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RESEARCH ARTICLE

International Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (iSPHYNCS): the impact of psychiatric comorbidities on daily life in central disorders of hypersomnolence—a vicious circle

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Summary

Presence of psychiatric comorbidities is well documented in narcolepsy type-1 (NT1) but there are limited data on patients with 'other central disorders of hypersomnolence' (OCH). This study aimed to investigate frequency of psychiatric comorbidities in patients with NT1 and OCH, and to evaluate their impact on quality of life and sleep as an additive factor in combination with hypersomnolence-related symptoms. This study was conducted within the scope of the international Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (iSPHYNCS), which aims to find new biomarkers in central disorders of hypersomnolence (CDH). Study participants underwent Mini International Neuropsychiatric Interview and completed questionnaires related to quality of life and sleep. Comparative analysis was conducted to investigate group differences, and multivariable regression models were used to reveal the impact of psychiatric comorbidities. Among a total of 90 patients, 26 were

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diagnosed with NT1 and 64 with OCH. In all, 38 patients showed at least one psychiatric disorder, 27% of NT1 and 48% of OCH, with female dominance (50% in females versus 23% in males, $p < 0.02$). Major depressive episodes ($n = 29$) were most common, followed by suicidality ($n = 13$). Patients with a psychiatric diagnosis were more fatigued ($\beta = 0.70$, $p < 0.05$), apathic ($\beta = -5.41$, $p < 0.002$), had more disturbed sleep ($\beta = 0.55$, $p < 0.02$), worse sleep ($\beta = 1.89$, $p < 0.001$) and general health ($\beta = -12.55$, $p < 0.02$) quality. Comorbid psychiatric disorders are frequent in patients with CDH and worsen the impact of hypersomnolence-related symptoms on daily activities regardless of the type of CDH. Psychiatric comorbidities may create a vicious circle with fatigue and avoidance of physical activities, which aggravates hypersomnolence-related symptoms.

KEYWORDS
central disorders of hypersomnolence, hypersomnia, narcolepsy, neuropsychiatric interview, psychiatric comorbidities, psychiatric disorders, quality of life, vicious circle

1 | INTRODUCTION

Excessive daytime sleepiness (EDS) and hypersomnolence are symptoms that are multi-factorial and can be the expression of underlying sleep disorders, neurological/systemic or psychiatric problems (Pallesen et al., 2007). The causal relationship between EDS/hypersomnolence and psychiatric disorders is often unclear. Fatigue is often associated with depressive disorders, whereas EDS and hypersomnolence are rather considered as core symptoms of central disorders of hypersomnolence (CDH), such as narcolepsy type-1 (NT1) or type-2 (NT2) (Ruoff et al., 2017). While fatigue is often confused with EDS, it is not only a frequent symptom of psychiatric disorders, but also of CDH (Bassetti et al., 2019; Ruoff et al., 2017).

Narcolepsy type-1, a well-defined disease in the group of CDH is mainly characterised by EDS, cataplexy, hypnagogic or hypnopompic hallucinations, sleep paralysis, and disturbed night-time sleep (Bassetti et al., 2019). To date, many studies have shown that major depressive episodes (Fortuyn et al., 2010; Ohayon, 2013; Ruoff et al., 2017), generalised anxiety and panic disorders (Fortuyn et al., 2010; Ohayon, 2013), obsessive–compulsive disorder (Ohayon, 2013), schizophrenia (Canellas et al., 2014) and other psychotic disorders (Canellas et al., 2014), eating disorders, mainly presented as night eating syndrome (Baldini et al., 2024; Dahmen et al., 2008), attention deficit and hyperactivity disorder (mainly in paediatric patients with NT1) (Lecendreux et al., 2015; Zamarian et al., 2015), and various cognitive problems (Zamarian et al., 2015) are more common in patients with NT1 compared to the normal population. Mood disorders, the most frequent psychiatric comorbidity in patients with NT1, have been reported up to 56.9% in large case series (Daniels et al., 2001; Ruoff et al., 2017). In a cohort study by Cohen et al. (2018), NT1 was associated with a 4.88-fold increased risk of all psychiatric disorders. Lee et al. (2017) diagnosed mood disorders in 32.7% of all patients compared to 6.3% in a control group (NT1 + NT2: $n = 1258$ versus 2580 controls). In a retrospective study, Black et al. (2017) found mood disorders in 37.9% of all patients with NT1/NT2 versus 13.8% in a control group (with obesity). Besides, fatigue, which has been reported in up to 62.5% of these patients, is associated with more severe depressive symptoms (Droogleever Fortuyn et al., 2012).

In many of these studies, patients with NT1 and NT2 were evaluated as a single 'narcolepsy' group and not analysed separately, though only NT1 is a clear-cut diagnosis with well-described biomarkers. There are limited studies evaluating whether there is an altered risk of fatigue and psychiatric comorbidities in patients with CDH other than NT1, such as NT2, idiopathic hypersomnia (IH) or insufficient sleep syndrome (ISS) (Black et al., 2017). Although psychiatric comorbidities, predominantly mood disorders, have been reported less often in NT2 and IH compared to NT1, (from 15% to 25%), these findings may vary in different case series (Barateau et al., 2017). In addition, fatigue and hypersomnolence symptoms may often be confused in patients with IH, although their rates could not be clearly demonstrated in the literature (Vernet et al., 2010). Therefore, there is a need for studies that focus on the differences between NT1 versus other central hypersomnias (OCH) disorders in terms of frequency, diversity and severity of comorbid psychiatric disorders, exhaustion and fatigue.

Moreover, studies on this topic have generally been carried out with different subjective assessment scales and there is no standardised psychiatric evaluation method validated for this specific group of patients. In this context, the Mini International Neuropsychiatric Interview (MINI), a diagnostic interview tool structured following both Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) and International Classification of Diseases 10th Revision (ICD-10) diagnostic criteria, examining 17 different major psychiatric disease groups, was considered to be a good alternative (Sheehan et al., 1998). To date, only one study used the MINI to assess psychiatric disorders in CDH (Alasim et al., 2020). In this study, the frequency of major depressive disorders, suicidality, psychotic disorders, bulimia nervosa and generalised anxiety disorders was increased in patients with narcolepsy compared to healthy controls (Alasim et al., 2020). However, patients with OCH were not included and NT1 versus NT2 was not separated in this study (Alasim et al., 2020).

With this background, our study had three main objectives: (1) comparison of the frequency and type of psychiatric comorbidities in patients with NT1 and OCH using a structured psychiatric assessment tool (MINI); (2) comparison of the level of physical activity, hypersomnolence-related symptoms, sleep and overall quality of life (QoL) in patients with NT1 versus OCH, and patients with versus without a psychiatric diagnosis; and (3) determination of the relationship between subjective complaints about hypersomnolence-related symptoms and the presence of a psychiatric diagnosis in patients with NT1 or OCH regardless of the type of CDH.

2 | METHODS

2.1 | Study design

This study was conducted in six different Swiss sleep centres within the scope of the prospective Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (SPHYNCS), that after the inclusion of other European centres has been renamed the international SPHYNCS (iSPHYNCS). We refer to the published study protocol for further details (Dietmann et al., 2021). Centres participating (alphabetical order): Bad Zurzach (Sleep Center); Klinik Barmelweid AG (Clinic and Sleep Center); Basel (Sleep Center Basel); Bern (Sleep Center and University Hospital Inselspital); Lugano (Sleep Center and Neurocenter of the Southern Switzerland, Regional Hospital [EOC]); St. Gallen (Sleep Center AG and Cantonal Hospital). The study was approved by local ethics committees (2019-00788). The study has been registered in the international clinical trials registry: https://clinicaltrials.gov/study/NCT04330963.

2.2 | Participants

Individuals between the age of 16–70 years, native speakers of German, French or Italian, presenting to the sleep centres with subjective complaints of EDS and/or hypersomnolence and giving their informed written consent were included to the study. Exclusion criteria were the presence of other sleep disorders or neurological or systemic diseases as more probable causes for EDS/hypersomnolence among others (Figure 1). This analysis contains data from the first 90 participants in the iSPHYNCS study who underwent the MINI evaluation (for the details of the study protocol and methodology, see Dietmann et al., 2021).

