Journal of Pediatric Psychology, 41(9), 2016, 1002–1010
doi: 10.1093/jpepsy/jsw025
Advance Access Publication Date: 11 April 2016
Original Research Article

OXFORD

Stressful Events in Early Childhood and Developmental Trajectories of Bedwetting at School Age

Carol Joinson,[1] PhD, Sarah Sullivan,[1,2] PhD, Alexander von Gontard,[3] MD, PhD, and Jon Heron,[1] PhD

[1]School of Social and Community Medicine, University of Bristol, [2]Epidemiology and Health Services Research, CLAHRC West, and [3]Department of Child and Adolescent Psychiatry, Saarland University Hospital

All correspondence concerning this article should be addressed to Carol Joinson, PhD, School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Clifton BS8 2BN, Bristol. E-mail: carol.joinson@bristol.ac.uk

Received November 30, 2015; revisions received March 3, 2016; accepted March 7, 2016

Abstract

Objective To examine whether early stressful events are associated with developmental trajectories of bedwetting. **Methods** This is a prospective cohort study comprising 8,761 participants from the Avon Longitudinal Study of Parents and Children. Stressful events were measured using a maternal questionnaire completed at 3 time points before their child was 4 years old. The association between stressful events and trajectories of bedwetting from 4 to 9 years was examined using multinomial regression. **Results** The association with stressful events was strongest for the frequent persistent bedwetting trajectory (wetting at least twice a week up to age 9). A 1 standard deviation increase in the stressful events score was associated with a 29% (13–47%) increase in the odds of experiencing frequent persistent bedwetting compared with normal attainment of nighttime bladder control. **Conclusions** Clinicians and parents should be aware that continence is a developmental outcome that is associated with high levels of stress in the family.

Key words: ALSPAC; bedwetting; developmental trajectory; latent class; nocturnal enuresis; stressful life events.

Introduction

Nocturnal enuresis (bedwetting) is a common childhood disorder, and the risk is higher in boys than girls (Fergusson, Horwood, & Shannon, 1986). The etiology of bedwetting is believed to be multifactorial, involving genetic (von Gontard, Schaumburg, Hollmann, Eiberg, & Rittig, 2001), neurobiological (Jarvelin, 1989), and psychological risk factors (Joinson, Sullivan, von Gontard, & Heron, 2015). It has also been suggested that environmental factors including stressors in early childhood could play an important role in the etiology of bedwetting (Douglas, 1973). Stressors that have been examined in earlier studies include acute life events (e.g., death of parent), chronic stressors (e.g., family financial problems), normative events (e.g., birth of a sibling), and non-normative (unpredictable) stressors (e.g., parent's serious injury). Exposure to early stressful events has been found to be associated with an increased risk of bedwetting in a small case control study of 7-year-olds (Jarvelin, Moilanen, Vikeväinen-Tervonen, & Huttunen, 1990), a small longitudinal study of children followed up to age 8 years (Kaffman & Elizur, 1977) and a cross sectional study of 6–16-year-olds (Kalo & Bella, 1996). Only one early prospective cohort study has examined the effects of stressful events on risk for subsequent bedwetting (Douglas, 1973). The study found that children who were exposed to "disturbing" events (e.g., family breakdown, moving house, accidents, separation from mother) in the first

4 years of life (especially at age 3–4 years) had an increased prevalence of bedwetting up to age 15 years. Children exposed to four or more disturbing events had around double the risk of experiencing bedwetting than those not exposed to such events (Douglas, 1973).

A limitation of earlier studies is that they examined only the presence or absence of bedwetting and did not take into account the heterogeneity in development of continence during childhood. There is now evidence for distinct patterns (longitudinal phenotypes) of development of nighttime bladder control during childhood that are characterized by normative development, delayed attainment, persistent bedwetting, or relapses (Croudace, Jarvelin, Wadsworth, & Jones, 2003; Joinson et al., 2009; Sullivan, Joinson, & Heron, 2015). No studies have examined whether these different patterns of incontinence in childhood are differentially associated with early stressful events. Another limitation of earlier studies is the lack of adjustment for a range of potential confounders that might explain the association between stressful events and bedwetting.

We use data from a large UK cohort to examine whether stressful events in early childhood are associated with bedwetting at school age. Different patterns (latent classes) of typical and atypical development of nighttime bladder control have been previously identified using longitudinal data derived from parental reports of frequency of bedwetting at ages 4–9 years in almost 11,000 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (Sullivan et al, 2015). In this article, we use these latent classes to examine whether exposure to stressful events in the first 4 years of life is associated with an increased risk of bedwetting at 4–9 years.

