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Validation of the Pediatric Narcolepsy Screening Questionnaire (PNSQ): A cross-sectional, observational study

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ABSTRACT

Objective/Background: This study evaluated psychometric properties of the Pediatric Narcolepsy Screening Questionnaire (PNSQ), developed in response to the difficulty of identifying pediatric narcolepsy.

Patients/Methods: The initial PNSQ was updated following debriefing interviews with parents of children with suspected/diagnosed narcolepsy. Subsequently, newly recruited caregivers were categorized into groups: clinician-confirmed narcolepsy, other sleep problems (OSP), and no sleep problems (controls). Caregivers completed the 11-item PNSQ assessing narcolepsy symptomatology. PNSQ psychometric properties were evaluated; mean PNSQ Total Score (TS) was compared inter-group using analysis of variance.

Results: The analysis population (N = 158) included patients with narcolepsy (n = 49), OSP (n = 55), and controls (n = 54); mean ± SD age was 13.8 ± 2.8, 10.2 ± 4.3, and 10.0 ± 3.8 years, respectively. Inter-item Pearson correlations (range, 0.22–0.75) indicated good construct validity. Principal component analysis confirmed unidimensionality. Item discriminative power was high for narcolepsy vs control (range, 0.693–0.936) and lower for narcolepsy vs OSP (range, 0.584–0.729). The latent trait was well covered (separation index = 0.868). Item 7 (vivid dreams/nightmares), having low discriminative power and specificity, was removed. Cronbach's alpha (final PNSQ) indicated high internal consistency reliability (raw alpha = 0.88). Mean ± SD PNSQ TS (range, 0–50) in the narcolepsy, OSP, and control groups were 34.98 ± 7.98, 25.20 ± 9.43, and 9.54 ± 9.38, respectively (nominal $P < 0.0001$). Classification by PNSQ TS was defined: PNSQ+ (likely narcolepsy, TS ≥ 29), PNSQ 0 (likely OSP, TS 19–28), and PNSQ− (narcolepsy unlikely, TS ≤ 18); patients with narcolepsy were classified as PNSQ+ (79.6%), PNSQ 0 (18.4%), and PNSQ− (2.0%).

Conclusions: The PNSQ demonstrated good psychometric properties and excellent performance discriminating narcolepsy, OSP, and control groups.

1. Introduction

Narcolepsy is a central hypersomnolence disorder characterized by excessive daytime sleepiness (EDS), cataplexy (specific to narcolepsy type 1 [NT1]), hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep [1–3]. The estimated overall prevalence of narcolepsy is 30.6–56.3 per 100,000 in the United States [4,5]. Evidence suggests that symptom onset occurs sometimes in childhood and most frequently during adolescence [6,7]. The prevalence of pediatric narcolepsy has been estimated at 10.0 per 100,000 in the United States [8]; however, pediatric narcolepsy can be difficult to diagnose and often goes undetected or misdiagnosed for many years [7,9]. Such diagnostic delays can hinder patient access to proper care, with negative consequences in

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Abbreviations

ANOVA	analysis of variance
AUC	area under the curve
CI	confidence interval
EDS	excessive daytime sleepiness
IRT	item response theory
NT1	narcolepsy type 1
NT2	narcolepsy type 2
OR	odds ratio
OSP	other sleep problems
PCA	principal component analysis
PNSQ	Pediatric Narcolepsy Screening Questionnaire
PRAC-Test©	PRAgmatic Content and face validity Test
ROC	receiver operating characteristic
SD	standard deviation
T1	threshold 1
T2	threshold 2

social and academic settings [10].

One of the reasons for delayed diagnosis may be the differential presentation of narcolepsy in children and adults. EDS is typically the first symptom to develop in children, and the full pentad of narcolepsy symptoms (EDS, cataplexy, hypnagogic and hypnopompic hallucinations, and disrupted nighttime sleep) rarely have their onset at the same time [3,7,9]. Cataplexy, seen in NT1, often manifests during childhood as a complex movement disorder with persistent hypotonia and prominent facial involvement, before developing into the atonia associated with emotional triggers characteristic of cataplexy in adults. Parents, caregivers, teachers, and school nurses are often unfamiliar with, and may not recognize, these symptoms. Furthermore, pediatric healthcare providers, to whom these patients often initially present, may also have difficulty identifying clinical manifestations of pediatric narcolepsy and may not appreciate the need for further evaluation. Diagnosis is also complicated by the fact that although existing instruments may identify EDS in pediatric patients with narcolepsy, they do not address the other possible symptoms of narcolepsy [11,12]. In addition, younger children, in particular, may not be able to articulate their own symptoms, and the behavioral and mood dysregulation associated with EDS can be misattributed, leading to misdiagnosis (eg, attention-deficit/hyperactivity disorder or anxiety/depression) [7,13–16].

To address these concerns, a brief screening tool, the Pediatric Narcolepsy Screening Questionnaire (PNSQ), was developed to help pediatricians identify children or adolescents who may have signs/symptoms of narcolepsy. Use of this screening tool would facilitate expedited referral to a sleep specialist. The PNSQ is completed by parents or caregivers of children/adolescents who are presenting with signs/symptoms suggestive of narcolepsy. Items assess the presence and frequency of narcolepsy signs/symptoms, with higher scores (range, 0–50) indicating more severe sleep problems and higher risk for narcolepsy. The PNSQ was developed based on input from an advisory committee of clinicians and researchers with an expertise in pediatric narcolepsy (organized by Jazz Pharmaceuticals).

The primary objective of this study was to evaluate the PNSQ based on results from psychometric analyses and conduct an evaluation of the psychometric properties of the final instrument. Secondary objectives were to define decision rules to classify patients at the individual level based on their PNSQ score, to document the ability of the PNSQ to differentiate patients with narcolepsy from those without narcolepsy, and to assess the ability of the PNSQ to screen for narcolepsy among pediatric patients presenting with sleep problems.

2. Methods

This study, conducted in the United States, included 3 phases: 1) a series of qualitative cognitive debriefing interviews, 2) a cross-sectional observational pilot phase soliciting clinicians' feedback, and 3) a cross-sectional psychometric validation study.

2.1. Preliminary cognitive debriefing interviews

Caregivers of children showing signs/symptoms of narcolepsy or with a diagnosis of narcolepsy were recruited by study physicians to participate in interviews. After caregivers had provided written consent to participate, trained researchers conducted the interviews by phone. Caregivers first completed an initial 12-item test version of the PNSQ (Supplemental Table 1) and then were asked questions regarding each item, which aimed to assess both their understanding and the relevance of each item, as well as to provide any feedback they had about the questionnaire overall. Materials were provided in the English language only. Answers were summarized and analyzed qualitatively using Microsoft Excel. The advisory committee (Judith A. Owens, MD; Debra A. Babcock, MD; Jean-Pierre Chanoine, MD; David Gozal, MD; Emmanuel Mignot, MD, PhD; Giuseppe Plazzi, MD, PhD; and Carol L. Rosen, MD) reviewed the results and recommendations and discussed and agreed on changes to the questionnaire.

