

Title	Enuresis and hyperactivity-inattention in early adolescence: Findings from a population-based survey in Tokyo (Tokyo Early Adolescence Survey).
Author(s)	Kanata, Sho; Koike, Shinsuke; Ando, Shuntaro; Nishida, Atsushi; Usami, Satoshi; Yamasaki, Syudo; Morimoto, Yuko; Toriyama, Rie; Fujikawa, Shinya; Sugimoto, Noriko; Sasaki, Tsukasa; Furukawa, Toshiaki A.; Hiraiwa-Hasegawa, Mariko; Kasai, Kiyoto
Citation	PLOS ONE (2016), 11(7)
Issue Date	2016-07-14
URL	<a href="http://hdl.handle.net/2433/216404">http://hdl.handle.net/2433/216404</a>
Right	© 2016 Kanata et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Type	Journal Article
Textversion	publisher

RESEARCH ARTICLE

# Enuresis and Hyperactivity-Inattention in Early Adolescence: Findings from a Population-Based Survey in Tokyo (Tokyo Early Adolescence Survey)

Sho Kanata<sup>1,2</sup>, Shinsuke Koike<sup>1,3,4</sup>, Shuntaro Ando<sup>1,5\*</sup>, Atsushi Nishida<sup>5</sup>, Satoshi Usami<sup>6</sup>, Syudo Yamasaki<sup>5</sup>, Yuko Morimoto<sup>5,7</sup>, Rie Toriyama<sup>1</sup>, Shinya Fujikawa<sup>1</sup>, Noriko Sugimoto<sup>1</sup>, Tsukasa Sasaki<sup>8</sup>, Toshiaki A. Furukawa<sup>9</sup>, Mariko Hiraiwa-Hasegawa<sup>7</sup>, Kiyoto Kasai<sup>1</sup>

**1** Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, **2** Department of Psychiatry, Teikyo University School of Medicine, Tokyo, Japan, **3** University of Tokyo Institute for Diversity and Adaptation of Human Mind (UTIDAHM), The University of Tokyo, Tokyo, Japan, **4** Center for Evolutionary Cognitive Sciences, Graduate School of Art and Sciences, The University of Tokyo, Tokyo, Japan, **5** Department of Psychiatry and Behavioral Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan, **6** Faculty of Human Sciences, Division of Psychology, University of Tsukuba, Tsukuba, Japan, **7** Department of Evolutionary Studies of Biosystems, School of Advanced Sciences, SOKENDAI (The Graduate University for Advanced Studies), Hayama, Japan, **8** Laboratory of Health Education, Graduate School of Education, The University of Tokyo, Tokyo, Japan, **9** Department of Health Promotion and Human Behavior, Kyoto University Graduate School of Medicine / School of Public Health, Kyoto University, Kyoto, Japan

\* [ando-st@igakuken.or.jp](mailto:ando-st@igakuken.or.jp)



CrossMark  
click for updates

**OPEN ACCESS**

**Citation:** Kanata S, Koike S, Ando S, Nishida A, Usami S, Yamasaki S, et al. (2016) Enuresis and Hyperactivity-Inattention in Early Adolescence: Findings from a Population-Based Survey in Tokyo (Tokyo Early Adolescence Survey). PLoS ONE 11(7): e0158786. doi:10.1371/journal.pone.0158786

**Editor:** Andrea Martinuzzi, IRCCS E. Medea, ITALY

**Received:** March 3, 2016

**Accepted:** June 22, 2016

**Published:** July 14, 2016

**Copyright:** © 2016 Kanata et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Data Availability Statement:** This study was planned and conducted in accordance with the ethics committee of the Tokyo Metropolitan Institute of Psychiatry. When applying to the research ethics committee for the data set, the authors did not request this to be released as public data. However, the data can be made available to all interested researchers upon request to Dr. Atsushi Nishida, Ph.D ([nishida-at@igakuken.or.jp](mailto:nishida-at@igakuken.or.jp)).

**Funding:** This work was supported by Grant-in-Aid for Scientific Research on Innovative Areas (23118002; Adolescent Mind & Self-Regulation to Kiyoto Kasai) from the Ministry of Education, Culture,

## Abstract

### Background

Enuresis (9% at age 9.5) negatively affects children's psychosocial status. Clinically-diagnosed enuresis (2% at the age) is associated with hyperactivity-inattention, and common neural bases have been postulated to underlie this association. It is, however, unclear whether this association is applicable to enuresis overall among the general population of early adolescents when considered comorbid behavioral problems. We aimed to examine whether enuresis correlates with hyperactivity-inattention after controlling for the effects of other behavioral problems.

### Methods

Participants were 4,478 children (mean age 10.2 ± 0.3 years old) and their parents from the Tokyo Early Adolescence Survey (T-EAS), a population-representative cross-sectional study conducted in Tokyo, Japan conducted from 2012 to 2015. Children's enuresis and behavioral problems, including hyperactivity-inattention (as measured by the Strength and Difficulties Questionnaire), were examined using parent-reporting questionnaires. Multivariate linear regression was used to explore whether enuresis predicts hyperactivity-inattention.

Sports, Science and Technology of Japan. The funder had no role in the study.