Methods

Participants

The sample comprised participants from the ALSPAC. Detailed information about ALSPAC is available on the study Web site (http://www.bristol.ac.uk/alspac), which includes a fully searchable dictionary of available data (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). Pregnant women resident in the former Avon Health Authority in southwest England, having an estimated date of delivery between April 1, 1991 and December 31, 1992 were invited to take part, resulting in a cohort of 14,541 pregnancies and 13,973 singletons/twins (7,217 boys and 6,756 girls) alive at 12 months (Boyd et al., 2013). Ethical approval for the study was obtained from the ALSPAC Law and Ethics committee and local research ethics committees. Written informed consent was obtained after the procedure(s) had been fully explained.

Exposure: Stressful Events in Early Childhood

Stressful events were measured using a maternally reported questionnaire comprising 42 life events (see Supplementary Appendix) that was derived for ALSPAC using previous inventories as a basis for item selection (Barnett, Hanna, & Parker, 1983; Brown and Harris, 1978). Mothers completed the questionnaire at three time points when the study children were approximately 1 year 9 months, 2 years 9 months, and 3 years 11 months. At the first time point mothers were asked, "Have any of these (*life events*) occurred since the baby was 8 months old?"; at the second time point, "Have any of these occurred since the study child was 18 months old?"; and at the third time point, "Have any of these occurred since the study child was $2^1/_2$ years old?". This allowed us to examine exposure to stressful life events in three time periods: 8 months to approximately 1 year 9 months; 18 months to approximately 2 years 9 months; and $2^1/_2$ years to approximately 3 years 11 months.

Outcome: Latent Classes of Bedwetting

At ages $4^1/_2$, $5^1/_2$, $6^1/_2$, $7^1/_2$, and $9^1/_2$ years (hereafter referred to as 4–9 years), parents were asked, "How often usually does your child wet the bed?" and were given the options "never"; "less than once a week"; "about once a week"; "2–5 times a week"; "nearly every night"; "more than once a night." Latent classes of bedwetting were previously derived by collapsing the bedwetting frequency data at each time point into three-level ordinal variables indicating no current bedwetting, infrequent bedwetting (less than once a week or about once a week) and frequent bedwetting (two to five times a week, nearly every night, or more than once a night). The latter category corresponds to the frequency of bedwetting required for a DSM-V diagnosis of nocturnal enuresis. Full details of the derivation of the latent classes are in (Sullivan et al., 2015).

The latent classes describe typical and atypical development of nighttime bladder control: "*normative development*" (71.5% of the sample)—low probability of bedwetting at any time point; "*infrequent delayed*" (14.3%)—delayed attainment of nighttime bladder control and decreasing probability of infrequent bedwetting from 4 to 9 years; "*infrequent persistent*" (8.6%)—relatively high probability of infrequent bedwetting from 4 to 9 years; "*frequent delayed*" (2.4%)—high probability of frequent bedwetting at age 4 years, which decreased and became more infrequent at 6–9 years; "*frequent persistent*" (3.2%)—relatively high probability of bedwetting at least twice a week from 4 to 9 years.

Potential Confounders

We adjusted for potential confounders that are reported in the empirical literature to be risk factors for stressful life events and bedwetting. These included a range of socio-demographic measures and maternal depression. The socio-demographic measures were derived from responses to a questionnaire, completed by mothers during the antenatal period, containing items on socioeconomic position and adversity. Binary variables were generated from these questions and each item was scored as 1 if an adversity was present and 0 if not. The items included social class based on the lower of the mother or partner's occupational social class using the 1991 British Office of Population and Census Statistics classification and dichotomized into non-manual (professional, managerial, or skilled professions) and manual (partly or unskilled occupations); early parenthood (<19 years vs. >=19 years), housing adequacy (yes/no—comprising crowding, periods of homelessness, living conditions, major defects/infestation), maternal education (defined as none vs. high school qualifications or greater), major financial difficulties (yes/no), family size (less than three children vs. >=more than or equal to three children), and the presence of a social network (yes/no—comprising emotional support, practical/financial support). We adjusted for maternal depression using the Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987), which was completed by mothers when their study child was 8 months old. The EPDS was dichotomized at the standard cutoff (score-> 12) used to indicate probable depressive disorder (Evans et al., 2001).

We also adjusted for gender and a maternal rating of the child's developmental level at 18 months, which was assessed using a questionnaire developed by ALSPAC including items from the Denver Developmental Screening Test (Frankenburg, Dodds, Archer, Shapiro, & Bresnick, 1992). The questionnaire assesses four domains of development (fine motor, gross motor, communication, and social skills) and scores on each domain were adjusted for age in weeks, standardized (using a linear regression model and extracting the residuals), and reversed where appropriate so that high values on all scores reflected a lower level of development. We used a total development score derived from the sum of the scores on each domain.