2.2. Assessment of clinician feedback

Six sleep specialists (including 4 pediatric sleep specialists and 1 narcolepsy specialist) currently treating multiple patients with EDS/fatigue indicative of sleep problems were recruited to evaluate the revised 11-item PNSQ (Table 1) using the PRAgmatic Content and face validity Test (PRAC-Test©) Short Form [17], a 32-item questionnaire that assesses the efficiency and usefulness of a measure; specifically, it was used to assess the intent to use the PNSQ in clinical practice as well as the main strengths and weaknesses of the tool. Clinicians recruited caregivers of children/adolescents making an office visit. After the caregivers provided their written consent, they were asked to complete the PNSQ. In addition, 10 pediatricians meeting the same criteria were recruited to complete the PRAC-Test© only. Clinicians were also provided the opportunity to communicate any comments or suggestions they had in order to make the PNSQ easier for caregivers to complete. All responses were analyzed descriptively.

2.3. Validation study

2.3.1. Ethical conduct

The participation of caregivers in the validation study was in accordance with the ethical principles having their origin in the Declaration of Helsinki. An ethics committee reviewed the final study protocol, including the study documents. Caregivers gave written consent to participate prior to enrollment. The study was conducted by a third-party vendor (Mapi, an ICON company), with a scientific goal of finalizing and assessing the psychometric properties of the PNSQ and minimizing potential bias associated with conflict of interest.

2.3.2. Participants

The study population consisted of 3 groups: caregivers of children or adolescents with clinician-confirmed diagnosed

Table 1
PNSQ items used in the pilot testing and validation study.

Item[a,b]	Item Content
1	How often do you have difficulty waking up your child in the morning or from naps (e.g., because he/she is still very tired or may get very irritable, agitated or start fighting when disturbed)?
2	How often does your child become drowsy or fall asleep when doing something in which he/she is not actively engaged (e.g., standing while waiting in line or sitting at a desk in school)?
3	How often does your child fall asleep immediately or almost immediately when he/she gets in a vehicle (e.g., car or public transport)?
4	How often does your child's sleepiness lead to difficulty functioning at school or at home (e.g., completing homework or chores, participating in activities)?
5	How often does your child, **without meaning to**, show unusual facial expressions (e.g., sticking out the tongue, jaw dropping, or having droopy eyelids)?
6	How often does your child fall down, become weak or floppy, or lose control of his/her head when laughing, joking, or watching funny movies, cartoons, or videos?
7[c]	How often does your child have vivid dreams or nightmares?
8	How often is your child's sleep disturbed (e.g., sleep talking, sleep walking, moving a lot in bed)?
9	Has your child ever experienced a rapid weight gain that you could not explain over a period of six months or less?
10	Does your child take more naps than other children of the same age or more than you think he/she should?
11	Has a teacher or a nurse at your child's school ever told you that your child has problems staying awake in class?

[a] For ordinal items (1–8), the response options are (1) Never; (2) Less than once a month; (3) 1–3 times a month; (4) 1–3 times a week; (5) 4–6 times a week; (6) Daily (or Nightly); (7) I don't know.
[b] For dichotomous items (9–11), the response options are: (1) Yes; (2) No; (3) I don't know.
[c] Item 7 was removed from the instrument following validation.

narcolepsy; caregivers of children or adolescents with other sleep problems (OSP) who had presented to their healthcare provider with complaints of a sleep problem, but for whom the healthcare provider had ruled narcolepsy out; and caregivers of children and adolescents who had never been diagnosed with narcolepsy and did not have OSP (controls).

Caregivers were adults (18 years of age or older), and children or adolescents were under 18 years of age. Caregivers were excluded from participation if they had a significant psychiatric disorder preventing them from responding to or understanding the instrument's questions, or who, in the opinion of the recruiter, would not comply with the requirements of the study, or would not be able to recall the child's signs/symptoms.

Caregivers of children with narcolepsy and OSP were recruited via sleep centers, advocacy groups, and social media, and caregivers of children in the control group were recruited via a market research agency. Enrollment was terminated when 50 caregivers from each group (narcolepsy, OSP, and controls) were enrolled. Caregivers were compensated with a $25 Visa gift card for their participation.

2.3.3. Data collection

Demographic information on caregivers, demographic and clinical information on children/adolescents, and a completed PNSQ questionnaire were collected from caregivers after screening and after diagnosis for the narcolepsy and OSP groups. The following demographic information on caregivers was collected: age, sex, highest level of education, relationship to child/adolescent, race/ethnicity, number of children, and employment status. The following demographic and clinical information on children and adolescents was collected: age, sex, race/ethnicity, highest level of education, current medical diagnoses, and current treatment for any medical condition.

For the narcolepsy group, confirmation of diagnosis of narcolepsy (and whether the narcolepsy was type 1 [with cataplexy; NT1] or type 2 [without cataplexy; NT2], if available) was collected by directly contacting the diagnosing physician. For the OSP group, confirmation of exclusion of narcolepsy (and, if available, the diagnosis and characterization of the disorder [delayed sleep phase syndrome, insomnia, anxiety, depression, other]) was collected by directly contacting the clinician seen for sleep problems. For the control group, caregivers were asked to confirm the absence of narcolepsy or OSP, and the absence of a visit to a clinician with excessive sleepiness as the chief complaint.

2.3.4. PNSQ instrument

The PNSQ used in the validation study was an 11-item, self-administered questionnaire designed for caregivers of children or adolescents presenting with signs/symptoms suggestive of narcolepsy, consisting of 8 questions (items 1–8) asking about the frequency of certain signs/symptoms of narcolepsy and 3 questions (items 9–11) asking about the presence (yes/no) of specific narcolepsy signs/symptoms (Table 1). For the 8 ordinal items, the response options were “never,” “less than once a month,” “1–3 times per month,” “1–3 times per week,” “4–6 times per week,” and “daily or nightly.” For items 2–8, “I don't know” was an additional response option.

2.3.5. Statistical analysis

Caregiver and child/adolescent characteristics were summarized descriptively for the narcolepsy, OSP, and control groups. Categorical responses to each PNSQ item were compared across groups with a chi-square test. Item scores were compared across groups using the non-parametric Kruskal-Wallis test, chosen based on the limited sample size and non-normal distribution. Due to an imbalance between the groups with regard to child age and caregiver level of education, 2 linear regression analyses were conducted for each item (1 adjusting for the child age and 1 adjusting for the caregiver education level). PNSQ inter-item and item-total Pearson correlation coefficients were calculated. Cronbach's alpha [18] was generated overall for all items and after deletion of each item, one at a time. A minimum alpha value of 0.80 is provided as a guideline for determining that a total score is internally consistent [19], although values of $\geq$0.70 are also generally considered acceptable [20]; alpha scores $\geq$0.90 may indicate an overly homogenous measure where items are redundant due to excessive similarity [21].

To assess the discriminative power of individual PNSQ items, 2 logistic regression models were produced for each PNSQ item, with corresponding odds ratios (ORs) and 95% confidence intervals (CIs), using the PNSQ item as the explanatory variable and the narcolepsy versus OSP groups as the predicted variable (in the first model) or the narcolepsy versus control groups as the predicted variable (in the second model). Additionally, receiver operating characteristic (ROC) curves were drawn for each PNSQ item, and area under the ROC curve (AUC) [22] was calculated.

A principal component analysis (PCA) was conducted to assess the unidimensionality of the PNSQ using the scree test [23] and eigenvalue larger than 1 as well as residual analysis [24,25]. A 2-parameter item response theory (IRT; a model that predicts

responses to an item based on 2 parameters, the difficulty level of the item on the measured concept, and the item discriminability [how well an item discriminates different subjects]) model [26] was applied to PNSQ items to allow estimation of item difficulty and discrimination parameters.