**Competing Interests:** The authors have declared that no competing interests exist.

## Results

The hyperactivity-inattention score was significantly higher in the enuretic group than the non-enuretic group (enuretic:  $M (SD) = 3.8 (2.3)$ , non-enuretic:  $M (SD) = 3.0 (2.1)$ , Hedge's  $g = 0.39$ ,  $p < .001$ ). This association remained significant even after controlling for other behavioral problems and including sex, age, intelligence quotient (IQ), low birth weight and parents' education ( $\beta = .054$  [95% CI: .028–.080],  $p < .001$ ).

## Conclusions

Enuresis was independently associated with hyperactivity-inattention in early adolescents among general population even when other behavioral problems were considered. These results suggest that, as with clinically-diagnosed cases, enuresis may predict need for screening and psychosocial support for hyperactivity-inattention.

## Introduction

Enuresis, or pathological bedwetting, is defined as an intermittent (i.e., not continuous) wetting with any frequency during sleep in children more than or equal to five years old, according to the International Children's Continence Society (ICCS) [1]. Epidemiological studies have shown that enuresis affects 25–30% of children at age 5 years, and 9.4% at 9.5 years [2,3]; whereas 5% of children at age 5 years and 2% at 10 [4] according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV/5), which requires twice or more in any one week [5,6]. Although the biological basis of enuresis is not fully understood, clinical studies have postulated that there exists neurodevelopmental immaturity, especially in the brainstem and motor cortex circuitry [7,8], as well as urological deficits [9].

Enuresis, especially in clinical situation, is known to be associated with a range of children's behavioral problems such as emotional problems, peer-relational problems, and conduct problems [10–12]. Hyperactivity-inattention, including attention-deficit hyperactivity disorder (ADHD), which is a pathologic condition on a hyperactivity-inattention spectrum [13], is the most common problem associated with enuresis, a link reported not only in clinical [14, 15], but also in epidemiological studies [16, 17]. A common neural basis is thought to underlie this association, perhaps through inhibitory regulation subserved by the anterior cingulate and the prefrontal cortexes [18], which develops through childhood and adolescence and matures in early adulthood [19, 20]. In clinical situations, these findings have been used for effective treatment of enuresis; the ICCS recommends screening enuretic children for hyperactivity-inattention, since simultaneous treatment for both leads to better outcomes in enuresis [10].

Children in early adolescence, at around 10 years old, perceive enuresis as a highly distressing problem, ranking it eighth among stressful life events [21], and children in eight years of age or older with persistent enuresis have psychosocial difficulties such as decreased self-esteem [22]. Appropriate care for enuresis is therefore very important, even if it does not appear in clinical situations or health professionals have not yet intervened. It is not, however, known whether hyperactivity-inattention may be independently associated with enuresis among general population as well as clinically-diagnosed enuresis [15]. Previous studies on the association have mainly been done in clinical situations, but low consulting rate for medical clinicians for enuresis [23] and restrictive criteria about frequency (twice or more per week according to the DSM-IV/5) [24] have excluded a considerable number of enuretic children from the studies [25].

A few epidemiological studies on early adolescents have suggested an association between enuresis and hyperactivity-inattention among general population. Byrd *et al.* reported that

children with any episodes of enuresis in the previous year showed higher extreme behavior scores, including hyperactivity-inattention, than non-enuretic children [3]. Joinson *et al.* reported that current enuresis was associated with increased hyperactivity-inattention even after children with frequent enuresis such as twice or more per week were excluded from the analyses [25]. These studies did not, however, examine and separate the overlap of behavioral problems despite their high comorbidity among enuretic children [26].

It therefore remains unclear whether there is an independent association between enuresis and hyperactivity-inattention among general population when other behavioral problems such as emotional and conduct problems are also considered [25]. Our study aimed to examine whether enuresis is independently associated with hyperactivity-inattention in early adolescence even after controlling for the effects of other behavioral problems.

## Materials and Methods

### Study procedures and participants

This study used data from Tokyo Early Adolescence Survey (T-EAS), a population-based cross-sectional survey focusing on children's health from bio-psycho-social multidisciplinary viewpoints. The T-EAS was also intended to serve as a baseline survey for a longitudinal study, which is now under way (Tokyo TEEN Cohort Study; TTC, <http://tcp.umin.jp/>). The TTC, especially focusing on children's self-regulation, aims to investigate development of children's mental health throughout adolescence, which serves as a foundation for their future health [27]. The T-EAS was conducted from October 2012 to January 2015, and the participants were recruited from three municipalities in Tokyo (Setagaya, Mitaka, and Chofu) using the Basic Resident Register. Out of 18,830 children born between 1st September 2002 and 31st August 2004 and living in the municipalities at the time of the survey, 14,553 children, together with their parents, were randomly selected and invited to participate in the survey. We were unable to contact 4,319 of these 14,553 child/parent groups. Of the 10,234 child/parent groups who were contacted, 5,756 refused to participate, leaving a total of 4,478 participating children, together with their parents (a response rate of 43.8%).

