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Is it possible to predict the response to therapy in enuretic children? The PiFe score

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Introduction Nocturnal enuresis (NE) is defined as the involuntary passage of urine during sleep in children over the age of five. Although the precise mechanisms of NE are unclear, factors like delayed development, genetic influences, excessive nighttime urine production, disrupted sleep, and bladder dysfunction play a role. This study aims to evaluate the role of comorbidities in NE and develop a scoring system to predict treatment response, with clinical applications.

Material and methods We recruited 374 patients aged 5–18 years undergoing pharmacological treatment (single or combined) for NE. Demographic and clinical data were collected through parent interviews. Statistical analyses included descriptive statistics and categorical analysis using χ^2 tests, followed by logistic regression.

Results Statistical associations were found between recurrence and learning disorders ($\chi^2 = 4.862$, $p = 0.027$), and between treatment response and learning disorders, encopresis, polythelia, language delay, and snoring. Logistic regression identified learning disorders (OR = 3.023), encopresis (OR = 2.156), polythelia (OR = 2.196), language delay (OR = 2.137), and snoring (OR = 1.560) as predictors of poor treatment response. We propose the PiFe score, a clinical tool to predict treatment outcomes in children with NE. This score integrates factors such as comorbidities, age, and symptom severity, helping to guide multidisciplinary interventions.

Conclusions This study emphasizes the importance of a holistic approach to managing NE. The PiFe score could be a useful tool for predicting treatment outcomes and guiding interventions. Further research is needed to validate and refine the scoring system.

Key Words: enuresis ‹› children ‹› treatment ‹› relapse ‹› prognostic factor

INTRODUCTION

Nocturnal enuresis (NE), commonly referred to as intermittent bedwetting, is defined by the International Children's Continence Society (ICCS) as the involuntary and episodic passage of urine during sleep in children over the age of five [1, 2]. NE affects over 10.0% of 6-year-olds, around 5.0% of 10-year-olds, and between 0.5% and 1.0% of adolescents and young adults [3].

Nocturnal enuresis is generally categorized into 2 main types: primary NE (PNE) and secondary NE (SNE). PNE is more common and refers to bedwetting in children who have never had an extended period (over 6 months) of night-time dryness. In contrast, SNE occurs when bedwetting reappears after a dry period of at least 6 months. NE can also be further divided into monosymptomatic NE (MNE) and non-monosymptomatic NE (NMNE). NMNE is marked by additional daytime lower urinary tract

symptoms (LUTS) such as urgency, daytime incontinence, hesitancy, and abnormal voiding frequency, which is defined as urinating either more than 8 times per day or fewer than 3 times per day.
Although the precise mechanisms behind NE remain unclear, it is widely recognized that multiple factors contribute to its onset and persistence, including delayed development, genetic influences, excessive nighttime urine production, disrupted sleep patterns, limited bladder capacity, and overactive bladder muscles [1, 4–10].
A key pathological mechanism appears to be a delayed maturation of the central nervous system, which may contribute to PNE, particularly when compared to age-matched controls, a concept further supported by neurophysiological data [11]. However, several factors seem to play a predominant role in the onset and progression of NE, particularly in terms of treatment response and relapse rates. Specifically, according to the ICCS, the response to NE treatment is classified into three categories based on the reduction in the number of wet nights. A complete response is defined as a reduction of 90.0% or more, or complete resolution of NE, typically indicated by 14 consecutive dry nights. A partial response refers to a decrease of 50.0% to 89.0% in the number of wet nights. If the reduction is less than 50.0%, it is considered no response [1, 2].
Several studies have explored the role of specific comorbidities in children with NE investigating their potential association with the onset and recurrence of the condition. Approximately 20.0–30.0% of children with NE have clinically significant comorbidities with a prevalence 2 to 4 times higher than that observed in control populations [12]. These comorbidities are more commonly found in children with SNE and those with NMNE [12–14].
However, despite emerging evidence, none of these comorbidities have been incorporated into standardized treatment protocols at this time. The presence of comorbidities often necessitates a multidisciplinary treatment approach, addressing both the NE and the associated conditions to achieve the best possible outcome for affected children.
The primary objective of our study was to evaluate the role of comorbidities in children with NE and to develop a scoring system of factors that may predict treatment response, with potential applications in clinical practice.