After the final PNSQ structure and scoring algorithm were proposed, the discriminant ability of the proposed total score was evaluated using logistic regression. The AUC characterizing the distinction between individuals with narcolepsy and individuals with OSP, and between individuals with narcolepsy and controls, was tested with narcolepsy (yes/no) as the predicted variable and the PNSQ score as the explanatory variable. PNSQ score thresholds (T1 and T2) were established to classify individuals into categories (PNSQ+, PNSQ 0, PNSQ−). T1 and T2 were obtained following results from logistic regressions and associated ROC curves in which the explanatory variable was the PNSQ score and the predicted variable was value = 1 if the child or adolescent was in the narcolepsy group and value = 0 if the child or adolescent was in the control group (for T1) or OSP group (for T2). The value maximizing the Youden Index, a statistic used to capture the performance of a dichotomous diagnostic test, often used in conjunction with ROC analysis, was selected for both thresholds. The formula to compute the Youden index is J = sensitivity + specificity −1, where the sensitivity is the true positive rate, and the specificity is the true negative rate.

Known groups validity was assessed with a description and comparison (ANOVA comparing the 3 groups and *t* tests comparing 2 groups at a time) of the PNSQ score across the narcolepsy, OSP, and control groups, and overall. The number and percentage of individuals belonging to each PNSQ category were compared across the narcolepsy, OSP, and control groups, and overall, using a chi-square test.

Statistical analyses were performed using SAS® software version 9.4 (SAS Institute, Inc., Cary, NC, USA) or higher, except for partial least square discriminant analyses (a multivariate method that is used for dimensionality reduction [ie, to reduce the number of factors needed to explain a categorical variable, while minimizing error]), which were performed using R Software (V3.4.3), and PCA/IRT models, which were performed using RUMM 2030. Due to no adjustments for multiplicity, the *P* values presented are nominal.

3. Results

3.1. Content validity testing and cognitive debriefing

Twenty caregivers (median [range] age, 38 [31–54] years; n = 19 female; n = 10 White [n = 1/10 Hispanic/Latino], n = 10 African American [n = 1/10 Hispanic/Latino]) took part in the cognitive debriefing interviews. Nineteen of the 20 children for whom the PNSQ was completed had a formal diagnosis of narcolepsy (median [range] age at diagnosis, 10 [7–17] years); median (range) age was 12 (7–17) years, and most were female (n = 12), African American (non-Hispanic/Latino, n = 9), or White (non-Hispanic/Latino, n = 7) and were being treated for narcolepsy (n = 14). Overall, caregivers had a very positive impression of the initial draft of the PNSQ and indicated that they liked the response choices. For items about sleep (regarding frequency of nightmares or multiple nocturnal awakenings), caregivers thought that older children should answer those items themselves, noting that older children no longer told them about their dreams/nightmares or woke them up or told them later if there was a problem. Limited suggestions for modifications were made and the majority of caregivers did not suggest deleting any items from the questionnaire.

Based on these findings, several changes to the initial 12-item PNSQ were made, including the rewording of instructions to emphasize the caregivers' subjective observation of their child's behavior, the addition of “Never” and “I don't know” to all frequency response questions, the deletion of 3 questions (Walking or running awkwardly, Waking up a lot at night, Early onset of puberty), and the addition of 2 questions (1 regarding sleep disturbances and 1 regarding a history of reported sleep problems by a teacher or school nurses). The updated version of the PNSQ therefore comprised 11 items.

3.2. Preliminary clinician feedback

Six sleep clinicians piloted the updated PNSQ and completed the PRAC-test©; an additional 10 pediatricians completed only the PRAC-test© with no patient/parent contact. Seventeen caregivers making a visit to the clinician's office were recruited to participate and asked to complete the PNSQ for their children. All clinicians and pediatricians thought the PNSQ was useful overall and would recommend it to their colleagues. No modifications were made to the PNSQ prior to the validation study, as it was well received by clinicians.

3.3. Validation study population

In total, 180 caregivers of patients were enrolled: 70 children and adolescents with narcolepsy, 59 with OSP, and 51 in the control group (Fig. 1). Analysis populations were defined, taking into account clinicians' diagnoses, leading to the following groups: controls (n = 54), patients with confirmed narcolepsy (n = 49), and patients reporting OSP (n = 55). In the narcolepsy group, 34 (69.4%) children and adolescents were reported by the clinician to have NT1 and 14 (28.6%) were reported to have NT2; for 1 (2.0%) child, the clinician was “not sure” of the type of narcolepsy. In the OSP group, all children were considered to have a sleep problem, but not narcolepsy. No children or adolescents (0%) in this OSP group were reported by the clinician to have delayed sleep phase syndrome, 5 (9.1%) had insomnia, 2 (3.6%) had anxiety, and 1 (1.8%) had depression; for 4 (7.3%) children and adolescents, the physician was unsure, for 11 (20.0%), the type of sleep problem was categorized as “other,” and for 32 (58.2%), the information was missing. Sensitivity analyses comparing patients with confirmed narcolepsy (n = 49) and patients with confirmed OSP (n = 18), as well as the patients reporting narcolepsy (n = 69) and patients reporting OSP (n = 55), showed similar results to those of the main analyses.

Sociodemographic characteristics of caregivers are presented in Table 2. Differences across groups were identified in terms of caregivers' level of education, employment status, and age. Although statistical testing was not performed, caregivers from the OSP group, compared with caregivers from the narcolepsy and control groups, had a numerically lower education level (60.0% non-graduated [ie, without a high school or college degree] compared with 24.5% and 27.8%, respectively), were less likely to be employed or self-employed (43.6%, compared with 79.6% and 66.7%, respectively), and were slightly younger (mean age, 38.6 years, compared with 43.1 and 43.4 years, respectively).

Characteristics of the children and adolescents are presented in Table 3. The most notable differences across groups were related to age and diagnosed health conditions. Children and adolescents in the narcolepsy group, compared with the OSP and control groups, were numerically older (mean age, 13.8 years, compared with 10.2 years and 10.0 years, respectively) and more likely to be treated for a diagnosed health condition (87.8%, compared with 58.2% and 18.5%, respectively; no statistical comparisons performed).

