-1) has been proved to diagnose Narcolepsy Type 1 (NT1) with high precision (Sensitivity = 0.93–0.99. Specificity = 1) [5]. An autoimmune-driven selective loss or inactivation of the hypocretin-producing neurons in the lateral hypothalamus is central to the development of disease [6, 7]. According to the 2014 edition of the International Classification of Sleep Disorders (ICSD-3), narcolepsy is divided into NT1 and Narcolepsy type 2 (NT2) based on the level of Csf-Hcrt-1 and the presence or lack of cataplexy[4]. Historically, narcolepsy was viewed by many as a disease within the psychiatric spectrum [8, 9]. Proof that narcolepsy was a somatic disease came when the landmark discovery of hypocretin deficiency in the cerebrospinal fluid of patients with narcolepsy was made in 2000 by Mignot et al. [10]. Several studies have shown a strong correlation between narcolepsy and psychiatric disorders. The psychiatric symptom spectrum in patients with narcolepsy and idiopathic hypersomnia (IH) is important because of its major impact on patient health and quality of life [11–14]. High but varying rates (4%–32%) of psychiatric comorbidity have been reported several times in patients with narcolepsy [15–19]. There are inconsistencies in the literature, and the causal relationship still needs exploration. Most importantly, earlier studies lack subtyping of hypersomnias [20, 21]. The causal and temporal dispersion in psychiatric comorbidity in patients with hypersomnia is insufficiently understood because the diagnostic spectrum of sleep disorders and psychiatric disorders overlap [8, 22]. Two main theories have been proposed as the cause of excess psychiatric disease in patients with NT1. One of them claims that the stress of having a persistent sleep disorder, which makes both social and professional life difficult, renders people more sensitive to psychiatric diseases. The other suggests, based on the linkage between the hypocretin (orexin) system and brain regions linked with mental disorders, that Csf-Hcrt-1 loss is one of the driving components of psychiatric disease [22–26]. Several studies have explored the psychiatric comorbidity in narcolepsy, but few include the measurement of Csf-Hcrt-1. Most research investigating psychiatric comorbidity in patients suffering form narcolepsy utilizes questionnaires instead of a diagnosis within the ICD-10 or DSM-5 [14, 17, 19, 27]. More importantly, almost no prior data regarding patients with IH exist, and a comparison between the three major disorders of central hypersomnia could lead to a better understanding of their pathophysiology.

Given these uncertainties, we aim to explore the patterns of psychiatric disease in patients with narcolepsy and IH by dividing them based on their hypocretin levels, evaluating their psychiatric comorbidities, and comparing them to matched population controls.

Materials and Methods

Study design

This study was designed as a case–control study. Initially, we examined the occurrence of psychiatric disorders 2 years after the diagnosis of the patients' sleep disorder. However, we found that all patients who developed psychiatric disorders did so before diagnosis of their sleep disorder. This led us to only base our model on psychiatric disorders before diagnosis of central hypersomnia.

Cases were defined by an NT1, NT2, or IH diagnosis in our sleep lab at the Danish Center of Sleep Medicine (DCSM). These patients were then identified in the Danish Civil Registration System (CRS) [28], which is possible since every citizen in Denmark is designated with a unique personal identification number at birth or immigration. Information regarding psychotropic medication was derived from the Danish National Prescription Registry (DNPR), and information regarding psychiatric diagnoses from the Danish Psychiatric Central Research Register (DPCR) [29, 30]. Patients were matched with controls from the general population according to sex, age, marital status, and municipality at the index year in a ratio of 1:4. The SAS SURVEYSELECT procedure was used for selecting a probability-based random control group.

Definition of sleep disorders

In this matched case–control study, we collected patients by retrieving all Csf-Hcrt-1 measurements requisitioned by trained sleep experts at the DCSM between 2004 and 2022 as a part of the standard evaluation for central hypersomnia. In this period, many patients were clinically evaluated for central hypersomnia but not selected for lumbar puncture if the suspicion of central hypersomnia was not present. Patients with a history of at least 3 months of EDS, defined as an irrepressible need to sleep or daytime lapses into sleep, were selected as candidates for the central hypersomnia evaluation. We retrieved the analyzed polysomnography (PSG) and MSLT data from our local database; these were all performed according to international standards and analyzed by expert technicians [31]. We confirmed all final diagnoses in the electronic patient journal, made by an expert clinician based on the 3rd edition of the International Classification of Sleep Disorders (ICSD-3) [4]. Information concerning the patients' clinical symptoms and demographic data was also found in the electronic patient files. We included all patients who received a diagnosis of NT1, NT2, or IH. Patients without an NT1, NT2, or IH diagnosis but with another primary sleep disorder explaining their hypersomnia, such as Kleine–Levine Syndrome, Sleep Apnea, Insomnia, Parasomnia, REM Sleep Behavior Disorder, or Restless Legs Syndrome, were excluded. All patients were rigorously interviewed about their sleep patterns, job schedules, and overall sleep hygiene. Some patients with NT1, NT2, and IH with comorbid sleep disorders, such as sleep apnea and restless legs syndrome; they were not excluded to make our patient sample clinically applicable. The personal identification numbers of these selected patients were searched in the Danish CRS [28]; if the patient was not found, they were excluded since it would not be possible to find a matched control.