Statistical Modeling

We generated a total life events score for each time period by adding all events (presence of life event = 1, absence = 0) and then standardized the score to allow us to interpret the change in odds of membership to the bedwetting latent classes per standard deviation (*SD*) increase in life events score. We estimated the association between stressful events and membership of the bedwetting latent classes using a series of univariable multinomial logistic regression models and employing the normative latent class as the reference category. Models were then adjusted for the confounders described above. Parameter estimates were obtained using the "Modal ML" three-step method (Vermunt, 2010) implemented in Mplus. This has been shown to produce less-biased estimates than traditional three-step methods such as probability weighting, while avoiding the problem of covariates impacting on the measurement model itself (Asparouhov & Muthen, 2013). Bias-adjusted estimates were obtained using the Mplus "auxiliary (r3step)" command.

Results

Bedwetting data were available for 10,810 children on at least one measurement occasion. Of these, 8,761 had data from at least three time points and 5,849 had complete data. The proportion of children with bedwetting decreased over time and proportions did not change markedly when the sample was restricted to participants with more data (Sullivan et al., 2015). For the analyses presented here, we focused on the sample with bedwetting data available from at least three time points ($n = 8{,}761$). Conclusions were consistent for the other two samples described earlier (available on request). While the sample with complete bedwetting data had the lowest rates of socioeconomic disadvantage, there was little variation in the other confounders and the risk factors across samples (Table I).

Association Between Stressful Events and Bedwetting Latent Classes

Table II presents the results of the analysis examining the associations between stressful events experienced in three time periods and latent class membership. Odds ratios were derived in relation to the normative latent class of nighttime bladder control, which was used as the reference category in this analysis. The results show the increase in odds of membership to each latent class per 1 *SD* increase in the stressful events score. There was evidence that stressful events occurring in the first two time periods were associated with membership of the infrequent delayed, infrequent persistent, and frequent persistent classes, but not the frequent delayed class. For instance, in the unadjusted model a 1 *SD* increase in the stressful events score for the first time period was associated with a 29% (13–47%) increase in the odds of belonging to the frequent persistent class compared with the normative class. Adjustment for confounders led to a small attenuation of these effects, but there was still evidence that

Table I. Means and Proportions of Risk Factors and Confounders in the Three Samples Considered for the Analysis

Risk factors and confounders	Complete data ($n = 5{,}489$)	Partially missing data ($n = 8{,}761$)	At least one bedwetting measure ($n = 10{,}810$)
Mean (SD) for stressful events score in each time period			
8 months to ~1 year 9 months	4.40 (2.81)	4.45 (2.87)	4.48 (2.93)
18 months to ~2 years 9 months	4.87 (2.97)	4.92 (3.03)	4.96 (3.10)
2½ years to ~3 years 11 months	4.56 (3.10)	4.61 (3.16)	4.66 (3.22)
Confounders			
Gender (male)	2,959 (50.6%)	4,508 (51.46%)	5,580 (51.6%)
Maturational level (mean total score at 18 months)	37.72 (5.5)	37.73 (5.6)	37.74 (5.7)
Socioeconomic variables			
Manual social class	705 (12.8%)	1,238 (15.4%)	1,661 (17.3%)
Early parenthood <20 years	213 (3.64%)	419 (4.8%)	648 (6.0%)
Housing inadequacy	408 (7.1%)	748 (8.6%)	982 (9.3%)
Low maternal education	580 (10.0%)	995 (11.6%)	1,342 (12.9%)
Financial difficulties	803 (13.9%)	1,297 (15.1%)	1,653 (16.0%)
Family size ≥ 3	251 (4.3%)	424 (4.9%)	600 (5.8%)
Poor social network	716 (12.3%)	1,129 (13.0%)	1,433 (13.6%)
Maternal depression (mean EPDS score at 8 months)	3.18 (2.89)	3.27 (2.95)	3.31 (2.99)

Note. Actual number with available data on each risk factor varies in each of the samples shown here. Manual social class includes manual and part/unskilled.

stressful events were associated with increased odds of membership to these classes. Odds ratios were generally highest for the frequent persistent class in the adjusted models, for example, a 1 *SD* increase in the stressful events score for the first time period was associated with a 27% (10–47%) increase in the odds of belonging to the frequent persistent class compared with the normative class in the adjusted model. Stressful events at the latest time period were only associated with increased odds of membership to the frequent persistent class. For example, a 1 *SD* increase in the stressful events score was associated with a 30% (11–52%) increase in the odds of belonging to the frequent persistent class compared with the normative class.