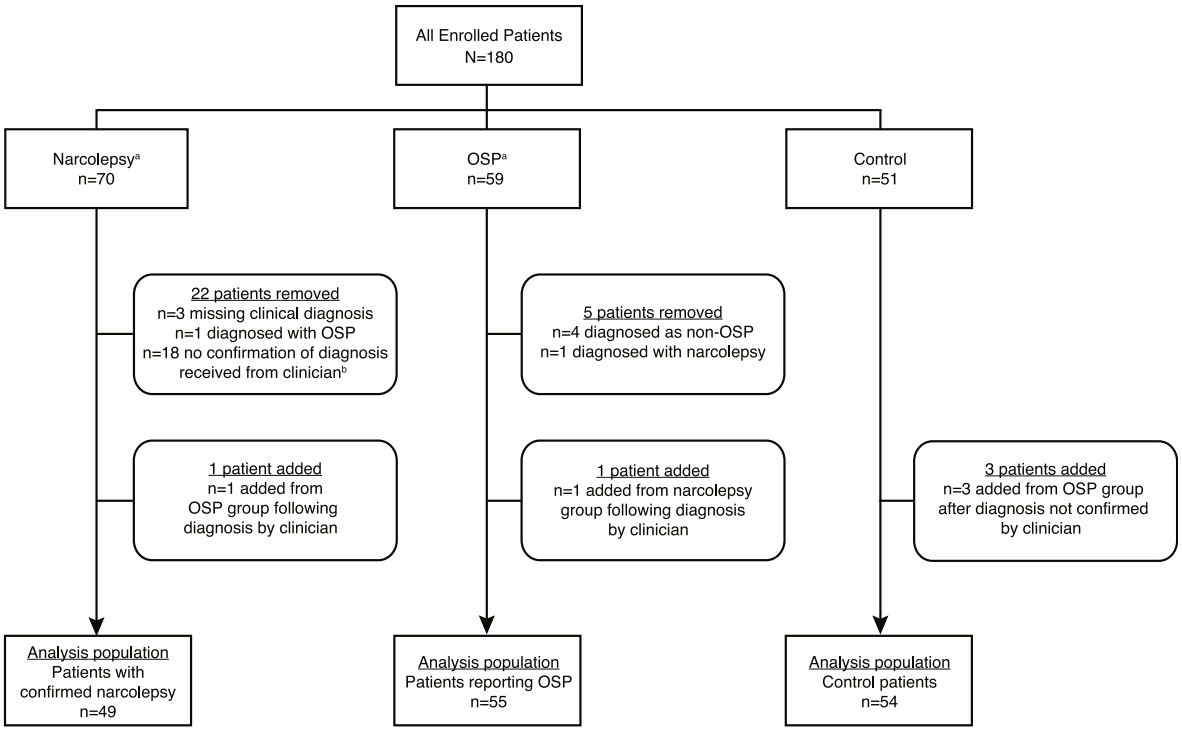

Fig. 1. Patient disposition.
OSP, other sleep problems.
[a] As declared by caregivers.
[b] After 3 reminders.

Table 2
Caregiver sociodemographic characteristics.

	Group		
Characteristic	Narcolepsy (n = 49)	OSP (n = 55)	Control (n = 54)
Age, years			
Mean (SD)	43.1 (5.7)	38.6 (7.6)	43.4 (7.0)
Min, max	33, 54	22, 56	28, 60
Female, n (%)	46 (93.9)	51 (92.7)	48 (88.9)
Race, n (%)			
Black or African American	5 (10.2)	5 (9.1)	13 (24.1)
White	39 (79.6)	49 (89.1)	39 (72.2)
Other/Multiple	5 (10.2)	1 (1.8)	2 (3.7)
Ethnicity, n (%)			
Hispanic or Latino	4 (8.2)	5 (9.1)	4 (7.4)
Not Hispanic or Latino	43 (87.8)	49 (89.1)	48 (88.9)
Missing	2 (4.1)	1 (1.8)	2 (3.7)
Relationship to child or adolescent, n (%)			
Mother	46 (93.9)	48 (87.3)	46 (85.2)
Father	3 (6.1)	4 (7.3)	6 (11.1)
Legal guardian	0 (0.0)	3 (5.5)	2 (3.7)
Number of children, n (%)			
1	3 (6.1)	11 (20.0)	8 (14.8)
2	16 (32.7)	13 (23.6)	22 (40.7)
3	20 (40.8)	16 (29.1)	11 (20.4)
4+	10 (20.4)	15 (27.3)	13 (24.1)
Highest education level, n (%)			
Non-graduated[a]	12 (24.5)	33 (60.0)	15 (27.8)
Graduated	34 (69.4)	22 (40.0)	37 (68.5)
Other	3 (6.1)	0 (0.0)	2 (3.7)
Employment status, n (%)			
Employed/Self-employed	39 (79.6)	24 (43.6)	36 (66.7)
Not employed	10 (20.4)	31 (56.4)	17 (31.5)
Missing	0 (0.0)	0 (0.0)	1 (1.9)

Max, maximum; min, minimum; OSP, other sleep problems; SD, standard deviation.
[a] Without a high school or college degree.

Table 3
Child and adolescent characteristics.

Characteristic	Group		
	Narcolepsy (n = 49)	OSP (n = 55)	Control (n = 54)
Narcolepsy type, n (%)			
Type 1	34 (69.4)	0	0
Type 2	14 (28.6)	0	0
Not sure	1 (2.0)	2 (3.6)	0
Missing	0	53 (96.4)	54 (100)
Age, years			
n (missing)	49 (0)	54 (1)	54 (0)
Mean (SD)	13.8 (2.8)	10.2 (4.3)	10.0 (3.8)
Min, max	6, 17	2, 17	1, 17
Age, categorical, n (%)			
<7 years old	1 (2.0)	14 (25.5)	12 (22.2)
7–12 years old	15 (30.6)	24 (43.6)	29 (53.7)
>12 years old	33 (67.3)	16 (29.1)	13 (24.1)
Missing	0 (0.0)	1 (1.8)	0 (0.0)
Female, n (%)	22 (44.9)	23 (41.8)	29 (53.7)
Race, n (%)			
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (1.9)
Black or African American	8 (16.3)	5 (9.1)	12 (22.2)
White	34 (69.4)	44 (80.0)	34 (63.0)
Other/Multiple	7 (14.3)	6 (10.9)	7 (13.0)
Ethnicity, n (%)			
Hispanic or Latino	6 (12.2)	8 (14.5)	9 (16.7)
Not Hispanic or Latino	40 (81.6)	47 (85.5)	43 (79.6)
Missing	3 (6.1)	0 (0.0)	2 (3.7)
Highest education level, n (%)			
No schooling completed	0 (0.0)	10 (18.2)	8 (14.8)
Preschool to 8th grade	23 (46.9)	36 (65.5)	37 (68.5)
Some high school, no diploma	25 (51.0)	8 (14.5)	9 (16.7)
High school equivalent (eg, GED)	0 (0.0)	1 (1.8)	0 (0.0)
Missing	1 (2.0)	0 (0.0)	0 (0.0)
Any diagnosed health condition(s), n (%)[a]			
Yes	31 (63.3)	39 (70.9)	17 (31.5)
No	18 (36.7)	16 (29.1)	37 (68.5)
Currently treated for any diagnosed health conditions, n (%)			
Yes	43 (87.8)	32 (58.2)	10 (18.5)
No	3 (6.1)	8 (14.5)	42 (77.8)
Missing	3 (6.1)	15 (27.3)	2 (3.7)

GED, Graduate Equivalency Degree; max, maximum; min, minimum; OSP, other sleep problems; SD, standard deviation.
[a] Excepting narcolepsy in the narcolepsy group.

3.4. Data collection

The percentage of caregivers with no missing data on the PNSQ was 98%, 70%, and 98% in the narcolepsy, OSP, and control groups, respectively. The number of items with missing data per caregiver ranged from 0 to 1 for the narcolepsy and control groups and from 0 to 3 for the OSP group. The items with the most missing data were item 6 (child falls down, becomes weak or floppy, loses control of his head; 5% of questionnaires), item 7 (child has vivid dreams or nightmares; 4%), and item 5 (child shows unusual facial expressions; 3%); for all other items, there were 2 or fewer questionnaires with missing data; items 9 (rapid weight gain that you could not explain) and 10 (child takes more naps than other children of the same age) had no missing data at all. When the "I don't know" response option was replaced by a missing item value, the percentage of caregivers with no missing data was 86%, 67%, and 83% in the narcolepsy, OSP, and control groups, respectively.