MATERIAL AND METHODS

Subjects

The 374 patients with NE under single or combined drug treatment were recruited; their age ranged between 5 and 18 years old (average = 8.68; standard deviation = 2.7). Overall M : F ratio was 2.4 : 1. The research was conducted ethically. Authors have given their written informed consent, and all parents gave written informed consent for themselves and for their children.

Measures

All demographic and clinical variables were collected through a standardized interview administered to parents. We classified the response to treatment as excellent if complete, good if partial, and absent in cases where the reduction in wet nights was less than 50.0%.

Statistical analysis

Descriptive statistics were calculated for all variables. The clinical parameters were analysed using a categorical approach, testing each variable for association with presence/absence of recurrence of symptoms and response to pharmacological therapy, using χ^2 statistics followed by logistic regression. Data are reported as frequencies (%), median ±semi-interquartile range, or mean ±SD; statistical significance is set at a nominal two-tail $p < 0.05$. No correction for repeated measures was applied, due to the non-independence of many clinical variables.
Statistical analyses were performed using SPSS software release 24.0 (SPSS Inc., Chicago, IL), and R software.

Bioethical standards

This study was conducted in accordance with the regulatory standards of Good Clinical Practice and with the World Medical Association Declaration of Helsinki and was approved by the Paediatric Unit of Campus Bio-Medico University Hospital (September 2024).

RESULTS

One hundred thirty-six 136 (36.4%) patients were taking desmopressin, 65 (17.4%) patients oxybutynin, and finally 173 (46.2%) patients were taking a combined therapy, desmopressin and oxybutynin; 227 (60.7%) patients did not experience a recurrence of symptoms, while 147 (39.3%) showed them. 80 (21.4%) patients showed an excellent response to therapy, 164 (43.9) a partial or good response, while 130 (34.7) no response to pharmacological treatment. One hundred fifty (40.1%) of the pa-

tients displayed predominantly nocturnal symptoms, 97 (25.9%) patients showed daytime symptoms, and 127 (34.0%) patients had symptoms both during the day and at night.

Table 1 and Table 2 summarize the sample features and the data in frequency and percentage for all the variables included in the study. No difference was found in distribution of presence/absence of recurrence of symptoms and response to pharmacological therapy regarding to sex. Interestingly, we found a significant statistical association between the presence of learning disorders (dyslexia and dysgraphia) and recurrence of symptoms ($\chi^2 = 4.862$, 1 df, $p = 0.027$).

Regarding the association between response to therapy and the clinical variables we found statistical significance for learning disorders ($\chi^2 = 6.386$, 2 df, $p = 0.041$), encopresis ($\chi^2 = 7.919$, 2 df, $p = 0.019$), polythelia ($\chi^2 = 7.435$, 2 df, $p = 0.024$), presence of language delay ($\chi^2 = 7.739$, 2 df, $p = 0.021$), and snoring ($\chi^2 = 7.504$, 2 df, $p = 0.023$); instead, the evidence of heart murmur and deep sleep do not reach statistical significance although show an interesting trend worthy of further investigation ($\chi^2 = 5.599$, 2 df, $p = 0.061$; $\chi^2 = 4.839$, 1 df, $p = 0.089$). No statistically significant association was found between pharmacological treatment and response to therapy ($\chi^2 = 4.464$, 4 df, $p = 0.347$), while a moderately significant association was found between therapy and recurrence of symptomatology ($\chi^2 = 5.969$, 2 df, $p = 0.051$).

Finally we performed logistic regression analyses, adjusted for age and sex, with the response to therapy as a dichotomous outcome, with the aim to estimate the risk probability/odds ratio (OR) associated with the clinical variables found to be significant; the OR estimate for learning disorders is 3.023 with a 95% confidence interval from 1.047 to 8.729; the OR estimate for encopresis is 2.156 (95% CI:

Table 1. *Patients characteristics and comorbidities*

Parameter		Mean/Median	SD; range
Mean age (year)		8.68	2.70; 4–18
		n	%
Gender	Male	264	70.5
	Female	110	29.5
	M/F ratio	2.4 : 1	
Pharmacological therapy	Desmopressin	136	36.4
	Oxybutynin	65	17.4
	Combined	173	46.2
Symptoms	Nocturnal	150	40.1
	Daytime	97	25.9
	Both	127	34.0
Recurrence of symptoms	Yes	147	39.3
	No	227	60.7
Response to therapy	Excellent	80	21.4
	Partial or good	164	43.9
	No response	130	34.8
Positive family history	Yes	221	59.1
	No	153	40.9
Left-handedness	Yes	32	8.6
	No	342	91.4
Allergies	Yes	53	14.2
	No	321	85.8
Sleep apnoea	Yes	13	3.5
	No	361	96.5
Bruxism	Yes	122	32.6
	No	252	67.4
Headache disorders	Yes	4	1.1
	No	370	98.9
Recurrent cystitis	Yes	9	2.4
	No	365	97.6
Cryptorchidism	Yes	8	2.1
	No	366	97.9
Dysgraphia	Yes	6	1.6
	No	368	98.4
Dyslexia	Yes	12	3.2
	No	362	96.8
Learning Disorders	Yes	15	4.0
	No	359	96.0
Encopresis	Yes	49	13,1
	No	325	86,9
ADHD symptoms	Yes	25	6.7
	No	349	93.3
Urinary tract infections	Yes	17	4.5
	No	357	95.5
Overweight or obesity	Yes	25	6.7
	No	349	93.3
Polythelia	Yes	46	12.3
	No	328	87.7
High blood pressure	Yes	11	2.9
	No	363	97.1
Speech delay	Yes	33	8.8
	No	341	91.2
Snore	Yes	131	35.0
	No	243	65.0
Heart murmur	Yes	50	13.4
	No	324	86.6
Somnambulism	Yes	3	0.8
	No	371	99.2
Somniloquy	Yes	107	28.6
	No	267	71.4
Restless sleep	Yes	16	4.3
	No	358	95.7
Deep sleep	Yes	350	93.6
	No	24	6.4
Encopresis	Yes	49	13.1
	No	325	86.9
Constipation	Yes	49	13.1
	No	325	86.9

ADHD – attention deficit hyperactivity disorder

Table 2. *Data in frequency and percentage for all the variables*

Variables (n = 374)	Response to therapy			Statistics	p-value
	Absent	Good	Excellent		
ADHD	10/130 (7.7%)	13/164 (7.9%)	2/80 (2.5%)	$\chi^2 = 2.863$; 2 df	0.239
Allergies	20/130 (15.3%)	22/164 (13.4%)	11/80 (13.75%)	$\chi^2 = 0.246$; 2 df	0.884
Bruxism	49/130 (37.6%)	49/164 (29.8%)	24/80 (30%)	$\chi^2 = 2.333$; 2 df	0.312
Constipation	21/130 (16.1%)	22/164 (13.4%)	6/80 (7.5%)	$\chi^2 = 3.283$; 2 df	0.194
Deep sleep	121/130 (93%)	150/164 (91.4%)	79/80 (98.7%)	$\chi^2 = 4.839$; 2 df	0.089
Dysgraphia	5/130 (3.8%)	1/164 (0.6%)	0/80 (0%)	$\chi^2 = 6.471$; 2 df	0.039
Dyslexia	7/130 (5.3%)	1/164 (0.6%)	4/80 (5%)	$\chi^2 = 6.375$; 2 df	0.041
Encopresis	25/130 (19.2%)	19/164 (11.5%)	5/80 (6.25%)	$\chi^2 = 7.919$; 2 df	0.019
Family history	78/130 (60%)	92/164 (56%)	51/80 (63.7%)	$\chi^2 = 1.371$; 2 df	0.504
Headache disorders	2/130 (1.5%)	1/164 (0.6%)	1/80 (1.2%)	$\chi^2 = 0.622$; 2 df	0.733
Heart murmur	23/130 (17.6%)	22/164 (13.4%)	5/80 (6.2%)	$\chi^2 = 5.599$; 2 df	0.061
High blood pressure	6/130 (4.6%)	5/164 (3%)	0/80 (0%)	$\chi^2 = 3.707$; 2 df	0.157
Left-handedness	13/130 (10%)	12/164 (7.3%)	7/80 (8.7%)	$\chi^2 = 0.672$; 2 df	0.715
Overweight\obesity	11/130 (8.4%)	11/164 (6.7%)	3/80 (3.7%)	$\chi^2 = 1.763$; 2 df	0.414
Polythelia	23/130 (17.6%)	12/164 (7.3%)	11/80 (13.7%)	$\chi^2 = 7.435$; 2 df	0.024
Recurrent cystitis	5/130 (3.8%)	3/164 (1.8%)	1/80 (1.2%)	$\chi^2 = 1.836$; 2 df	0.399
Restless sleep	9/130 (6.9%)	6/164 (3.6%)	1/80 (1.25%)	$\chi^2 = 4.166$; 2 df	0.125
Sleep apnea	6/130 (4.6%)	4/164 (2.4%)	3/80 (3.7%)	$\chi^2 = 1.047$; 2 df	0.593
Snore	55/130 (42.3%)	57/164 (34.7%)	19/80 (23.7%)	$\chi^2 = 7.504$; 2 df	0.023
Somnambulism	0/130 (0%)	2/164 (1.2%)	1/80 (1.2%)	$\chi^2 = 1.612$; 2 df	0.047
Somniloquy	41/130 (31.5%)	50/164 (30.4%)	16/80 (20%)	$\chi^2 = 3.733$; 2 df	0.155
Speech delay	17/130 (13%)	7/164 (4.2%)	9/80 (11.2%)	$\chi^2 = 7.739$; 2 df	0.021
Urinary tract infection	8/130 (6.1%)	7/164 (4.2%)	2/80 (2.5%)	$\chi^2 = 1.576$; 2 df	0.455