2.3 | Outcome parameters

The impact of EDS and/or hypersomnolence on night-time sleep and QoL was investigated with both various standardised subjective assessment scales and additional questions (Figure 1), which were selected from the large number of assessment scales used in the iSPHYNCS study in accordance with the objectives of this sub-study; including the Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Narcolepsy Severity Scale (NSS), Idiopathic Hypersomnia Severity Scale (IHSS), Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI), Sleep Inertia Questionnaire (SIQ), 36-item Short-Form Health Survey (SF36), and Apathy Evaluation Scale-Self-rated (AES-S). Aside from validated scales, additional questions were used, which were adapted from previous publications (Daniels et al., 2001; Maski et al., 2017), to address additional potentially disabling symptoms and restrictions in daily life caused by hypersomnolence-related symptoms. All study participants underwent a comprehensive structured diagnostic neuropsychiatric assessment through MINI – German (version 7.0.2, $n = 76$), French (version 5.0.0, $n =$ six) and Italian (version 5.0.0, $n =$ eight) versions (Sheehan et al., 1997; Sheehan et al., 1998), which had been designed as a diagnostic interview for the major psychiatric disorders according to DSM-IV and ICD-10. The MINI evaluation was performed by dedicated, experienced members of the study team either face-to-face or by telephone. Demographics were recorded, along with the level of physical activities and body mass index (BMI).

2.4 | Objective assessments and subgroups

A 1-night polysomnography, multiple sleep latency test, maintenance of wakefulness test, 14-day actigraphy and sleep diary records were analysed in all study participants for the differential diagnosis of CDH. Cerebrospinal fluid-hypocretin measurements and human leucocyte antigen phenotyping were used as biomarkers to achieve a clear-cut diagnosis of NT1. Differential diagnoses of CDH were determined according to the International Classification of Sleep Disorders–Third Edition (ICSD-3; American Academy of Sleep Medicine [AASM], 2014). For the purpose of this study, all participants were divided into two groups: NT1 and OCH (non-NT1). The OCH group included patients with the diagnoses of NT2, IH, ISS, hypersomnia associated with a psychiatric disorder and excessive daytime sleepiness not otherwise specified.

2.5 | Statistical analysis

Categorical variables were expressed as numbers (% total), while continuous variables were expressed as median (interquartile range [IQR], first quartile–third quartile). In comparing NT1 and OCH groups, Fisher's exact test or chi-square for categorical variables test (selection was made based on sample size) and Mann–Whitney *U* test for continuous variables (which were non-normally distributed) were used. Further prediction analysis for continuous and ordinal variables was made by a general linear model. Multivariable regression analysis was performed to evaluate if the presence/absence of psychiatric comorbidity was associated with the scores of subjective assessment scales and the severity of daily life troubles due to hypersomnolence-related symptoms, regardless of the type of CDH and the effect of sex. RStudio IDE 2022.07.0 was used for the statistical analysis and data visualisation.

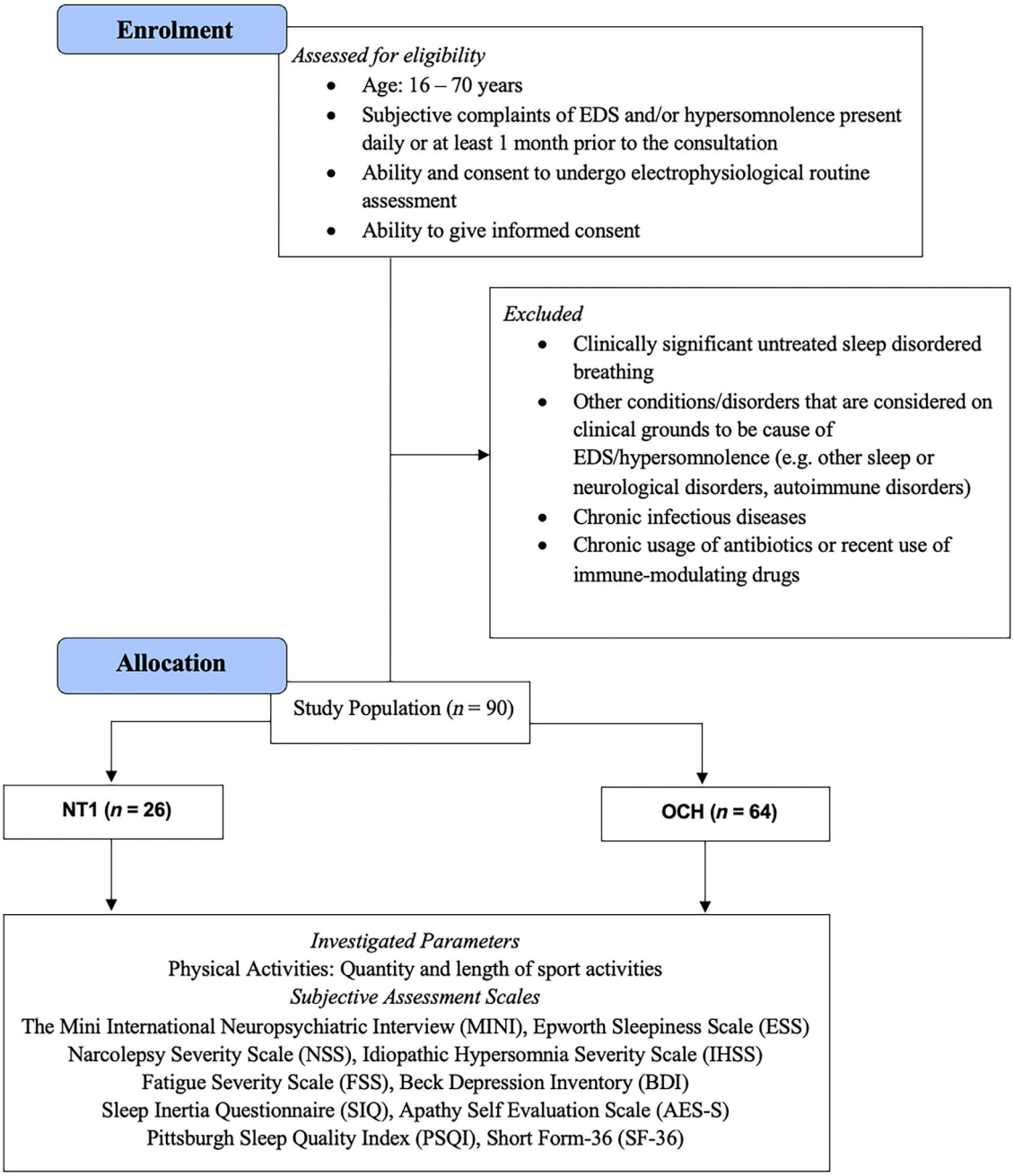

FIGURE 1 The inclusion and exclusion criteria of the International Swiss Primary Hypersomnolence and Narcolepsy Cohort Study (iSPHYNCS) and the list of investigated parameters. EDS, excessive daytime sleepiness; NT1, narcolepsy type-1; OCH, other central hypersomnias.

3 | RESULTS

A total of 90 patients with a diagnosis of CDH (26 males, 64 females, mean [standard deviation, SD] age 28.86 [9.14] years) were included. According to the objective evaluation criteria defined in the Methods, the primary ICSD-3 diagnosis of 26 patients was NT1, while 64 were diagnosed with OCH. The OCH group included patients with the primary diagnoses of NT2 (n = six), IH (n = 29), ISS (n = 10), and hypersomnia associated with a psychiatric diagnosis (n = nine). The remainder of the group (n = 10) consisted of borderline cases that did not exactly meet the ICSD-3 criteria and were reported as excessive daytime sleepiness which could not be classified more precisely. The mean (SD) delay of diagnosis was 115.20 (87.37) months in NT1 and 90.37 (80.63) months in OCH, while this difference was not statistically significant (p = 0.110). The MINI evaluation demonstrated at least one psychiatric disorder in 42.0% of the whole study population

TABLE 1 Comparison of the Mini International Neuropsychiatric Interview psychiatric diagnoses distributions according to the central disorders of hypersomnolence type (narcolepsy type-1 versus other central hypersomnias) and sex (male versus female).