3.5. Responses to PNSQ items

The distributions of responses on individual PNSQ items per group are shown in Fig. 2. On the ordinal items (items 1–8), fewer caregivers in the narcolepsy group compared with the control group reported that the signs/symptoms being assessed "never" occurred, and more caregivers in the narcolepsy group compared with the control group reported that these signs/symptoms occurred "daily" or "nightly." In the OSP group, the frequency of the signs/symptoms was generally evenly distributed across all response options. On the dichotomous items (items 9–11), most caregivers in the narcolepsy group reported that the signs/symptoms being assessed were present, and most caregivers in the control group reported that the signs/symptoms were absent. Caregivers in the OSP group mostly denied unexplained weight gain (item 9) and were about evenly split between "yes" and "no" on items 10 and 11.

For all items, P values from the non-parametric Kruskal-Wallis test comparing mean item scores across groups were all <0.0001 (except for item 7, which was $P = 0.0005$). As there were differences among the groups in terms of the child age and the education level of the caregiver, linear regression models were performed to control for these potential confounders. The regression showed that, even after adjustment for these potential confounders, the differences in mean item scores across groups remained significant.

3.6. Internal consistency reliability

Inter-item correlation coefficients >0.7 (Table 4) were obtained for 4 item pairs. Other inter-item correlations were of small (≤0.40) to medium (>0.40 to <0.70) amplitude. Item-total correlations ranged from 0.43 (item 9) to 0.82 (items 2 and 4). Cronbach's alpha of the PNSQ was 0.88 (raw) and 0.90 (standardized) overall (Supplemental Table 2). When deleting 1 item at a time, the range

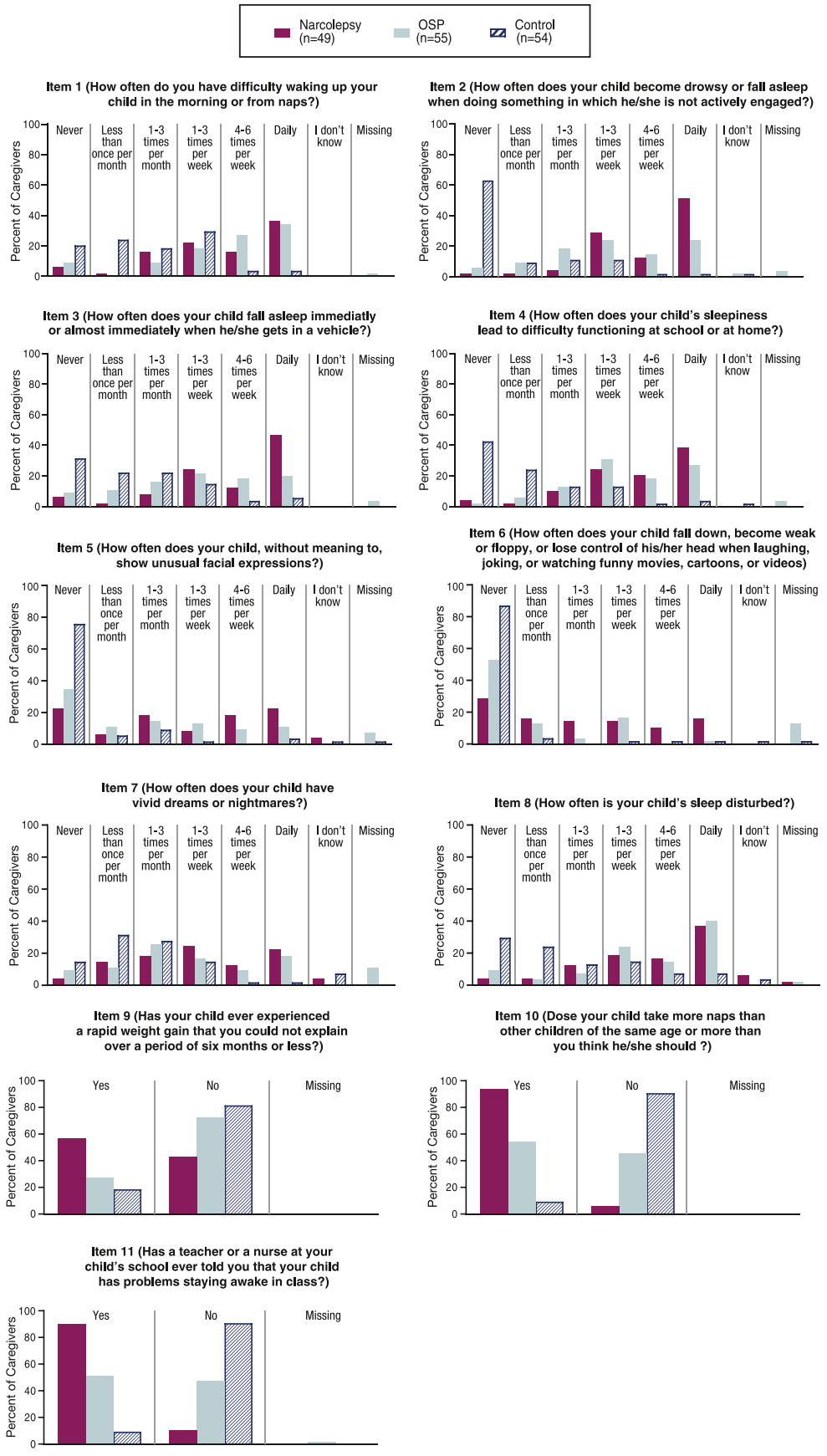

Fig. 2. Responses to PNSQ items.
OSP, other sleep problems; PNSQ, Pediatric Narcolepsy Screening Questionnaire.

Table 4
Inter-item Pearson correlations.[a]

		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7[b]	Item 8	Item 9	Item 10	Item 11
		Difficulty waking up	Drowsy or falls asleep when not actively engaged	Falls asleep in vehicle	Sleepiness leads to difficulty functioning	Unusual facial expressions	Weak or floppy when laughing or joking	Vivid dreams or nightmares	Disturbed sleep	Rapid weight gain	More naps than peers	Teacher mentioned sleepiness
Item 1	Difficulty waking up	1.00										
Item 2	Drowsy or falls asleep when not actively engaged	0.56	1.00									
Item 3	Falls asleep in vehicle	0.50	0.73	1.00								
Item 4	Sleepiness leads to difficulty functioning	0.66	0.75	0.63	1.00							
Item 5	Unusual facial expressions	0.42	0.57	0.44	0.53	1.00						
Item 6	Weak or floppy when laughing or joking	0.34	0.54	0.39	0.45	0.72	1.00					
Item 7[b]	Vivid dreams or nightmares	0.50	0.48	0.34	0.57	0.48	0.39	1.00				
Item 8	Disturbed sleep	0.39	0.48	0.36	0.54	0.36	0.31	0.44	1.00			
Item 9	Rapid weight gain	0.23	0.35	0.29	0.40	0.22	0.39	0.22	0.44	1.00		
Item 10	More naps than peers	0.36	0.67	0.58	0.62	0.44	0.39	0.33	0.33	0.39	1.00	
Item 11	Teacher mentioned sleepiness	0.33	0.71	0.50	0.63	0.48	0.43	0.27	0.33	0.33	0.63	1.00

[a]Colors represent inter-item correlation coefficients: ≤0.40 = light green, >0.40 to <0.70 = medium green, ≥0.70 = dark green.
[b]Item 7 was removed from the instrument following validation.

of raw alphas decreased slightly but remained high and was 0.86–0.89, and the range of standardized alphas was 0.88–0.90.

