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ORIGINAL CONTRIBUTION

Stressful events and psychological difficulties: testing alternative candidates for sensitivity

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Abstract The current study investigated the longitudinal, reciprocal associations between stressful events and psychological difficulties from early childhood to mid-adolescence. Child age, sex, prenatal maternal anxiety, and difficult temperament were tested as sources of sensitivity, that is, factors that may make children more sensitive to stressful life events. Analyses were based on data from 10,417 children from a prospective, longitudinal study of child development. At ages 4, 7, 9, 11, and 16 years, stressful events and psychological difficulties were measured. Prenatal anxiety was measured at 32 weeks of gestation and difficult temperament was measured at 6 months. Children exposed to stressful events showed significantly increased psychological difficulties at ages 7 and 11 years; there was consistent evidence of a reciprocal pattern: psychological difficulties predicted stressful events at each stage. Analyses also indicated that the associations between stressful events and psychological difficulties were stronger in girls than in boys. We found no evidence for the hypothesis that prenatal anxiety or difficult temperament increased stress sensitivity, that is, moderated the link between life events and psychological difficulties. The findings extend prior work on stress exposure and psychological difficulties and highlight the need for additional research to investigate sources of sensitivity and the mechanisms that might underlie differences in sensitivity to stressful events.

Keywords Stressful events · Psychological difficulties · Sensitivity · ALSPAC · Prenatal anxiety

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Introduction

Exposure to stress has been related to a heightened vulnerability to the development of later psychopathology [1–3]. For example, Kendler and colleagues provided evidence that stressful life events had a substantial causal relationship with the onset of episodes of major depression [2]. However, not everyone exposed to stressful events will develop behavioural or mental problems. In the current paper we examine several possible sources of variation in the link between stressful events and psychological difficulties in a large longitudinal cohort study. In line with the idea that individuals differ in sensitivity to their environment, we test the hypothesis that the association between stressful events and psychological difficulties is moderated by child age, sex, prenatal stress exposure, and difficult temperament.

Stressful life events and children's psychological difficulties

Several theoretical frameworks have proposed alternative mechanisms that may account for the presumed individual

differences that moderate the effects of stress on psychological well-being. For example, risk exposures may accumulate and amplify the impact of (subsequent) stress on 'sensitive individuals' (the 'diathesis stress/dual risk' theory [4]). Recent research has suggested that, in addition to suffering more from an adverse environment, sensitive or susceptible children may also benefit relatively more from a positive environment (the 'differential susceptibility' and 'biological sensitivity to context' theory [5–7]). For example, using a randomised controlled trial, Scott and O'Connor [8] showed that children who exhibited emotionally dysregulated behaviour pre-treatment were more responsive to improvements in parental care that were experimentally induced. These models imply that individual characteristics can moderate the association between environmental influences and child outcomes, making certain children more sensitive than others, probably for better and certainly for worse. Nonetheless, debate remains about the factors that might moderate the link between stress and well-being and the robustness of this effect.

The developmental process that we focus on in this study is the link between stress and psychological difficulties. This is a natural target for studies of developmental sensitivity because it has a long history in developmental science [9]. The current study adds to the existing literature by using five occasions of measurement, from preschool age to mid-adolescence. Moreover, the longitudinal design allowed us to examine the reciprocal associations between stress exposure and psychological difficulties. Although this has hardly been studied so far, studying reciprocal associations is significant because there is some evidence that depressive symptoms may evoke stressful conditions and events rather than the other way around [2, 10, 11]. For example, Kendler et al. [2] showed that about one-third of the association between stressful events and onsets of depression was non-causal, suggesting that individuals predisposed to major depression select themselves into high-risk environments. Consequently, it seems plausible that influences between stress exposure and behavioural and emotional difficulties can also be bidirectional. Accordingly, we will model the reciprocal relations between stressful events and psychological difficulties using a cross-lagged approach.

Factors moderating the link between stressful events and psychological difficulties in children

Several factors have been identified that may moderate the link between stressful life events and psychological difficulties [12, 13]. The proposed study adds to the growing literature on individual differences in sensitivity to stress in several ways. First, we adopt a longitudinal design, a feature that has been missing in most studies in this area. Second, we consider several alternative sources of individual sensitivity: age, sex, prenatal maternal anxiety, and temperament.

Age as a source of sensitivity

The extent to which there are developmental changes in an individual's sensitivity to environmental exposures such as stress is a major area of research interest, but questions remain about when in development children may be most sensitive to their environment [14]. One hypothesis is that early life is a period of greatest sensitivity because the infant brain is most adversely affected by the psychological/biological effects of stress and that these effects are carried forward in development [15–17].