Discussion

Most children are expected to attain nighttime bladder control by 4–6 years (Fergusson et al., 1986). We find evidence that the risk of experiencing problems attaining bladder control at 4–9 years is greater if the child is exposed to stressful events in early childhood. These results are consistent with previous studies reporting a link between early stressful events and bedwetting (Douglas, 1973; Jarvelin et al., 1990; Kaffman & Elizur, 1977; Kalo & Bella, 1996). This, however, is the first prospective study to examine whether early stress is associated with distinct patterns of atypical development of nighttime bladder control. Our findings were mostly in agreement with a dose response relationship, in which increasing levels of exposure to early stress were associated with increasing severity (frequency and persistence) of bedwetting. We did not find evidence for distinct etiologies for the latent classes. It is possible that distinct risk factors would emerge if we further refined our bedwetting classes by incorporating additional symptom information such as concurrent daytime wetting and indicators of bladder dysfunction.

Strengths and Limitations

The study is based on a large contemporary cohort and takes advantage of repeated measures of frequency of bedwetting and the availability of a range of confounders. We have extended previous work by using developmental trajectories of frequency of bedwetting throughout childhood as our outcomes rather than simply the presence or absence of bedwetting at a particular age.

We did not examine the effect of specific life events, nor did we distinguish between life events that are acute (e.g., death of parent) versus more chronic in nature (e.g., financial problems) or between normative stressors (e.g., marriage, pregnancy) and non-normative (unpredictable) stressors (e.g. accidents). Some studies have found evidence that single events, especially parental divorce or separation, are particularly important risk factors for enuresis (Jarvelin et al., 1990; Kaffman & Elizur, 1977). We additionally examined single stressful events (e.g., divorce and separation), but we did not find individual associations with bedwetting (available on request). It is difficult to isolate the effect of single stressful events because they are often interrelated (e.g., parental divorce/separation may be related to financial problems). Consistent with

Table II. Odds Ratios and 95% Confidence Intervals for the Association Between Stressful Events and Latent Class Membership

Stressful events	*N*	Class			
		Infrequent delayed	Infrequent persistent	Frequent delayed	Frequent persistent
Stressful events					
8 months to ~1 year 9 months					
Unadjusted	8,193	1.14 (1.04, 1.26) $p = .008$	1.21 (1.10, 1.32) $p < .001$	0.99 (0.81, 1.20) $p = .911$	1.29 (1.13, 1.47) $p < .001$
Adjusted 1: Gender, developmental level	7,827	1.15 (1.04, 1.28) $p = .006$	1.21 (1.10, 1.33) $p < .001$	0.99 (0.81, 1.20) $p = .923$	1.30 (1.14, 1.49) $p < .001$
Adjusted 2: Socio-demographic factors	7,266	1.14 (1.02, 1.28) $p = .017$	1.18 (1.07, 1.31) $p = .001$	0.98 (0.79, 1.21) $p = .815$	1.31 (1.14, 1.50) $p < .001$
Adjusted 3: Maternal depression	7,025	1.12 (1.00, 1.25) $p = .042$	1.16 (1.04, 1.30) $p = .007$	0.96 (0.77, 1.18) $p = .689$	1.27 (1.10, 1.47) $p = .001$
18 months to ~2 years 9 months					
Unadjusted	7,635	1.17 (1.07, 1.28) $p = .001$	1.18 (1.08, 1.30) $p < .001$	0.97 (0.79, 1.18) $p = .732$	1.19 (1.02, 1.38) $p = .032$
Adjusted 1: Gender, developmental level	7,266	1.17 (1.06, 1.29) $p = .002$	1.21 (1.09, 1.33) $p < .001$	0.97 (0.79, 1.19) $p = .784$	1.20 (1.03, 1.40) $p = .019$
Adjusted 2: Socio-demographic factors	6,735	1.18 (1.06, 1.31) $p = .002$	1.21 (1.09, 1.34) $p < .001$	1.00 (0.80, 1.25) $p = .998$	1.22 (1.04, 1.43) $p = .012$
Adjusted 3: Maternal depression	6,519	1.17 (1.05, 1.30) $p = .004$	1.20 (1.08, 1.33) $p = .001$	0.98 (0.79, 1.21) $p = .819$	1.21 (1.03, 1.42) $p = .024$
2½ years to ~3 years 11 months					
Unadjusted	8,196	1.08 (0.98, 1.18) $p = .111$	1.10 (1.00, 1.21) $p = .049$	0.84 (0.69, 1.03) $p = .089$	1.25 (1.10, 1.43) $p = .001$
Adjusted 1: Gender, developmental level	7,749	1.09 (0.99, 1.20) $p = .067$	1.12 (1.01, 1.24) $p = .028$	0.88 (0.72, 1.08) $p = .223$	1.29 (0.99, 1.67) $p < .001$
Adjusted 2: Socio-demographic factors	7,138	1.12 (1.01, 1.24) $p = .033$	1.10 (0.99, 1.22) $p = .069$	0.87 (0.70, 1.08) $p = .193$	1.33 (1.14, 1.54) $p < .001$
Adjusted 3: Maternal depression	6,900	1.10 (0.99, 1.22) $p = .083$	1.08 (0.97, 1.20) $p = .169$	0.85 (0.69, 1.06) $p = .153$	1.30 (1.11, 1.52) $p = .001$