Using a parent-reported questionnaire children were excluded from the analyses if they needed care for urological and neurological deficits other than enuresis, or if they had taken medication for these conditions in the previous 2 weeks ( $n = 44$ ). Of the 4,434 participants, data from 90 participants were not used for the final regression analysis owing to missing values, leaving complete data from 4,344 child/parent groups available for the final analyses. There was no significant difference in demographic characteristics between those included and not included in the final analyses ( $p > .10$ ).

### Measures

Specially trained interviewers visited participants' homes and collected data. They obtained informed consent for participation, distributed questionnaires to the children and parents, and conducted psychological tests for the children.

**Enuresis.** Parents were asked about their children's enuresis using the question "Does your child currently wet the bed at night?" with the following options: (1) Never, (2) Sometimes, (3) Once or twice a week, (4) Three or four times a week, and (5) Using diapers. The answers were converted to a dichotomous variable, and children with any enuresis (answers (2)–(5)) were defined as an enuretic group with the others (an answer (1)) defined as a non-enuretic group.

Children who experienced enuresis frequent more than once a week (answers (3)–(5)), or had a diagnosis and medication for enuresis were regarded as a frequent enuresis group.

**Children's behavioral problems.** We employed the Japanese version of the Strength and Difficulties Questionnaire (SDQ) [28], a widely-used parent-reported questionnaire developed to evaluate behavioral conditions of children and adolescents [29]. The SDQ has four difficulty subscales (hyperactivity-inattention, emotional symptoms, conduct problems, and peer-relationship problems), and each of the subscales has five questions with 3-point Likert scales (0: Not true, 1: Somewhat true, 2: Absolutely true). The scores are summed for each subscale, so that each has a possible score from 0 to 10.

**Other variables.** Sex, age, intelligence quotient (IQ), low birth weight, and parents' educational backgrounds were included in the analyses since they are known to relate to children's enuresis and behavioral problems [4,28,30–32]. Children's IQ was estimated by a short version of the Wechsler Intelligence Scale for Children (WISC-III), which consists of two subsets (Information and Picture Completion) [33]. We developed a formula (Estimated IQ = 3.3\*Information + 2.0\*Picture Completion + 45.6) to estimate children's IQ from the two subsets using data from 28 children who were tested using the full version of WISC-III by expert psychologists one year after participation in T-EAS. The IQ calculated by the formula explained 78% of the variance in IQ from the full version of WISC-III. Birth weight was collected from the Maternal and Child Health Handbook, which are distributed to all pregnant women by the local government in Japan to record maternal and child medical and health information during pregnancy and after birth. We used a dichotomous variable for low birth weight (< 2,500 g), in line with the tenth version of the International Classification of Diseases [34]. To assess parents' educational backgrounds, we asked about their highest level of education using six items [35]: (1) Junior high school (or less), (2) High school (leaving before graduation), (3) High school (graduated), (4) Vocational school or two-year college, (5) Four-year college or university, and (6) Postgraduate education (or more).

## Statistical analysis

We examined differences between the enuretic and non-enuretic groups in the SDQ subscales and other variables using *t*-tests, and calculated the effect sizes using Hedge's *g*. We then carried out multivariate linear regression analyses to examine whether enuresis is independently associated with hyperactivity-inattention; the independent variable was enuresis, and the dependent variable was the SDQ subscale score for hyperactivity-inattention. The analyses had two models. Model 1 included potential confounding variables such as sex, age, estimated IQ, low birth weight, and parents' educational backgrounds, which were forced into the model simultaneously. Model 2 added the other SDQ subscales as well as the confounders in model 1. To assess the independent association between enuresis and the other SDQ subscales, we repeated the same analyses for each of the other SDQ subscales. As previous studies have shown sex differences in prevalence both of enuresis and behavioral problems [3, 4, 28], the effect of interactions between sex and enuresis on each subscale of the SDQ were also evaluated in both models. Finally, as sensitivity analyses, the statistical procedures above were repeated after excluding the frequent enuresis group.

The threshold for statistical significance was set to  $p < .05$  (two-sided) for all analyses. All statistical analyses were carried out using SPSS (Statistical Package for Social Science; IBM Corp., Armonk, NY USA), version 21.0 for Macintosh.

## Ethical approval

Ethical approval for this study was obtained from the research ethics committees of Tokyo Metropolitan Institute of Medical Science (Approval number: 12–35), SOKENDAI (The Graduate University for Advanced Studies) (2012002), and the Graduate School of Medicine and

Faculty of Medicine, The University of Tokyo (10057). Informed consent was obtained from both children and parents and written informed consent was obtained from the parents.

## Results

### Prevalence of enuresis

Enuresis was reported for 407 (9.2%) children out of 4,434 participants (Table 1). Of these, 61 children (1.4% of the total) were placed in the frequent enuresis group. Boys were more likely to show both enuresis (OR = 2.66 [95% CI: 2.12–3.33],  $p < .001$ ), and frequent enuresis (OR = 2.30 [95% CI: 1.31–4.05],  $p = .0036$ ).

### Differences in behavioral problems and other variables between the enuretic and non-enuretic groups

The enuretic group had a significantly higher hyperactivity-inattention score than the non-enuretic group (enuretic: mean (SD) = 3.8 (2.3), non-enuretic: 3.0 (2.1),  $p < .001$ , Table 2).

