Nocturnal enuresis in early adolescence and neurodevelopmental delay in infancy: a population-based study

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Abstract

Objectives: The neurodevelopmental delay hypothesis may explain the mechanism of nocturnal enuresis (NE), but whether the hypothesis holds in early adolescence remains unknown, considering NE frequency. Therefore, we aimed to identify whether the neurodevelopmental delays in infancy were associated with the frequency of NE in early adolescence.

Methods: Data were extracted from the Tokyo Early Adolescence Survey, in which 4,478 children (10.2 years) and their parents participated. Developmental delays were extracted from the Maternal and Child Health Handbook. The NE frequency was obtained from a parent-answered questionnaire (frequent; ≥2 times a week). Multinomial logistic regression analysis was performed to determine whether delayed developmental milestones in infancy were predictive of frequent/infrequent NE in early adolescence.

Results: Developmental delays, particularly those related to motor development but not verbal, such as holding their head up (odds ratio; OR [95% confidence interval (CI)]=2.1[1.1–4.2]), crawling (2.1[1.0–4.4]), walking with support (4.0[1.9–8.4]), walking independently (5.8[2.2–15.4]), and drawing a circle (5.0[2.0–12.3]) were significantly associated with an increased risk of frequent NE in early adolescence (all ps<.05). However, an association with infrequent NE was not found.

Conclusions: This population-based epidemiological study revealed that motor developmental delays increased the risk of frequent NE in early adolescents, except for infrequent NE; this finding reinforces the neurodevelopmental delay hypothesis, which provides a biological explanation for the involuntary nature of enuresis. All children in early adolescence with frequent NE should be evaluated and treated by a medical expert.

Introduction

Nocturnal enuresis (NE)—defined as intermittent wetting during sleep in children—can be a health problem if it persists beyond the age of 5 years [1, 2]. NE is an important issue because of its high prevalence and related psychosocial burdens, particularly during early adolescence. The prevalence of NE is as high as 9% at the age of 10 years [3, 4]. NE is associated with various psychological problems [5, 6] including low self-esteem or well-being [7], or anxiety-depressive symptoms [8, 9], and behavioral problems such as higher tendency of hyperactivity [4, 9, 10] or conduct problems [11]. These associations are particularly pronounced beyond the age of 8 years [7]. Notably, NE is reported as a highly common distressing life event during early adolescence, and ranked 8th among stressful life events, such as not getting along with friends or low academic achievement [12].

Despite these concerns, the mechanism by which NE remains until early adolescence is unclear [13]. Over the past several decades, the causes of NE have been pursued. There are molecular genetic aspects [14], neurobiological mechanisms (lack of inhibition of CNS emptying reflex, difficult arousal) [15], and a wide range of contributions from behavioral aspects such as sleep [16] or hyperactivity tendencies [4], have been pointed out, but ultimately remain unresolved.

The neurodevelopmental delay hypothesis offers one possible explanation for NE [17–19]: an immature central nervous system (CNS) as well as urological deficits underly NE in children [20]. Clinical neurophysiological and neuroimaging studies have indicated an association between enuresis (pathological NE) and CNS immaturity, particularly in the brainstem and motor cortex circuitry [21–23]. However, epidemiological evidence supporting this hypothesis is limited since children with NE are less likely to consult a doctor [24] even if their NE is as frequent as twice a week, which could be described as a pathological level [2]. NE frequency is another essential factor in the association between NE and delayed neurodevelopment [25], as it reflects the severity of neurodevelopmental delay. In the clinical setting, the

International Children's Continence Society (ICCS) requires at least one episode per month [1], while the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) regards wetting ≥ 2 a week as NE [2]. Considering the gap between the prevalence of NE and its consultation rates [3, 4, 24], determining whether wetting frequency affects the association between NE and neurodevelopmental delay among the general population will help elucidate the nature of NE. Therefore, delays in reaching developmental milestones in infancy (rolling over, standing, speaking) could predict NE in early adolescence; nevertheless, there is a limited number of epidemiological studies exploring the association [17, 18, 25–27], while no studies have investigated whether the association between each chronological neurodevelopmental delay and NE is applicable among children aged ≥ 10 years, considering NE frequency. Therefore, we aimed to explore this association, hypothesizing that children who exhibited delays in developmental milestones up to the age of 3 years would experience NE at the age of 10 years.