ADHD – attention deficit hyperactivity disorder

the child and their caregivers. Although previous studies have examined the prevalence of specific comorbidities in children with NE compared to control groups, the potential impact of these comorbidities on treatment efficacy and the risk of relapse remains insufficiently explored.

This study was specifically designed with the aim of developing a clinical score to predict therapeutic response and relapse rates based on the presence of specific comorbidities. The present study examined a cohort of 374 children and adolescents aged between 5 and 18 years (mean age = 8.68 years), all of whom were receiving single or combined pharmacological treatment for NE. In terms of treatment, the majority of the cohort (46.2%) was receiving combined therapy with desmopressin and oxybutynin. Desmopressin alone was used in 36.4% of patients, while 17.4% were treated with oxybutynin alone. Notably, 227/374 (60.7%) of the patients did not experience a recurrence of symptoms, suggesting that most children responded favourably to pharmacological intervention. However, 147/374 (39.3%) of the patients did experience recurrence, which underscores the chronic nature of NE in some individuals despite treatment.

The therapeutic outcomes were varied. Approximately 21.4% of patients showed an excellent response to therapy, while 43.9% had a partial or good response, and 34.7% had no response to the pharmacological treatment. These results are in line with previous studies that report a mixed efficacy of treatment for NE, with some children achieving full resolution of symptoms while others continue to struggle. Thus, a significant observation was that no statistically meaningful association was found between the type of pharmacological treatment (desmopressin, oxybutynin, or combination therapy) and treatment outcomes ($p = 0.347$). This suggests that, at least in this cohort, the specific drug regimen may not substantially affect the overall therapeutic result. However, a borderline significant association between therapy and symptom recurrence ($p = 0.051$) implies that the treatment regimen might still influence the likelihood of symptom relapse, necessitating further investigation.

Based on all the evidence available in the literature and utilizing the data at our disposal, we assessed the impact of specific comorbidities, either alone or in combination, on the response and outcomes in children with NE. Psychological factors, such as exposure to stress, may influence the onset and recurrence of NE, especially in SNE [15–17]. Children with ADHD tend to have higher rates of NE, potentially due to challenges with attention, bladder control, and disrupted sleep [18]. The prevalence of NE in patients with ADHD has been estimated to be 28.0–3.02% [19]. The coexistence of these conditions has clinical significance: children with

Table 3. *Single and combined odds ratio measures*

Variables	Odds ratio	95% CI
Learning disorders	3.023	1.047–8.729
Learning disorders + polythelia	2.390	1.390–4.110
Learning disorders + language delay	2.380	1.310–4.330
Learning disorders + encopresis	2.340	1.380–3.970
Learning disorders + encopresis + polythelia	2.280	1.520–3.420
Learning disorders + encopresis + polythelia + language delay	2.250	1.580–3.200
Polythelia	2.196	1.166–4.133
Polythelia + encopresis	2.173	1.164–4.053
Polythelia + language delay	2.173	1.106–4.273
Encopresis	2.156	1.174–3.961
Encopresis + language delay	2.148	1.349–3.419
Language delay	2.137	1.039–4.396
Learning disorders + encopresis + polythelia + language delay + snoring	1.902	1.468–2.463
Polythelia + snoring	1.748	1.214–2.517
Encopresis + snoring	1.747	1.219–2.503
Learning disorders + snoring	1.720	1.140–2.600
Language delay + snoring	1.673	1.193–2.350
Snoring	1.560	0.998–2.436

ADHD and NE are harder to treat, tend to have lower adherence to treatment, and experience less favorable outcomes for incontinence management. Anxiety, especially social or generalized anxiety, may also contribute to NE by increasing stress, which can influence both the psychological and physiological aspects of bladder control [14, 20].