**Table 1. Demographic data of the participants (Total N = 4,434).**

Variables	n / Mean	(%) / SD
<b>Sex, male</b>	2347	(52.9)
<b>Age</b>	10.2	0.3
<b>Estimated IQ</b>	107.8	14.0
<b>Birth Weight, g</b>	3025	412
Low Birth Weight (< 2,500 g)	354	(8.1)
<b>Father's education</b>		
Junior high school or less	16	(0.4)
High school (leaving before graduation)	90	(2.1)
High school (graduated)	606	(14.3)
Vocational school or two-year college	574	(13.6)
Four-year college or university	2419	(57.2)
Postgraduate education or more	527	(12.5)
<b>Mother's education</b>		
Junior high school or less	11	(0.3)
High school (leaving before graduation)	41	(0.9)
High school (graduated)	678	(15.4)
Vocational school or two-year college	1909	(43.4)
Four-year college or university	1614	(36.7)
Postgraduate education or more	141	(3.2)
<b>Enuresis</b>		
None	4014	(90.8)
Sometimes	353	(8.0)
Once or twice a week	20	(0.5)
Three or four times a week	7	(0.2)
Using diapers	27	(0.6)
<b>Strength Difficulties Questionnaire</b>		
Hyperactivity-inattention	3.03	2.14
Emotional symptoms	1.57	1.69
Conduct problems	1.84	1.53
Peer relationship problems	1.52	1.57

Abbreviations: SD, Standard Deviation; IQ, Intelligence quotient.

doi:10.1371/journal.pone.0158786.t001

**Table 2. Comparison of behavioral problems in the enuretic and non-enuretic groups.**

	Non-enuretic (n = 3997)		Enuretic (n = 407)		t	p-value	Effect size
	Mean	SD	Mean	SD			
	SDQ						
Hyperactivity-inattention	2.96	2.11	3.79	2.26	7.11	< .001***	0.39
Emotional symptoms	1.55	1.67	1.84	1.85	3.10	< .001***	0.18
Conduct problems	1.80	1.51	2.18	1.66	4.43	< .001***	0.25
Peer relationship problems	1.49	1.55	1.81	1.74	3.51	< .001***	0.20

Effect size was Hedge’s *g*. Statistical significances were tested by *t*-test for two means.

Abbreviations: SD, Standard Deviation; SDQ, the Strength and Difficulties Questionnaire

\*\*\* *p* < .001

doi:10.1371/journal.pone.0158786.t002

This difference corresponded with Hedge’s *g* = 0.39. The other SDQ subscale scores were also higher among the enuretic group (*g* = 0.18 vs. 0.26, *p* < .001). There were no significant differences in children’s age, estimated IQ, and parental education (*p* > .20) between the two groups. These results did not change significantly even after excluding the frequent enuresis group (hyperactivity-inattention, enuretic: mean (SD) = 3.8 (2.3), non-enuretic: 3.0 (2.1), *g* = 0.38, *p* < .001).

### Independent association between enuresis and behavioral problems

Enuresis was associated with increased scores in hyperactivity-inattention and all the other SDQ subscales after controlling for demographic variables (hyperactivity-inattention:  $\beta = .087$  [95% CI: .057–.117], *p* < .001, other subscales:  $\beta = .048$ –.059, *p* < .005, Table 3, model 1). In model 2, which additionally adjusted for the other SDQ subscales, enuresis was associated only with increased hyperactivity-inattention ( $\beta = .054$  [95% CI: .028–.080], *p* < .001, model 2), but not with the other SDQ subscales (*p* > .15). Sensitivity analyses, which excluded the frequent enuresis group, showed similar results in both models (hyperactivity-inattention:  $\beta = .049$  [95% CI: .023–.076], *p* < .001, other subscales: *p* > .15, model 2).

**Table 3. Multivariate linear regression analyses predicting behavioral problems from enuresis.**

	Model 1 <sup>a)</sup>			Model 2 <sup>b)</sup>		
	$\beta$	95% C.I.	p-value	$\beta$	95% C.I.	p-value
SDQ						
Hyperactivity inattention	.087	[.057–.117]	< .001***	.054	[.028–.080]	< .001***
Emotional symptoms	.052	[.022–.083]	< .001***	.020	[–.008–.048]	.16
Conduct problems	.059	[.029–.090]	< .001***	.012	[–.015–.039]	.37
Peer relationship problems	.048	[.017–.079]	.0022**	.015	[–.014–.043]	.31

Final number included in analyses *n* = 4,344. Dependent variable was each SDQ subscale, and independent variable was enuresis. All the variables were forced into the model simultaneously, and multi-collinearity was not indicated (*VIF* < 1.5).

a) Adjusted for age, sex, estimated IQ, father’s education, mother’s education, low birth weight.

b) Adjusted for all of the other subscales of the SDQ as well as those in model 1.