Materials And Methods

All methods below were carried out in accordance with relevant guidelines and regulations.

Ethical approval

Ethical approval was obtained from the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (10057), the research ethics committees of the Tokyo Metropolitan Institute of Medical Science (Approval number: 12-35), and SOKENDAI (The Graduate University for Advanced Studies) (2012002). Informed consent was obtained from both children and their parents, and written informed consent was obtained from the parents.

Study procedures and participants

We used the data from the Tokyo Early Adolescence Survey (T-EAS), a population-based cross-sectional survey conducted in three municipalities in Tokyo (Setagaya, Mitaka, and Chofu) [28]. The T-EAS was designed to function as a baseline survey for the Tokyo Teen Cohort study (TTC), a longitudinal cohort study for which the fourth wave of data collection is underway (http://ttcp.umin.jp/). The T-EAS was conducted from October 2012 to January 2015, and participants were recruited by the Basic Resident Register in the municipalities. Children aged 10 years born between September 1, 2002, and August 31, 2004 and lived in the municipalities during the survey period and their parents (mothers; 98.5%) were invited to join in the T-EAS. Among 10,234 potential child-parent pairs, 5,756 pairs refused to participate in the T-EAS. Finally, 4,478 children were included, together with their parents (response rate: 43.8%) [28].

Trained investigators conducted the survey over the course of two visits. At the first visit, we obtained written informed consent from the parents and assent from the children to participate in the T-EAS. The child-parent pairs were required to answer questionnaires separately by the second visit. There were columns on the questionnaire for the parent to copy records from the Maternal and Child Health Handbook (MCH Handbook). The MCH Handbook is distributed to almost all (>98%) [29] pregnant women in Japan by local municipalities to record maternal and child health information during pregnancy, the perinatal period, and after-birth [30]. At the second visit, the participating child-parent pairs were asked to complete the other self-reported questionnaires separately. These questionnaires pertained to sensitive contents such as mental health problems and placed in an envelope immediately after completion. During the second visit, the investigator also performed physical measurements and psychological examinations.

Children were excluded from the analyses if they needed special care for urological or neurological deficits other than NE or had taken medication for these conditions in the 2 weeks prior to participation (n = 44). Of the 4,434 participants, the data from 90 were not used for the final logistic regression analysis due to missing values. Finally, the data of 4,344 child-parent pairs were available for analysis. Demographic characteristics such as age and estimated intelligence

quotient (IQ) (bilateral *t*-test), sex prevalence and parental educational background (chi-square test) did not significantly differ between included and excluded children ($p>.05$).

Measures

Delay in developmental milestones

To collect data regarding developmental delays, we created columns for copying the MCH Handbook records in the T-EAS questionnaire for the parents. The developmental milestones studied were as follows: 'Holding their head up' (at 3 months of age), 'Rolling over' and 'sitting' (6-7 months), 'Crawling' and 'standing' (9-10 months), 'Walking with support' and 'Understanding some words' (12 months), 'Walking independently' and 'Speaking a few words' (18 months), 'Talking in two-word sentences' (24 months), and 'Drawing a circle' and 'Saying their name' (36 months). We asked the parents, for instance, "Did your child hold his/her head up at 3 months old?". In their answer, the parents would refer to the corresponding column in the MCH Handbook. Answer options were Yes (0) and No (1), and dichotomous variables for each delay were created according to the answers.