Alternatively, specific brain regions might have their own particular sensitive periods to the effects of stress [15, 16, 18]; that is, sensitivity may not be a linear, monotonic feature of development. For example, adolescence may also be a sensitive period because of anatomical and neurohormonal changes during these years [19]. Indeed, evidence has been found for increased biological sensitivity to stress during adolescence, both in the brain [20] and with regard to physiological stress reactivity [21] and temperament [22]. Less is known about adolescent-specific sensitivity to stressful events and psychological difficulties. Some evidence has been found for a stronger association in children compared with adolescents [13], but findings were inconsistent and only studied in a few cases based on broad age ranges. Thus, our first aim is to investigate the association between stressful events and psychological difficulties and compare the strength of the effects at different stages in childhood and adolescence. Using five waves of data collected longitudinally from early childhood until the age of 16 years, we will examine whether or not specifically vulnerable age periods can be distinguished.

Alternative sources of sensitivity

Child characteristics or early exposures might also increase children's sensitivity to stress exposure. Child sex is probably the most widely researched moderator in studies on the association between stressful events and problem behaviours [13, 23]. Results are not totally consistent, but there is a suggestion that boys may be more sensitive during early childhood [24], whereas girls display more sensitivity during adolescence [25]. Consequently, our second aim is to investigate whether the association between stressful events and psychological difficulties is similar for boys and girls.

Previous studies have shown influences of maternal prenatal anxiety and stress on foetal brain development, affecting behavioural, emotional, cognitive development,

and stress physiology that may underlie psychological symptoms [26–29]. The developmental programming model that underlies much of this research predicts that prenatal maternal anxiety would heighten sensitivity to future stress. The presumed mechanism is through the programming of stress axes, especially the HPA axis, a process that has been reported both in experimental animal work and in human studies [28]. In the present study we will investigate if prenatal anxiety moderates the effect of environmental influences on psychological difficulties.

Another factor that may account for increased sensitivity to the effect of environmental influences on psychological difficulties is difficult temperament. Difficult temperament has been a focus of several studies on sensitivity, in particular from the perspective of the differential susceptibility hypothesis, both in human samples [12, 30] and in rhesus monkeys [31]. These studies suggest that difficult temperament moderates the association between stress exposure and child difficulties. Accordingly, we hypothesised that children with a difficult temperament show a stronger link between stress exposure and psychological difficulties than children without a difficult temperament.

Methods

Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal, prospective study of women, their parents, and an index child. A detailed description of recruitment, dropout, and other methodologies can be found in Golding and colleagues [32]. For the current study, five waves of data on stressful events and psychological difficulties were used. Inclusion criteria for these analyses were that (1) the child was the first born or only child in the family participating in ALSPAC, (2) the gestational age at delivery was at least 32 weeks, (3) weight at birth was at least 1,500 g. This resulted in a sample of 10,417 children (68.43 % of the children enrolled in ALSPAC during mothers' pregnancy).

Psychological difficulties

Psychological difficulties were measured using the Strengths and Difficulties Questionnaire (SDQ). The questionnaire was completed by the mothers for their children at the age of 4, 7, 9, 11, and 16 years. The SDQ asks about psychological attributes, some positive and others negative. We used the total difficulties score, based on 20 items on emotional symptoms, conduct problems, hyperactivity/inattention and peer relationship problems. The SDQ's emphasis on strengths as well as difficulties makes it particularly acceptable to community samples. Moreover, because of the limited number of items it has been widely used in epidemiological, developmental, and clinical research [33]. It has well-established consistency and diagnostic predictability. Reliability of the SDQ is good, whether judged by internal consistency (mean $\alpha = 0.73$) or cross-informant correlation (mean: 0.34). Internal consistency of the total problem scale was slightly lower in the current sample, ranging from 0.55 to 0.70 across waves. Also longitudinally, the SDQ has been found to be adequate, with test–retest stability after 4–6 months on average 0.62 [34]. In the current sample, test–retest stability of the SDQ across the different waves was substantial, although proportionally decreasing with increasing time intervals: total problems T1–T2 $r = 0.58$, T1–T3 $r = 0.52$, T1–T4 $r = 0.45$, T1–T5 $r = 0.43$, T2–T3 $r = 0.70$, T2–T4 $r = 0.64$, T2–T5 $r = 0.59$, T3–T4 $r = 0.72$, T3–T5 $r = 0.66$, T4–T5 $r = 0.75$.