Abbreviations: SDQ Strength and Difficulties Questionnaire; IQ Intelligence quotient; C.I. Confidence Interval

\*\* *p* < .01,

\*\*\* *p* < .001.

doi:10.1371/journal.pone.0158786.t003

There were no significant interaction effects between enuresis and sex on the SDQ subscales in these multivariate linear regression analyses ( $p > .20$ ). Interaction terms were therefore removed from the final analyses shown in [Table 3](#).

## Discussion

This study showed that enuresis was independently associated with hyperactivity-inattention in the general population of early adolescents even when considering other behavioral problems such as emotional symptoms, conduct problems, and peer-relationship problems. These results were essentially unchanged even after the frequent enuresis group was excluded.

To the best of our knowledge, this is the first study that has showed the independent association between enuresis and hyperactivity-inattention among a large general population in early adolescence. The result was consistent with a previous case-control clinical study showing independent association of hyperactivity-inattention with enuresis [15]. Our results could have adequate reliability and validity since the prevalence and sex ratio of enuresis is consistent with previous studies [3, 4]. We also observed significant associations between enuresis and other behavioral problems such as emotional and conduct problems in the unadjusted model (model 1), in line with a previous epidemiological study [25]. The sensitivity analyses excluding the frequent enuresis group did not significantly change the results. Therefore, enuresis may not be clearly divided into pathologic/non-pathologic groups according to its frequency, although the DSM-IV/5 defines enuresis based on the frequency [24].

No independent association with enuresis was observed for the other behavioral problems in this study. The clinical case-control study cited above, however, reported that not only hyperactivity-inattention but all the other behavioral problems in the SDQ were also independently associated with enuresis [15]. This difference in the results might be due to the small number of participants recruited from clinical patients in the previous study. Stronger distress associated with enuresis in clinical situation, rather than enuresis without consulting to clinicians, might lead to the association of enuresis with other behavioral problems as well as hyperactivity-inattention [36].

Although the mechanisms for the association between enuresis and hyperactivity-inattention remain unclear, we can propose some possible explanations based on previous studies. From a psychosocial viewpoint, children's increased hyperactivity-inattention could be a relapse of coping behavior resulted from the psychological burdens of enuresis [9, 36]. These burdens become much stronger in early adolescence, from around 10 years, since enuresis increasingly begins to carry social and peer-relational meanings at that point [21, 37]. From a biological viewpoint, neurophysiological and neuroimaging studies have recently suggested common developmental immaturities in the central nervous system for both enuresis and hyperactivity-inattention [18, 38]. A neurophysiological case-control study showed that deficits in prepulse inhibition were greater in children with clinically-diagnosed enuresis or attention deficit hyperactivity disorder (ADHD) than healthy controls, and greatest in children with both conditions [39]. These results could imply that the two conditions share dysregulation of inhibitory signal processing system in the pons, where exists the pontine micturition center [40], modulated by limbic cortico-striato-pallido-thalamic circuitry and prefrontal neural circuitry [41]. There has been no neuroimaging study focusing on the direct association between enuresis and hyperactivity-inattention. Functional magnetic resonance imaging studies during Go/No-Go tasks, however, have shown impaired activities in the anterior cingulate and the prefrontal cortexes, which are responsible for self-regulatory behavior against emotional reward cues [18–20], in patients with both clinical enuresis [42] and ADHD [43].



The results of this study may provide some clues for appropriate care for children showing enuresis and not consulting to clinicians. In clinical situations, for effective treatment of enuresis, the ICCS recommends screening for psycho-behavioral problems, especially hyperactivity-inattention, among enuretic children and provision of psychosocial care for both issues [10]. This study's findings suggest that this recommendation could also be applicable to enuresis in non-clinical situations, and that screening for hyperactivity-inattention and psychosocial care for the problem might prove effective care for enuretic children in early adolescence. This implication could be true of not only clinicians and parents but also school teachers and social welfare workers, who often face children with enuresis and hyperactivity-inattention in non-clinical situations (at home, school, and community).

This study has several limitations. First, our survey included no physical examination by medical specialists for urological and neurological disorders. Instead we relied on the parents' reports. This might not have been sufficient, as physical examinations are recommended in studying incontinence problems [38]. This meant that we were unable to guarantee exclusion of children with urinary disorders other than enuresis. Second, the SDQ scores might be biased towards high scores in the enuretic group, since parents of enuretic children, who perceive higher stress than ones of non-enuretic children [12], could negatively affect their evaluation of children's behavioral problems [44]. This limitation would, however, not explain the independent association of enuresis with hyperactivity-inattention, and not with other behavioral problems. Third, even though hyperactivity-inattention and ADHD are characterized as a continuous spectrum [13], it requires careful attention that children with high score of hyperactivity-inattention in the SDQ does not necessarily receive a diagnosis of ADHD. Finally, the cross-sectional nature of this study means that we cannot draw conclusions about any causal relationship between children's enuresis and hyperactivity-inattention. Future studies would benefit from drawing on both prospective and longitudinal viewpoints to clarify the causality. We plan to investigate this in the current longitudinal study.

## Conclusion

Enuresis was associated with increased hyperactivity-inattention among the general population of early adolescents even after controlling for other behavioral problems. The lines of evidence on treatments for clinical enuresis, such as screening and psychosocial support for hyperactivity-inattention [10], might therefore also be applicable to early adolescents showing enuresis even if not appearing to clinical situations.