Several studies suggest that children with NE are more likely to experience language delays or disorders, particularly in the areas of phonology, expressive language, and verbal communication [21]. Previous studies showed a higher percentage of language disorders in enuretic children, as Ferrara et al. [22] which documented 16.7% of children affected by language disturbances, 8.3% by dyslexia and 8.3% by delayed language or Esposito et al. [23] which observed learning difficulties in 18 children with NE compared to 7 healthy children and a significantly higher likelihood of mild academic impairment in enuretic children. In this way, the Quebec Longitudinal Study of Child Development, led by Touchette et al. [24], revealed that NE impacts early developmental milestones. For example, enuretic children reached motor skills, such as sitting unsupported for 10 minutes by 5 months, and language skills, such as speaking 2 words, at later ages compared to non-enuretic children while Birenbaum et al. [21] documented a higher prevalence of oral language disorders, particularly phonological issues, and speech difficulties in these children. Language disorders and NE may both reflect a delay in development, potentially influencing one another.

This is further supported by other research showing that children with NE perform worse than the control group in areas such as abstract thinking, clear expression of thoughts, understanding cause-and-effect relationships, short-term memory, and problem-solving skills [25]. Sleep disorders, such as obstructive sleep apnoea or other parasomnias, are also commonly seen in children with NE, and these conditions may worsen bedwetting by interfering with the normal regulation of bladder function during sleep [26, 27]. Children with NE were more than 1.5 times as likely to experience parasomnias, sleep-disordered breathing (SDB), and night awakenings, indicating a higher prevalence of sleep problems compared to those without NE. Several studies have shown that the sleep of these children is more fragmented compared to that of their non-enuretic peers [28, 29]. This fragmentation leads to sleep deprivation, which results in increased daytime sleepiness and a higher arousal threshold, preventing the child from waking up when the bladder is full. Other studies report findings that are completely different from the previous ones, describing enuretic children as "light sleepers" or attributing to them a sleep pattern not dissimilar to that of non-enuretic children [30, 31].

The sleep of children with NE has been studied multiple times, but the results are inconsistent: some authors, studying the EEG recordings of enuretic children during sleep, found correlations between urine loss and non-REM sleep, particularly the delta wave phase; other authors, however, did not find this specific type of relationship between enuretic episodes and sleep stages [32]. NE has also been associated with obstructive sleep apnoea syndrome (OSAS): nocturnal polyuria is considered a cardiovascular response to the negative pressure in the upper respiratory airways, characteristic of OSAS. The association of these two conditions in paediatrics is further supported by other evidence: improvement or complete resolution of enuretic episodes is observed after the treatment of respiratory disorders with adenotonsillectomy or the use of intranasal corticosteroids [33]. Additionally, untreated OSAS patients produce more urine and sodium during the night, likely due to increased secretion of atrial natriuretic peptide, caused by stimulation of the right atrial receptors exposed to significant changes in intrathoracic pressure, typical of OSAS. Polyuria and natriuresis resolve following effective treatment of OSAS [34–36]. Smaller studies have also investigated other comorbidities in children with NE, with future research needed to expand and strengthen the association. Children with encopresis and functional constipation have a higher incidence of urinary disorders, including NE, infections, vesicoureteral reflux, and hydronephrosis [37, 38].

For example, encopresis occurs more often in enuretic children than in the general population, both in males (5.1% vs 0.2%) and females (3.8% vs 0%) [18, 19]. It could be explained by the prolonged and frequent anal contractions seen in children with constipation which lead to involuntary bladder contractions, thereby causing incontinence. Other studies have also demonstrated an association between NE and headache, heart murmur, high blood pressure, left-handedness, overweight/obesity, and polythelia [39–42]. Most of these comorbidities have been widely recognized as being associated with the onset, severity, and treatment response rate of enuresis. However, some factors – such as left-handedness and polythelia – require further investigation in larger populations to establish more robust associations. Based on our centre's experience, these comorbidities are nevertheless observed in the majority of enuretic patients. We investigat-

ed the presence of these specific comorbidities commonly associated with NE in children, as reported in the literature and outlined in Tables 1 and 2.