Adjusted 1: Gender, developmental level at 18 months (total development score derived from the sum of the scores on each domain).

Adjusted 2: Social class (manual vs. nonmanual), early parenthood (<19 years vs. ≥ 19 years), housing adequacy (yes/no), maternal education (none vs. high school qualifications or greater), major financial difficulties (yes/no), family size (less than three children vs. More than or equal to three children), presence of a social network (yes/no).

Adjusted 3: Maternal depression—Edinburgh Postnatal Depression Scale score at 8 months.

the early prospective study (Douglas, 1973), we find that it is the total burden of exposure to stressful events during early childhood, rather than any single event, that is important in determining risk for subsequent bedwetting.

In agreement with earlier studies examining stressful life events, we generated a total life events score for each time period by adding all events (Araya et al., 2009). This differs to the approach taken by Jarvelin et al. (1990), who weighted the life events according to the parents' perceived "seriousness" of the event. There is evidence that appraisals of the negative impact of life events are systematically elevated in individuals with depression (Espejo, Hammen, & Brennan, 2012). A mother's own subjective appraisal of the impact of a life event may not reflect the child's own experience of the impact.

In this article, we focused on exposure to stressful life events in early childhood and we did not examine the effects of more proximal stressors on risk for bedwetting. There is evidence that proximal exposure to stressful life events increases the risk of secondary enuresis (relapse in bedwetting after a period of at least 6 months' dryness; Fergusson, Horwood, & Shannon, 1990; Jarvelin et al., 1990). There is also a possibility that the association between stress and bedwetting is bidirectional. The occurrence of bedwetting after the age at which most children would be expected to be dry at night can often lead to increased levels of stress in the family. Intolerance and punishment are not uncommon among parents of children with incontinence (Butler & McKenna, 2002) and such reactions could increase stress in the child, resulting in further episodes of bedwetting.

Potential Mechanisms Explaining the Link Between Stressful Events and Bedwetting

Bedwetting is conceptualized as a "biobehavioral" problem (Houts, 1991) with biological, behavioral, and psychosocial factors contributing to the etiology. The age of 2–4 years is believed to be a sensitive period for learning bladder control (Douglas, 1973; Jarvelin et al., 1990; MacKeith, 1968). It is possible that parents experiencing high levels of stress may have less time and sensitivity to cope with the demands of toilet training (Jarvelin et al., 1990), and this could adversely affect their child's transition to continence. There is evidence that delayed or inadequate toilet training is associated with an increased risk of bladder dysfunction (e.g., urgency, urge incontinence, emptying difficulties, bladder instability, and/or dyscoordinated micturition; Bakker & Wyndaele, 2000; Hellstrom, 2000; Hodges, Richards, Gorbachinsky, & Krane, 2014). Bladder dysfunction is not only a contributing factor for daytime wetting, but it is also associated with bedwetting (Franco, von Gontard, & DeGennaro, 2013; Nevéus et al., 2000). There is also evidence that the stress hormone cortisol suppresses the release of antidiuretic hormone (Bähr, Franzen, Oelkers, Pfeiffer, and Diederich, 2006), a lack of which leads to polyuria (increased volume of urine in the bladder; Aikawa, Kasahara, Uchiyama, 1998).

It is notable that higher levels of stressful events at the latest time point (up to around age 4 years) were associated with the frequent persistent class, but not the infrequent bedwetting classes. There is evidence that during the period of transition to bladder control, the risk of developing continence problems may be greater if the transition period is prolonged and if the child is older (Hellstrom, 2000). Later initiation of toilet training could prolong the child's exposure to potential stressors and this could interfere with the process of learning bladder control. We examined whether toilet training was initiated later (after 24 months) among children in the frequent persistent class compared with the infrequent bedwetting classes. The proportions with later initiation of toilet training were 42.2% in the frequent persistent class compared with 36.8% in the infrequent delayed class and 41.2% in the infrequent persistent class. To properly examine this, we would need to further refine the late initiation group to identify those with toilet training initiated after 2½ years, after 3 years, and beyond, but the data did not permit this.

