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Research paper

Prenatal maternal negative life events associated with child emotional and behavioral problems in the French EDEN cohort

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ABSTRACT

Introduction: Prenatal negative life events (NLEs) have been linked to adverse health outcomes in children. However, few studies examine this relationship during late childhood using trajectory analyses. Additionally, the impact of specific NLEs domains on child development remains unclear. This study aims to longitudinally explore the association between NLEs (cumulative score and specific NLEs domains) and child outcomes from birth to late childhood.

Methods: 1135 mother-child pairs from the French EDEN cohort were followed from 24 to 28 weeks of pregnancy up to 11 years of age. Maternal self-reports of prenatal NLEs were collected immediately after birth, then analyzed as a cumulative score and by NLEs domain. Children's emotional and behavioral symptoms were assessed at 4 timepoints through the Strengths and Difficulties Questionnaire.

Results: Children of mothers exposed to ≥3 NLEs were more likely to follow trajectories of high levels of peer relationship problems (aOR [95 % CI] = 5.69 [1.74–18.69]), emotional symptoms (aOR [95 % CI] = 3.05 [1.08–8.63]), and conduct problems (aOR [95 %] = 3.53 [1.20–10.42]). Among the domains of NLEs, only events related to housing, finance, and living conditions were significantly associated with high emotional and behavioral difficulties trajectories (aOR [95%CI] = 2.71[1.26–5.81]).

Limitations: Potential attrition bias due to a higher dropout rate for children experiencing early indications of emotional and behavioral difficulties.

Conclusion: Findings support the relationship between prenatal NLEs and child outcomes, underscoring the importance of assessing prenatal stressors across life domains to identify mothers who might be in need of support.

1. Introduction

In recent years, there has been growing interest in assessing the adverse effects of prenatal stress on later child development. This extensive research is theoretically based on the developmental origins of health and disease (DoHAD) framework and the fetal programming hypothesis, which postulate that stressors occurring at critical periods during fetal development can induce intrauterine changes in the function of metabolic and neurological pathways in the offspring (Barker, 2007; Glover et al., 2018). These changes may have long-lasting effects on the child, potentially leading to various mental health difficulties, including emotional and behavioral problems (Glover et al., 2018). Given the high prevalence of maternal stress experienced during pregnancy (ranging between 6 and 74 % of expectant mothers) (Doty et al., 2022) and inadequate access to perinatal mental health care (Webb et al., 2022), this topic holds significant public health importance.

Evaluating the adverse effects of prenatal stress can be challenging due to the lack of consensus regarding its clinical definition. Prenatal stress is a complex and multidimensional concept that encompasses various factors, including cognitive, emotional, and biological responses to stressful stimuli (Doyle and Cicchetti, 2018; Quatraro and Grussu, 2020). These are often assessed among mothers via subjective indicators

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such as self-reported depression, anxiety, and perceived stress (Epel et al., 2018). The concept of prenatal stress further includes the stressors themselves, considered as objective measures of stressful life events, which are circumstances or environmental conditions that require adjustment with a generally clear onset and offset usually signifying major life changes (Carlson, 2014). Research on prenatal stress mostly focuses on negative life events (NLEs).

Research on NLEs during pregnancy is based on the notion that cumulative stress can arise from multiple significant life changes (Quatraro and Grussu, 2020). The majority of studies assess NLEs based primarily on the total number of events experienced (cumulative score of events) (Allen et al., 2020; Booth et al., 2021; Kingsbury et al., 2016; MacKinnon et al., 2018; Senter et al., 2021), since stressors rarely occur in isolation. Fewer studies have taken an interest in the type of event (Robinson et al., 2011; Mukherjee et al., 2017) and in the ensuing NLEs domains (Stanhope and Hogue, 2020). Assessment of life event domains is important, since various NLEs may impact women's health differently (Liu and Tronick, 2013; Salm Ward et al., 2017; Stanhope and Hogue, 2020). Research suggests that stressors impacting an individual's core identity may result in more severe psychological and physiological effects. These events are usually related to interpersonal problems, loss of social status, and employment difficulties (Cohen et al., 2019). Recent antenatal screening tools have been used to identify high-risk populations by assigning different weights to stressors according to their impact on maternal mental health, with domestic violence being considered the most impactful (Amuli et al., 2021). However, types of NLEs are assessed differently across studies making it harder to compare results and replicate findings when using objective measures. For example, Robinson et al. (2011) categorized NLEs into independent (events whose occurrence is outside the individual's control) versus dependent (events that an individual at least partly contributes to). Other studies categorized events into financial difficulties, traumatic experiences, relational events, and emotional events (Qobadi et al., 2016). Currently, there is a gap in the literature exploring the domains of prenatal NLEs and their potential differential effects on mother-child health. There is also a need to study the specific types of prenatal NLEs experienced by expectant mothers in France.