An important finding of this study was the link between learning disorders (such as dyslexia and dysgraphia) and the recurrence of NE symptoms ($\chi^2 = 4.862$, $p = 0.027$). Learning disorders were also significantly associated with poorer therapy outcomes ($\chi^2 = 6.386$, $p = 0.041$). These results may indicate that children with learning difficulties may require more individualized or intensive treatment approaches to effectively address both NE and associated conditions. Additional clinical variables significantly associated with therapy response included encopresis ($\chi^2 = 7.919$, $p = 0.019$), polythelia ($\chi^2 = 7.435$, $p = 0.024$), language delay ($\chi^2 = 7.739$, $p = 0.021$), and snoring ($\chi^2 = 7.504$, $p = 0.023$). These findings suggest that comorbidities and developmental delays may influence treatment outcomes. Specifically, the presence of encopresis, a condition involving involuntary fecal incontinence, seems to be a key factor in predicting response to therapy. This implies that children with multiple toileting issues may face greater challenges in overcoming NE, potentially due to underlying physiological or behavioral factors. Logistic regression analysis, adjusted for age and sex, provided deeper insights into the risk factors for therapy response. Learning disorders, encopresis, polythelia, language delay, and snoring were all associated with an increased likelihood of poor treatment outcomes. The OR for these variables suggest a higher risk of treatment failure in children with these conditions.

This highlights the importance of clinicians considering these factors when developing treatment plans and monitoring progress. Thus, based on these findings, we propose a new score, the PiFe score, for the management of enuretic children, which represent a clinical tool designed to predict therapy outcomes or identify factors that influence the success of treatment in children with NE. PiFe could stand for Predictive index For enuresis therapy. This could refer to a system or model used to predict the effectiveness of NE treatments based on various clinical factors, such as comorbidities, age, severity, and other relevant variables. Based on our experience, the PiFe score should include the following variables:

- family history;
- ADHD and other psychological disorders;
- constipation and encopresis;
- recurrent cystitis and urinary tract infection;
- sleep disorders: deep sleep, restless sleep, sleep apnoea, snore, somnambulism, somniloquy, bruxism;
- learning disorders: dysgraphia, dyslexia, speech delay;
- headache disorder;
- heart murmur;
- left-handedness;
- overweight/obesity;
- polythelia.

Each comorbidity could be assigned a score of 1, with a total score of 21 (Table 4). The risk of relapse and non-response to therapy would be low if the PiFe is ≤7, moderate if the PiFe is between 8 and 14, and high if the PiFe is ≥15.

The more comorbidities or risk factors present in an enuretic child, the higher the likelihood of relapse and lack of response, regardless of the treatment used. The PiFe score can help us determine which multidisciplinary approaches and interventions will be most effective in each specific case.

One important limitation of this study is that the proposed scoring system was developed using data from a single retrospective cohort, with no external validation or prospective assessment to date. The absence of validation in independent populations raises concerns about the reproducibility and robustness of the score across different clinical

Table 4. *Comorbiditis and score*

Comorbidity	Score
Family history	1
ADHD or spectrum disorders	1
Anxiety or other behavioural problems	1
Constipation	1
Encopresis	1
Urinary tract infections	1
Deep sleep	1
Restless sleep	1
Sleep apnea	1
Snore	1
Somnambulism	1
Somniloquy	1
Bruxism	1
Dysgraphia	1
Dyslexia	1
Speech delay	1
Headache disorder	1
Heart murmur	1
Left-handedness	1
Overweight/Obesity	1
Polythelia	1

ADHD – attention deficit hyperactivity disorder

settings and patient groups. As such, the generalizability of our results remains uncertain. We fully recognize this limitation and stress the importance of conducting future research aimed at externally validating the score in diverse and prospective cohorts. These additional studies will be crucial to determine whether the scoring system retains its predictive accuracy and practical value when applied in varied clinical environments and real-world scenarios.

CONCLUSIONS

The present study highlights the complex interplay between NE and various clinical and developmental factors. It emphasizes the need for a holistic approach to the management of NE, one that considers not only the pharmacological treatment but also the broader context of each child's health and development. Further research, particularly larger-scale studies, is needed to confirm these associations and explore potential mechanisms underlying the observed relationships and to confirm the validity of our new score.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

This study was conducted in accordance with the regulatory standards of Good Clinical Practice and with the World Medical Association Declaration of Helsinki and was approved by the Pediatric Unit of Campus Bio-Medico University Hospital (September 2024).

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