There was a relative lack of evidence for associations between the risk factors and the frequent delayed class. This might be owing to this being the smallest class, leading to larger standard errors and hence, a lack of precision in our estimates of the effect of the risk factors on membership to this class. Alternatively, it is possible that this pattern of wetting has a slightly different etiology. Three central nervous system (CNS) factors are believed to contribute to the development of enuresis: nocturnal polyuria (production of abnormally large amounts of urine at night), a lack of arousal, and a lack of inhibition of the emptying reflex of the bladder during sleep (von Gontard & Neveus, 2006). Overall, bedwetting has a spontaneous remission rate of approximately 15% per year (Forsythe & Redmond, 1974). In the delayed classes, this rate is lower, that is, children take a longer time to achieve continence. It could be speculated that this is a less severe condition (characterized by a maturational delay) in contrast to the persistent classes (characterized by a maturational disorder). With increasing maturational development, children in the frequent delayed class would be expected to progressively attain improved bladder stability, increased CNS recognition of bladder fullness, and the ability to suppress bladder contractions (Watanabe & Azuma, 1989). Children are more easy to arouse with increasing maturity (Busby, Mercier, & Pivik, 1994), and lack of

arousal is one of the possible pathophysiological aspects of nocturnal enuresis (Koff, 1996; Wolfish, Pivik, & Busby, 1997). From a clinical perspective, this developmental delay would be expected to resolve over time and these children would eventually attain nighttime continence, albeit at a later age than their typically developing peers.

It is possible that the effects of stressors could be mediated through comorbid behavioral and emotional problems. Although some earlier studies (many based on small samples) find no increased rates of psychological problems in children who wet the bed, there is now a wide and growing literature providing evidence that children with bedwetting have higher levels of both internalizing (e.g., depression and anxiety) and externalizing symptoms (e.g., attention/activity and conduct problems) (Joinson, Heron, Emond, & Butler, 2007). Stressors not only increase the risk for relapses in bedwetting (see von Gontard, Baeyens, Van Hoecke, Warzak, & Bachmann, 2011a for a review), but also the risk of psychological disorders in children (Harland et al., 2002). These, in turn, could be responsible for the persistence of enuresis. A review paper cites evidence linking psychological distress to bladder dysfunction (Cortes, Sahai, Pontari, & Kelleher, 2012). The authors suggest that this link may be owing to alterations in neurotransmitters having direct or indirect effects on bladder function.

Gene–environment interactions also need to be considered. Previous analyses of the ALSPAC cohort have demonstrated that the risk for bedwetting is significantly increased if parents were also affected by enuresis (von Gontard, Heron, & Joinson, 2011b). With a heritability of 0.7, bedwetting is a highly genetically determined disorder (von Gontard et al., 2001). This genetic risk is present in all types of enuresis and can be modulated and activated by stressors (von Gontard et al., 2001).

Conclusions

There is well-established evidence that early exposure to stress interferes with brain development and is associated with a range of adverse developmental and health outcomes (Shonkoff & Garner, 2012). Our findings add to the evidence that continence is a developmental outcome that is associated with exposure to high levels of stress in the family. Family stress has also been found to be an important prognostic factor in the treatment of enuresis among children referred to a community-based enuresis clinic (Devlin & O'Cathain, 1990). Health practitioners have a role to play in identifying families experiencing high levels of stress and directing them to appropriate sources of support. There is a need to educate parents about the long-term consequences of stress and the potential benefits of preventing or reducing sources of stress in early childhood (Garner & Shonkoff, 2012). Families at high risk of stress should be offered anticipatory guidance, especially for sensitive developmental transition periods such as toilet training, because they may find the demands even more challenging. Provision of support to families under stress could help parents navigate sensitive transitions in child development and promote healthy development during the early years.

Supplementary Data

Supplementary data can be found at: http://www.jpepsy.oxfordjournals.org/.

Acknowledgments

This study is based on the ALSPAC. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, and nurses. The UK Medical Research Council, the Wellcome Trust (grant reference: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC.

Funding

This research was specifically funded by a grant from the Medical Research Council (Increasing understanding of risk factors and outcomes associated with continence problems in children and adolescents. MRC reference: MR/L007231/1).
Conflicts of interest: None declared.

References

Aikawa, T., Kasahara, T., & Uchiyama, M. (1998). The arginine–vasopressin section profile of children with primary nighttime enuresis. *European Urology, 33*, 41–44.