## Acknowledgments

The authors are grateful to the participants, recruitment staff, the interviewers, and all of the TTC staff. Sho K was in charge of designing, analyzing and writing the manuscripts, being supervised by Shinsuke K, SA, AN, and KK. SU took charge of supervision of statistical analyses. All the authors critically reviewed the manuscript and approved the final version to be submitted. All of the authors declared that there are no conflicts of interest in relation to this study with respect to the research, authorship, and/or publication.

This work was supported by Grant-in-Aid for Scientific Research on Innovative Areas (23118002; Adolescent Mind & Self-Regulation) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

## Author Contributions

Conceived and designed the experiments: S. Kanata S. Koike SA AN SU SY YM RT SF NS MH KK. Performed the experiments: S. Kanata S. Koike SA AN SY YM RT SF NS MH KK.

Analyzed the data: S. Kanata S. Koike SA AN SU. Contributed reagents/materials/analysis tools: S. Kanata S. Koike SA AN SU SY YM RT SF NS MH KK. Wrote the paper: S. Kanata S. Koike SA AN SU SY YM RT SF NS TS TF MH KK.

## References

1. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. *NeuroUrol Urodyn.* 2016; 35(4):471–81. doi: [10.1002/nau.22751](https://doi.org/10.1002/nau.22751) PMID: [25772695](https://pubmed.ncbi.nlm.nih.gov/25772695/)
2. Sullivan S, Joinson C, Heron J. Factors predicting atypical development of nighttime bladder control. *J Dev Behav Pediatr.* 2015; 36(9):724–33. doi: [10.1097/DBP.0000000000000229](https://doi.org/10.1097/DBP.0000000000000229) PMID: [26468941](https://pubmed.ncbi.nlm.nih.gov/26468941/)
3. Byrd RS, Weitzman M, Lanphear NE, Auinger P. Bed-wetting in US children: epidemiology and related behavior problems. *Pediatrics.* 1996; 98(3):414–9. PMID: [8784366](https://pubmed.ncbi.nlm.nih.gov/8784366/)
4. Butler RJ, Heron J. The prevalence of infrequent bedwetting and nocturnal enuresis in childhood. A large British cohort. *Scand J Urol Nephrol.* 2008; 42(3):257–64. doi: [10.1080/00365590701748054](https://doi.org/10.1080/00365590701748054) PMID: [18432533](https://pubmed.ncbi.nlm.nih.gov/18432533/)
5. American Psychiatric Association (1995). *The diagnostic and statistical manual of mental disorders, 4th. ed. (DSM-IV)*. Washington D.C.: American Psychiatry Press.
6. American Psychiatric Association (2014). *The diagnostic and statistical manual of mental disorders, 5th. ed. (DSM-5)*. Washington D.C.: American Psychiatry Press.
7. Freitag CM, Röhling D, Seifen S, Pukrop R, von Gontard A. Neurophysiology of nocturnal enuresis: Evoked potentials and prepulse inhibition of the startle reflex. *Dev Med Child Neurol.* 2006; 48(4):278–84. PMID: [16542515](https://pubmed.ncbi.nlm.nih.gov/16542515/)
8. von Gontard A, Freitag CM, Seifen S, Pukrop R, Röhling D. Neuromotor development in nocturnal enuresis. *Dev Med Child Neurol.* 2006; 48(9):744–50. PMID: [16904021](https://pubmed.ncbi.nlm.nih.gov/16904021/)
9. Butler RJ. Childhood nocturnal enuresis: Developing a conceptual framework. *Clin Psychol Rev.* 2004; 24(8):909–31. PMID: [15533278](https://pubmed.ncbi.nlm.nih.gov/15533278/)