		Central disorders of hypersomnolence			Sex		
MINI category	Overall, *n/N* (%) (*N* = 90)	NT1, *n/N* (%) (*n* = 26)	OCH, *n/N* (%) (*n* = 64)	*p* NT1 vs OCH	Male, *n/N* (%) (*n* = 26)	Female, *n/N* (%) (*n* = 64)	*p* Male vs female
Any psychiatric diagnosis	38/90 (42.0)	7/26 (27.0)	31/64 (48.0)	0.061	6/26 (23.0)	32/64 (50.0)	0.019*
Any major depressive events	29/88 (33.0)	5/25 (20.0)	24/63 (38.0)	0.100	4/26 (15.0)	25/62 (40.0)	0.023*
Current major depressive event	5/88 (5.7)	0/25 (0)	5/63 (7.9)	0.300	2/26 (7.7)	3/62 (4.8)	0.600
Past major depressive event	24/87 (28.0)	5/25 (20.0)	19/62 (31.0)	0.300	2/25 (8.0)	22/62 (35.0)	0.009**
Recurrent major depressive event	9/85 (11.0)	2/25 (8.0)	7/60 (12.0)	0.900	0/25 (0)	9/60 (15.0)	0.053
Any suicidal attempts	13/86 (15.0)	4/25 (16)	9/61 (15.0)	0.900	3/26 (12.0)	10/60 (17.0)	0.700
Current panic disorder	9/85 (11.0)	0/25 (0)	9/60 (15)	0.053	3/25 (12.0)	6/60 (10.0)	0.700
Any psychotic events	5/80 (6.2)	1/24 (4.2)	4/56 (7.1)	0.900	1/25 (4.0)	4/55 (7.3)	0.900
Any eating disorders	4/82 (4.9)	0/23 (0)	4/59 (6.8)	0.600	0/23 (0)	4/59 (6.8)	0.600
Current social phobia	3/84 (3.6)	0/25 (0)	3/59 (5.1)	0.600	0/25 (0)	3/59 (5.1)	0.600
Current generalised anxiety disorder	2/84 (2.4)	1/25 (4.0)	1/59 (1.7)	0.500	0/25 (0)	2/59 (3.4)	0.900
Current agoraphobia	1/82 (1.2)	0/24 (0)	1/58 (1.7)	0.900	0/24 (0)	1/58 (1.7)	0.900
Current obsessive-compulsive disorder	1/85 (1.2)	0/25 (0)	1/60 (1.7)	0.900	1/26 (3.8)	0/59 (0)	0.300
Current substance use disorder	1/83 (1.2)	0/25 (0)	1/58 (1.7)	0.900	1/25 (4.0)	0/58 (0)	0.300

Note: group comparisons for categorical variables were performed with Fisher's exact test.
Abbreviations: MINI, Mini International Neuropsychiatric Interview; NT1, narcolepsy type-1; OCH, other central hypersomnias.
*$p < 0.05$; **$p < 0.01$.

($n = 38$), of which 31 had the diagnosis of OCH and seven NT1 (Table 1, 48.0% versus 27.0%, respectively, $p = 0.061$). Major depressive disorders were the most common psychiatric diagnoses, followed by suicidal attempts, panic disorder, any psychotic events and eating disorders, respectively. The differences between OCH and NT1 did not reach significance also at the level of individual categories for each psychiatric disorder. Any psychiatric events (50.0% versus 23.0%, $p = 0.019$), any major depressive disorder (40.0% versus 15.0%, $p = 0.023$) and past major depressive events (35.0% versus 8.0%, $p = 0.009$) were significantly more common in females than males (Table 1). There was no significant difference in mean delay for the diagnosis of CDH between the patients with and without a psychiatric diagnosis (mean [SD] 82 [61] versus 104 [87] months, $p = 0.451$). In all, 26.9% of patients with NT1 and 53.1% of patients with OCH were drug naïve (45.6% of the study population). Primary medication at the time of study enrolment was modafinil in 21.1% of all participants, methylphenidate in 11.1%, sodium oxybate in 3.3% and pitolisant in 1.1%, the latter two were taken only by patients with NT1. The rest of the treated study population ($n = 16$ [17.7%]) was under antidepressants, like duloxetine, venlafaxine or clomipramine. As the study inclusion was generally performed shortly after first diagnosis, most patients had started their medication only recently. There was no significant difference in distribution of medications between patients with and without a psychiatric diagnosis ($p = 0.513$).

3.1 | Physical activities

Patients with OCH were significantly less engaged in sports than patients with NT1 (69.0% versus 96.0%, $p = 0.005$), although the median BMI value was higher in NT1 group (26.1 versus 23.3 kg/m^2, $p = 0.011$; Table 2). On the other hand, patients with a psychiatric diagnosis were significantly less active in sports than those without (66.0% versus 85.0%, $p = 0.046$; Table 2). Also, the duration of sport activities was shorter in patients with a psychiatric diagnosis in comparison to without ($p = 0.005$, Table 2). Moreover, SF36 Physical Functioning scores were lower in patients with a psychiatric diagnosis compared to patients without a psychiatric diagnosis (90.0 versus 100.0, $p = 0.001$; Table 3) regardless of the type of CDH.

3.2 | Subjective sleep and daily life assessment questionnaires

Patients with NT1 stated significantly higher scores in ESS ($p = 0.044$), and NSS for EDS ($p = 0.005$), hallucinations ($p = 0.002$) and sleep paralysis ($p = 0.003$) compared to patients with OCH. Patients with OCH were significantly more fatigued ($p = 0.017$), had more severe sleep inertia ($p = 0.013$), and less QoL in terms of physical functioning ($p = 0.039$), energy/fatigue

TABLE 2 Table for comparison of demographic characteristics and physical activity habits according to the central disorders of hypersomnolence type (narcolepsy type-1 versus other central hypersomnias) and presence of any psychiatric diagnosis (present versus not present).

		Central disorders of Hypersomnolence			Presence of any psychiatric diagnosis		
Variable	Overall ($N = 90$)	NT1 ($n = 26$)	OCH ($n = 64$)	p NT1 vs OCH	Present ($n = 38$)	Not present ($n = 52$)	p Present vs not present
Age, years, median (IQR)	27.0 (22.0–35.0)	26.0 (19.0–34.0)	28.0 (23.0–35.0)	0.300	26.0 (21.0–35.0)	28.0 (22.0–35.0)	0.700
Sex, male, *n/N* (%)	26/90 (29.0)	11/26 (42.0)	15/64 (23.0)	0.120	6/38 (16.0)	20/52 (28.0)	0.021*
Body mass index, kg/m^2, median (IQR)	23.7 (21.7–27.5)	26.1 (22.6–30.7)	23.3 (20.5–26.2)	0.011*	24.2 (21.0–28.5)	23.3 (21.8–26.2)	0.600
Sport Activities, yes, *n/N* (%)	69/90 (77.0)	25/26 (96.0)	44/64 (69.0)	0.005**	25/38 (66.0)	44/52 (85)	0.046*
Quantity of sport activities, *n/N* (%)				0.200			0.200
Never	21/76 (28.0)	1/21 (4.8)	20/55 (36.0)		13/30 (43.0)	8/46 (17.0)	
<once a week	3/76 (3.9)	1/21 (4.8)	2/55 (3.6)		1/30 (3.3)	2/46 (4.3)	
2–3 times a week	30/76 (39.0)	14/21 (67.0)	16/55 (29.0)		7/30 (23.0)	23/46 (50.0)	
4–6 times a week	18/76 (24.0)	4/21 (19.0)	14/55 (25.0)		7/30 (23.0)	11/46 (24.0)	
Daily	4/76 (5.3)	1/21 (4.8)	3/55 (5.5)		2/30 (6.7)	2/46 (4.3)	
Duration of sport activities, *n/N* (%)				0.051			0.005**
Never	21/90 (23.0)	1/26 (3.8)	20/64 (31.0)		13/38 (34.0)	8/52 (15.0)	
<30 min	7/90 (7.8)	3/26 (12.0)	4/64 (6.2)		4/38 (11.0)	3/52 (5.8)	
30–60 min	39/90 (43.0)	14/26 (54.0)	25/64 (39.0)		16/38 (42.0)	23/52 (44.0)	
>60 min	23/90 (26.0)	8/26 (31.0)	15/64 (23.0)		5/38 (13.0)	18/52 (35.0)	

Note: All categorical and ordinal variables were shown as *n/N* (percentage, %) and all continuous variables were shown as median (IQR). Group comparisons for categorical variables were performed with Fisher's exact test and for continuous and ordinal variables with Mann–Whitney *U* test. Quantity and length of sport activities were regarded as ordinal variables.

Abbreviations: IQR, interquartile range (first quartile–third quartile); NT1, narcolepsy type-1; OCH, other central hypersomnias.

*$p < 0.05$; **$p < 0.01$.