A growing body of evidence demonstrates that maternal prenatal NLEs predict a wide range of unfavorable child neurodevelopmental outcomes going beyond the perinatal period. In a recent review, Van den Bergh et al. (2020) highlighted the importance of the prenatal period and NLEs in predicting neurodevelopmental difficulties later on in life, such as negative affect, delayed cognitive development, attention-deficit/hyperactivity disorder (ADHD) symptoms, and emotional and behavioral problems. Likewise, some specific prenatal NLEs, such as bereavement and natural disasters (e.g. flood, earthquakes, storms) show important independent deleterious effects on child neurodevelopment (Li et al., 2023; Yong Ping et al., 2020).

Symptoms in offspring are usually measured at either one time point during childhood (Rudd et al., 2022) or at multiple time points (Robinson et al., 2011). Nevertheless, there is a need to expand research on longitudinal data. Analyzing child emotional and behavioral problems as trajectories has been recommended by several researchers, because risk factors of behavioral symptoms over time might differ depending on the developmental profile (e.g. persisting symptoms vs early-onset symptoms vs adolescent-onset symptoms) (MacKinnon et al., 2018) and child behavior may change throughout childhood and adolescence (Becker et al., 2015). Few of the studies that have used developmental trajectories analyzed data from the ALSPAC cohort in the United Kingdom and have shown that a higher number of NLEs during pregnancy is linked to mental health problems during adolescence (Kingsbury et al., 2016; MacKinnon et al., 2018). Particularly, MacKinnon et al. (2018) revealed that a greater number of NLEs during pregnancy are associated with a higher level of externalizing symptoms trajectory among children between the ages of 6 and 16. However, the authors did not explore differences between NLEs domains.

To address these gaps, the first objective of this study was to assess associations between maternal prenatal NLEs and child emotional and behavioral developmental trajectories from 3 to 11 years of age. We hypothesized that children of women who experienced more stressful NLEs during pregnancy would present persistent high emotional and behavioral symptoms, and that these associations would remain after adjustment for confounders. The second study objective was to describe whether frequency of prenatal NLEs and specific NLEs domains were associated with child emotional and behavioral developmental trajectories.

2. Methods

2.1. Study sample

The French EDEN mother-child cohort aims to investigate the prenatal and early postnatal environmental, nutritional, and psycho-social determinants of child health and development. Between February 2003 and January 2006, the maternity wards of two university hospitals in Nancy and Poitiers, France, recruited pregnant women with <24 weeks of amenorrhea. Exclusion criteria were pre-pregnancy diabetes, multiple pregnancies, inability to speak French, and planning to relocate from the region within the next three years. A total of 2002 women (53 %) accepted to participate and were enrolled in the cohort. The ongoing cohort has followed families for >11 years, with children undergoing five clinical examinations (at birth, at 1, 3, 5–6 and 11 years). Socio-demographic characteristics, environmental exposures, child behavioral, cognitive, and developmental data were also collected using health records, self-administered questionnaires, and midwife-administered questionnaires during and between examinations. During follow-up, attrition rates were higher in younger mothers and in women with lower educational attainment. Compared to a national sample, women from the EDEN cohort presented a higher educational level (Heude et al., 2016). For the current study, we included mother-child pairs for whom developmental trajectories for emotional and behavioral problems from 3 to 11 years had been previously determined (Kallas et al., 2023). By applying these criteria, a total of 1135 mother-child pairs were included in our sample.

The longitudinal EDEN cohort received ethical approval from the Ethical Research Committee of Bicêtre Hospital and the French Data Protection Authority. Written informed consent was obtained from parents at the time of enrollment for themselves and their newborns after delivery. All research was conducted per the Declaration of Helsinki.

2.2. Variables

2.2.1. Prenatal negative life events

Prenatal NLEs were assessed through a 13 item self-report questionnaire (including an open-ended question) inquiring about negative events commonly occurring during pregnancy. This questionnaire was completed by mothers just after delivery. Based on their answers to the closed and open-ended questionnaire, mothers' events were summed to create a new NLEs score (range 0–5). Continuous scores for NLEs are commonly used in literature (Ahmad et al., 2022). However, as our study had very few women reporting a high number of NLEs (4 and 5 events), they were grouped with those reporting 3 NLEs, resulting in a categorical cumulative NLEs score with values: 0, 1, 2, and ≥ 3 NLEs.