Life events

Stressful events were measured using a questionnaire on life events that may have brought changes to their life and that occurred since the previous assessment. Some questionnaires were combined to match the SDQ assessments. This resulted in five waves of life event data covering events that occurred from birth–age 4, age 5–7, age 8–9, age 10–11 and age 12–16. All data were obtained from the mother, except data on events that occurred between ages 12 and 16 which were obtained from the adolescent. Events were included that (1) were measured at all waves, (2) have previously been found to be likely to be experienced as stressful and bring change to someone's life [35], and (3) are family related events that can be reliably reported by the mother as well as by the adolescent. The seven events included were illness of a family member, illness of a relative, death of a family member, death of a relative, loss of a job by a parent, problems with the law of one of the parents, and death of a pet [35]. Internal consistency of the stress sum scale was modest (ranging from $\alpha = 0.25$ at T1, to 0.34 at T2 and T4), which seems to be in accordance with what could be expected given that the scale consists of relatively independent events. Test–retest correlations of the stress scores across the different waves were modest: T1–T2 $r = 0.27$, T1–T3 $r = 0.22$, T1–T4 $r = 0.22$, T1–T5 $r = 0.10$, T2–T3 $r = 0.25$, T2–T4 $r = 0.20$, T2–T5 $r = 0.08$, T3–T4 $r = 0.35$, T3–T5 $r = 0.10$, T4–T5 $r = 0.13$.

Prenatal maternal anxiety

Maternal anxiety was measured at 32 weeks in pregnancy using the 16 anxiety items from the Crown–Crisp index, a validated self-rating inventory [36]. In this sample, the internal consistency was 0.82 [37]. We focus on 32 weeks'

gestation; previously we found a greater effect of prenatal anxiety in late rather than early pregnancy [37]. There is no well-established clinical cutoff for this measure; we therefore identified as highly anxious those mothers who scored in the top 15 %.

Temperament

Temperament was assessed at 6 months with the Carey Infant Temperament Scales [38]. The original version, consisting of nine domains, was developed from the work of Thomas and Chess [39] on childhood temperament. In our sample the original nine domains were measured, but 11 of the questions were not used in the ALSPAC study because of poor response rate in the pilot work; the average internal consistency of the ITQ domains was >0.80. We focused on the domain most closely related to 'difficult temperament' as referred to in the literature: mood. The mood scale consisted of nine items rated on a six-point scale. Parents complete each question using a six-point scale response, from "almost never" to "almost always". Similar to prenatal anxiety, we identified children as having a difficult temperament using a cutoff at 15 %. The scale has demonstrated good test–retest reliability and internal consistency, and normative data exist [38].

Statistical analyses

Changes in psychological difficulties and stressful events as well as main effects of prenatal anxiety, difficult temperament and child sex were analysed using repeated measures ANOVAs. Bidirectional relations between stressful events and psychological difficulties from early childhood into adolescence were studied using path analyses with cross-lagged effects. Analyses were done using the statistical software package software Mplus Version 5 [40]. In the model, stability of stressful events and the psychological difficulties over time and the within-wave correlations were included.

First, we examined an (unconstrained) model that included stability paths (both the direct paths and the paths T1–T3, T2–T4, and T3–T5) and within-wave correlations of stressful events and psychological difficulties (Model 1). Within-wave correlations refer to Wave 1 cross-sectional correlations and to correlated change in Wave 2, Wave 3, and Wave 4. Then, cross-lagged paths were added to the model and improvement of goodness of fit of the model was tested. This was done in three steps. First, we added cross-lagged paths from stressful events to psychological difficulties (Model 2). Second, we added cross-lagged paths from psychological difficulties to stressful events without including the cross-lagged paths from stressful events to psychological difficulties (Model 3). Third, we examined the bidirectional relations (Model 4). In Models 1–4, the paths linking stressful events and psychological difficulties were allowed to vary across age. Then, we compared Model 4 with a model in which all paths were constrained to be equal across waves (Model 5). If Model 5 fitted the data better than Model 4, then this would indicate that the association between stressful events and psychological difficulties was comparable across all ages (i.e. age did not modify this link or act as a differential sensitivity variable). This provided a test of age as a moderator of the link between stressful life events and psychological difficulties. For the model that fitted the data best, we reported the model including only the significant paths (Model 6). In exploratory analyses, we also included lag-2 and lag-3 paths, but these additional paths provided no evidence for reliable prediction and were therefore dropped.

Additionally, multi-group analyses were used to test the three remaining candidates of differential sensitivity: child sex, prenatal maternal anxiety, and difficult temperament. For the developmental model that fitted the data best above, we investigated if concurrent relations and cross-lagged paths varied as a function of (1) high/low maternal anxiety, (2) boys and girls, and (3) high/low difficult temperament (Models 7–12).

To determine the goodness of fit of the models we used the Comparative Fit Index (CFI) and the root mean-square error of approximation (RMSEA). CFI should be larger than 0.90 and the RSMEA smaller than 0.10. Model comparisons were conducted using Robust χ^2 difference tests [41]. We selected the most parsimonious model in case of non-significant differences in Robust χ^2.