($p = 0.009$) and bodily pain ($p = 0.038$) compared to patients with NT1 (Table 3). On the other hand, patients with a psychiatric diagnosis were more fatigued ($p < 0.001$), more apathic ($p = 0.003$), had more disturbed night-time sleep ($p = 0.050$) and had worse sleep ($p = 0.002$) and QoL than those without a psychiatric diagnosis (Table 3). The sub-parameters of the SF36, which indicate the different dimensions of QoL, are shown in Figure 2 as four separate groups: NT1 with/without a psychiatric diagnosis and OCH with/without a psychiatric diagnosis in comparison with the normative data for the Swiss population. This graph demonstrates that most results concerning QoL (i.e., in terms of functioning and limitations) were related with the presence of a psychiatric diagnosis than the type of hypersomnia. When the effect of psychiatric diagnosis on the subjective assessment scale scores independent from sex and the type of CDH via multivariable regression model, it was seen that fatigue, disturbed night-time sleep, sleep inertia and decreased quality of sleep and QoL were significantly affected by presence of a psychiatric diagnosis (Figure 3a).

3.3 | Subjective complaints concerning typical hypersomnolence-related symptoms

In the Additional Question Group-I ('Of all the symptoms you experience, which 1–3 symptoms have the greatest impact on your life?' see Supporting Information S1, adapted from Maski et al. 2017), patients with NT1 indicated EDS (58%), memory and cognition problems (33%), pronounced sleep attacks (33%), generalised tiredness/fatigue (25%), cataplexy (25%) and unstable/reduced mood (25%) as the symptoms that most adversely affected their lives. On the other side, the prominent complaints of patients with OCH were generalised tiredness/fatigue (69%), memory and cognition problems (52%), EDS (48%), unrefreshed awakening (47%), unrestful night sleep (18%), and unstable/reduced mood (11%). However, these complaints did not significantly differ between those with and without a psychiatric diagnosis neither in NT1 nor in OCH groups.

Further subjective complaints were addressed with the Additional Question Group-II for certain daily life activities limited by symptoms of their disease ('Are there certain activities that are important to you

TABLE 3 Table for comparison of scores obtained from different sleep and quality of life scales according to the central disorders of hypersomnolence type (narcolepsy type-1 versus other central hypersomnias) and presence of any psychiatric diagnosis (present versus not present).

		Central disorders of hypersomnolence			Presence of any psychiatric diagnosis		
Variable, median (IQR)	Overall ($N = 90$)	NT1 ($n = 26$)	OCH ($n = 64$)	p NT1 vs OCH	Present ($n = 38$)	Not present ($n = 52$)	p Present vs not present
Epworth Sleepiness Scale	15.0 (12.0–18.0)	17.0 (14.0–19.0)	14.0 (12.0–17.0)	0.04 NT1 vs OCH 4*	15.0 (12.0–18.0)	15.0 (12.0–18.0)	0.900
Fatigue Severity Scale	4.7 (3.7–5.7)	3.8 (2.7–5.5)	5.1 (4.2–5.8)	0.017*	5.7 (4.3–6.2)	4.2 (3.1–5.4)	<0.001***
NSS–Excessive Daytime Sleepiness	12.0 (7.0–17.0)	16.0 (12.0–19.0)	11.0 (6.0–16.0)	0.005**	13.0 (7.0–19.0)	12.0 (7.0–16.0)	0.300
NSS–Cataplexy	0 (0–6.0)	9.0 (6.0–10.0)	0 (0–0)	<0.001***	0 (0–5.0)	0 (0–6.0)	0.900
NSS–Hypnagogic Hallucinations	0 (0–4.0)	4.0 (0–5.0)	0 (0–2.0)	0.002**	0 (0–4.0)	0 (0–3.0)	0.300
NSS–Sleep Paralysis	0 (0–2.0)	2.0 (0–4.0)	0 (0–0)	0.003**	0 (0–4.0)	0 (0–1.0)	0.072
NSS–Disturbed Nighttime Sleep	1 (0–2.0)	1.0 (1.0–2.0)	1.0 (0–2.0)	0.110	2 (0–2.0)	0 (0–1.0)	0.050*
Beck Depression Inventory	11.0 (5.0–19.0)	11.0 (4.0–16.0)	11.0 (5.0–20.0)	0.400	18.0 (12.0–26.0)	7.0 (4.0–11.0)	<0.001***
Apathy Evaluation Scale-Self-rated	37.0 (31.0–42.0)	39.0 (34.0–41.0)	37.0 (31.0–42.0)	0.700	34.0 (30.0–37.0)	40.0 (34.0–62.0)	0.003**
Sleep Inertia Scale	60.0 (40.0–71.0)	45.0 (32.0–66.0)	64.0 (51.0–72.0)	0.013*	70.0 (64.0–80.0)	45.0 (34.0–62.0)	<0.001***
Pittsburgh Sleep Quality Index	6.0 (5.0–8.0)	7.0 (6.0–8.0)	6.0 (5.0–8.0)	0.300	7.0 (6.0–8.0)	6.0 (4.0–7.0)	0.002**
SF36–Physical Functioning	95.0 (80.0–100)	98.0 (95.0–100)	90.0 (75.0–100)	0.039*	90.0 (60.0–95.0)	100 (89.0–100)	0.001**
SF36–Limitations due to Physical Functioning	50.0 (0–100)	75.0 (31.0–100)	50.0 (0–100)	0.400	50.0 (0–75.0)	75.0 (25.0–100)	0.070
SF36–Limitations due to Emotional Problems	100 (33.0–100)	100 (33.0–100)	100 (33.0–100)	0.800	33.0 (0–100)	100 (67.0–100)	<0.001***
SF36–Energy/Fatigue	30.0 (20.0–54.0)	48.0 (26.0–65.0)	25.0 (20.0–41.0)	0.009**	20.0 (10.0–35.0)	40.0 (25.0–55.0)	<0.001***
SF36–Emotional Well-Being	70.0 (55.0–84.0)	76.0 (64.0–80.0)	68.0 (52.0–84.0)	0.900	60.0 (48.0–76.0)	80.0 (64.0–84.0)	<0.001***
SF36–Social Functioning	75.0 (50.0–100)	75.0 (50.0–100)	75.0 (50.0–88.0)	0.500	50.0 (38.0–88.0)	75.0 (62.0–100)	0.003**
SF36–Pain	90.0 (68.0–100)	100 (81.0–100)	90.0 (58.0–100)	0.038*	90.0 (58.0–100)	100 (70.0–100)	0.024*
SF36–General Health	65.0 (50.0–75.0)	60.0 (50.0–75.0)	65.0 (49.0–75.0)	0.800	55.0 (40.0–70.0)	70.0 (55.0–80.0)	0.005**

Note: all continuous variables were shown as median (IQR). Group comparisons for continuous variables were performed with Mann–Whitney U test.
Abbreviations: IQR, interquartile range (first quartile–third quartile); NSS, Narcolepsy Severity Scale; NT1, narcolepsy type-1; OCH, other central hypersomnias; SF36, 36-item Short-Form Health Survey.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

but are not able to do as much as you would like because of your symptoms?' see Supporting Information S2, adapted from Daniels et al. 2001), and Additional Question Group-III, representing five questions from the IHSS (Dauvilliers et al., 2019; see Supporting Information S3). Patients with a psychiatric diagnosis, regardless of their CDH diagnosis, complained more about their symptoms interfering with daily activities, than those without. Irrespective of the type of hypersomnia, the presence of a psychiatric comorbidity had a negative impact on most of the daily life activities (trouble to achieve his/her actual potential: $\beta = 0.58$, $p < 0.020$; trouble to make friends: $\beta = 0.69$, $p < 0.008$; impact of hypersomnolence on general health: $\beta = 0.66$, $p < 0.010$; impact of hypersomnolence on intellectual functioning: $\beta = 0.90$, $p < 0.001$; impact of hypersomnolence on mood: $\beta = 1.05$, $p < 0.001$; impact of hypersomnolence on daily activities: $\beta = 0.55$, $p < 0.050$; impact of hypersomnolence on driving: $\beta = 1.04$, $p < 0.020$; Figure 3b).