10. von Gontard A, Baeyens D, van Hoecke E, Warzak WJ, Bachmann C. Psychological and psychiatric issues in urinary and fecal incontinence. *J Urol.* 2011; 185(4):1432–6. doi: [10.1016/j.juro.2010.11.051](https://doi.org/10.1016/j.juro.2010.11.051) PMID: [21349549](https://pubmed.ncbi.nlm.nih.gov/21349549/)
11. van Hoecke E, De Fruyt F, de Clercq B, Hoebeke P, Vande Walle J. Internalizing and externalizing problem behavior in children with nocturnal and diurnal enuresis: A five-factor model perspective. *J Pediatr Psychol.* 2006; 31(5):460–8. PMID: [15905418](https://pubmed.ncbi.nlm.nih.gov/15905418/)
12. de Bruyne E, van Hoecke E, van Gompel K, Verbeken S, Baeyens D, Hoebeke P, et al. Problem behavior, parental stress and enuresis. *J Urol.* 2009; 182(4 Suppl):2015–20. doi: [10.1016/j.juro.2009.05.102](https://doi.org/10.1016/j.juro.2009.05.102) PMID: [19695644](https://pubmed.ncbi.nlm.nih.gov/19695644/)
13. Whalen CK, Jamner LD, Henker B, Delfino RJ, Lozano JM. The ADHD spectrum and everyday life: Experience sampling of adolescent moods, activities, smoking, and drinking. *Child Dev.* 2002; 73(1):209–27. PMID: [14717253](https://pubmed.ncbi.nlm.nih.gov/14717253/)
14. Baeyens D, Roeyers H, Hoebeke P, Verté S, van Hoecke E, Walle J Vande. Attention deficit/hyperactivity disorder in children with nocturnal enuresis. *J Urol.* 2004; 171(6):2576–9. PMID: [15118422](https://pubmed.ncbi.nlm.nih.gov/15118422/)
15. Coppola G, Costantini A, Gaita M, Saraulli D. Psychological correlates of enuresis: A case-control study on an Italian sample. *Pediatr Nephrol.* 2011; 26(10):1829–36. doi: [10.1007/s00467-011-1880-3](https://doi.org/10.1007/s00467-011-1880-3) PMID: [21533628](https://pubmed.ncbi.nlm.nih.gov/21533628/)
16. Shreeram S, He J-P, Kalaydjian A, Brothers S, Merikangas KR. Prevalence of enuresis and its association with attention-deficit/hyperactivity disorder among U.S. children: Results from a nationally representative study. *J Am Acad Child Adolesc Psychiatry.* 2009; 48(1):35–41 doi: [10.1097/CHI.0b013e318190045c](https://doi.org/10.1097/CHI.0b013e318190045c) PMID: [19096296](https://pubmed.ncbi.nlm.nih.gov/19096296/)
17. Park S, Kim B- N, Kim J- W, Hong S- B, Shin M- S, Yoo HJ, et al. Nocturnal enuresis is associated with attention deficit hyperactivity disorder and conduct problems. *Psychiatry Investig.* 2013; 10(3):253–8. doi: [10.4306/pi.2013.10.3.253](https://doi.org/10.4306/pi.2013.10.3.253) PMID: [24302948](https://pubmed.ncbi.nlm.nih.gov/24302948/)
18. von Gontard A, Equit M. Comorbidity of ADHD and incontinence in children. *Eur Child Adolesc Psychiatry.* 2014; 24:127–40. doi: [10.1007/s00787-014-0577-0](https://doi.org/10.1007/s00787-014-0577-0) PMID: [24980793](https://pubmed.ncbi.nlm.nih.gov/24980793/)
19. Casey BJ, Duhoux S, Malter Cohen M. Adolescence: What do transmission, transition, and translation have to do with it? *Neuron.* 2010; 67(5):749–60. doi: [10.1016/j.neuron.2010.08.033](https://doi.org/10.1016/j.neuron.2010.08.033) PMID: [20826307](https://pubmed.ncbi.nlm.nih.gov/20826307/)
20. Kasai K. Toward an interdisciplinary science of adolescence: Insights from schizophrenia research. *Neurosci Res.* 2013; 75(2):89–93. doi: [10.1016/j.neures.2012.12.001](https://doi.org/10.1016/j.neures.2012.12.001) PMID: [23262062](https://pubmed.ncbi.nlm.nih.gov/23262062/)