Definition of psychiatric disorders

A psychiatric disease was defined as a diagnosis received in the secondary mental health care sector and thus recorded in the DPCR. Only patients with a sleep diagnosis from 2004 to 2021 (2022 has not yet been validated in the registers) were included to ensure consistent reporting. Two reasons exist for the choice of this time span. Firstly, Denmark began using the International Classification of Diseases 10th revision (ICD-10) in 1994 [32], and secondly, the national registers have not been updated until 2022. The occurrence of psychiatric comorbidity was defined as having any kind of psychiatric disorder 10 years before being diagnosed with a sleep disorder. A prospective approach would have been favorable, but due to the long diagnostic delay of narcolepsy [33] at 5–15 years evaluating the psychiatric diagnosis 10 years before the diagnosis of the sleep disorder was chosen. All patients with a diagnosis of non-organic sleep disorders defined as F51 in the ICD-10

were identified and removed from our analysis. This resulted in the removal of 7 patients with NT1, 7 patients with IH, and 1 patient with NT2.

From the DNPR, we identified patients who had redeemed prescriptions for psychoactive drugs, defined as any filled prescriptions with the Anatomical Therapeutic Chemical Classification System (ATC) codes N06A (antidepressants) and N05B (anxiolytics). The patients had to redeem at least two prescriptions within one year to be defined as having a psychiatric disorder. N06A was used to indicate a diagnosis of mood disorder, whereas N05B was used to indicate neurotic and stress-related disorders. Methylphenidate (N06BA04), modafinil (N06BA07), venlafaxine (N06AX16), sodium oxybate (N07XX04), and tricyclic antidepressants (N06AA) were excluded as indicators of psychiatric disorders due to their established use in the treatment of narcolepsy and IH [1, 2]. The exclusion of N05A (antipsychotics) was necessary to avoid overestimating the prevalence of schizophrenia spectrum disorders because of the frequent off-label use of antipsychotics [34]. In addition, very few patients with schizophrenia spectrum disorders are treated in the primary sector, making the data in DPCR the most reliable. The Danish registers have been found to have a good validity of diagnosis in schizophrenia [35] (for a schematic overview of the definitions used for each psychiatric diagnosis, see Supplementary Table S1).

The Danish healthcare system has a free public access. Private sleep clinics in Denmark exist but do not treat patients with central hypersomnias. The diagnosis and treatment of these rare patients are only conducted in specialized sleep labs around the country; these are all within the public system.

Statistical analyses

Group differences in categorical features were compared with the chi-squared test if there were more than five patients available; otherwise, the Fisher exact test was used. Continuous variables were compared via the Mann–Whitney Wilcoxon test. Odds ratios were calculated based on a multivariate logistic regression model used to assess the potential influence of the specific hypersomnia subtype on the comorbidity of a psychiatric disorder while controlling for the effects of age and sex. Odds ratios were calculated based on the multivariate logistic regression model. p-values < .05 were considered significant. Analyses were performed using SAS 9.4 TS Level 1M5 (SAS, Inc., Cary, NC, USA).

A logistic regression model identical to the one described here was deployed on the data 2 years prospectively initially; however, this model was not included since no patients were diagnosed with psychiatric disorders after their sleep disorder diagnosis.

Case versus control model.

The goal of this model was to compare the prevalence of psychiatric comorbidity in cases (NT1, NT2, or IH) to the general population. Psychiatric comorbidity status was compared to a matched control sample up to 10 years before the sleep diagnosis. The controls were drawn from the National Patient Register to ensure that it was representative and well matched to the case group. The presence or absence of a psychiatric condition diagnosed within the 10 years before the index date was captured by the outcome variable. This model was used to compare the incidence of psychiatric disorders in hypersomnia cases to the general population during the decade preceding sleep diagnoses. To assess total psychiatric comorbidity, one overall model was developed. Models were then focused on the psychiatric diagnostic groups of the ICD-10.

Case versus case model.

In this model, the primary objective was to examine the prevalence of psychiatric comorbidities diagnosed up to 10 years prior among the hypersomnia cases, using the NT1 group as the reference category. The outcome variable represented the presence or absence of a psychiatric comorbidity identified within the decade leading up to the index date, which is when the cases were diagnosed with NT1, NT2, or IH. The independent variable denoted the patient group, categorized as NT1 (reference group), NT2, or IH. An overarching model was initially constructed to assess total psychiatric comorbidity. Subsequent models were then deployed for the psychiatric diagnostic groups of the ICD-10, providing insights into which psychiatric diagnostic groups were most prevalent among the three groups.

Both models underwent adjustments for potential confounders, including age and gender, to ensure reliable and unbiased estimates. The application of logistic regression facilitated the derivation and interpretation of odds ratios, which offer clinical insights into the magnitude of the associations.

Results

The systematic collection of patients based on a Csf-Hcrt-1 measurement identified 505 patients, out of whom 226 were diagnosed with NT1, 115 with NT2, and 164 with IH. These numbers were reduced according to the flowchart in Figure 1. The final population included 179 patients with NT1, 100 patients with NT2, and 139 patients with IH. The baseline characteristics of these patients are summarized in Table 1, along with their primary clinical presentations and Csf-Hcrt-1 measurements.