Results

Preliminary analyses

First, we compared children with postnatal data (responders, $n = 10{,}417$) with children who only had data on prenatal anxiety and child sex (non-responders, $n = 3{,}114$). The comparison showed that the proportion of boys was slightly higher in the non-responders than in the responders (53.2 vs. 51.3 %), $\chi^2(1) = 3.22$, $p = 0.073$. The groups did not differ with regard to prenatal anxiety, $\chi^2(1) = 0.67$, $p = 0.414$. Full information maximum likelihood (FIML) was used to deal with missing data. In the Mplus FIML procedure, individual missing data patterns are assessed, and means and covariances for each missing data pattern are calculated to inform the observed information matrix [40]. The observed information matrix is used to generate estimates.

Descriptives

Descriptive statistics are presented in Table 1. As the waves were unequally distributed over time, we reported the number of events corrected for the number of months since the previous assessment [(number of events/time gap in months) × 100]. In the analyses, we used this corrected life event variable. Intraclass correlation coefficients for the SDQ total difficulties score across age ranged from 0.43 to 0.75 ($p < 0.001$) and for the life events across age from 0.08 to 0.26 ($p < 0.001$). Bivariate correlations between the different variables under study are reported in Table 2.

Repeated measures ANOVAs showed a significant decrease in psychological difficulties from Wave 1 to Wave 5 [F (4, 2,572) = 219.41, $p < 0.001$, $\eta^2 = 0.254$]. No association was found between change in difficulties and prenatal anxiety [F(4, 2,571) = 1.02, $p = 0.393$, $\eta^2 = 0.002$) or child sex [F (4, 2,571) = 1.87, $p = 0.114$, $\eta^2 = 0.003$]. Also the number of stressful events children were exposed to changed over time, although not in a clear linear pattern [Table 1, F (4, 2,849) = 1,264.26, $p < 0.001$, $\eta^2 = 0.640$].

Path analyses

First, we compared a model including all stability paths and within-wave correlations with a model including cross-lagged paths from events to difficulties (Table 3, Model 2) and with a model including cross-lagged paths from difficulties to events (Table 3, Model 3). Model fit increased significantly from Model 1 to both Models 2 and 3 (Table 3, that is, a significant drop in Chi square). The model fit further improved when bidirectional cross-lagged paths were added (Model 4 vs. Models 1, 2 and 3; see Table 3), indicating bidirectional links over time between stressful events and psychological difficulties.

Model fit was significantly worse in Model 5, which constrained all paths to be equal across waves; that is, the associations between stressful life events and psychological difficulties significantly varied as a function of age. Repeated measures findings reported above indicated change in levels of psychological difficulties and numbers of stressful events over time. We deleted all insignificant paths (that is, all dashed lines in Fig. 1), and used this model (Model 6) for our further analyses. The fit indexes indicated that the measurement model fit the data adequately (CFI = 0.988; RMSEA = 0.031; Table 3).

Next, we tested whether the concurrent associations and cross-lagged paths between stressful events and psychological difficulties were moderated by prenatal anxiety, child sex, and infant difficult temperament. No moderating effects were found for maternal prenatal anxiety (Models 7 and 8) and difficult temperament (Models 9 and 10), that is, no significant drop in Chi square. Paths varied significantly between boys and girls, indicating a moderating role of child sex (Models 11 and 12). Model estimates of the cross-lagged paths were stronger in girls than in boys early in life, and some of the paths did not remain significant in boys during middle childhood and adolescence (Fig. 2a, b).