Araya, R., Hu, X., Heron, J., Enoch, M. A., Evans, J., Lewis, G., & Nutt, D. (2009). Effects of stressful life events, maternal depression and 5-HTTLPR genotype on emotional symptoms in pre-adolescent children. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 150*, 670–682.

Asparouhov, T., & Muthen B. O. (2013). Auxiliary variables in mixture modeling: 3-step approaches using Mplus. *Mplus Web Notes: No 15*. Retrieved from http://www.statmodel.com/examples/webnotes/webnote15.pdf. Retrieved 19 May 2015.

Bähr, V., Franzen, N., Oelkers, W., Pfeiffer, A. F. and Diederich, S. (2006). Effect of exogenous glucocorticoid on osmotically stimulated antidiuretic hormone secretion and on water reabsorption in man. *European Journal of Endocrinology, 155*, 845–848.

Bakker, E., & Wyndaele, J. J. (2000). Changes in the toilet training of children during the last 60 years: The cause of an increase in lower urinary tract dysfunction?. *BJU International*, *86*, 248–252.

Barnett, B. E., Hanna, B., & Parker, G. (1983). Life event scales for obstetric groups. *Journal of Psychosomatic Research, 27*, 313–320.

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., … Davey Smith, G. (2013). Cohort profile: The 'Children of the 90s'–the index offspring of the Avon Longitudinal Study of Parents and Children. International Journal of *Epidemiology*, *42*, 111–127.

Brown, G. W., & Harris, T. (1978). *Social origins of depression: A study of psychiatric disorder in women*. London: Tavistock.

Busby, K. A., Mercier, L., & Pivik, R. T. (1994). Ontogenetic variations in auditory arousal threshold during sleep. *Psychophysiology*, *31*, 182–188.

Butler, R. J., & McKenna, S. (2002). Overcoming parental intolerance in childhood nocturnal enuresis: A survey of professional opinion. *BJU International, 89*, 295–297.

Cortes, E., Sahai, A., Pontari, M., & Kelleher, C. (2012). The psychology of LUTS: ICI-RS 2011. *Neurourology and Urodynamics*, *31*, 340–343.

Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry, 150*, 782–786.

Croudace, T. J., Jarvelin, M. R., Wadsworth, M. E., & Jones, P. B. (2003). Developmental typology of trajectories to nighttime bladder control: Epidemiologic application of longitudinal latent class analysis. *American Journal of Epidemiology, 157*, 834–842.

Devlin, J. B., & O'Cathain, C. (1990). Predicting treatment outcome in nocturnal enuresis. *Archives of Disease in Childhood, 65*, 1158–1161.

Douglas, J. W. B. (1973). Early disturbing events and later enuresis. In I. Kolvin, R. C. MacKeith, & S. R. Meadow (Eds.), *Bladder control and enuresis* (pp. 109–117). London: William Heinemann Medical Books.

Espejo, E. P., Hammen, C., & Brennan, P. A. (2012). Elevated appraisals of the negative impact of naturally occurring life events: A risk factor for depressive and anxiety disorders. *Journal of Abnormal Child Psychology, 40*, 303–315.

Evans, J., Heron, J., Francomb, H., Oke, S., & Golding, J.; ALSPAC Study Team. (2001). Cohort study of depressed mood during pregnancy and after childbirth. *British Medical Journal, 323*, 257–260.

Fergusson, D. M., Horwood, L. J., & Shannon, F. T. (1986). Factors related to the age of attainment of nighttime bladder control: An 8-year longitudinal study. *Pediatrics*, *78*, 884–890.

Fergusson, D. M., Horwood, L. J., & Shannon F.T. *(1990)*. Secondary enuresis in a birth cohort of New Zealand children. *Paediatric and Perinatal Epidemiology*, *4*, 53–63.

Forsythe, W. I., & Redmond, A. (1974). Enuresis and spontaneous cure rate: Study of 1129 enuretics. *Archives of Disease in Childhood, 49*, 259–263.

Franco, I., von Gontard, A., & DeGennaro, M. (2013). Evaluation and treatment of nonmonosymptomatic nocturnal enuresis: A standardization document from the International Children's Continence Society. *Journal of Pediatric Urology, 9*, 234–243.

Frankenburg, W. K., Dodds, J., Archer, P., Shapiro, H., & Bresnick, B. (1992). The Denver II: A major revision and restandardization of the Denver Developmental Screening Test. *Pediatrics, 89*, 91–97.

Garner, A. S., & Shonkoff, J. P. (2012). Early childhood adversity, toxic stress, and the role of the pediatrician: Translating developmental science into lifelong health. *Pediatrics, 129*, e224–e231.