Odds ratios for the case versus control and case versus case models

The results from the logistic regression for the case versus control model are visualized in Figure 2, Figure 3, and Figure 4. The case versus case model is in Figure 5. Tables displaying the specific values for all ORs, 95% confidence intervals, and p-values are found in Supplementary Tables S2 and S3. The model concerning cases versus controls showed that NT2 and IH compared with controls were significantly associated with having a psychiatric disorder, but NT1 was not. The OR for NT1 (OR = 1.5, 95% CI = 1.0 to 2.2) was not significant, but the ORs for NT2 (OR = 6.1, 95% CI = 3.6 to 10.4) and IH (OR = 5.2, 95% CI = 3.4 to 8.0). The similarity between NT2 and IH with the subsequent difference to NT1 is exemplified in the ORs regarding the psychiatric diagnostic groups. IH was associated with all psychiatric diagnostic groups except for behavioral syndromes (F50–59), personality disorders (F60–69), and developmental disorders (F80–89). Patients with NT2 were associated with all psychiatric diagnostic groups except behavioral syndromes (F50–59) and developmental disorders (F80–89). Patients with NT1 were not significantly different from controls in any psychiatric diagnostic groups. The strongest associations for NT2 and IH were schizophrenia spectrum disorders (NT2: OR = 8.5, 95% CI = 2.6 to 27.7 IH: OR = 3.3, 95% CI = 1.0 to 10.9), mood disorders (NT2: OR = 6.7, 95% CI = 3.8 to 12.1 IH: OR = 5.9, 95% CI = 3.7 to 9.6), and behavioral and emotional disorders with onset usually occurring in childhood (F90–F98) (NT2: OR = 4.3, 95% CI = 1.6 to 11.1 IH: OR = 4.0, 95% CI = 1.3 to 12.4).

Figure 5 shows that IH compared with NT1 was associated with any psychiatric disorder (OR = 3.2, 95% CI = 2.0 to 5.3). NT2 compared with NT1 was associated with any psychiatric disorder (OR = 3.8, 95% CI = 2.2 to 6.4). It is important to note the wide

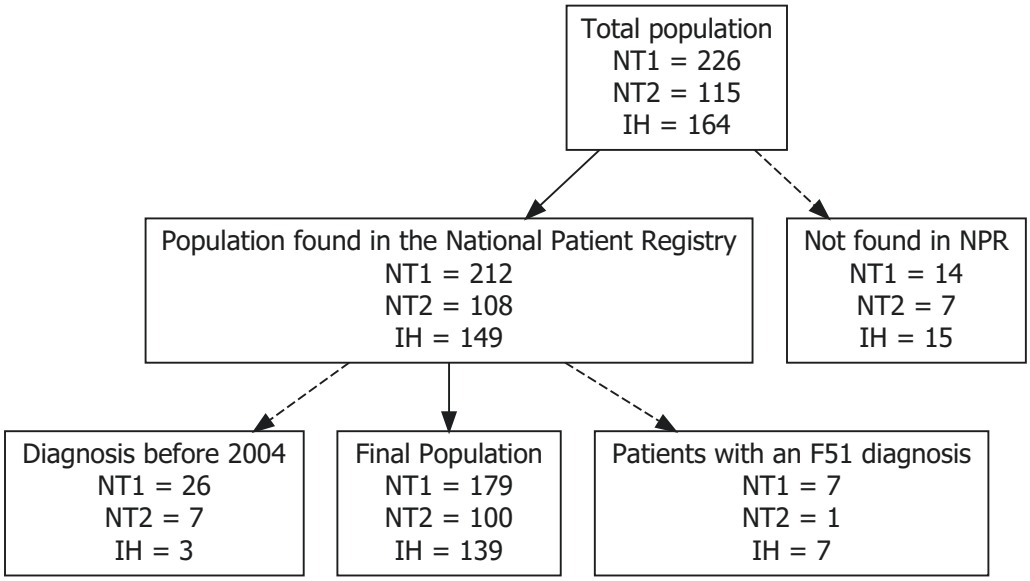


Figure 1. Patient flowchart from all patients collected to the number of patients included. This figure is a schematic representation of the initial identification of all available patients meeting the inclusion criteria and the subsequent exclusion. A patient that is not able to be found in the National Patient Register (NPR) could be due to not being born in Denmark and therefore not having a searchable identification number. Secondly, we excluded patients who were diagnosed before 2004 due to the 10-year design of this study.

confidence intervals produced by the low number of available patients.

For patients with NT2 and NT1 as reference regarding psychiatric diagnostic groups, there was a significant association in schizophrenia spectrum disorders (OR = 7.4, 95% CI = 1.8 to 29.5), mood disorders (OR = 6.3, 95% CI = 3.2 to 12.1), neurotic disorders (OR = 2.3, 95% CI = 1.1 to 4.7), and behavioral and emotional disorders with onset usually occurring in childhood (OR = 4.4, 95% CI = 1.3 to 14.2). IH compared with NT1 was only associated with mood disorders (OR = 5.4, 95% CI = 2.9 to 9.9).

The influence of age

Age distribution.

An analysis of different age groups was performed and can be found in the Supplementary Tables S4 and S5. Patients were separated into three groups: those aged 18 and up, those aged 30 and up, and all patients combined. When these patients were compared to matched controls, the pattern was similar, i.e. independent of age group.

In Supplementary Table S3, the frequency of total psychiatric disease in the different age groups is found. In the NT1 population, no age groups significantly differed from the control group, but their rates were slightly higher.

