

Trend of nocturnal enuresis in children with attention deficit/hyperactivity disorder: a nationwide population-based study in Taiwan

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ABSTRACT

Abstract Attention-deficit/hyperactivity disorder (ADHD) and nocturnal enuresis are common disorders with extensive psychosocial suffering in affected children, and healthcare burden on parents. Whether the childhood psychological disorders and nocturnal enuresis are factors contributing to ADHD have not been clearly established. This study conducted a population-based case–control study using data sets from the National Health Research Insurance database, and identified 14 900 children diagnosed with ADHD. Risk factors that have been associated with or possibly related to ADHD development were included in this study. Performance of in groups of ADHD with enuresis was compared with controls. With adjustment for potential covariates, participants with enuresis exhibited a 2.24-fold greater risk of subsequent ADHD development compared with controls (95% CI 1.84 to 2.73). Participants with enuresis and comorbidity had a significantly greater risk of ADHD than those with no enuresis and no comorbidity (adjusted OR=8.43, 95% CI 4.38 to 16.2). Children who are assessed for ADHD should be evaluated for the presence of enuresis or other neurobehavioral comorbidities. Multidisciplinary treatment may benefit children with ADHD and minimize psychological burden on parents.

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in pediatric populations, and thought to be associated with structural and chemical alterations in the prefrontal cortex. It is associated with abnormalities in the frontal lobes, makes sense that any neurological disorder that originates in these regions would increase the risk for ADHD.¹ The symptoms are characterized of persistent patterns of inattention and/or hyperactivity-impulsivity that interfere with functioning or development. The symptoms have persisted for at least 6 months to a degree that is inconsistent with developmental level and that negatively impacts directly on social and academic/occupational activities.^{2–3} Growing evidence indicates association between ADHD and other comorbid psychological disorders, which may present from childhood into adulthood.^{4–5}

Significance of this study

What is already known about this subject?

- ▶ Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in pediatric populations, and thought to be associated with structural and chemical alterations in the prefrontal cortex.
- ▶ Nocturnal enuresis is a genetically determined maturation deficit of the central nervous system, which is modulated by psychological and environmental factors.
- ▶ Despite being a physiologically benign condition, children with nocturnal enuresis may have significantly impaired self-esteem.

What are the new findings?

- ▶ This study robustly demonstrates the association of nocturnal enuresis in children with ADHD in a large population.
- ▶ Children with enuresis had a 2.53-fold greater risk of developing ADHD.
- ▶ Children with both enuresis and neurobehavioral comorbidities had greatest risks of developing ADHD than those with only enuresis or the comorbidities.

How might these results change the focus of research or clinical practice?

- ▶ Children with enuresis and ADHD may benefit from a comprehensive psychological assessment and multidisciplinary approach.

Nocturnal enuresis (NE) or bedwetting has been found to be associated with increased risks of social, emotional and behavioral comorbidities.^{6–7} It is a predominantly genetically determined maturation deficit of the central nervous system, which is modulated by psychological and environmental factors.^{8–9}

Small bladder, nocturnal polyuria and arousal problems are the most commonly accepted causes in the medical world. Although there is strong evidence that central factors do play a role, these are not yet extensively investigated.^{8–9} As common neurobehavioral disorders

in childhood, it has been found that boys exhibit NE more often than girls.^{10 11} Despite being a physiologically benign condition, children with NE may have significantly impaired self-esteem.

ADHD and NE are well known to be associated with extensive psychosocial suffering in affected children, including poor self-image, diminished achievement in school; these conditions are also associated with increased economic impact on the family and healthcare burden on society.^{12 13} Associations between NE and ADHD via decreased prepulse inhibition of startle have been debated.¹⁴ The children with ADHD may feel different and unaccepted. ADHD appear to have a higher incidence of NE despite no evidence that either one causes the other.

Although the exact pathogenesis of ADHD and NE remains unclear, genetic and environmental factors as well as aberrant neurodevelopment importantly affect the development of both disorders. This study examined the relationship between ADHD, NE and other childhood psychological disorders by using a population-based case-control study.

METHODS

Data sources

The National Health Insurance (NHI) program was initiated in 1995. By the end of 2007, 22.6 million of Taiwan's population of 22.96 million people was covered by the program. The National Health Insurance Research Database (NHIRD) records participants' gender and date of birth, all clinical visits and hospitalization, prescribed drugs and dosages, and diagnoses of diseases coded in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study used claims data information for a randomly selected half of all insured children aged 18 years or less in Taiwan. The National Health Research Insurance (NHRI) protected the confidentiality and privacy of all participants, and transferred health insurance data to the authors after ethical approval was obtained. Owing to personal electronic data privacy

regulations, the insurers' records are encrypted before being released to researchers; thus, informed consent was not required in this study. Our study was approved by the Ethics Review Board of China Medical University (CMU-REC-101-012).