We also counted each participant's total number of developmental milestone delays described above (range: 0-12), as an indicator of severity and consistency of children's developmental delay. Participants without any information about their developmental milestones (n = 31 (0.7%)) were excluded from this procedure.

Nocturnal enuresis

The participating parents were asked about their children's NE with the following question: "Does your child currently wet the bed at night?", which was scored on a 5-point scale: (1) never, (2) sometimes, (3) once or twice a week, (4) three or four times a week, and (5) using diapers. We classified the answers into three groups. Children with answer (1) were assigned to the 'none' group, children with (2) to 'infrequent wetting,' and children with (3-5) to 'frequent wetting' since they could meet the diagnostic criteria for enuresis according to the DSM-5 [2].

Other potentially confounding factors

Sex, age, child's intelligence quotient (IQ), low birth weight, and parents' educational backgrounds were included in the analyses as potential confounding factors [31–36]. IQ was estimated using a short form of the Wechsler Intelligence Scale for Children (WISC-III), consisting of two subsets (Information and Picture Completion) [37]. A formula for estimating the child's IQ (estimated IQ = 3.3 × Information + 2.0 × Picture Completion + 45.6) was obtained from the results of the full version of the WISC-III performed by clinical psychologists in 28 children, 1 year after participation in the T-EAS. The IQ calculated by the formula explained 78% of the variance in IQ from the full version. Birth weights were collected from the MCH Handbook. We created a dichotomous variable for low birth weight (<2,500 g), in line with the 10th Version of the International Classification of Diseases [38]. The parents' educational backgrounds were assessed according to their highest levels of education, scored on a 6-point scale [39]: (1) Junior high school (or lower), (2) high school (leaving before graduation), (3) high school (graduated), (4) vocational school or 2-year college, (5) 4-year college or university, and (6) postgraduate education (or higher).

Statistical analysis

Following the demographic statistics calculation, we created a cross-tabulation table for developmental milestones in infancy and NE status in early adolescence (none, infrequent wetting, and frequent wetting). Chi-square tests were conducted to examine distribution differences. Subsequently, the total number of developmental delays recorded in the MCH Handbook was tabulated for each participant. We examined whether the distribution and average number of developmental delays differed among NE groups using the chi-square test and analysis of variance with a post hoc

Bonferroni procedure. Finally, multinomial logistic analyses were performed, which employed developmental delay as an independent variable and NE as a dependent variable using the None group as reference. We created two models. In the crude model, the odds ratio (OR) of each developmental delay was calculated without adjustment. In the adjusted model, we adjusted for sex, age, estimated IQ, low birth weight, and parents' educational background. All variables were simultaneously forced into the model, and multi-collinearity not indicated (*VIF*<1.5). The Statistical Package for Social Science version 24 was used for all statistical analyses.

Results

The basic demographic data of the participants is shown in Table 1. Among the participating children, 408 (9.2%) experienced NE at the age of 10. Of these children, 351 (86.7%) belonged to the infrequent wetting group, and the remaining 57 (13.3%) to the frequent wetting group. There was a significant sex difference in the distributions of NE status ($\chi^2(4) = 77.6$, $p<.001$); boys (none: 2043 (87.2%), infrequent wetting: 258(11.0%), frequent wetting: 42(1.8%)) experienced more frequent wetting than girls (none: 1971(94.8%), infrequent wetting: 93(4.5%), frequent wetting: 15(0.7%)). The odds ratio of NE prevalence among boys to girls was 2.7 (12.8% vs. 5.2%, 95% confidence interval [CI]: 2.1–3.3, $p<.001$).

Delays in developmental milestones were observed in 1.7–21.9% of children throughout infancy; the most common was a delay in sitting by oneself at 6 months (21.9%) and the most uncommon a delay in independent walking at 18 months (1.7%).