For NT2 aged 18 and up, the prevalence of any psychiatric disorder was 51.1% compared with the matched control group (15.2%). Among patients with NT2 aged 30 years and older, the prevalence increased to 58.1% and 17% in the control group, respectively. Both relationships were statistically significant.

In patients with IH aged 18 and up, the prevalence of any psychiatric disorders was 45.4% compared to 16.5% in controls. In the group over the age of 30, the prevalence was 47.2%, compared to 17.4% in the control group. Both relationships were statistically significant.

Supplementary Table S5 depicts the uneven age distribution. There were four times as many patients with NT1 below the age of 18 compared with NT2 and IH.

Absolute occurrence of psychiatric comorbidity.

Supplementary Table S6 shows the number of patients found in each psychiatric diagnostic group within each of the hypersomnia diagnoses can be found.

Discussion

Psychiatric comorbidity in patients with central hypersomnia

Previous research has found a strong correlational link between central hypersomnias, including narcolepsy, and psychiatric disorders. For the first time, we show that subtypes of central hypersomnia have a profound effect on occurrences of psychiatric comorbidities: NT2 and IH groups had a close relationship to psychiatric comorbidity, whereas NT1 did not. When compared to previous studies, these findings indicate a lower prevalence of psychiatric disorders in NT1 [14, 17, 36]. However, one previous study of Danish patients with narcolepsy, as well as some smaller studies, found nonsignificantly higher rates of psychiatric disorders in NT1 [15, 20, 21]. One possible explanation for these differences is that, while patients with NT1 tend to score high on depression-related questionnaires, they frequently do not have a formal diagnosis of depression or any other psychiatric disorder [20]. When examining the subgroups of each psychiatric disorder, the groups become small weakening the conclusions; however, the trends observed are important. These are that NT2 and IH are more affected by psychiatric comorbidity than NT1. It is also clear that schizophrenia spectrum disorders, mood disorders, and neurotic disorders are not highly prevalent among patients with NT1 compared with healthy controls or other hypersomnia disorders. The fact that NT2 and IH are tightly related to psychiatric disorders is a clue to the differing underlying pathophysiology of these central hypersomnia compared to the patients with NT1. Our data suggest that psychiatric comorbidity could be involved in the pathophysiology of these disorders. One interesting finding

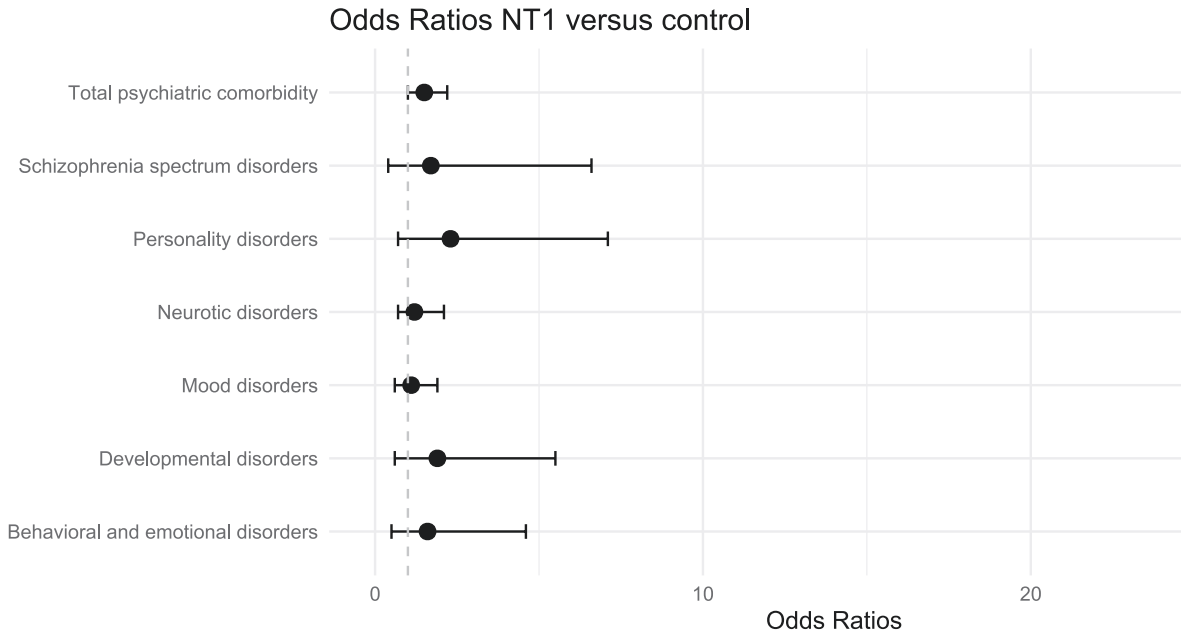
Table 1. Descriptive and Clinical Characteristics