Study population

We conducted a population-based case-control study using data sets obtained from NHIRD from 1 January 1996 to 31 December 2008 (figure 1). This study identified 26 642 children newly diagnosed with ADHD, ICD-9-CM code: 314.xx aged 7–18 years, who were registered in the NHIRD data set of ambulatory and inpatient care from 1 January 2004 to 31 December 2008. The index date was the date of diagnosis ADHD. For each case, four controls were identified with no history of ADHD. Controls were frequency-matched for sex, age (to 1 year) and index year. Diagnosis of ADHD was based on more than three times in the inpatient hospitalization and/or outpatient department visits with diagnosis of ADHD. In Taiwan, diagnosis of ADHD and NE were based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); assessments of ADHD and NE were made by pediatric psychologists, pediatric neurologist or psychiatrists in charge at medical institutions.

Examined demographic factors were sex, age, urbanization, and parents' occupational status. Age was categorized into two levels: 7–12 and 13–18 years. Urbanization level was defined according to the NHRI report. City districts and townships in which participants were registered for insurance purposes were grouped into four levels of urbanization based on population density (persons/km²), population ratios of people with an educational level of college or above, of people aged over 65 years, and of agricultural workers, and number of physicians per 100 000 people.¹⁵ Level 1 indicates the most urbanized areas; level 4 indicates the least urbanized areas. We classified occupational status into three levels: white collar, blue collar, and other.

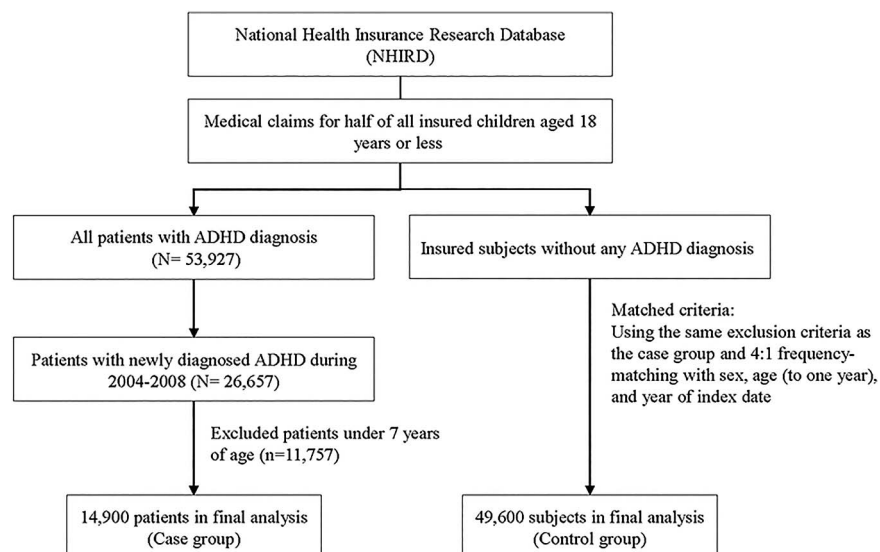


Figure 1 Flow diagram of participant selection. ADHD, attention deficit hyperactivity disorder.

Table 1 Demographics and comorbidities between children with physician diagnosed ADHD and non-ADHD

	Non-ADHD group N=59 600 n (%)	ADHD group N=14 900 n (%)	p Value
Sex			0.99
Girls	12 268 (20.6)	3067 (20.6)	
Boys	47 332 (79.4)	11 833 (79.4)	
Age (years)			0.99
7–12	50 712 (85.1)	12 678 (85.1)	
13–18	8888 (14.9)	2222 (14.9)	
Mean (SD)	10.0 (2.49)	10.0 (2.49)	0.21
Urbanization			<0.001
Level 1 (highest)	16 483 (27.8)	5396 (36.4)	
Level 2	17 581 (29.7)	4550 (30.7)	
Level 3	11 360 (19.2)	2614 (17.7)	
Level 4 (lowest)	13 780 (23.3)	2252 (15.2)	
Parents' occupation			<0.001
White collar	35 156 (59.0)	9555 (64.1)	
Blue collar	16 633 (27.9)	3526 (23.7)	
Others	7811 (13.1)	1819 (12.2)	
Comorbidity			
Nocturnal enuresis	286 (0.48)	171 (1.15)	<0.001
Epilepsy	505 (0.85)	422 (2.83)	<0.001
Mental retardation	289 (0.48)	507 (3.40)	<0.001
Autism	142 (0.24)	261 (1.75)	<0.001
Tourette syndrome	63 (0.11)	126 (0.85)	<0.001
Sleep disorder	16 (0.03)	28 (0.19)	<0.001
Emotional problem	93 (0.16)	331 (2.22)	<0.001
Reaction to acute stress	6 (0.01)	15 (0.10)	<0.001
Adjustment disorder	30 (0.05)	122 (0.82)	<0.001