Cross-tabulations between developmental delays in infancy and NE at 10 years are shown in Table 2. Children with developmental delays ('Holding their head up' at 3 months and all items after 12 months) were more likely to experience NE in their early adolescence than children without delays ($\chi^2(2) = 7.4$, $ps<.024$). When the risk ratio (RR) for NE due to developmental delays were calculated, the frequent wetting group had RRs > 1 at all milestones (Holding one's head up: RR = 2.0, Rolling over 1.3, Sitting oneself 1.1, Crawling 2.2, Pulling oneself up 2.1, Walking along something 4.1, Understanding some words 3.5, Walking on one's own 6.8, Saying one word 2.7, Saying two-word sentences 2.6, Drawing a circle with crayons5.9, Saying one's name 4.8).

Figure 1 shows the distribution of the number of developmental delays according to NE group. Among all children (n = 4,403), 2,542 (57.7%) had no delays, 1,007 (22.9%) had one, 413 (9.4%) had two, and the remaining 441 (10.0%) had ≥3. The frequent wetting group tended to experience a greater number of delays during infancy than the other two groups ($\chi^2(22) = 152.5$, $p<.001$). The mean number of delays for the three groups was 0.8±1.3 (none), 0.8±1.2 (infrequent wetting), and 1.8±2.9 (frequent wetting), with significant between-group differences ($F(2, 4400) = 13.1$, $p<.001$). In post hoc analysis, significant differences were observed between the none and the frequent wetting groups, and the infrequent and frequent wetting groups (both $ps<.001$), but the difference between the none and infrequent wetting groups was not significant.

Table 3 presents the results of multinomial logistic regression analysis predicting infrequent or frequent NE at 10 years when experiencing developmental delay in infancy. In both the crude and adjusted models, various developmental delays significantly predicted a 2.1–5.8-fold increased risk of frequent NE. This was particularly apparent for items related to motor development, such as 'Holding their head up', 'Crawling', 'Walking with support', 'Walking independently', and 'Drawing a circle' ($ps<.05$). According to infrequent NE, only an item from verbal development ('Speaking a few words') increased the risk of infrequent NE, but the OR was relatively low, and the lower limit of the CI was almost 1.0, indicating not robust significance. (OR=1.61, 95% CI: 1.01–2.56, $p=.045$).

Discussion

This study aimed to identify the neurodevelopmental delays in infancy associated with infrequent/frequent NE among early adolescents. Our results indicated that developmental delays in infancy were significantly associated with an increased risk of frequent NE in early adolescence; this association was particularly strong for certain milestones related to motor development. On the other hand, developmental delays did not generally increase the risk of infrequent NE. In addition, children who experienced frequent NE tended to exhibit a greater number of developmental delays than did those who experienced no NE or infrequent NE.

The results of the present study are in agreement with those of previous epidemiological studies which targeted younger age groups or used single-point measures for neurodevelopmental delays [3,17,18,25–27]. Regarding the prevalence and sex differences in NE, our research found a 9.2% prevalence at age 10 years, and boys were 2.7-fold more likely than girls to experience NE. These results are consistent with a representative population-based study conducted in the UK (the ALSPAC study) [3]. As for the association between developmental delay and frequent NE, a Canadian population-based cohort study by Touchette *et al.* revealed that relative to those that did not, children still NE at 4.5 years of age exhibited delayed motor development at 5 months in boys and delayed verbal development at 17 months in girls [27]. Using the ALSPAC samples, Sullivan *et al.* reported that developmental delay in gross/fine motor and communication/social skills in 1.5-year-olds predicted an increased risk of NE up to the age of 9 years [25].

The present study is novel in suggesting that motor developmental delay is more prominently associated with frequent NE than is verbal developmental delay. This tendency seems to be more evident in our results than the abovementioned studies suggested [25,27]. These findings could be due to the detailed and cumulative examination of chronological development from 3 to 36 months, and the relatively old age of the children. Our finding is consistent with previous findings examining physiological functioning, cognitive functioning, or behavioral problems. NE is associated with motor performance difficulties such as repetitive movements, suggesting CNS maturational deficits [19]. Children with NE up to the age of 7.5 years tend to have a lower IQ than non-wetting children, particularly in the performance IQ subset [33]. One of the most common problems associated with NE is hyperactivity-inattention [4,40,41], including the pathological attention-deficit-hyperactivity disorder [10,42–46].