Baseline table			
	NT1	**IH**	**NT2**
Number of patients (*n*)	179	139	100
Gender and age at PSG date			
Gender (%)			
Female	58.7	71.9	58.0
Male	41.3	28.1	42.0
Age groups at PSG (%)			
< 18	21.6	5.0	5.1
18–29	33.5	39.6	49.0
30–49	24.0	40.3	38.8
50+ years	21.0	15.1	7.1
Missing data (%)	6.7	0.0	2.0
Clinical data			
ESS group (%)			
ESS ≤ 10	11.4	10.3	23.3
11 ≤ ESS ≤ 12	8.9	5.6	13.7
13 ≤ ESS ≤ 15	29.3	24.3	37.0
16 ≤ ESS ≤ 24	50.4	59.8	26.0
Missing data	31.3	23.0	27.0
Fragmented			
Not fragmented	30.3	73.9	62.5
Fragmented	69.7	26.1	37.5
Missing data	7.8	–	–
Cataplexy (%)			
No cataplexy or missing data	23.5	93.5	78.0
Clear-cut cataplexy	45.3	–	5.0
Partial cataplexy	21.8	–	8.0
Occasional or atypical cataplexy	9.5	3.6	9.0
Missing data	0.0	0.0	0.0
Sleep attacks during the day (%)			
No sleep attacks	6.8	23.2	25.0
Sleep attacks	93.2	76.8	75.0
Missing data	17.3	19.4	20.0

Biochemical measures						
Hypocretin (HCRT)	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
	55.7	46.8	404.4	63.4	385.7	78.7
Missing data (*n*)	<5	–	0	0.0	<5	–

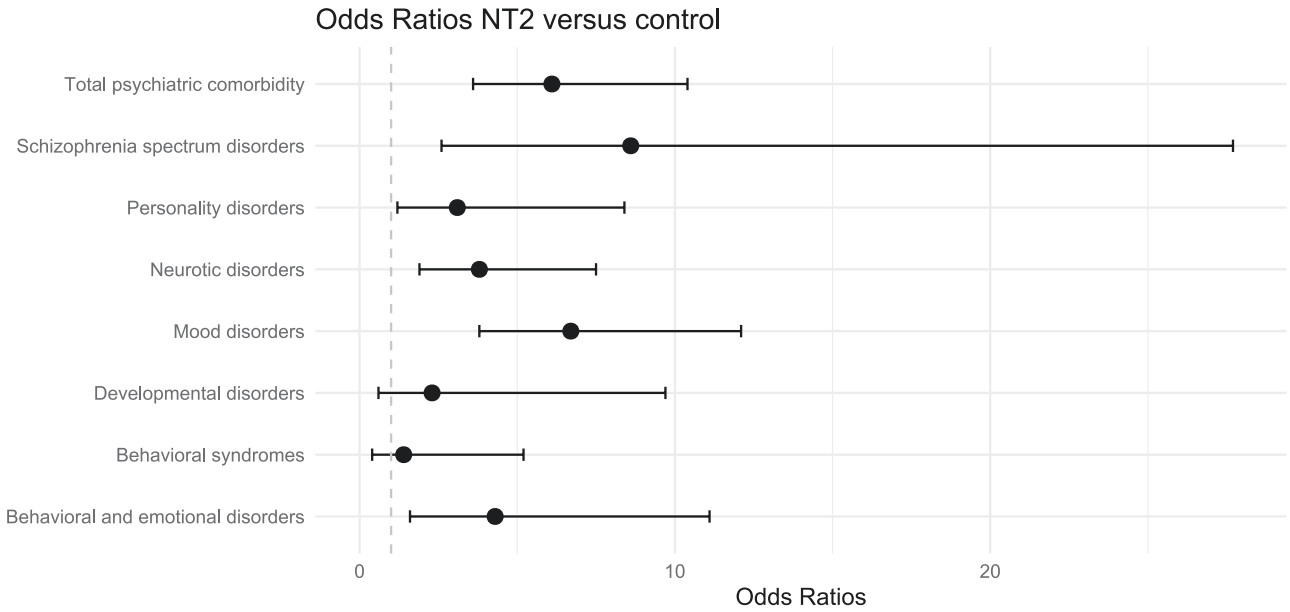
In this table, the general characteristics, clinical variables, and hypocretin measures are presented. All variables are from the date of the PSG except for the hypocretin measurement, which is routinely scheduled after the analysis of the electrophysiological evaluations. NT1, Narcolepsy type 1; NT2, Narcolepsy type 2; IH, idiopathic hypersomnia.
Sleep fragmentation was defined during the clinical diagnostic interview with the patient, asking them if they experienced disturbed nighttime sleep and, if so, how many awakenings they experienced during the night.
The definition of the different cataplexy categories was defined through the diagnostic interview as well by asking the patient questions regarding 1. The frequency of attacks, 2. The experience during an attack.
Cataplexy was defined clinically during the diagnostic interview based on the frequency and which muscles were paralyzed during an attack. A patient was defined as clear-cut cataplexy if they described their attack as sudden loss of muscle tone due to a trigger such as laughter resulting in complete muscle paralysis in seconds without the loss of consciousness. The same definition was used for patients with partial cataplexy, with the difference being only partial muscle paralysis. Lastly, we combined the groups of occasional or atypical cataplexy where the patient had either an unusual pattern of cataplexy or extremely rare cataplexy. We defined occasional cataplexy as less than five attacks per year.

is that mood and neurotic disorders were highly prevalent in patients with NT2 and IH but in patients' with NT2 schizophrenia was very common. Mood and neurotic disorders could be second to these patients' generally increased disease burden or an undiagnosed and untreated hypersomnia diagnosis. The large diagnostic delay in these patients could be one of the driving components in the development of their psychiatric disorders. The development of sleep disorders like NT2 and IH secondary to a severe psychiatric disorder could, however, also be the case in some of these patients. Since we do not know the exact pathophysiology of these patients, it is difficult to exclude this possibility.