Table 1 Means and SD split for sex, prenatal anxiety, and temperament

	Sex		Prenatal maternal anxiety		Difficult temperament	
	Boys *M* (SD)	Girls *M* (SD)	Low *M* (SD)	High *M* (SD)	Low *M* (SD)	High *M* (SD)
Total difficulties						
Age 4	9.30 (4.68)	8.39 (4.40)**	8.56 (4.43)	10.68 (4.95)**	8.54 (4.41)	10.65 (4.55)**
Age 7	7.76 (4.91)	6.78 (4.46)**	6.99 (4.55)	9.13 (5.31)**	6.96 (4.50)	8.99 (4.72)**
Age 9	6.82 (5.01)	6.04 (4.34)**	6.15 (4.51)	8.28 (5.49)**	6.13 (4.49)	8.10 (4.79)**
Age 11	6.57 (4.90)	5.64 (4.36)**	5.81 (4.46)	8.01 (5.43)**	5.80 (4.46)	7.84 (4.58)**
Age 16	6.30 (4.46)	5.81 (4.34)**	5.79 (4.25)	8.03 (5.07)**	5.80 (4.23)	7.84 (4.52)**
Stressful events						
Age 0–4 (time gap 47 months)	6.32 (2.80)	6.37 (2.85)	6.23 (2.80)	7.11 (2.86)**	6.23 (2.80)	7.15 (2.78)**
Age 4–7 (time gap 34 months)	4.11 (3.48)	4.33 (3.61)*	4.10 (3.49)	4.90 (3.78)**	4.10 (3.50)	4.85 (3.66)**
Age 7–9 (time gap 29 months)	6.31 (4.45)	6.57 (4.45)*	6.31 (4.41)	7.23 (4.59)**	6.34 (4.42)	7.06 (4.57)**
Age 9–11 (time gap 24 months)	6.40 (5.18)	6.94 (5.33)**	6.53 (5.21)	7.56 (5.52)**	6.54 (5.22)	7.37 (5.46)*
Age 11–16 (time gap 64 months)	2.24 (1.87)	2.65 (1.97)**	2.44 (1.90)	2.78 (2.10)**	2.43 (1.92)	2.88 (2.05)*

* Subgroups differ significantly at $p < 0.05$

** Subgroups differ significantly at $p < 0.01$

Table 2 Correlations between psychological difficulties, life events, prenatal anxiety, difficult temperament and sex

	SDQ					Prenatal anxiety	Difficult temperament	Sex
	Age 4	Age 7	Age 9	Age 11	Age 16			
Events 0–4	0.122***	0.137***	0.128***	0.107***	0.118***	0.109***	0.109****	0.009
Events 4–7	0.067***	0.093***	0.091***	0.080***	0.073***	0.078***	0.070***	0.030*
Events 7–9	0.040**	0.080***	0.080***	0.098***	0.077***	0.070***	0.053***	0.029*
Events 9–11	0.049***	0.096**	0.087***	0.093***	0.094***	0.068***	0.052**	0.052***
Events 11–16	0.043**	0.057***	0.114***	0.078***	0.077***	0.058**	0.072**	0.102***
Prenatal anxiety	0.163***	0.156***	0.155***	0.161***	0.164***	1.00	0.562***	0.004
Infant temperament	0.158***	0.144**	0.139***	0.143***	0.144***		1.00	−0.003
Sex	−0.100***	−0.103***	−0.082***	−0.100***	−0.056**			1.00

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

Table 3 Longitudinal model fit indices and model comparison tests

	Model fit indices model comparison tests					Satorra–Bentler scaled Chi-square model comparison tests			
	(*df*)	MLr χ^2	χ^2 (*df*)	CFI	RMSEA		TRdχ^2	Δdf	*p*
1. Model with stability paths and within-wave correlation	26	300.60	11.56	0.984	0.032				
2. Model 1 + cross-lagged paths from events to difficulties	22	274.90	12.50	0.985	0.033	Model 2 vs. Model 1	25.70	4	<0.001
3. Model 1 + cross-lagged paths from difficulties to events	22	220.83	10.03	0.990	0.028	3 vs. 1	79.77	4	<0.001
4. Model 3 + all cross-lagged paths	18	173.49	9.64	0.991	0.029	4 vs. 1	127.11	8	<0.001
						4 vs. 2	101.41	4	<0.001
						4 vs. 3	47.34	4	<0.001
5. Model 4 fully constrained (all paths fixed across waves)	38	1,191.16	31.35	0.920	0.062	4 vs. 5	1,017.67	20	<0.001
6. Model 4 only sign. paths	22	181.62	8.26	0.992	0.026				
7. Model 4 + prenatal anxiety	66	202.37	3.07	0.993	0.020				
8. Model 4 + prenatal anxiety constrained	44	206.75	4.70	0.992	0.027	8 vs. 7	4.38	22	0.999
9. Model 4 + different temperament	66	172.03	2.60	0.988	0.040				
10. Model 4 + different temperament constrained	44	154.38	3.51	0.990	0.038	10 vs. 9	17.65	22	0.727
11. Model 4 + sex	66	365.07	5.53	0.986	0.029				
12. Model 4 + sex constrained	44	220.76	5.02	0.992	0.028	12 vs. 11	144.31	22	<0.001

Conclusion and discussion

The current analysis from a large, longitudinal community sample of approximately 10,000 children studies between the ages of 4 and 16 years builds on and extends research on the links between exposure to stressful life events and behavioural problems. Our results indicate that there is increased sensitivity to the effects of stressful life events on psychological difficulties during early childhood and pre-adolescence, and in girls. We found no evidence to suggest that prenatal maternal anxiety or difficult infant temperament moderated the associations between stressful life events and psychological difficulties, cross-sectionally or longitudinally. Furthermore, reciprocal associations were found between stressful events and psychological difficulties from early childhood to adolescence.