ADHD, attention deficit hyperactivity disorder.

White-collar workers were defined as those with occupations characterized by longer indoor work hours, such as civil services and institution workers, enterprise, business and industrial administration personnel, etc. Blue-collar workers were defined as those with occupations characterized by longer work hours, such as farmers, fishermen, vendors, and industrial laborers. Other occupations included mainly retired, unemployed, and low income populations.

Risk factors known to be associated with or possibly related to the development of ADHD were included in this study. Since the prevalence of ADHD is age-dependent, selections of common comorbid disorders/symptoms in childhood were defined as risk factors. We recorded disease history before the index date, including NE (ICD-9 code 788.36).

Statistical analysis

Summary statistics are expressed as frequency and percentage for categorical data and mean±SD for continuous variables, as appropriate. Differences in demographic factors between the two study populations were compared using Student's t-tests for continuous variables and χ^2 tests for categorical variables. Associations between NE and risk of ADHD were estimated using univariate logistic regression analysis and multivariate logistic regression analysis. The logistic regression model was adjusted for parents' occupational status, urbanization levels, and comorbidity. Stratification analysis was also performed to assess the effect of NE under different demographic factors by logistic regression. Crude and adjusted ORs are presented with 95% CIs. All data analyses were performed using SAS V9.3 (SAS Institute, Cary, North Carolina, USA); $p<0.05$ in a two-sided test was considered statistically significant.

RESULTS

The study included 14 900 children with ADHD and 59 600 individuals without ADHD with a similar average age (10.0 years) and sex ratio (boys: 79.4%; [table 1](#)). Children with ADHD were more likely to reside in urban areas (67.1%) and have parents with white collar occupations (64.1%). Compared with the control group, children with ADHD tended to have NE (1.15% vs 0.48%), epilepsy (2.83% vs 0.85%), mental retardation (3.40% vs 0.48%), autism (1.75% vs 0.24%), Tourette syndrome (0.85% vs 0.11%), sleep disorder (0.19% vs 0.03%), emotional problems (2.22% vs 0.16%), acute reaction to stress (0.10% vs 0.01%), and adjustment disorder (0.82% vs 0.05%).

[Table 2](#) presents the risk of ADHD in participants with NE, stratified by sex and age. Sex-specific analysis showed that participants with NE were at the greatest risk of ADHD among girls (adjusted OR=2.80, 95% CI 1.82 to 4.31) and boys (adjusted OR=2.12, 95% CI 1.70 to 2.66).

Table 2 Logistic regression estimated ORs of ADHD in children with nocturnal enuresis stratified by sex and age

	Non-ADHD group		ADHD group		OR (95% CI)	
	n	Per cent	n	Per cent	Crude	Adjusted†
Sex						
Girls	56	0.46	42	1.37	3.03 (2.03 to 4.53)***	2.80 (1.82 to 4.31)***
Boys	230	0.49	129	1.09	2.26 (1.82 to 2.80)***	2.12 (1.70 to 2.66)***
Age, years						
7–12	251	0.49	144	1.14	2.31 (1.88 to 2.84)***	2.20 (1.78 to 2.73)***
13–18	35	0.39	27	1.22	3.11 (1.88 to 5.16)***	2.52 (1.46 to 4.36)***

*** $p<0.001$.

†Model mutually adjusted for sex, age, parents' occupational status, urbanization levels and comorbidity (including nocturnal enuresis, epilepsy, mental retardation, autism, Tourette syndrome, sleep disorder, emotional problem, reaction to acute stress, and adjustment disorder).

ADHD, attention deficit hyperactivity disorder.