A conditional logistic model for case versus control. NT1 = Narcolepsy Type 1. Each of the listed categories for psychiatric disorders is defined as a chapter in the ICD-10. Total psychiatric comorbidity is the combined occurrence of all psychiatric disorders. One is highlighted by the dashed line.

Figure 2. Logistic regression model for NT1 versus control. A conditional logistic model for case versus control. NT1, Narcolepsy type 1. Each of the listed categories for psychiatric disorders is defined as a chapter in the ICD-10. Total psychiatric comorbidity is the combined occurrence of all psychiatric disorders. One is highlighted by the dashed line.



A conditional logistic model for case versus control. NT2 = Narcolepsy Type 2. Each of the listed categories for psychiatric disorders is defined as a chapter in the ICD-10. Total psychiatric comorbidity is the combined occurrence of all psychiatric disorders. One is highlighted by the dashed line.

Figure 3. Logistic regression model for NT2 versus control. A conditional logistic model for case versus control. NT2, Narcolepsy type 2. Each of the listed categories for psychiatric disorders is defined as a chapter in the ICD-10. Total psychiatric comorbidity is the combined occurrence of all psychiatric disorders. One is highlighted by the dashed line.

It is important to remember that hypersomnia diagnosis is very rare, but psychiatric diagnoses are quite common, making it possible that some patients received a psychiatric diagnosis based on their hypersomnia complaints. However, this cannot account for the large overlap between NT2 and IH and low occurrence in patients with NT1. We believe that

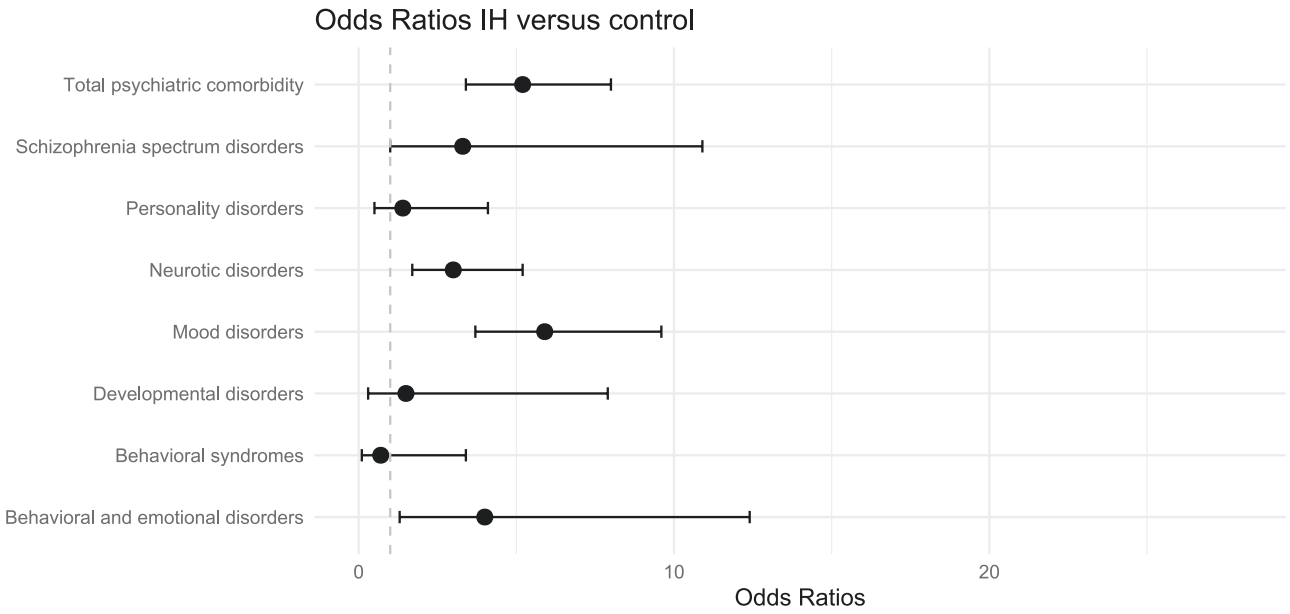


Figure 4. Logistic regression model for IH versus control. A conditional logistic model for case versus control. IH, idiopathic hypersomnia. Each of the listed categories for psychiatric disorders is defined as a chapter in the ICD-10. Total psychiatric comorbidity is the combined occurrence of all psychiatric disorders. One is highlighted by the dashed line.

our findings point to a pathophysiological difference between NT2, IH, and NT1.

The BOND study, which was based on an American claims database, was the most comparable to our study. The BOND study discovered a significantly higher frequency of patients with narcolepsy in all subtypes of psychiatric disease, with mood disorders and anxiety disorders being the most common. This seems to reflect our findings in the patients with NT2 and IH quite accurately, whereas the Danish patients with NT1 did not achieve significant ORs for any psychiatric disorder. The primary distinction between our study and the BOND study was that we have a diagnosis for the specific subtype of hypersomnia as well as a measurement of their Csf-Hcrt-1. We used the ICD-10, while they used the DSM-V. Although the BOND study included a larger number of patients (9.312), Csf-Hcrt-1 values were not available. One study did report Csf-Hcrt-1 and psychiatric comorbidity in a population of young patients with NT1 but did not include any patients with central hypersomnia and normal Csf-Hcrt-1 [13].