Reciprocal associations between stressful events and psychological difficulties

Relations between stressful events and psychological difficulties were bidirectional. Although literature has

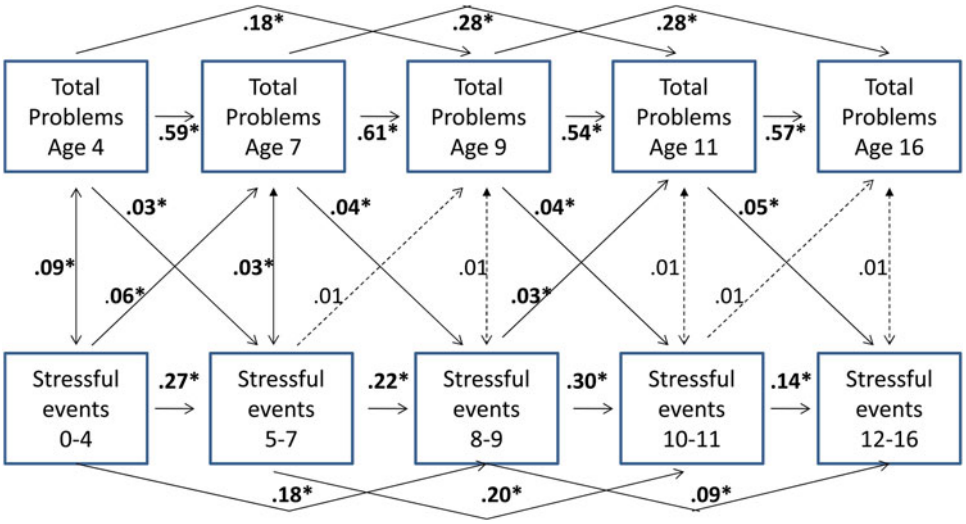

Fig. 1 Stability paths, within-wave correlations, and bidirectional cross-lagged paths with beta coefficients. *Dashed lines* refer to non-significant paths and were deleted from further analyses. *Asterisks* indicates path coefficient (β) <0.05