3.7. Discriminative power of PNSQ items

The AUCs for each ROC curve are presented in Table 5. For the narcolepsy group compared with the control group, the AUC exceeded 0.8 for 9 of the 11 items, indicating strong discriminative power. Item 9 and item 7 presented the smallest AUC (0.693 [95% CI, 0.606–0.781] and 0.757 [0.663–0.852], respectively); however, the lower bound of the 95% CI was >0.5 for both, indicating moderate discriminative power.

For the narcolepsy group compared with the OSP group, the AUC exceeded 0.6 for 7 of the 11 items. The smallest AUCs were presented by item 1 (0.596 [0.490–0.702]), item 4 (0.584 [0.478–0.691]), item 7 (0.599 [0.492–0.707]), and item 8 (0.591 [0.484–0.697]); for each of these items, the lower bound of the 95% CI was <0.5, suggesting limited power to discriminate between these groups.

3.8. Unidimensionality and latent trait analysis

The scree plot and proportion of variance explained with the PCA according to the number of factors considered are shown in Fig. 3. The hypothesized unidimensionality of the PNSQ was confirmed, as the trajectory of the scree plot indicates a clear drop in the eigenvalue from the second factor of the PCA, and the percentage of variance explained with the first factor was >50%. In the IRT model using PNSQ item scores, the person separation index (0.868) indicated an "excellent" fit of the model. Category

Table 5
Discriminative power of PNSQ items.

Item	AUC[a]	95% CI	Description
Narcolepsy group compared with control group			
1	0.807	0.726–0.888	Difficulty waking up
2	0.936	0.890–0.982	Drowsy or falls asleep when not actively engaged
3	0.852	0.779–0.926	Falls asleep in vehicle
4	0.888	0.823–0.953	Sleepiness leads to difficulty functioning
5	0.818	0.738–0.897	Unusual facial expressions
6	0.820	0.746–0.895	Weak or floppy when laughing or joking
7[b]	0.757	0.663–0.852	Vivid dreams or nightmares
8	0.805	0.719–0.891	Disturbed sleep
9	0.693	0.606–0.781	Rapid weight gain
10	0.923	0.871–0.975	More naps than peers
11	0.903	0.845–0.961	Teacher mentioned sleepiness
Narcolepsy group compared with OSP group			
1	0.596	0.490–0.702	Difficulty waking up
2	0.709	0.613–0.804	Drowsy or falls asleep when not actively engaged
3	0.689	0.590–0.788	Falls asleep in vehicle
4	0.584	0.478–0.691	Sleepiness leads to difficulty functioning
5	0.637	0.532–0.741	Unusual facial expressions
6	0.729	0.643–0.815	Weak or floppy when laughing or joking
7[b]	0.599	0.492–0.707	Vivid dreams or nightmares
8	0.591	0.484–0.697	Disturbed sleep
9	0.649	0.558–0.741	Rapid weight gain
10	0.697	0.622–0.771	More naps than peers
11	0.695	0.616–0.774	Teacher mentioned sleepiness

AUC, area under the curve; CI, confidence interval; OSP, other sleep problems; PNSQ, Pediatric Narcolepsy Screening Questionnaire.
[a] AUCs were obtained from Receiving Operator Characteristic (ROC) curves derived from logistic regression (predicted variable: narcolepsy compared with control or narcolepsy compared with OSP; explanatory variable: PNSQ item [1 model for each item]).
[b] Item 7 was removed from the instrument following validation.

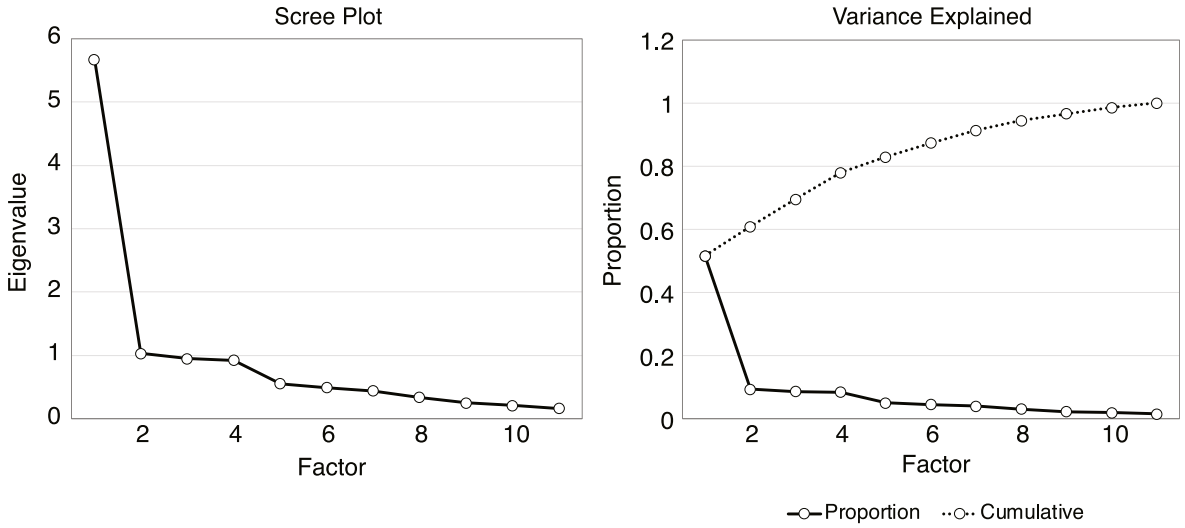

Fig. 3. Scree plot from PCA.
PCA, principal component analysis.

probability curves for each PNSQ item indicated that for each ordinal item (1–8), response options "never" and "daily" or "nightly" were dominant for the lower and higher values, respectively, on the latent trait, while intermediate response options "less than once per month" and "4–6 times per week" were rarely preferred. The person-item threshold distribution (Fig. 4) indicated good coverage of the latent trait by the PNSQ items, with an increased number of item parameters around the value 0.2–0.4 of the latent trait.

3.9. Item selection and derivation of thresholds

Based on its low discriminative power and poor performance in the IRT model, as well as the fact that caregivers expressed difficulty responding to this question during the cognitive debriefing interviews (ie, indicating older children may not share their nightmares) and the relative non-specificity of the item (ie, most children may experience nightmares), PNSQ item 7 ("How often does your child have vivid dreams or nightmares?") was removed, leading to a final PNSQ of 10 items, and a scoring algorithm for the 10 selected items. For ordinal items (1–8), response options were weighted from 0 ("never") to 5 ("daily" or "nightly"). For dichotomous items (9–11), a score of 0 was given for "no" and a score of 5 was given for "yes." This led to a total PNSQ score, ranging from 0 to 50, with a higher value indicating more severe sleep problems and higher probability of narcolepsy.