To evaluate NLEs by domain, we identified 9 domains through a comprehensive review of existing literature (Li et al., 2021; Liu and Tronick, 2013) and consensus within the research team. These domains are as follows: 1) Death of a loved one, 2) Events related to the couple's relationship, 3) Housing/financial problems or change of living situation, 4) Work/academic stress, 5) Pregnancy-related events, 6) Stressful social events, 7) Health issues, 8) Legal problems, 9) Other events. We created binary variables for each of these NLEs domains, assigning a

value of 1 to indicate that a participant reported at least one NLE from that specific domain and 0 if they did not.

In the questionnaire, participants indicated whether yes or no they had experienced the following events during pregnancy: 1) Death of a relative: partner, parent, sibling, 2) Separation of their couple, 3) Eviction of their home, need to relocate, 4) Fire, flood or major disaster in their home, 5) Serious traffic accident, whether they were a motorist, cyclist or pedestrian, 6) Loss of their job, 7) Partner's loss of their job, 8) They have had problems with the law, 9) Their partner has had problems with the law, imprisonment, 10) Their partner has had problems with alcohol or drugs, 11) Their partner has hit them or otherwise physically abused them, 12) Their partner has used force to have sex with them 13) Their partner has harassed them or controlled all their activities.

The open-ended question was answered by 360 participants. It asked participants if they experienced any additional upsetting events that were not mentioned in the list, with the possibility of reporting multiple events. The qualitative nature of this question allowed for the inclusion of events that had a significant impact on the woman's life during pregnancy. To facilitate their inclusion, answers were first grouped into specific categories, which were then assigned to broader thematic categories. In total, 33 broad categories were identified. Each category receives the value of 1 if the event occurred and 0 if it did not occur. For a more detailed breakdown of the categories grouped under the NLEs domains, please refer to Supplementary Table 1.

2.2.2. Child emotional and behavioral problems

Emotional and behavioral problems in children were measured using the French validated version of the parent-reported Strengths and Difficulties Questionnaire (SDQ) at 3, 5.5, 8 and 11 years of age (Shojaei et al., 2009). This 25-item questionnaire is a widely used tool for assessing child and adolescent mental health problems in clinical, community, and research settings. It evaluates 5 distinct dimensions: conduct problems, hyperactivity and inattention, emotional symptoms, peer problems, and prosocial behavior (Goodman, 1997). The subscale scores have a range of 0 to 10. A "total difficulties" score is computed by adding up the scores of the 4 subscales denoting difficulties. This score ranges from 0 to 40, with higher values indicating higher levels of experienced difficulties. Regarding the prosocial subscale, the items were reverse coded. This means that the scoring was adjusted so that a higher score reflects a higher level of positive social behavior. The SDQ presents satisfactory to good internal consistency, test-retest stability, and parent-child agreement in the different subscales (Essau et al., 2012; Muris et al., 2003).

For each subscale, 3 trajectory models of stable symptoms over time were identified, denoting low, intermediate, and high-level symptoms (Kallas et al., 2023). Group-based trajectory modelling (GBTM) was used to identify trajectories using the PROC TRAJ package of SAS software (version 9.4; SAS Institute, Inc., Cary, NC, USA). The model selection was guided by Bayesian information criteria (BIC), which paired fit statistics with overall interpretability. The number and polynomial shape of the trajectories were considered. To compare competitive models that include different numbers of trajectories, we preferred the improvement of $2^*\Delta BIC > 10$ (Bayes factor). The criteria for adequate model fit were an Average Posterior Probability (APP) >0.75 and odds of correct classification (OCC) >5.0 for each group. In this sample, 13.2 % of children belonged to the high-level emotional symptoms, 7.8 % to the high-level peer relationship problems, 15 % were allocated to the high trajectory of conduct problems, 14.6 % to the high trajectory of hyperactivity and inattention, and 7.6 % belonged to the low-level trajectory of prosocial behavior.