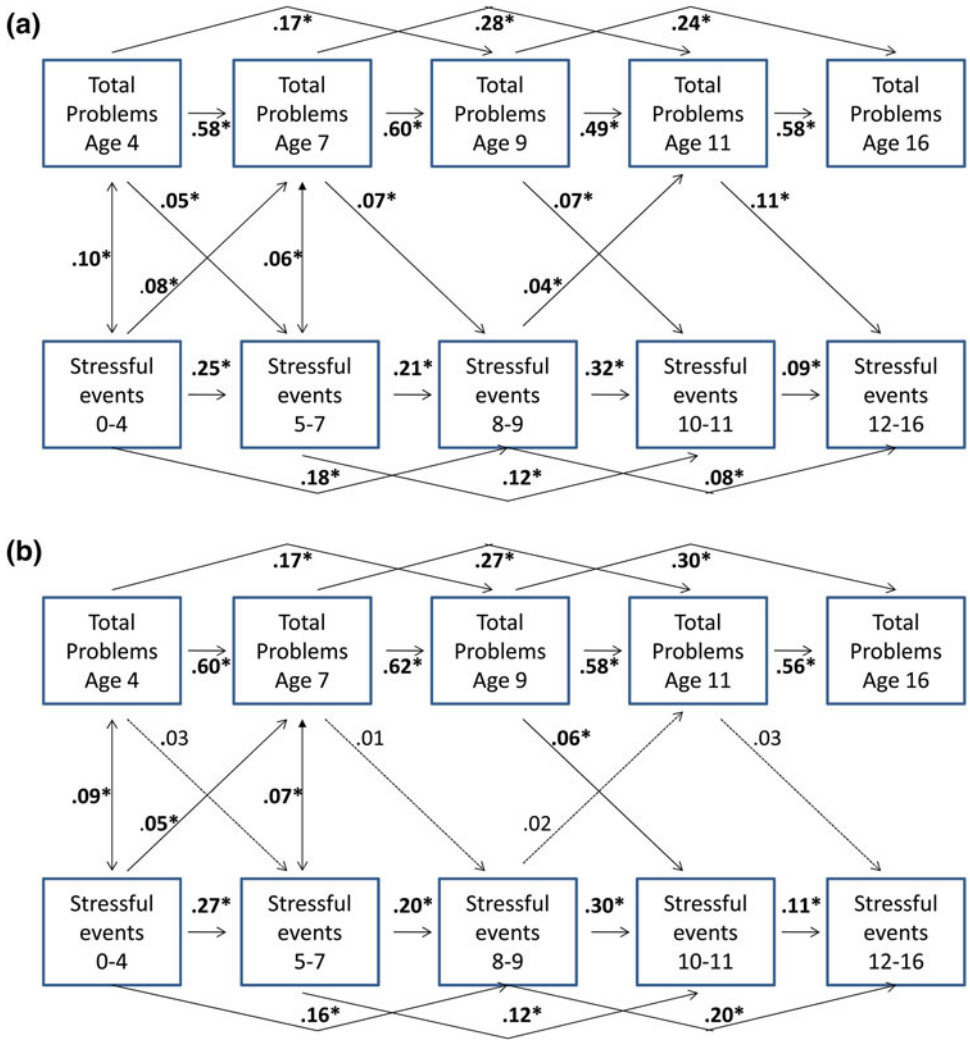

Fig. 2 **a** Girls stability paths, within-wave correlations, and bidirectional cross-lagged paths with beta coefficients. *Asterisk* indicates path coefficient (β) <0.05. **b** Boys stability paths, within-wave correlations, and bidirectional cross-lagged paths with β coefficients. *Asterisks* indicates path coefficient (β) <0.05

traditionally focused on stressful events as a precursor of difficulties, a few studies suggest that difficulties can also predict subsequent events [10, 11]. Our results support and extend these findings by demonstrating a dynamic association from early childhood to mid-adolescence. Psychological difficulties, including disruptive and

irritable behaviour, predicted the subsequent experience of stressful events that might have been viewed as 'independent' events, or events that were outside of the control of the child. Children's psychological difficulties may have a major impact on the family environment and dynamics, resulting in a complex intertwining of psychological difficulties of the child, and stressful events within the family; this offers further support for the notion that children are active agents in creating their environments. It should be noted that the magnitude of the cross-lagged effects might also be influenced by the fact that stressful events are less stable than psychological difficulties. Taken together, our findings clearly emphasise the need for developmentally sensitive assessment of how the child is affected by and has a direct role in creating his/her environment.

Factors moderating the link between stressful events and psychological difficulties

The effect of stressful events on psychological difficulties varied across age; in contrast, age did not moderate the link between psychological difficulties and stressful events. This age-based comparison assessing the magnitude of association between stressful events and psychological difficulties is new to the literature and indicates that there is no simple, monotonic increase or decrease with age [15–19].

In our study, participants exposed to stressful events showed more psychological difficulties at the ages of 7 and 11 years. At the ages 9 and 16, participants exposed to stressful events did not show more psychological difficulties. What explains this inconsistency? First, there is the possibility of false-negative (age 9 and 11) or false-positive (age 7 and 11) findings. Another possibility is that our findings are an indication of age sensitivity. Both human and experimental animal studies have suggested that both children and animals are more sensitive to their environment during some times than others. Early life is a period during which increased sensitivity to stress has been found consistently [42]. Our findings on children of age 0–7 are consistent with this. Later in childhood, sensitivity may either gradually decrease, or it might be that adolescence is another period of increased sensitivity, as proposed by Spear [19]. In both cases, it seems plausible that we did not find a significant effect at the age of 9 years. With regard to the adolescent years, however, our findings might imply that 'adolescent sensitivity' mainly applies to the early and not to the late-adolescent years. Alternatively, the measurement gap between early and late adolescence might have been too big to show effects, especially because adolescence has been shown to be a vulnerable period in another study investigating a related outcome [22] In addition, we note that although paths at specific ages were significant and others were not, the difference in effect sizes was not substantial. Further studies are needed to confirm early adolescent sensitivity by replication of the current findings as well as by exploring the influence of other possible sources of sensitivity.

Boys and girls were equally sensitive during early childhood, but girls were more sensitive during adolescence [23]. The sex difference might be explained by the possibility that boys may be more sensitive to particular events such as violence and poverty [13] which were not included in our study. A somewhat related possible explanation is that the events included in the current study occurred within the family environment, and girls may be more sensitive to social/familial stresses than boys [13].

Previous studies have found long-term effects of prenatal maternal anxiety on children's development [24, 27, 28, 43, 44]. For example, a previous ALSPAC study showed that children whose mothers experienced high levels of anxiety in late pregnancy exhibited higher rates of psychological difficulties at 81 months of age, providing evidence that prenatal maternal anxiety has a programming effect on the foetus which lasts at least until middle childhood [45]. Our study is one of the first human investigations to examine whether or not exposure to prenatal maternal anxiety has a programming effect with regard to future stress sensitivity, that is, whether prenatal maternal anxiety increases children's sensitivity to subsequent stressful events. We found no such evidence, despite a large sample size and notwithstanding the reliable links between prenatal maternal anxiety and children's psychological difficulties that have been found in this sample. This suggests that the programming effects of prenatal maternal anxiety are not the same for future psychopathology and for future stress sensitivity. It is not clear if the lack of sensitivity observed here contradicts the findings in rodents [28], and what it means for the programming hypothesis that underlies the prenatal anxiety paradigm used in research. Future research is needed to replicate our findings and to further examine the programming effects of prenatal maternal anxiety.