The thresholds obtained from logistic regressions and associated ROC curves (Fig. 5) were 18 for T1 (AUC [95% CI], 0.96

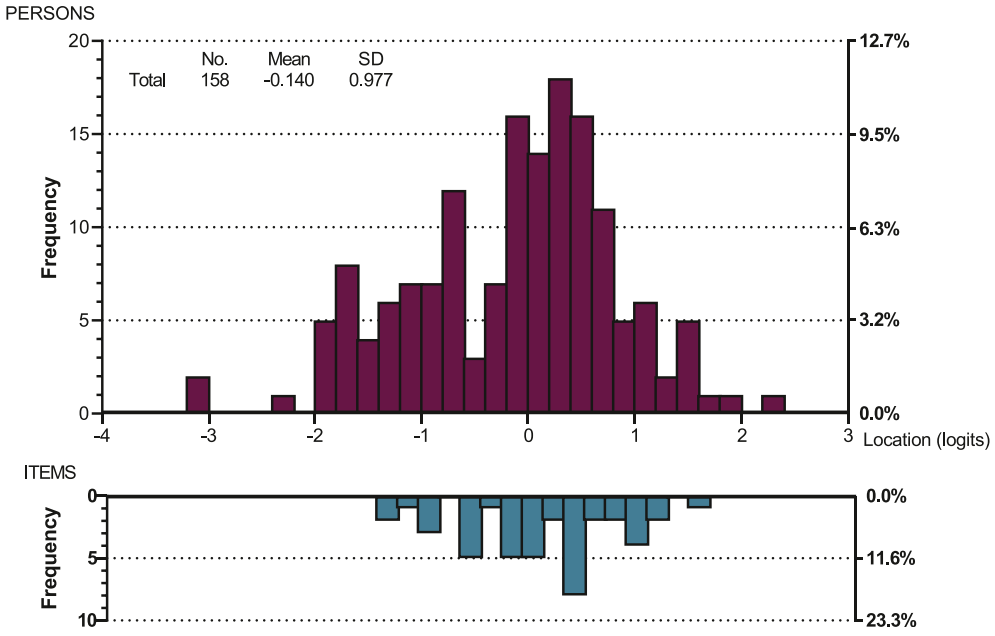

Fig. 4. IRT/partial credit model.
IRT, item response theory; SD, standard deviation.

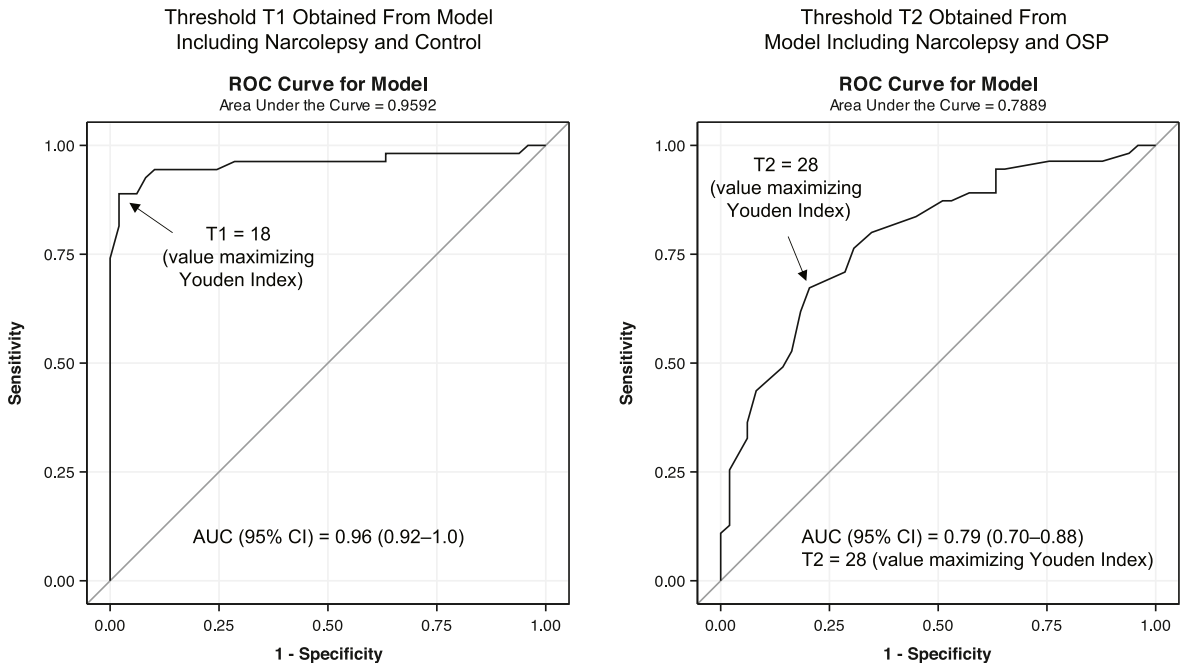

Fig. 5. Discriminative power of the PNSQ score and derivation of thresholds to categorize patients.
AUC, area under the curve; CI, confidence interval; OSP, other sleep problems; ROC, receiver operating characteristic; T1, threshold 1; T2, threshold 2.

[0.92–1.0]; Youden Index, 0.868) and 28 for T2 (AUC [95% CI], 0.79 [0.70–0.88]; Youden Index, 0.469). The thresholds allowed for the classification of individuals into 3 groups, as follows: PNSQ+ (PNSQ score >28 [T2]), indicating an individual presenting with severe sleep problems suggestive of possible narcolepsy, with further investigation needed; PNSQ 0 (PNSQ score >18 [T1] and ≤28 [T2]), indicating an individual presenting with sleep problems possibly requiring further investigation; and PNSQ– (PNSQ score ≤18 [T1]), indicating an individual for whom sleep problems are either absent or minor and limited, and who is unlikely to have narcolepsy.

3.10. Discriminative power of the PNSQ

Mean (SD) PNSQ scores in the narcolepsy, OSP, and control groups were 35.0 (8.0), 25.2 (9.4), and 9.5 (9.4), respectively (Table 6). Comparisons of mean PNSQ scores across the 3 groups (ANOVA; $P < 0.0001$) and pairwise comparisons of the groups (*t* tests; all $P < 0.0001$) indicated significant differences.

In the narcolepsy group, the majority of individuals were classified as PNSQ+ (79.6%); most of the remainder were classified as PNSQ 0 (18.4%), and 1 was classified as PNSQ– (2.0%; Table 6). In the OSP group, 32.7%, 47.3%, and 20.0% were classified as PNSQ+, PNSQ 0, and PNSQ–, respectively. In the control group, the large majority of individuals were classified as PNSQ– (88.9%), with the remainder evenly split between PNSQ+ and PNSQ 0 (both 5.6%). As expected, the number and percentage of individuals belonging to each PNSQ category differed significantly across groups (chi-square test; $P < 0.0001$).

Table 6
Final PNSQ total scores across groups.

	Narcolepsy (n = 49)	OSP (n = 55)	Control (n = 54)	*P* Value[a]
Score (0–50)[b]				
Mean (SD)	34.98 (7.98)	25.20 (9.43)	9.54 (9.38)	<0.0001
Median	34.00	26.00	6.50	
Min, max	14.00, 49.00	5.00, 46.00	0.00, 46.00	
Classification[c], n (%)				
PNSQ + [d]	39 (79.6)	18 (32.7)	3 (5.6)	<0.0001
PNSQ 0[e]	9 (18.4)	26 (47.3)	3 (5.6)	
PNSQ–[f]	1 (2.0)	11 (20.0)	48 (88.9)	

ANOVA, analysis of variance; max, maximum; min, minimum; OSP, other sleep problems; PNSQ, Pediatric Narcolepsy Screening Questionnaire; SD, standard deviation.
[a] From ANOVA comparing the 3 groups.
[b] Calculated for the 10-item instrument, excluding item 7.
[c] Threshold T1 = 18 and T2 = 28.
[d] PNSQ score > T2.
[e] PNSQ score > T1 and ≤T2.
[f] PNSQ score ≤ T1.