In the present study, as opposed to frequent NE, infrequent NE was only associated with a delay of ‘Speaking a few words’. The contribution of neurodevelopmental factors to NE may differ depending on its frequency. It is notable that these inferences above do not imply the lack of necessity of care or treatment for infrequent NE. Most NE occurs less than twice a week [47], and wetting children are indeed burdened in psychosocial aspects regardless of NE frequency [7,12]. The ICCS defines frequent enuresis as four or more times a week, but at the same time claiming that low-frequency NE could also be a treatment target if the children experience any difficulties [1].

The results of the present study could support the neurodevelopmental delay model of NE [17–19]. In that case, frequent NE among early adolescents could reflect the immaturity of the CNS and its autonomic functions [48]. Disseminating the involuntary nature of NE to the people typically in contact with children (e.g. their parents, teachers, workers in welfare, etc.) could lead to more protective care for children who experience particularly frequent NE. For example, all children in early adolescence with frequent NE may benefit from evaluation and treatment by medical professionals [49]. In this context, the term "developmental delay" needs to be critically interpreted. The wording assumes that children with slow-to-achieve milestones will "eventually catch up" with their typically developing peers. However, the possibility also exists that NE may signify a relatively permanent neurodevelopmental problem rather than a temporary neurodevelopmental delay, such as developmental coordination disorder (DCD) in DSM-5 [2], since NE may be a manifestation of one of the neurological soft signs [19].

Using a population-representative sample, we conducted a reliable analysis and discussion on NE, which generally has a low consultation rate hindering the evaluation of the actual situation [24]. One of the strengths of the present study is

that recall bias was avoided due to the efficacy of the MCH Handbook, which is sequentially recorded along with children's development. Therefore, although this study had a cross-sectional follow-back design, the recall bias could be regarded nearly as low as in a prospective cohort study. The efficacy of the MCH Handbook as a reliable source for the monitoring of children's development should be afforded more attention. However, there are several limitations to the present study. Due to the T-EAS structure as an epidemiological survey for the general population, information on physical diseases, particularly in the field of urology and neurology, was collected only from the parents' self-reported questionnaires. In addition, this study did not employ the definitions of frequent NE in the DSM-5 or the ICCS. Therefore, the exclusion criteria might not have been sufficient, as professional physical examinations are recommended in clinical studies on elimination disorders [50].

Findings from magnetic resonance imaging studies of clinical enuresis focusing on the brainstem and inhibitory regulation system, subserved by the anterior cingulate and prefrontal cortices, have gradually accumulated [10,51,52]. Based on population neuroscience principles [53,54], applying these clinical findings to sub-clinical children and adolescents could be fruitful for elucidating the neural basis of NE.

Conclusion

This population-based epidemiological study revealed that developmental delays in infancy, particularly delays in motor development, increased the risk of frequent NE in early adolescence. In contrast, there was barely any association between neurodevelopmental delay and infrequent NE. Possibly the contribution of neurodevelopmental factors to NE differs based on its frequency. Despite several limitations, the results of the present study have significant implications. All children in early adolescence with frequent NE should be evaluated and treated by a medical expert.

Declarations

Conflict of Interest Disclosures: The authors have no conflicts of interest relevant to this article to disclose.

Data Sharing Statement: When applying to the TTC research ethics committee for the present data set, the authors did not request the data to be shared publicly. However, the data can be available to all researchers on request to the corresponding author (SA; sandou-tky@umin.ac.jp).