Besides the data from larger registers, studies utilizing questionnaire-based approaches have revealed that a significant amount of patients with narcolepsy have depressive feelings, which has a major impact on quality of life [12, 13, 37, 38]. In general, questionnaires are a good screening tool for psychiatric disorders, but their diagnostic accuracy is not high [39, 40].

Development of psychiatric disorders in hypersomnia

The main finding of this paper was the commonality of psychiatric comorbidity among patients with NT2 and IH before the diagnosis of their sleep disorder. As formerly suggested, the cause is complex and probably multimodal. We believe these results reflect true psychiatric disorders that could be developed by the debilitating nature of the hypersomnia disorders or have an impact on the patient, rendering them more prone to developing a hypersomnia disorder. Due to the nature of the methodology used, this is only speculative and further research is necessary to pin down the causality of excess psychiatric comorbidity in patients with hypersomnolence. Studies comparing schizophrenic spectrum disorders and NT1 have revealed overlapping symptoms but distinct differences in phenotypical expression [41]. Schizophrenia does not seem to play any significant role in the comorbidity in Danish patients with NT1. Interestingly, patients with NT2 showed the highest frequency of comorbid schizophrenia spectrum disorders, which points to a possible connection between these two separate entities. Earlier studies on patients with NT2 are few, and the underlying pathophysiology remains unknown. One substantial study did observe fewer clinical challenges and fewer brain abnormalities in NT2 compared with NT1 [42]. The authors used Csf-Hcrt-1 as a marker of NT1, but they did not report the levels found in their patients. Future research should focus on elucidating the disease mechanism in NT2.

It is plausible that the comparable incidence of depression among patients in the patients with NT1 and the matched controls may be attributed to the notion that the hypocretin system does not singularly contribute to the onset of depressive disorders but rather operates within a multifaceted system [9]. The data suggests that low Csf-Hcrt-1 does not drive the development of psychiatric disorders in disorders central hypersomnolence. Since we are examining the patients retrospectively, we of course do not exactly know the timely relation between the development of the psychiatric disorder and the loss of Csf-Hcrt-1. Therefore, a complete ruling out of its role is not possible.

What seems to be suggested by our data is that NT2 and IH have a strong link to psychiatric disorders, and possibly patients suffering from psychiatric disorders of the mood disorder and neurotic types have an increased risk of developing NT2 and IH. This might be caused by a fundamental pathophysiological relationship between NT2 and IH with psychiatric disorders. One