4. Discussion

The results of this comprehensive psychometric validation study demonstrate that the PNSQ is able to identify patients with a higher likelihood of narcolepsy compared with those with no sleep problems, and patients less likely to have narcolepsy but with a possibility of other sleep problems. The findings support the use of the PNSQ as a tool to assist healthcare providers in identifying pediatric patients who should be further evaluated for a possible diagnosis of narcolepsy. Given the difficulties surrounding the diagnosis of pediatric narcolepsy [7,9], this questionnaire meets a significant unmet need for a screening tool to help providers in primary care settings identify potential narcolepsy. It should be noted that, at the time this manuscript was undergoing peer review, a new tool (the Pediatric Hypersomnolence Survey) was published in *Neurology* [27]. The PNSQ is brief, easy to administer, and was well accepted by both caregivers and clinicians during preliminary studies. The PNSQ is designed as a screening and not a diagnostic tool, intended to facilitate referral to an appropriate specialist for further evaluation. Furthermore, the PNSQ was also not designed to distinguish between NT1 and NT2.

The present study compared patients with a clinician-confirmed diagnosis of narcolepsy to healthy controls and to those reporting other sleep problems, even in the absence of a formal diagnosis. Although it was important to evaluate the PNSQ among patients

with a confirmed diagnosis of narcolepsy, the inclusion of a broader, less well-defined set of patients in the OSP group was felt to be reflective of the diagnostic process where many patients may present with sleep problems that have not yet led to a defined diagnosis. Sensitivity analyses comparing the broadly defined narcolepsy and OSP groups, and the patients with confirmed narcolepsy and confirmed OSP, produced similar results to the main analysis.

The distribution of responses to the PNSQ items demonstrated that there were clear differences between the narcolepsy and control groups on most individual PNSQ items, particularly the dichotomous (yes/no) items (items 9, 10, and 11). The OSP group was mostly intermediate between the narcolepsy and control groups, which could be due to the more heterogeneous nature of sleep problems in this group, suggesting that in clinical practice, further assessment is necessary for such patients. Some items showed fewer differences between groups in the distributions of responses (eg, item 1 [difficulty waking up your child], item 7 [vivid dreams and nightmares], and item 8 [disturbed sleep]). The similarity in responses on items 7 and 8 may be due to children's inability to articulate their sleep symptoms and/or caregivers' lack of awareness of their child's sleep experience [13]. Unidimensionality of the PNSQ was confirmed by the large percentage of variance explained by the first PCA factor and the scree plot of eigenvalues. PNSQ inter-item and item-total Pearson correlation coefficients indicated good construct validity, with little redundancy between items.

When assessing the discriminative power of the PNSQ items, the majority of the AUCs were highly discriminative (>0.80) for comparisons between narcolepsy and controls (except for items 7 and 9). When comparing patients with narcolepsy and other sleep problems, most items discriminated well, but AUC values with 95% CI lower bounds <0.5, indicating performance worse than random chance [28], were obtained for items 1, 4, 7, and 8. This may indicate that scores on these items may relate to shared signs/symptoms between the narcolepsy and OSP groups. Given that the total PNSQ score provides some discriminative power between patients with OSP and narcolepsy, the aforementioned items may be important in the context of the total score even if their individual discriminatory power is lower. Although the inclusion of multiple response options was intended to make the instrument more sensitive, the partial credit analyses indicated that the large number of response options per item did not increase the precision of the PNSQ.

After analyses of the 11 individual PNSQ items, only item 7 was removed, as it was found to show both low specificity and poor discriminative power. Based on the remaining 10 items, the PNSQ total score range is 0–50, with 3 categories defined: PNSQ+ (>28), PNSQ 0 (>18 and ≤28), and PNSQ− (≤18). The overall discriminative power of the final 10-item PNSQ was demonstrated through analyses of known groups validity (ie, the ability of a measure to discriminate between separate populations when a difference between them is expected). The chi-square test confirmed that the number and percentage of individuals belonging to each PNSQ category differed across groups.

A particular strength of this study was the high response rate with few missing data. Most items (8 of 11) had fewer than 2 instances of missing data; items 5 (regarding involuntary unusual facial expressions), 6 (regarding cataplexy), and 7 (regarding vivid dreams and nightmares) had more missing data, primarily from the OSP group. As the OSP group included children with heterogeneous sleep problems and potentially at an earlier stage in the diagnostic process, caregivers may have been uncertain about whether behaviors they observed fit signs/symptoms of cataplexy, and the lower response rate also could have resulted from the aforementioned inability of children to articulate their sleep symptoms and/or caregivers' lack of awareness of their child's sleep experience [13].

Some limitations of the study are noted. Firstly, the 3 categories of respondents were based solely on provider diagnoses, with no sleep testing performed to confirm the presence or absence of narcolepsy, and the presence of heterogeneity among the OSP group. In addition to the small sample size, numerical differences were observed in the demographic makeup among the caregivers and children/adolescents; specifically, education and employment were lower in the OSP caregiver group; the impact of this difference is unclear. Patients in the narcolepsy group were older, on average, compared with the OSP and control groups, which is likely the consequence of the duration needed to formally diagnose narcolepsy [7]. For the narcolepsy group, the diagnosis was known by the caregiver prior to completion of the questionnaire, and this may have facilitated the identification of the narcolepsy signs/symptoms. Lastly, the PNSQ does not contain a question regarding the symptoms of REM sleep behavior disorder, which often precedes the development of NT1 in pediatric patients [29]. Nevertheless, the results show that the PNSQ differentiates very well between patients with narcolepsy and healthy controls. As expected, the discriminative power of the PNSQ was lower between patients with narcolepsy and those with other sleep problems, but the AUC of 0.79 suggests that the PNSQ did provide meaningful information in discriminating these patients. The next steps will involve prospectively implementing the scale in clinical practice to provide further evidence regarding the usefulness of the PNSQ as a prospective screening tool for pediatric patients requiring formal narcolepsy diagnosis testing, and the generation of evidence to determine the predictive validity of the PNSQ in specific age groups.

5. Conclusion

In conclusion, this study allowed finalization of the PNSQ content and assessment of its psychometric performance. The final PNSQ is a 10-item questionnaire to screen for potential narcolepsy in children and adolescents presenting to clinicians with sleep problems before referral to a sleep specialist. Overall, the distribution of scores on individual PNSQ items showed clear differences between the narcolepsy and control groups, with intermediate levels in the OSP group. The PNSQ exhibited good psychometric properties and excellent performance in discriminating between narcolepsy and control groups, and thresholds were derived to identify individuals who would benefit from additional clinical narcolepsy evaluation. The PNSQ fulfills its intended purpose of identifying children who would benefit from further evaluation for narcolepsy.

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Declaration of competing interest

Susan Morris is a former employee of Jazz Pharmaceuticals who, in the course of her employment, received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc.

Giuseppe Plazzi is a former consultant to Jazz Pharmaceuticals and has participated in advisory boards for UCB Pharma, Bioprojet, Idorsia, Jazz Pharmaceuticals, and Takeda.

Christine de la Loge is a paid consultant to ICON plc.

Alexia Marrel is an employee of ICON plc.

Judi Profant is a former full-time employee of Jazz Pharmaceuticals who, in the course of this employment, received stock options

exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

Teresa L. Steininger is a full-time employee of Jazz Pharmaceuticals who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

Junji Lin is a full-time employee of Jazz Pharmaceuticals who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2022.05.017.

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