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Tables

Table 1. Demographic data of the participants

Variables		number of collected data	*n* / Mean	(%) / *SD*
Sex, Boys		4434	2347	(52.9)
Age, years		4425	10.2	0.3
Estimated IQ		4430	107.8	14.0
Father's education		4232		
Junior high school or lower			16	(0.4)
High school (leaving before graduation)			90	(2.1)
High school (graduated)			606	(14.3)
Vocational school or 2-year college			574	(13.6)
Four-year college or university			2419	(57.2)
Postgraduate education or higher			527	(12.5)
Mother's education		4394		
Junior high school or lower			11	(0.3)
High school (leaving before graduation)			41	(0.9)
High school (graduated)			678	(15.4)
Vocational school or 2-year college			1909	(43.4)
Four-year college or university			1614	(36.7)
Postgraduate education or higher			141	(3.2)
Nocturnal enuresis		4422		
None			4014	(90.8)
Infrequent nocturnal enuresis			351	(7.9)
Frequent nocturnal enuresis			57	(1.3)
Records on the Maternal and Child Health Handbook				
Birth weight, g		4360	3025	412
Low birth weight infant (<2,500 g)			354	(8.1)
Children not achieved developmental milestones				
3 months	Holding their head up	4268	466	(10.9)
6 months	Rolling over	4315	362	(8.4)
	Sitting	4211	923	(21.9)
9 months	Crawling	4302	375	(8.7)
	Standing	4301	443	(10.3)
12 months	Walking with support	4239	212	(5.0)

	Understanding some words	4218	92	(2.2)
18 months	Waking independently	4341	75	(1.7)
	Speaking a few words	4332	183	(4.2)
24 months	Talking in two-word sentences	4162	358	(8.6)
36 months	Drawing a circle	4287	88	(2.1)
	Saying their name	4278	104	(2.4)

SD, standardized deviation; IQ, intelligence quotient

Table 2. Cross-tabulation between developmental delays in infancy and nocturnal enuresis at 10 years

			Nocturnal enureis at 10 years							
			None		Infrequent		Frequent			
Months	**Developmental milestones**		***n***	**(%)**	***n***	**(%)**	***n***	**(%)**	$\chi^2(2)$	*p*
3	Holding their head up	achieved	3460	(91.3)	287	(7.6)	44	(1.2)	7.4	.024*
		not achieved	410	(88.0)	45	(9.7)	11	(2.4)		
6	Rolling over	achieved	3575	(90.7)	317	(8.0)	50	(1.3)	1.6	.44
		not achieved	333	(92.0)	23	(6.4)	6	(2.7)		
	Sitting	achieved	2972	(90.7)	263	(8.0)	42	(1.3)	0.4	.83
		not achieved	841	(91.1)	69	(7.5)	13	(1.4)		
9	Crawling	achieved	3557	(90.8)	313	(8.0)	47	(1.2)	5.8	.054
		not achieved	338	(90.1)	27	(7.2)	10	(2.7)		
	Standing	achieved	3491	(90.7)	311	(8.1)	46	(1.2)	5.8	.055
		not achieved	402	(90.7)	30	(6.8)	11	(2.5)		
12	Walking with support	achieved	3649	(90.8)	322	(8.0)	46	(1.1)	21.6	<.001***
		not achieved	190	(90.0)	11	(5.2)	10	(4.7)		
	Understanding some words	achieved	3740	(90.9)	325	(7.9)	51	(1.2)	7.4	.024*
		not achieved	82	(90.1)	5	(5.5)	4	(4.4)		
18	Walking independently	achieved	3864	(90.8)	341	(8.0)	51	(1.2)	30.5	<.001***
		not achieved	67	(90.5)	1	(1.4)	6	(8.1)		
	Speaking a few words	achieved	3773	(91.2)	315	(7.6)	51	(1.2)	15.2	<.001***
		not achieved	151	(83.0)	25	(13.7)	6	(3.3)		
24	Talking in two-word sentences	achieved	3450	(90.9)	299	(7.9)	45	(1.2)	9.2	.010*
		not achieved	315	(88.2)	31	(8.7)	11	(3.1)		
36	Drawing a circle	achieved	3807	(90.9)	333	(7.9)	49	(1.2)	22.1	<.001***
		not achieved	75	(86.2)	6	(6.9)	6	(6.9)		
	Saying their name	achieved	3781	(90.8)	332	(8.0)	51	(1.2)	16.6	<.001***
		not	91	(88.3)	6	(5.8)	6	(5.8)		