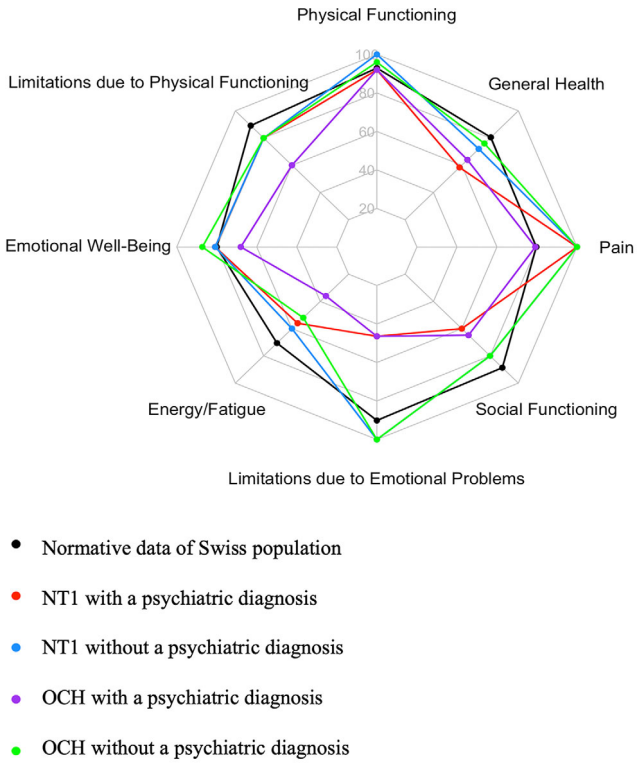

FIGURE 2 Graphical representation of the 36-item Short-Form Health Survey (SF36) scale results in patients with narcolepsy type-1 (NT1) and other central hypersomnias (OCH) with and without a psychiatric diagnosis and normative data for Swiss population.

4 | DISCUSSION

In this study, the presence of psychiatric diagnoses and their effects on daily life activities were investigated in CDH, and the prevalence of psychiatric comorbidities in NT1 was 27% and 48% in OCH. The reported high prevalence of psychiatric disorders in OCH was in line with the few available reports (Nevsimalova et al., 2022; Ruoff et al., 2017; Vernet et al., 2010) and, to our knowledge, presented the first systematic assessment of psychiatric disorders in OCH, studying the spectrum of psychiatric disorders with a systematic structured interview. Whereas in NT1 the highest prevalence was found for depression and anxiety disorders, in OCH psychiatric disorders showed a broader spectrum ranging from mood disorders to eating and behavioural disorders. The presence of psychiatric comorbidities was found to be more closely associated with physical inactivity, fatigue, apathy, disturbed night-time sleep and poor QoL, independent of the CDH sub-diagnosis. Moreover, in both NT1 and OCH, patients with a psychiatric diagnosis complained that hypersomnolence-related symptoms affected their QoL more and restricted their daily activities more than those without a psychiatric comorbidity. Although the severity of sleepiness evaluated by the ESS was similar, those patients with a psychiatric diagnosis described the impact of hypersomnolence on their daily physical and mental functions as significantly stronger than those without. To our knowledge, these are the first data about the striking deteriorating effect of psychiatric comorbidities in CDH on daily life activities and QoL.

In this study, we obtained a lower incidence of psychiatric disorders in NT1 compared to the literature for narcolepsy (NT1 and NT2 combined) and compared to the prevalence of depressive symptoms in NT1/NT2 according to a recently published meta-analysis (Li et al., 2021; Schuld et al., 2000). We hypothesise that the lower prevalence of psychiatric disorders in NT1 could be due to the separation of NT1-NT2, as well as the fact that the iSPHYNCS encompasses relatively young patients with a new diagnosis of CDH and might develop psychiatric comorbidities later. Patients with NT1, although having a higher BMI and being more severely affected by sleepiness, were more engaged in sports activity compared to patients with OCH. It can be speculated that patients with NT1 may use sports activities as an 'activating' strategy, whereas patients with OCH may experience too much fatigue to engage in sports.

4.1 | Central disorders of hypersomnolence and psychiatric comorbidities – Assessment tools

Regarding the CDH and psychiatric comorbidities, the mainstream literature was on NT1; however, psychiatric disorders in the OCH were not well described (Galušková & Šonka, 2021; Lopez et al., 2017). Concerning IH, the prominent psychiatric symptoms were mainly mood disorders and have been reported between 15% and 25% in different studies (Black et al., 2017; Trotti & Arnulf, 2021). Also, it was shown that patients with IH had more fatigue, anxiety and depression when compared to matched healthy controls (Vernet & Arnulf, 2009). Similarly, in a recent study, the most common complaint following EDS in a NT1 group was fatigue, whereas, in a IH group, it was sleep inertia, fatigue, depression and anxiety (Nevsimalova et al., 2022). In all studies mentioned, the psychiatric diagnosis was not based on a structured psychiatric assessment tool that enables establishing a concrete psychiatric diagnosis according to the ICD-10 criteria. Alasim et al. (2020) first used the MINI scale for psychiatric evaluation in narcolepsy and found an increased frequency of major depressive disorder and generalised anxiety disorder in NT1 compared to healthy controls (NT1 = NT2 > healthy controls). Although there is no specific scale developed for CDH, the MINI scale is suitable for practical clinical application as it systematically inquiries about psychiatric diagnoses. In former studies, scales and questionnaires predominantly related to mood or anxiety disorders were used, as follows: Generalized Anxiety Disorder seven-item (GAD-7) (Spitzer et al., 2006), Minnesota Multiphasic Personality Inventory-second edition (MMPI-2) (Munley, 2002), Patient Health Questionnaire (PHQ) for Depression (Kroenke et al., 2001), Beck Anxiety Inventory (Leyfer et al., 2006), BDI-II (Arnarson et al., 2008), and Depression, Anxiety and Stress Scale-21 items (DASS-21) (Norton, 2007). Unsurprisingly in these studies, anxiety and depression were well studied, but no further evaluation concerning other psychiatric disorders was performed. In our study, we did not only find an elevated amount of depression