Table 3 OR and 95% CI for association between parents' occupation, residential area, comorbidities and the development of physician diagnosed ADHD

	Crude OR (95% CI)	Adjusted OR† (95% CI)
Parents' occupation		
White collar	Reference	Reference
Blue collar	0.78 (0.75 to 0.81)***	0.88 (0.84 to 0.92)***
Others	0.86 (0.81 to 0.91)***	0.94 (0.89 to 0.99)*
Urbanization		
Level 1 (highest)	2.00 (1.90 to 2.12)***	1.93 (1.82 to 2.05)***
Level 2	1.58 (1.50 to 1.67)***	1.56 (1.47 to 1.65)***
Level 3	1.41 (1.32 to 1.50)***	1.36 (1.27 to 1.45)***
Level 4 (lowest)	Reference	Reference
Comorbidity		
Nocturnal enuresis		
No	Reference	Reference
Yes	2.41 (1.99 to 2.91)***	2.24 (1.84 to 2.73)***

*** p<0.001; *p<0.05.

†Multivariate Cox proportional hazards regression model including parents' occupational status, urbanization and comorbidity (including nocturnal enuresis, epilepsy, mental retardation, autism, Tourette syndrome, sleep disorder, emotional problem, reaction to acute stress, and adjustment disorder).

ADHD, attention deficit hyperactivity disorder.

Age-specific analysis indicated that participants with NE were at consistently increased risk of ADHD compared to participants without NE in all age groups (adjusted OR=2.20, 95% CI 1.78 to 2.73 for 7–12 years; and 2.52, 1.46–4.36 for 13–18 years).

Table 3 presents crude and adjusted ORs for potential factors influencing risk of ADHD development. After adjusting for potential covariates, participants with NE exhibited a 2.24-fold greater risk of subsequent ADHD development compared with participants with no NE (95% CI 1.84 to 2.73). Compared with participants with parents of white collar occupational status, participants with blue collar families were associated with reduced risk of ADHD (adjusted OR=0.88, 95% CI 0.84 to 0.92). Participants who resided in urban level 1 (adjusted OR=1.93, 95% CI 1.82 to 2.05), level 2 (1.56, 1.47 to 1.65), and level 3 (1.36, 1.27 to 1.45) showed the greatest risk of developing ADHD.

We observed a significant interaction effect of NE and comorbidity on risk of ADHD. Children with NE and

comorbidity were at a significantly greater risk of ADHD than those with no NE and no comorbidity, as shown in table 4 (adjusted OR=8.43, 95% CI 4.38 to 16.2).

DISCUSSION

The strength of the present study lies in its use of a nationwide population-based case-control database. The high recruitment rate of the nationwide database and case-control design suggest high validity, and extended availability enabled us to eliminate various possible coding biases. These results indicate strong associations between ADHD and NE, adding substantial evidence for the reported relationship. These correlations are known to affect incidence of ADHD; our results also demonstrate the correlation between gender and stratified age of enuresis, although disorders' severity is not available from the Longitudinal Health Insurance database (LHID).

The interaction effect in ADHD is higher associated with further comorbidities (OR 7.55/9.36) than with NE only (OR=2.7). In general, individuals affected by ADHD often have other behavior disorders that impact their ability to function successfully. There has been increasing awareness that many adults and children with ADHD may also meet criteria for one or more other psychiatric diagnoses. Previous clinical and population-based studies of large nationally representative samples have found that individuals with ADHD often present with other mental health problems, and may have more than one coexisting condition.^{14 15 16} The current study supported the finding that NE is a relatively common condition among children and significantly associated with ADHD and neurobehavioral disorders. Children with NE experience greater academic difficulty, and more externalizing problems, compared with children without NE. Taken together, these results suggest that children who are assessed for NE should also be evaluated for the presence of ADHD and other neurobehavioral disorders.¹⁷

The etiologies of NE and ADHD are multifactorial and heterogeneous, which contributes to their development and may account for their association.¹⁴ Previous research has suggested that developmental delays in the central nervous system, including deficits in arousal, inhibition of the micturition reflex, and prepulse inhibition, may contribute to both NE and ADHD.¹⁸ Although NE and ADHD operate along different neural pathways and networks, these conditions share common pathways such as the insula, the anterior cingulate cortex, and cortical

Table 4 The interaction effect between nocturnal enuresis and comorbidity in association with ADHD

		Non-ADHD	ADHD	OR†(95% CI)	p For interaction
Nocturnal enuresis	Comorbidity‡				0.0003
No	No	58327	13221	Reference	
No	Yes	987	1508	6.82 (6.27 to 7.41)***	
Yes	No	271	145	2.39 (1.95 to 2.93)***	
Yes	Yes	15	26	8.43 (4.38 to 16.2)***	

***p<0.001.

‡Patients with any one of epilepsy, mental retardation, autism, Tourette syndrome, sleep disorder, emotional problem, acute reaction to stress, and adjustment disorder were classified as the comorbidity group.