		achieved	

* $p<.05$, *** $p<.001$

Table 3. Odds ratios and 95% confidence intervals for the association between development delay at 3 - 36 months and infrequent or frequent bedwetting at 10 years

			Crude model		Adjusted model	
Months	**Developmental milestones**	**Nocturnal enuresis**	OR [95% CI]	*p*	OR [95% CI]	*p*
3	Holding their head up	Infrequent	1.32 [0.95–1.84]	.10	1.31 [0.92–1.85]	.13
		Frequent	2.11 [1.08–4.12]	.029*	2.10 [1.06–4.16]	.034*
6	Rolling over	Infrequent	0.78 [0.50–1.21]	.26	0.84 [0.53–1.33]	.45
		Frequent	1.29 [0.55–3.03]	.56	1.16 [0.45–2.95]	.76
	Sitting	Infrequent	0.93 [0.70–1.22]	.59	0.85 [0.63–1.14]	.27
		Frequent	1.09 [0.58–2.05]	.78	1.13 [0.60–2.14]	.70
9	Crawling	Infrequent	0.91 [0.60–1.37]	.64	0.95 [0.62–1.45]	.80
		Frequent	2.24 [1.12–4.47]	.022*	2.11 [1.01–4.38]	.046*
	Standing	Infrequent	0.84 [0.57–1.24]	.37	0.85 [0.56–1.29]	.45
		Frequent	2.08 [1.07–4.04]	.031	1.99 [0.99–4.01]	.054
12	Walking with support	Infrequent	0.66 [0.35–1.22]	.18	0.77 [0.41–1.44]	.41
		Frequent	4.18 [2.07–8.40]	<.001***	4.01 [1.90–8.44]	<.001***
	Understanding some words	Infrequent	0.70 [0.28–1.74]	.45	0.57 [0.20–1.57]	.28
		Frequent	3.58 [1.26–10.13]	.016*	3.50 [1.21–10.09]	.021*
18	Walking independently	Infrequent	0.17 [0.02–1.22]	.078	0.20 [0.03–1.44]	.11
		Frequent	6.78 [2.82–16.35]	<.001***	5.80 [2.19–15.38]	<.001***
	Speaking a few words	Infrequent	1.98 [1.28–3.07]	.0022**	1.61 [1.01–2.56]	.045*
		Frequent	2.94 [1.24–6.96]	.014*	1.95 [0.75–5.03]	.17
24	Talking in two-word sentences	Infrequent	1.14 [0.77–1.67]	.52	0.89 [0.59–1.35]	.59
		Frequent	2.68 [1.37–5.23]	.0039**	1.92 [0.94–3.94]	.075
36	Drawing a circle	Infrequent	0.91 [0.40–	.83	0.74 [0.32–	.49

		2.12]		1.73]	
	Frequent	6.22 [2.58–14.95]	<.001***	5.00 [2.04–12.28]	<.001***
Saying their name	Infrequent	1.34 [0.91–1.96]	.13	1.25 [0.83–1.88]	.28
	Frequent	2.10 [0.96–4.61]	.063	1.50 [0.62–3.62]	.37