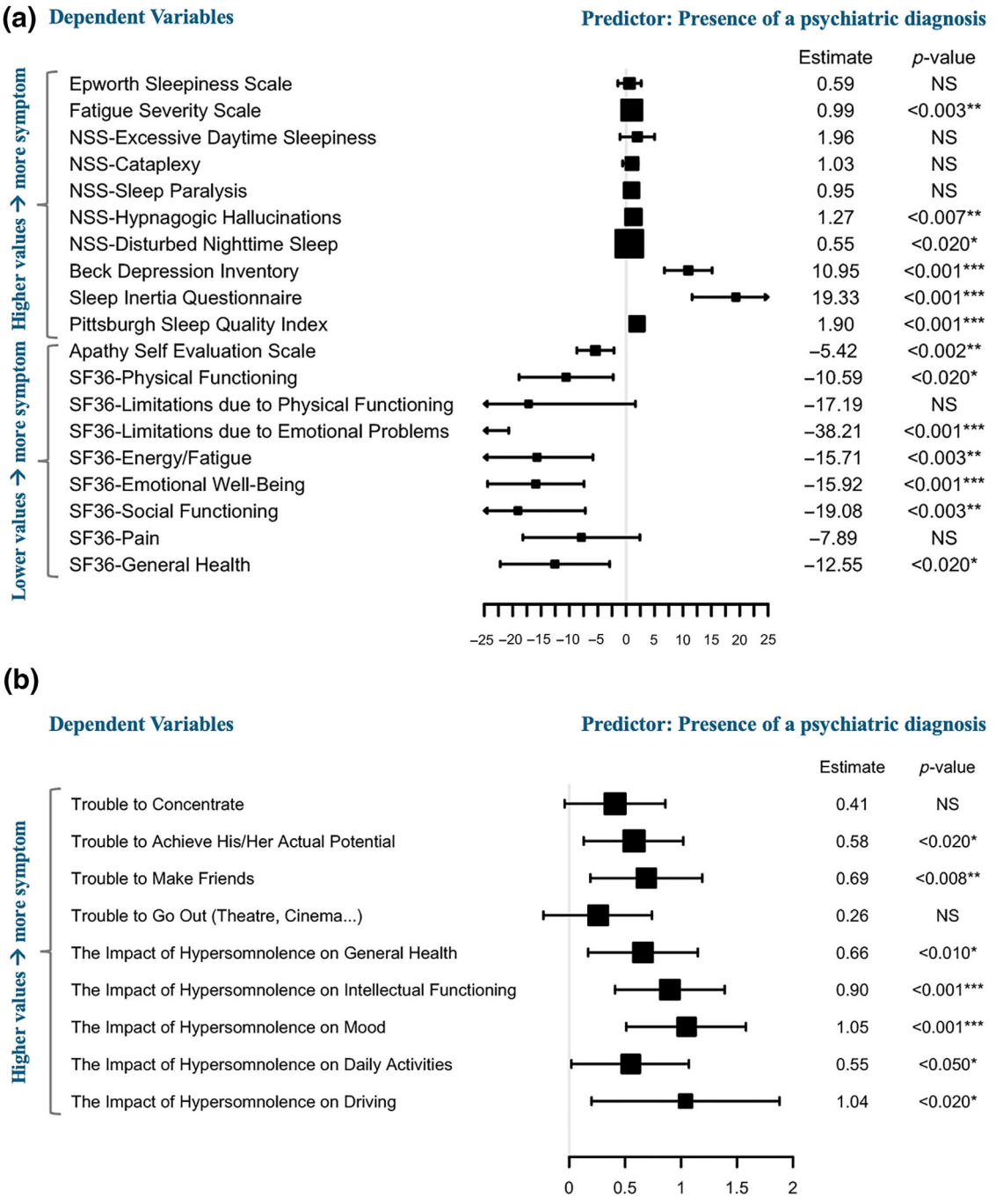

FIGURE 3 Forest plot representation of multivariable regression models. Both models were corrected for the of central disorders of hypersomnolence type and sex. (a) Dependent variables: subjective assessment scale scores; Predictor: the presence of a psychiatric diagnosis (NSS, Narcolepsy Severity Scale; SF36, 36-item Short-Form Health Survey). (b) Dependent variables: the impact of hypersomnolence-related symptoms on daily activities; Predictor: The presence of a psychiatric diagnosis.

or anxiety disorders in NT1 and/or OCH but also a greater diversity of psychiatric disorders in the OCH group, which raises the question, if other psychiatric disorders might contribute to an overlap of symptoms in patients with hypersomnolence in OCH. Also, the question arises, if patients within the OCH group classified as hypersomnia due to a psychiatric disorder according to the ICSD, might have other psychiatric symptoms or relapsing symptoms at the time of the study.

4.2 | Central disorders of hypersomnolence and psychiatric comorbidities – Possible pathophysiology

In NT1, the previously described autoimmune process resulting in orexin/hypocretin deficiency (Latorre et al., 2018) could be related to the pathophysiology of psychiatric disorders. Morse and Sanjeev (2018) considered whether a causal relationship could exist, as

hypocretin and dopamine significantly overlap in their effect on the basal forebrain, prefrontal cortex and the thalamic paraventricular nucleus as parts of the central reward circuitry. Supporting this notion, the modulation of reward circuits and executive function in patients with NT1 has been demonstrated in a study on food-response-associated tasks (van Holst et al., 2018). Ventral and dorsal medial prefrontal cortex responses to an attentional and a general executive control task, respectively, were altered in patients with NT1 compared to healthy controls or patients with IH. Mensen et al. (2015) also demonstrated that NT1 is associated with a blunted response to reward delivery. Nonetheless, it is suspected that behavioural traits, e.g., in patients with NT1, might also contribute to psychiatric illness. We suppose that secondary phenomena such as fear of cataplexy and exposure to hypnagogic hallucinations might presumably play a great role and worsen the burden of narcolepsy-related symptoms, as these phenomena promote social withdrawal and a lack of physical activity in the community. This would also fit in with the observation of Barateau et al. (2020) that depression and suicidal thoughts in NT1 improved under therapy, along with the improvement of the typical symptoms of narcolepsy. In our study QoL in NT1 was only a little restricted by disease-specific symptoms if affected persons were still able to engage in physical activities, as long they did not have an additional psychiatric disorder. On the other hand, OCH is discriminated from NT1 by normal hypocretin levels. Presumably, this group of disorders is caused by heterogeneous pathophysiologies, which are to date unknown. Also, as in our study, OCH might go along with a high prevalence of psychiatric comorbidities, even higher than NT1, and obvious restrictions in physical activities, despite normal hypocretin levels and the absence of severe narcolepsy symptoms like cataplexy or hallucinations.

4.3 | Central disorders of hypersomnolence and psychiatric comorbidities – The possibility of a vicious circle

In light of the presented data, by comparing the QoL in patients with CDH with or without psychiatric comorbidity and according to the subjective complaints, we assume a vicious circle in which interrelations are challenging to differentiate. We presume that patients with hypersomnolence with a psychiatric disorder could lack motivation for physical exercise or social activities. Conversely, as confirmed in many studies (Bei et al., 2017; Schuch et al., 2016) lack of physical activity has a negative effect on mood and fatigue. We, therefore, postulate a vicious circle in patients with CDH with comorbid psychiatric disease. Hypersomnolence may lead to fatigue, which might be intensified by longer sleep per se (Bei et al., 2017) or possibly in the context of negative self-assessment. This leads to the reduction of physical and social activity, and thereby to a reduction of their mood-stabilising effects. A similar vicious circle has been shown in depression, where reduced activity increases depressive symptoms (Bei et al., 2017). This, in turn, can increase the physical and social isolation. Psychiatric disorders further increase the level of fatigue and the associated impact of

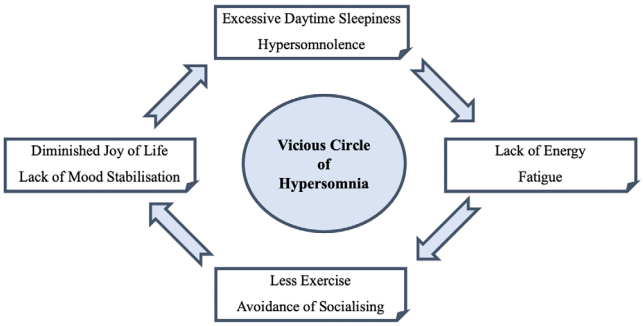

FIGURE 4 The vicious circle of hypersomnolence representing the relationship between increased daytime sleepiness and/or hypersomnolence, fatigue and psychiatric comorbidities.

hypersomnolence-related symptoms on QoL (Figure 4). This circle gives a chance for treatment if it can be recognised and interrupted. If a patient is at risk or already has a psychiatric comorbidity, good cooperation with psychotherapists and psychiatrists should take place. We propose the development of cognitive behavioural therapies for patients with CDH based on the proposed circle and similar to existing therapies for insomnia (Bei et al., 2017). Adapted to the patient's individual situation, these therapies could include improving the awareness of self-critical thoughts, improvement of self-care and self-efficacy, as well as optimising the daily structure, combined with an individual optimisation of habitual bedtimes, and increasing daily activity as a strategy to fight fatigue. This increase in activity could range from short physical activities to social interactions. We state that those measures taken in the course of the disease could be of great importance, both in the prevention of secondary psychiatric diseases and in interrupting pathological processes in a timely manner.

We propose to extend the vicious circle hypothesis for CDH in the future by considering the impact of cognitive disturbances on daily life activities, which were already defined for different types of CDH and particularly for NT1 (Filardi et al., 2021; Harel et al., 2024; Naumann et al., 2006; Witt et al., 2018). Apart from sustained attention, the iSPHYNCS does not include cognitive testing. However, this aspect is important when planning cognitive behavioural therapies for this group of patients, as certain cognitive functions, such as emotional processing, reasoning, or cognitive flexibility have been shown to be impaired in patients with CDH (Filardi et al., 2021) and can overlap to some extent with psychiatric complaints. The effect of cognitive disturbance on the vicious circle hypothesis proposed in this study needs to be evaluated further.

4.4 | Limitations and future perspectives

This study did not investigate the effect of the presence or absence of psychiatric diagnosis on the QoL in healthy controls without CDH. Due to low numbers of patients with specific diagnoses within the OCH, in combination with a low certainty of most OCH diagnoses, we decided not to perform sub-analyses for specific disorders within the

OCH. It is, therefore, not possible to make a statement about the individual diseases merged in this group. The small total sample size is a limitation of this study, and the results need to be replicated in larger cohorts. As the data on whether the psychiatric diagnosis or CDH manifested first were not obtained, and there was no long-term follow-up of the patients, a before-and-after or causal relationship between psychiatric diagnoses and CDH could not be established. Also, whether the diagnostic delay for CDH diagnoses may contribute to the development of psychiatric comorbidities or vice versa needs further evaluation.