Harland, P., Reijneveld, S. A., Brugman, E., Verloove-Vanhorick, S. P., & Verhulst, F. C. (2002). Family factors and life events as risk factors for behavioural and emotional problems in children. *European Child & Adolescent Psychiatry*, *11*, 176–184.

Hellstrom, A. L. (2000). Influence of potty training habits on dysfunctional bladder in children. *Lancet, 356*, 1787.

Hodges, S. J., Richards, K. A., Gorbachinsky, I., & Krane, L. S. (2014). The association of age of toilet training and dysfunctional voiding. *Research and Reports in Urology*, *6*, 127–130.

Houts, A. C. (1991). Nighttime enuresis as a bio-behavioural problem. *Behaviour Therapy*, *22*, 133–151.

Jarvelin, M. R. (1989). Developmental history and neurological findings in enuretic children. Developmental Medicine and Child *Neurology*, *31*, 728–736.

Jarvelin, M. R., Moilanen, I., Vikeväinen-Tervonen, L., & Huttunen, N. P. (1990). Life changes and protective capacities in enuretic and non-enuretic children. *Journal of Child Psychology and Psychiatry, 31*, 763–774.

Joinson, C., Heron, J., Butler, R., & Croudace, T. (2009). Development of nighttime bladder control from 4 – 9 years: Association with dimensions of parent rated child maturational level, child temperament and maternal psychopathology. *Longitudinal and Life Course Studies, 1*, 73–94.

Joinson, C., Heron, J., Emond, A., & Butler, R.; ALSPAC Study Team. (2007). Psychological problems in children with bedwetting and combined (day and night) wetting: A UK population-based study. *Journal of Pediatric Psychology, 32*, 605–616.

Joinson, C., Sullivan, S., von Gontard, A., & Heron, J. (2015). Early childhood psychological factors and risk for bedwetting at school age in a UK cohort. *Eur Child Adolesc Psychiatry*. [Epub ahead of print].

Kaffman, M., & Elizur, E. (1977). Infants who became enuretics: A longitudinal study of 161 kibbutz children. *Monographs of the Society for Research in Child Development, 42*, 1–61.

Kalo, B. B., & Bella, H. (1996). Enuresis: Prevalence and associated factors among primary school children in Saudi Arabia. *Acta Paediatrica, 85*, 1217–1222.

Koff, S. A. (1996). Cure of nocturnal enuresis: Why isn't desmopressin very effective? *Pediatric Nephrology, 10*, 667–670.

MacKeith, R. C. (1968). A frequent factor in origins of primary nocturnal enuresis: Anxiety in the third year of life. *Developmental Medicine and Child Neurology*, *10*, 465–470.

Nevéus, T., Läckgren, G., Tuvemo, T., Hetta, J., Hjälmås, K., & Stenberg, A. (2000). Enuresis–background and treatment. *Scandinavian Journal Of Urology and Nephrology. Supplementum*, *206*, 1–44.

Shonkoff, J. P., & Garner, A. S.; Committee on Psychosocial Aspects of Child, Family Health; Committee on Early Childhood, Adoption, Dependent Care; Section on Developmental and Behavioral Pediatrics. (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics, 129*, e232–e246.

Sullivan, S., Joinson, C., & Heron, J. (2015). Factors predicting atypical development of nighttime bladder control: A prospective cohort study. *Journal of Developmental and Behavioral Pediatrics, 36*, 724–733.

Vermunt, J. K. (2010). Latent class modeling with covariates: Two improved three-step approaches. *Political Analysis, 18*, 450–469.

von Gontard, A., Baeyens, D., Van Hoecke, E., Warzak, W. J., & Bachmann, C. (2011a). Psychological and psychiatric issues in urinary and fecal incontinence. *The Journal of Urology, 185*, 1432–1436.

von Gontard, A., Heron, J., & Joinson, C. (2011b). Family history of nocturnal enuresis and urinary incontinence – Results from a large epidemiological study. *The Journal of Urology, 185*, 2303–2307.

von Gontard, A., & Neveus, T. (2006). *Management of disorders of bladder and bowel control in childhood*. London: MacKeith Press.

von Gontard, A., Schaumburg, H., Hollmann, E., Eiberg, H., & Rittig, S. (2001). The genetics of enuresis – A review. *The Journal of Urology, 166*, 2438–2443.

Watanabe, H., & Azuma, Y. (1989). A proposal for a classification system of enuresis based on overnight simultaneous monitoring of electroencephalography and cystometry. *Sleep*, *12*, 257–64.

Wolfish, N. M., Pivik, R. T., & Busby, K. A. (1997). Elevated sleep arousal thresholds in enuretic boys: Clinical implications. *Acta Paediatrica*, *86*, 381–384.