OR, odds ratio; CI, confidence interval; * p<.05, ** p<.01, *** p<.00

Figures

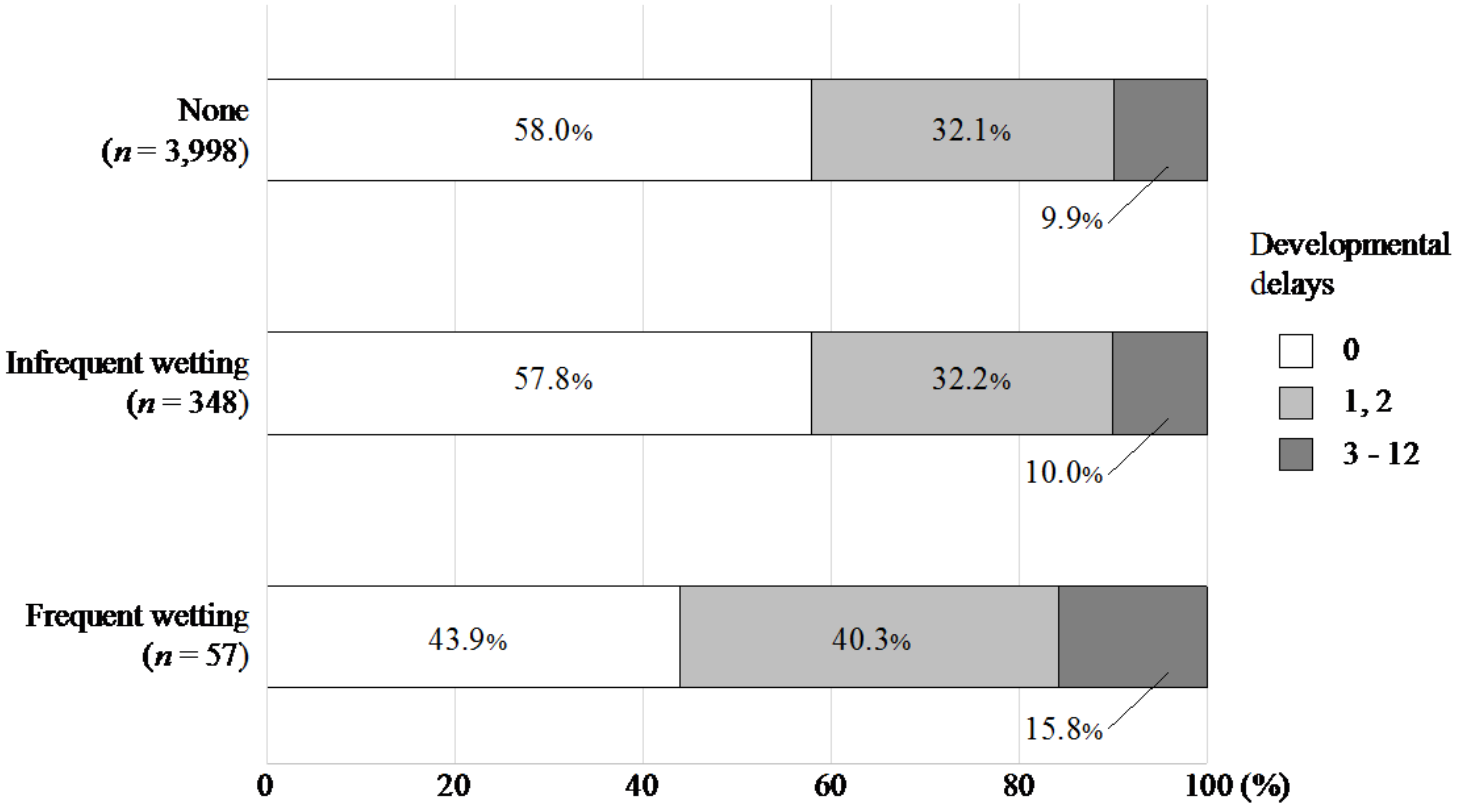

Figure 1

Distribution of the number of developmental delays according to bedwetting frequency (*N*=4,403)

The greatest number of developmental delays is observed in the Frequent wetting group. There is no difference in the distribution of the number of developmental delays between the None group and the Infrequent wetting group.