Possible interactions between psychiatric comorbidities and CDH and the effect of medication used to treat those diseases might also be considered. Medication for CDH might have positive or negative psychotropic effects and some psychiatric medications are well known for their benefit and potency in patients with CDH (Hanin et al., 2021; Langford & Gross, 2011; Sarkanen et al., 2014). Medication might have influenced the QoL of some participants, which could not be evaluated in detail in our study due to the small sample size. However, the vicious circle of hypersomnia associated with psychiatric complaints highlights the importance of a personalised and tailored pharmacotherapeutic approach in the field of CDH, in addition to psychotherapeutic strategies.

5 | CONCLUSION

In summary, our findings confirm the high incidence of psychiatric disorders in CDH and provide detailed information about the differences between NT1 and OCH regarding psychiatric comorbidities and their impact on daily life. Our analysis also supports the need for an interdisciplinary approach to CDH in terms of psychiatric comorbidities, as they exacerbated the impact of hypersomnolence-related symptoms on daily activities, regardless of the type of CDH. Based on our results, we postulate a vicious circle of hypersomnia and psychological vulnerability. More awareness and knowledge about the complex associations could serve as a basis for cognitive behavioural interventions, similar to the cognitive behavioural treatment of insomnia. For that, patients with CDH need to be evaluated for psychiatric symptoms systematically, both at the first consultation and during follow-ups, with open questions and eventually with questionnaires, ideally in an interdisciplinary consultation together with a sleep psychiatrist allowing additional psychotherapeutic interventions in individual or group therapy settings.

From a future perspective further larger studies, including healthy controls, are necessary to describe the specific patterns in the CDH subgroups more precisely. It is also important to increase knowledge about the pathophysiology and the associations between CDH and psychiatric disorders. In this context continuing the iSPHYNCS study might help to find out about this correlation between CDH, biomarkers and psychiatric disorders especially also in relation to the course of time.

AUTHOR CONTRIBUTIONS

Merve Aktan Suzgun: Writing – original draft; writing – review and editing; visualization; investigation; data curation. **Elena S. Wenz:** Conceptualization; writing – review and editing; methodology; data curation. **Julia van der Meer:** Conceptualization; data curation; software; formal analysis; project administration; writing – review and editing. **Livia G. Fregolente:** Writing – review and editing; data curation; software; formal analysis; methodology; investigation. **Jan D. Warncke:** Investigation; conceptualization; methodology; project administration; resources; writing – review and editing; funding acquisition. **Silvia Miano:** Writing – review and editing; data curation; investigation; conceptualization; funding acquisition. **Jens Acker:** Conceptualization; investigation; data curation; writing – review and editing; funding acquisition. **Mathias Strub:** Conceptualization; investigation; data curation; writing – review and editing; funding acquisition. **Elisabeth Olliges:** Conceptualization; investigation; data curation; writing – review and editing; funding acquisition. **Ramin Khatami:** Data curation; writing – review and editing; conceptualization; investigation; funding acquisition; supervision. **Markus H. Schmidt:** Supervision; writing – review and editing; project administration. **Claudio L. A. Bassetti:** Writing – review and editing; supervision; project administration; funding acquisition; conceptualization. **Sigrid von Manitius:** Conceptualization; writing – review and editing; funding acquisition; data curation; supervision.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PATIENT CONSENT

Each patient was enrolled in the study after an informed consent. Permission to Reproduce Material from Other Sources: no material was used from other sources.

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REFERENCES

Alasim, H., AlQazlan, S., Albanyan, S., Alsalhi, A., Buraik, A., Olaish, A. H., Almeneessier, A. S., Alosaimi, F. D., AlHadi, A., & BaHammam, A. S. (2020). Comorbid psychiatric disorders among patients with narcolepsy. *Sleep & Breathing*, *24*(2), 629–636.

American Academy of Sleep Medicine (AASM). (2014). *International classification of sleep disorders (ICSD)* (3rd ed.). AASM.

Arnarson, T. O., Olason, D. T., Smári, J., & Sigurethsson, J. F. (2008). The Beck depression inventory second edition (BDI-II): Psychometric properties in Icelandic student and patient populations. *Nordic Journal of Psychiatry*, *62*(5), 360–365.

Baldini, V., Venezia, N., Iriti, A., Quattrocchi, S., Zenesini, C., Biscarini, F., Atti, A. R., Menchetti, M., Franceschini, C., Varallo, G., De Ronchi, D., Plazzi, G., & Pizza, F. (2024). Eating disorders in narcolepsy type 1: Evidence from a cross-sectional Italian study. *Journal of Sleep Research*, *33*(5), e14150.

Barateau, L., Lopez, R., Chenini, S., Pesenti, C., Rassu, A. L., Jaussent, I., & Dauvilliers, Y. (2020). Depression and suicidal thoughts in untreated and treated narcolepsy: Systematic analysis. *Neurology*, *95*(20), e2755–e2768.

Barateau, L., Lopez, R., Franchi, J. A., & Dauvilliers, Y. (2017). Hypersomnolence, hypersomnia, and mood disorders. *Current Psychiatry Reports*, *19*(2), 13.

Bassetti, C. L. A., Adamantidis, A., Burdakov, D., Han, F., Gay, S., Kallweit, U., Khatami, R., Koning, F., Kornum, B. R., Lammers, G. J., Liblau, R. S., Luppi, P. H., Mayer, G., Pollmächer, T., Sakurai, T., Sallusto, F., Scammell, T. E., Tafti, M., & Dauvilliers, Y. (2019). Narcolepsy-clinical spectrum, aetiopathophysiology, diagnosis and treatment. *Nature Reviews. Neurology*, *15*(9), 519–539.

Bei, B., Manber, R., Allen, N. B., Trinder, J., & Wiley, J. F. (2017). Too long, too short, or too variable? Sleep Intraindividual variability and its associations with perceived sleep quality and mood in adolescents during naturalistically unconstrained sleep. *Sleep*, *40*(2), zsw067.

Black, J., Reaven, N. L., Funk, S. E., McGaughey, K., Ohayon, M. M., Guilleminault, C., & Ruoff, C. (2017). Medical comorbidity in narcolepsy: Findings from the burden of narcolepsy disease (BOND) study. *Sleep Medicine*, *33*, 13–18.

Canellas, F., Lin, L., Julià, M. R., Clemente, A., Vives-Bauza, C., Ollila, H. M., Hong, S. C., Arboleya, S. M., Einen, M. A., Faraco, J., Fernandez-Vina, M., & Mignot, E. (2014). Dual cases of type 1 narcolepsy with schizophrenia and other psychotic disorders. *Journal of Clinical Sleep Medicine*, *10*(9), 1011–1018.

Cohen, A., Mandrekar, J., St Louis, E. K., Silber, M. H., & Kotagal, S. (2018). Comorbidities in a community sample of narcolepsy. *Sleep Medicine*, *43*, 14–18.

Dahmen, N., Becht, J., Engel, A., Thommes, M., & Tonn, P. (2008). Prevalence of eating disorders and eating attacks in narcolepsy. *Neuropsychiatric Disease and Treatment*, *4*(1), 257–261.

Daniels, E., King, M. A., Smith, I. E., & Shneerson, J. M. (2001). Health-related quality of life in narcolepsy. *Journal of Sleep Research*, *10*(1), 75–81.

Dauvilliers, Y., Evangelista, E., Barateau, L., Lopez, R., Chenini, S., Delbos, C., Beziat, S., & Jaussent, I. (2019). Measurement of symptoms in idiopathic hypersomnia: The idiopathic hypersomnia severity scale. *Neurology*, *92*(15), e1754–e1762.

Dietmann, A., Wenz, E., van der Meer, J., Ringli, M., Warncke, J. D., Edwards, E., Schmidt, M. H., Bernasconi, C. A., Nirkko, A., Strub, M., Miano, S., Manconi, M., Acker, J., von Manitius, S., Baumann, C. R., Valko, P. O., Yilmaz, B., Brunner, A. D., Tzovara, A., … Bassetti, C. L. A. (2021). The Swiss primary Hypersomnolence and narcolepsy cohort study (SPHYNCS): Study protocol for a prospective, multicentre cohort observational study. *Journal of Sleep Research*, *30*(5), e13296.

Droogleever Fortuyn, H. A., Fronczek, R., Smitshoek, M., Overeem, S., Lappenschaar, M., Kalkman, J., Renier, W., Buitelaar, J., Lammers, G. J., & Bleijenberg, G. (2012). Severe fatigue in narcolepsy with cataplexy. *Journal of Sleep Research*, *21*(2), 163–169.