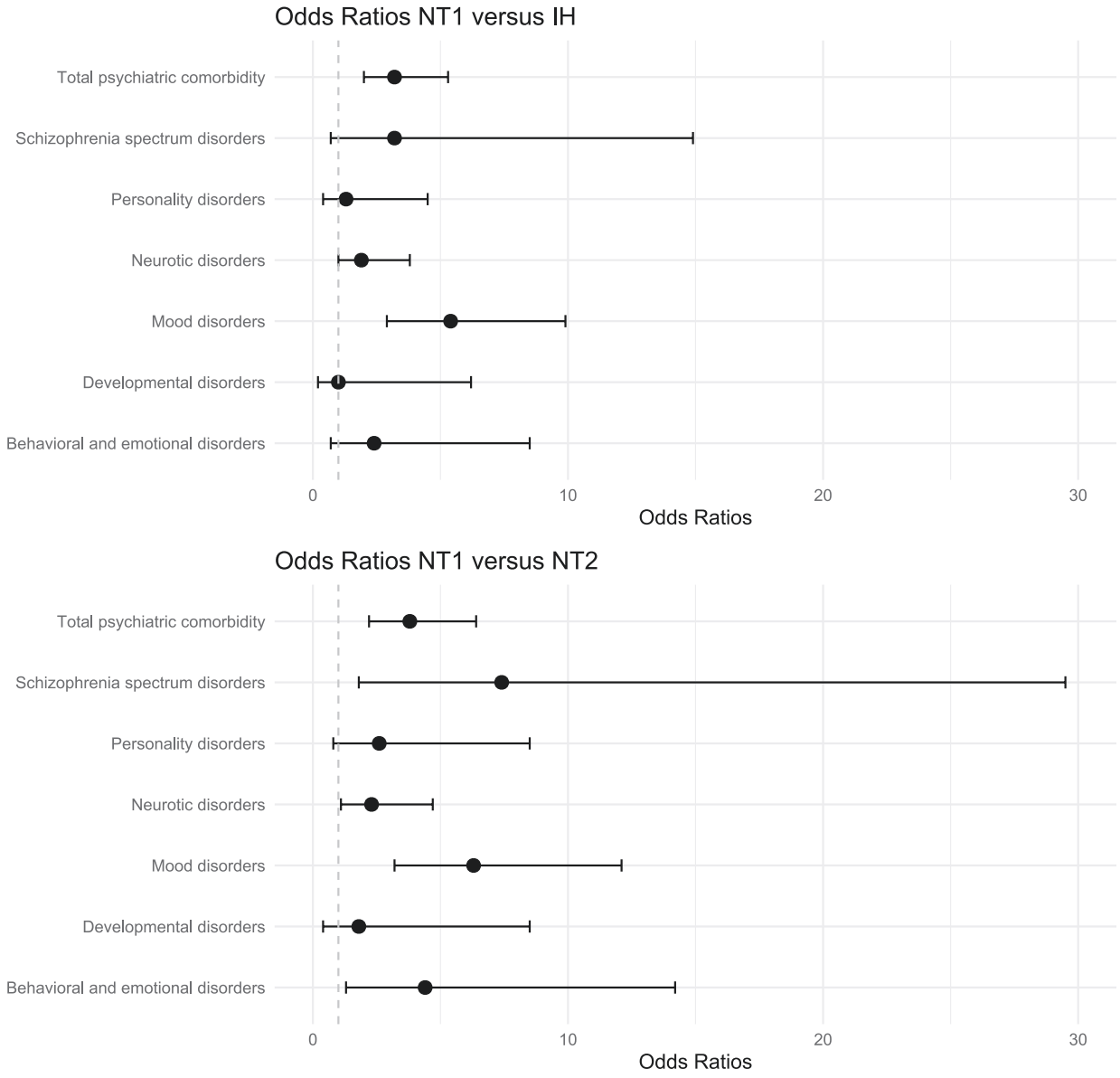


Figure 5. Logistic regression for psychiatric diagnosis (case versus case). Based on a model for each psychiatric diagnosis was used with the psychiatric diagnosis as the dependent variable and sleep diagnosis type (IH, NT1, and NT2) as independent (reference = NT1) also adjusting for age and gender in all models (not reported).

factor is the clinical experience that treatment of hypersomnolence is more effective in patients with NT1 compared to NT2 and IH. The difference is probably due to the fundamentally different nature of the disorders. The difficulty in proper treatment of patients with NT2 and IH and, thereby, increased pressure from their sleep disorders might be one of the causes for their increased psychiatric comorbidity [43]. Generally, EDS leads to low performance in daily life at school or work. In combination with an increased financial impact, this could explain a part of the higher psychiatric comorbidity in NT2 and IH [44].

Limitations

Diagnoses from the CSR are primarily hospital diagnoses, and the validity is generally high [35]. One potential limitation is the absence of expert medical evaluations, particularly in the context of pediatric diagnoses, which may be comparatively inadequate. Information about special offers for children (psychological assistance, educational offers, and special school offers) was not available. These factors could lead to under-diagnosis of psychiatric disorders and conditions in the child population, which would then lead to under-diagnosis in NT1. This study is limited by the sample size compared with other studies, making the findings in the subclassification of psychiatric disorders uncertain. The strength of the study is the systematic evaluation of all patients and the availability of Csf-Hcrt-1. The sleep diagnoses used in this study were all confirmed in the same sleep center using the same criteria defined in the ICSD-3. Defining psychiatric disorders as redeeming certain psychoactive medications might result in a misdiagnosis of psychiatric disorders and, subsequently, an overestimation of their frequency.

Expanding the time of observation beyond the 10 years of data available in this study would increase the accuracy of the data, but more importantly, prospective studies such as the Swiss Primary Hypersomnolence Cohort Study are needed to further increase our knowledge [45]. The age distribution in the three sleep disorder groups was skewed, with more patients with NT1 being younger than 18 years old. This could confound the lower number of psychiatric disorders in the patients with NT1, although the pattern of fewer psychiatric disorders in NT1 compared with both NT2 and IH persisted when using all available patients. Future studies should focus on the incidence of psychiatric disorders in patients with diseases of central hypersomnias to better grasp the causality.

Conclusion

Our findings highlight the severity of having central hypersomnia since this was associated with psychiatric comorbidity. Contrary to our expectation, Csf-Hcrt-1 deficient patients had a low rate of psychiatric disorders before diagnosis of their sleep disorder. Our findings indicate a need for a subdivision of patients with central hypersomnia and a deeper understanding of the pathophysiology driving NT2 and IH.

The rates of psychiatric disorders found in NT2 and IH indicate a relationship with the underlying pathophysiology. Possibly increasing the likelihood of developing NT2 or IH after a psychiatric diagnosis. The stress and debilitative nature of the NT2 and IH disorders may be important risk factors for developing psychiatric comorbidity. This is still not entirely clear, and future research should focus on elucidating the primary causes of psychiatric disorders in these patients. Improving timely diagnosis and finding more efficient treatments for NT2 and IH might ameliorate the impact of the disease.

Supplementary material

Supplementary material is available at *SLEEP Advances* online.

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Disclosure Statement

There were no conflicts of interest to report for any of the authors.

Author Contributions

Niels Christian Haubjerg Østerby (Conceptualization [lead], Data curation [lead], Formal analysis [equal], Funding acquisition [lead], Investigation [equal], Methodology [equal], Project administration [lead], Visualization [equal], Writing—original draft [equal], Writing—review & editing [lead]), Lone Baandrup (Supervision [equal], Writing—original draft [supporting], Writing—review & editing [equal]), and Poul Jennum (Funding acquisition [supporting], Methodology [supporting], Project administration [supporting], Resources [lead], Supervision [lead], Writing—original draft [equal], Writing—review & editing [equal])

Data Availability

The data used in this paper is stored locally at our Department of Sleep Medicine in Denmark, but the data extracted from the registers are only accessible upon authorized access from the custodians of the national registers. The local data is accessible in an anonymized form upon a reasonable request.

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