†Model adjusted for sex, age, parents' occupational status, and urbanization levels. ADHD, attention deficit hyperactivity disorder.

structures (prefrontal cortex). These pathways are also involved in emotion regulation processes, especially the anterior cingulate cortex.^{19–20} Further, these pathways' involvement has been suggested by previous studies that used acoustic evoked potentials, which found that children with NE and ADHD processed emotions more intensely, displaying interaction effects on the central nervous system that cannot be explained by each disorder alone.¹⁵

One possible explanation that NE may occur as a result of ADHD is that children who suffer from ADHD have less control over their bodily signals as they are easily distracted.^{21–23} On a psychological level, children with ADHD are more likely to be careless compared to children without ADHD, and may find it difficult to ameliorate this neurobehavioral problem.²⁴ Hence, the stress or pressure caused by these situations raises the likelihood of bedwetting. It is possible that either condition may simply occur due to a genetic predisposition to a common set of characteristics. Most children with enuresis appear physically, intellectually and emotionally normal. NE is likely associated with a combination of factors including heredity, slower neurological maturation, small bladder capacity, a tendency to produce too much urine at night, and the inability to recognize a full bladder while asleep.²⁵ Of sleep problems, the patients with enuresis have varied widely sleep pattern and are difficult to interpret. Sleep EEG studies have also reported an association of NE with slow brain-wave activity in children.²⁶ On the contrary other investigators have demonstrated that bedwetting may occur at different stages of sleep and children who wet the bed have normal sleep patterns.²⁷

Children with ADHD were more likely to reside in urban areas. Previous study reported that higher incidence of ADHD in children reside in urban areas. The possible reasons may as follows. First, children living in urban area have higher incidence rate of allergic disorders, which are one of the well-known common comorbidities of ADHD. Second, the caregivers may be more aware and easier to access to healthcare in urban area.⁵ Consistent with previous population-based studies, the present study observed NE to be male-predominated, and associated with increased prevalence of other neurobehavioral problems.^{28–29} In the present study, the distribution of ADHD and NE were both found to be male and school-age predominant. When stratifying the data by age, NE was found to be significantly associated with ADHD in all age groups, reflecting the close connection of the two neurobehavioral disorders. Given the strong association between ADHD and NE, primary care clinicians should routinely inquire about children's mastery of urinary continence in ADHD populations.^{30–31} This information will help clinicians and caregivers to direct effective interventions. It is also important for clinicians and caregivers to be aware of the challenging behavioral patterns associated with ADHD, which may affect the effectiveness of treatments of NE and its comorbidities.³²

Both ADHD and NE are fairly common, it would be important to have more systematic studies that looked at the relationship. There has been increasing awareness that children with ADHD may also meet criteria for one or more other psychiatric diagnoses. For years, clinicians have anecdotally noted an increased incidence of NE in children with ADHD,³³ and others have observed that their patients

with ADHD have an increased association with of NE.³⁴ The syndrome of ADHD is frequently associated with coexisting psychiatric and physical disorders, and this comorbidity does not appear to represent an artifact of assessment. In the assessment as well as treatment process, it is important to diagnosis and manages all comorbidities in order to maximize treatment. Since comorbid conditions are associated with greater psychiatric and physical impairments, early vigorous intervention is warranted.

This study is limited by the unavailability of information regarding clinical conditions, laboratory data, and images and information regarding severity of disorders. Neither the recording of the associated severity of neuropsychiatric comorbidities, nor socioeconomic factors like parents' income and educational background, were available to enhance the possibility of drawing causal conclusions. These data cannot clarify treatment of a subclinical state or a state in a latent period, or whether these states affected the results. According to the International Children Continence Society, NE is classified into primary and secondary NE. However, different types of NE are not grouped because of ICD-9 coding. Regarding to overall rates of NE in other population-based samples, the rates in current study seem relatively low. It is supposed not all the children with ADHD or NE will seek medical intervention; result in a lower rate in the NHIRD.

CONCLUSION

The results of our population-based case-control study suggest that NE is closely correlated with ADHD. This suggests that children who are assessed for ADHD should be evaluated for the presence of enuresis or other neurobehavioral comorbidities. Also children with NE should be evaluated the tendency of ADHD. Children with enuresis and ADHD may benefit from a comprehensive psychological assessment and multidisciplinary approach.

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