Filardi, M., D'Anselmo, A., Agnoli, S., Rubaltelli, E., Mastria, S., Mangiaruga, A., Franceschini, C., Pizza, F., Corazza, G. E., & Plazzi, G. (2021). Cognitive dysfunction in central disorders of hypersomnolence: A systematic review. *Sleep Medicine Reviews*, *59*, 101510.

Fortuyn, H. A., Lappenschaar, M. A., Furer, J. W., et al. (2010). Anxiety and mood disorders in narcolepsy: A case-control study. *General Hospital Psychiatry*, *32*(1), 49–56.

Galušková, K., & Šonka, K. (2021). Idiopathic hypersomnia and depression. *Prague Medical Report*, *122*(3), 127–139.

Hanin, C., Arnulf, I., Maranci, J. B., Lecendreux, M., Levinson, D. F., Cohen, D., & Laurent-Levinson, C. (2021). Narcolepsy and psychosis: A systematic review. *Acta Psychiatrica Scandinavica*, *144*(1), 28–41. 1.

Harel, B. T., Gattuso, J. J., Latzman, R. D., Maruff, P., Scammell, T. E., & Plazzi, G. (2024). The nature and magnitude of cognitive impairment in narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia: A meta-analysis. *SLEEP Advances*, *5*(1), zpae043.

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*, *16*(9), 606–613.

Langford, J., & Gross, W. L. (2011). Psychosis in the context of sodium oxybate therapy. *Journal of Clinical Sleep Medicine*, *7*(6), 665–666.

Latorre, D., Kallweit, U., Armentani, E., Foglierini, M., Mele, F., Cassotta, A., Jovic, S., Jarrossay, D., Mathis, J., Zellini, F., Becher, B., Lanzavecchia, A., Khatami, R., Manconi, M., Tafti, M., Bassetti, C. L., & Sallusto, F. (2018). T cells in patients with narcolepsy target self-antigens of hypocretin neurons. *Nature*, *562*(7725), 63–68.

Lecendreux, M., Lavault, S., Lopez, R., Inocente, C. O., Konofal, E., Cortese, S., Franco, P., Arnulf, I., & Dauvilliers, Y. (2015). Attention-deficit/hyperactivity disorder (ADHD) symptoms in pediatric narcolepsy: A cross-sectional study. *Sleep*, *38*(8), 1285–1295.

Lee, M. J., Lee, S. Y., Yuan, S. S., Yang, C. J., Yang, K. C., Lee, T. L., Sun, C. C., Shyu, Y. C., & Wang, L. J. (2017). Comorbidity of narcolepsy and depressive disorders: A nationwide population-based study in Taiwan. *Sleep Medicine*, *39*, 95–100.

Leyfer, O. T., Ruberg, J. L., & Woodruff-Borden, J. (2006). Examination of the utility of the Beck anxiety inventory and its factors as a screener for anxiety disorders. *Journal of Anxiety Disorders*, *20*(4), 444–458.

Li, X., Sanford, L. D., Zong, Q., Zhang, Y., Tan, L., Li, T., Ren, R., Zhou, J., Han, F., & Tang, X. (2021). Prevalence of depression or depressive symptoms in patients with narcolepsy: A systematic review and meta-analysis. *Neuropsychology Review*, *31*(1), 89–102.

Lopez, R., Barateau, L., Evangelista, E., & Dauvilliers, Y. (2017). Depression and hypersomnia: A complex association. *Sleep Medicine Clinics*, *12*(3), 395–405.

Maski, K., Steinhart, E., Williams, D., Scammell, T., Flygare, J., McCleary, K., & Gow, M. (2017). Listening to the patient voice in narcolepsy: Diagnostic delay, disease burden, and treatment efficacy. *Journal of Clinical Sleep Medicine*, *13*(3), 419–425.

Mensen, A., Poryazova, R., Huegli, G., Baumann, C. R., Schwartz, S., & Khatami, R. (2015). The roles of dopamine and Hypocretin in reward: A electroencephalographic study. *PLoS One*, *10*(11), e0142432.

Morse, A. M., & Sanjeev, K. (2018). Narcolepsy and psychiatric disorders: Comorbidities or shared pathophysiology? *Medical Sciences (Basel)*, *6*(1), 16.

Munley, P. H. (2002). Comparability of MMPI-2 scales and profiles over time. *Journal of Personality Assessment*, *78*(1), 145–160.

Naumann, A., Bellebaum, C., & Daum, I. (2006). Cognitive deficits in narcolepsy. *Journal of Sleep Research*, *15*(3), 329–338.

Nevsimalova, S., Skibova, J., Galuskova, K., Prihodova, I., Dostalova, S., Maurovich-Horvat, E., & Šonka, K. (2022). Central disorders of Hypersomnolence: Association with fatigue, depression and sleep inertia prevailing in women. *Brain Sciences*, *12*(11), 1491.

Norton, P. J. (2007). Depression anxiety and stress scales (DASS-21): Psychometric analysis across four racial groups. *Anxiety, Stress, and Coping*, *20*(3), 253–265.

Ohayon, M. M. (2013). Narcolepsy is complicated by high medical and psychiatric comorbidities: A comparison with the general population. *Sleep Medicine*, *14*(6), 488–492.

Pallesen, S., Nordhus, I. H., Omvik, S., Sivertsen, B., Tell, G. S., & Bjorvatn, B. (2007). Prevalence and risk factors of subjective sleepiness in the general adult population. *Sleep*, *30*(5), 619–624.

Ruoff, C. M., Reaven, N. L., Funk, S. E., McGaughey, K., Ohayon, M. M., Guilleminault, C., & Black, J. (2017). High rates of psychiatric comorbidity in narcolepsy: Findings from the burden of narcolepsy disease (BOND) study of 9,312 patients in the United States. *The Journal of Clinical Psychiatry*, *78*(2), 171–176.

Sarkanen, T., Niemelä, V., Landtblom, A. M., & Partinen, M. (2014). Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. *Frontiers in Neurology*, *5*, 136.

Schuch, F. B., Vancampfort, D., Rosenbaum, S., Richards, J., Ward, P. B., & Stubbs, B. (2016). Exercise improves physical and psychological quality of life in people with depression: A meta-analysis including the evaluation of control group response. *Psychiatry Research*, *241*, 47–54.

Schuld, A., Hebebrand, J., Geller, F., & Pollmächer, T. (2000). Increased body-mass index in patients with narcolepsy. *Lancet*, *355*(9211), 1274–1275.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59*(Suppl 20), 22–33. quiz 34–57.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M. F., & Dunbar, G. C. (1997). The validity of the MINI international neuropsychiatric interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, *12*(5), 232–241.

Spitzer, R. L., Kroenke, K., Williams, J. B., & Löwe, B. (2006). A brief measure for assessing generalized anxiety disorder: The GAD-7. *Archives of Internal Medicine*, *166*(10), 1092–1097.

Trotti, L. M., & Arnulf, I. (2021). Idiopathic hypersomnia and other hypersomnia syndromes. *Neurotherapeutics*, *18*(1), 20–31.

van Holst, R. J., Janssen, L. K., van Mierlo, P., Lammers, G. J., Cools, R., Overeem, S., & Aarts, E. (2018). Enhanced food-related responses in the ventral medial prefrontal cortex in narcolepsy type 1. *Scientific Reports*, *8*(1), 16391.

Vernet, C., & Arnulf, I. (2009). Idiopathic hypersomnia with and without long sleep time: A controlled series of 75 patients. *Sleep*, *32*(6), 753–759.

Vernet, C., Leu-Semenescu, S., Buzare, M. A., & Arnulf, I. (2010). Subjective symptoms in idiopathic hypersomnia: Beyond excessive sleepiness. *Journal of Sleep Research*, *19*(4), 525–534.

Witt, S. T., Drissi, N. M., Tapper, S., Wretman, A., Szakács, A., Hallböök, T., Landtblom, A.-M., Karlsson, T., Lundberg, P., & Engström, M. (2018). Evidence for cognitive resource imbalance in adolescents with narcolepsy. *Brain Imaging and Behavior*, *12*(2), 411–424.

Zamarian, L., Högl, B., Delazer, M., Hingerl, K., Gabelia, D., Mitterling, T., Brandauer, E., & Frauscher, B. (2015). Subjective deficits of attention, cognition and depression in patients with narcolepsy. *Sleep Medicine*, *16*(1), 45–51.

SUPPORTING INFORMATION

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

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