Similarly, in contrast to previous research [12], the associations between stressful events and psychological difficulties did not vary according to the child's temperament, as measured with the Carey scales. It is unlikely that our lack of finding might be explained by measurement differences because the Carey scales include items that have been included in other research, such as irritability, reactivity, and fearfulness. Our failure to detect any interaction might be explained by an alternative measurement factor. Studies reporting temperament to moderate the impact of stress on behavioural outcomes have tended to assess more proximal measures of stress exposure, such as

parenting, which may be a more sensitive marker of stress exposure and therefore more likely to show moderation effects.

Our results provide evidence for reciprocal associations between stressful events and psychological difficulties and suggest that this sensitivity might be age dependent and, to a more limited degree, sex dependent. This finding supports the idea that individuals differ in sensitivity to stress exposure, but that there may be a limited number of factors that reliably moderate the impact of stress on behavioural adjustment. In addition, we were limited in our ability to contrast alternative types of interactions, such as the 'diathesis stress/dual risk' and 'differential susceptibility' models [4, 6]. That is because we were limited by having only adverse experiences and did not have robust measures of positive experiences, which is required to differentiate the diathesis stress and differential susceptibility models. Future studies could extend our work by including positive environmental experiences to investigate sensitivity to positive environments as proposed by the differential susceptibility model.

Our study has several strengths, including the number of participants, the longitudinal design, and our focus on the reciprocal character of the association between stress and psychological difficulties. Some limitations should be mentioned as well. First, we used the parent version of the SDQ at all ages. The SDQ prediction has been found to work best when SDQs have been completed by all possible informants. However, especially during adolescence, self report SDQ provides an additional (although not better) source of information, particularly for emotional disorders [46]. Future research should include both parent and adolescent ratings from (middle/late) childhood onwards to avoid mono-method bias. Additionally, in the current study we focused on prenatal maternal anxiety as a sensitivity moderator, whereas it seems likely that in particular those children who were exposed to prenatal anxiety were also exposed to some maternal anxiety during childhood. Consequently, SDQ score there may be affected by some respondent bias associated with maternal anxiety at the time of response. Second, the time period between the last two waves was longer than between the other waves. This, in combination with the fact that at age 16 stressful events were reported by the adolescent instead of the mother, may partly explain the drop in the number of events exposed to from the age of 9–11 to 11–16 years. The large time period may have caused memory bias, and some of the events, e.g. problems with the law of one of the parents, might be somewhat underreported by adolescents. Nonetheless, within a longitudinal population cohort some changes in reporter cannot be avoided. Whereas parental measures may be superior to child measures with regard to child and early adolescent characteristics (including stressful life events), from middle adolescence onwards adolescent reports become increasingly valuable given that adolescents may not share detailed information about certain life events with their parents. Although we only included events in the current study that are likely to be reliably reported both by the parent and the adolescent, it would be interesting to include both parent and adolescent reports of stressful events in future research. Consequently, the results with regard to the last wave should be interpreted with caution. Nonetheless, because the association between stressful events and difficulties was not substantially different at this age from other ages, this source of method variance, sometimes inevitable in longitudinal studies across major developmental periods, did not seem to substantially confound study hypotheses. Also, for the current study we focused on only seven stressful events because of the need to include the same events at all occasions; these events have been identified as stressful and bringing change to someone's life [35] and were methodologically feasible to use in a population study spanning 16 years from early childhood to adolescence, but further work is needed to examine more severe and traumatic events. In addition, future research might translate our study to a more experimental design to disentangle causation of our associations in more detail than we could, using a cross-lagged model. Moreover, these studies may include additional potential sensitivity moderators than the factors we included in the current study (e.g. genetic characteristics), to test alternative hypotheses. Another limitation is that, because the effects are small as is common in the type of research, the clinical implications are modest.

In conclusion, the longitudinal design allowed us to examine the reciprocal associations between stressful events and psychological difficulties at different ages, and whether evidence could be found for factors accounting for differences in sensitivity. Our results suggest that early childhood and pre-adolescence are sensitive periods to the influence of stressful events, especially for girls. Future research is needed to specify particular mechanisms that may account for why child age and sex moderate the longitudinal links between stressful events and psychological difficulties.

Conflict of interest None.

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