21. Butler RJ, Heron J. An exploration of children's views of bed-wetting at 9 years. *Child Care Health Dev.* 2008; 34(1):65–70. doi: [10.1111/j.1365-2214.2007.00781.x](https://doi.org/10.1111/j.1365-2214.2007.00781.x) PMID: [18171446](https://pubmed.ncbi.nlm.nih.gov/18171446/)
22. Redsell SA, Collier J. Bedwetting, behaviour and self-esteem: A review of the literature. *Child Care Health Dev.* 2001; 27(2):149–62. PMID: [11251613](https://pubmed.ncbi.nlm.nih.gov/11251613/)
23. Nappo S, Del Gado R, Chiozza ML, Biraghi M, Ferrara P, Caione P. Nocturnal enuresis in the adolescent: A neglected problem. *BJU Int.* 2002; 90(9):912–7. PMID: [12460356](https://pubmed.ncbi.nlm.nih.gov/12460356/)
24. von Gontard A. Elimination disorders: a critical comment on DSM-5 proposals. *Eur Child Adolesc Psychiatry.* 2011; 20(2):83–8. doi: [10.1007/s00787-010-0152-2](https://doi.org/10.1007/s00787-010-0152-2) PMID: [21221682](https://pubmed.ncbi.nlm.nih.gov/21221682/)
25. Joinson C, Heron J, Emond A, Butler RJ. Psychological problems in children with bedwetting and combined (day and night) wetting: A UK population-based study. *J Pediatr Psychol.* 2007; 32(5):605–16. PMID: [17071625](https://pubmed.ncbi.nlm.nih.gov/17071625/)
26. Zink S, Freitag CM, von Gontard A. Behavioral comorbidity differs in subtypes of enuresis and urinary incontinence. *J Urol.* 2008; 179(1):295–8. PMID: [18006020](https://pubmed.ncbi.nlm.nih.gov/18006020/)
27. Sawyer SM, Afifi RA, Bearinger LH, Blakemore S-J, Dick B, Ezech AC, et al. Adolescence: A foundation for future health. *Lancet.* 2012; 379:1630–40. doi: [10.1016/S0140-6736\(12\)60072-5](https://doi.org/10.1016/S0140-6736(12)60072-5) PMID: [22538178](https://pubmed.ncbi.nlm.nih.gov/22538178/)
28. Matsuishi T, Nagano M, Araki Y, Tanaka Y, Iwasaki M, Yamashita Y, et al. Scale properties of the Japanese version of the Strengths and Difficulties Questionnaire (SDQ): A study of infant and school children in community samples. *Brain Dev.* 2008; 30(6):410–5. doi: [10.1016/j.braindev.2007.12.003](https://doi.org/10.1016/j.braindev.2007.12.003) PMID: [18226867](https://pubmed.ncbi.nlm.nih.gov/18226867/)
29. Goodman R. The Strengths and Difficulties Questionnaire: A Research Note. *J Child Psychol Psychiatry.* 1997; 38(5):581–6. PMID: [9255702](https://pubmed.ncbi.nlm.nih.gov/9255702/)
30. Oppel W, Harper P, Rider R. Social, psychological, and neurological factors associated with nocturnal enuresis. *Pediatrics.* 1968; 42(4):627–41. PMID: [5681281](https://pubmed.ncbi.nlm.nih.gov/5681281/)
31. Joinson C, Heron J, Butler RJ, von Gontard A, Butler U, Emond A, et al. A United Kingdom population-based study of intellectual capacities in children with and without soiling, daytime wetting, and bed-wetting. *Pediatrics.* 2007; 120(2):e308–16. PMID: [17609308](https://pubmed.ncbi.nlm.nih.gov/17609308/)
32. van Hoecke E, Baeyens D, Vande Walle J, Hoebeke P, Roeyers H. Socioeconomic status as a common factor underlying the association between enuresis and psychopathology. *J Dev Behav Pediatr.* 2003; 24(2):109–14. PMID: [12692456](https://pubmed.ncbi.nlm.nih.gov/12692456/)
33. Inada N, Kamio Y. Short forms of the Japanese version WISC-III for assessment of children with autism spectrum disorders. *Jpn J Child Adolesc Psychiatr.* 2010; 51:11–9.
34. World Health Organization. Tenth revision of the international classification of diseases and related health problems. Geneva: World Health Organization 1992.
35. Hollingshead AB. Four factor index of social status (Unpublished Working Paper, 1975). *Yale J Sociol.* 2011; 8:21–52.
36. Butler RJ. Annotation: Night wetting in children: psychological aspects. *J Child Psychol Psychiatry.* 1998; 39(4):453–63. PMID: [9599774](https://pubmed.ncbi.nlm.nih.gov/9599774/)
37. Butler RJ, Redfern E, Forsythe W. The child's construing of nocturnal enuresis: A method of inquiry and prediction of outcome. *J Child Psychol Psychiatry.* 1990; 31(3):447–54. PMID: [2318925](https://pubmed.ncbi.nlm.nih.gov/2318925/)
38. Nevéus T, Läckgren G, Tuvemo T, Hetta J, Hjälmås K, Stenberg A. Enuresis—background and treatment. *Scandinavian journal of urology and nephrology Supplementum.* 2000; 1–44.
39. Ornitz EM, Russell AT, Hanna GL, Gabikian P, Gehricke JG, Song D, et al. Prepulse inhibition of startle and the neurobiology of primary nocturnal enuresis. *Biol Psychiatry.* 1999; 45(11):1455–66. PMID: [10356628](https://pubmed.ncbi.nlm.nih.gov/10356628/)
40. Baeyens D, Roeyers H, Hoebeke P, Antrop I, Mauel R, Vande WJ. The impact of attention deficit hyperactivity disorders on brainstem dysfunction in nocturnal enuresis. *J Urol.* 2006; 176(2):744–8. PMID: [16813934](https://pubmed.ncbi.nlm.nih.gov/16813934/)
41. Braff DL, Geyer MA., Swedlow NR. Human studies of prepulse inhibition of startle: Normal subjects, patient groups, and pharmacological studies. *Psychopharmacology.* 2001; 156:234–58. PMID: [11549226](https://pubmed.ncbi.nlm.nih.gov/11549226/)
42. Lei D, Ma J, Du X, Shen G, Tian M, Li G. Altered brain activation during response inhibition in children with primary nocturnal enuresis: An fMRI study. *Hum Brain Mapp.* 2012; 33(12):2913–9. doi: [10.1002/hbm.21411](https://doi.org/10.1002/hbm.21411) PMID: [21998078](https://pubmed.ncbi.nlm.nih.gov/21998078/)
43. Bush G. Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2011; 69(12):1160–7. doi: [10.1016/j.biopsych.2011.01.022](https://doi.org/10.1016/j.biopsych.2011.01.022) PMID: [21489409](https://pubmed.ncbi.nlm.nih.gov/21489409/)
44. Najman JM, Williams GM, Nikles J, Spence S, Bor W, O'Callaghan M, et al. Bias influencing maternal reports of child behaviour and emotional state. *Soc Psychiatry Psychiatr Epidemiol.* 2001; 36:186–94. PMID: [11518032](https://pubmed.ncbi.nlm.nih.gov/11518032/)