2.2.3. Covariates

Potential confounders were identified in an extensive literature review (Arnold et al., 2023; Belhadj Kouider et al., 2014; Raudino et al., 2012; Takács et al., 2021). The following factors were taken into account: Child biological sex; *Sociodemographic variables* included maternal migrant status (none, first generation and second generation), maternal education (years), having a family income of <1500 euros/month (yes vs no), and maternal employment status (employed vs unemployed and not studying); *Maternal characteristics* included maternal age (years), parity (primiparous vs not primiparous), previous psychological consultation (yes vs no), maternal history of childhood behavioral difficulties (yes vs no), and previous antidepressant medication (yes vs no) as a proxy for depression history. In addition, having experienced at least one Adverse Childhood Event prior to the age of 14 years (placement in a public assistance program, material deprivation, parental conflict or violence, child abuse or neglect) was included as a binary variable (yes vs no); *Support indicators* included social support from the partner (yes vs no) and social support from their social network (yes vs no). Additionally, cohabitation with the father of the child was included as a binary variable (yes vs no) and represented as a proxy for relationship status.

2.3. Statistical analysis

All analyses were conducted using R Studio (version 4.3.0; R Core Team).

Description of baseline characteristics of the study sample was effectuated according to the categories of the cumulative NLEs score: 0, 1, 2, ≥3 NLEs. Pearson's chi-2 tests were performed for the bivariate analyses of categorical variables when the necessary conditions for performing this analysis were respected. Fisher's exact tests were performed when conditions were not respected (<5 expected observations) and for continuous variables.

In the present study, 218 (18.9 %) participants had missing data at 1 time point for any of the covariables. Multiple imputation by Fully Conditional Specification (FCS) was chosen to approach missing data of the covariates and the exposure through the multivariate imputation by chained equations (MICE) algorithm (Lee et al., 2021). The number of imputed datasets was assigned to 20, given the moderate percentage of missingness. The results were pooled from the multiple imputed datasets. The "mice" package in R software was utilized. Refer to the Supplementary table 2 for detailed information on how the variables were imputed.

First, multinomial logistic regressions were conducted to estimate the odds ratios and 95 % confidence intervals for membership in SDQ trajectory groups based on exposure to 0, 1, 2 and ≥3 NLEs. Separate multinomial regressions were conducted for each SDQ subscale. The low-level symptoms trajectory served as the reference category for the difficulties subscales, while the high-level symptoms trajectory was the reference for the prosocial behavior subscale. We conducted adjusted analyses by including in the model the covariates that were not a part of the causal pathway (Ananth and Schisterman, 2017) but had an association to the outcome with a significance level of $p < 0.20$ or a strong theoretical link. All analyses were adjusted for the previously cited covariates.

Second, NLE domains were described according to their frequency in the sample population. Third, separate multinomial logistic regressions were performed for evaluating the association of NLE domains with the total difficulties' developmental trajectories. The SDQ subscales were not evaluated, as there was no established theoretical rationale for linking the various facets of the NLE with each SDQ subscale separately.

3. Results

3.1. Sample characteristics

A total of 1135 mother-child dyads were included in the present study. Compared to the excluded participants, the included women were less likely to be first- or second-generation migrants, to have lower levels of education, to be unemployed during pregnancy, and to come from a household with a monthly income of <1500 euros. They were also on

average older, more likely to be first-time mothers and less likely to have used antidepressants before pregnancy. Study participants were less likely to have had behavioral problems or adverse childhood experiences. In addition, they were more likely to be living with the father of their child and to receive emotional and instrumental support from their partner, as well as emotional support from their social circle. See Supplementary Table 3 for characteristics of excluded participants. Moreover, only 18 participants from the excluded sample provided data on NLEs, therefore it was not possible to confirm whether the excluded participants ($n = 877$) had higher levels of exposure.

Characteristics of included participants according to the number of prenatal NLEs are shown in Table 1. Of the initial sample of 1135 participants, only 14 participants (1 %) had missing values on NLEs, resulting in 1121 participants included in the description of the study sample. 32 % of women reported at least 1 NLE during pregnancy: 238 women (21.3 %) reported 1 NLE, 92 (8 %) reported 2 NLEs, and 32 (2.8 %) reported 3 or more NLEs during pregnancy.

In general, women with the highest level of exposure to NLEs (≥3 NLEs) were more likely to be unemployed during pregnancy and to belong to a household whose monthly income was lower than 1500 euros per month. Additionally, they had a lower probability of living with the father of their child, as well as a lower likelihood of reporting emotional support from their partner and practical support from their family and friends. They were more likely to have experienced adversity during their own childhood and reported presenting more behavioral problems as children. Furthermore, women with 2 or more NLEs were more likely to have had psychological consultation prior to pregnancy. Among mothers reporting 3 or more antenatal NLEs, there is a higher proportion of girls than boys.

3.2. Association between number of prenatal NLEs and child developmental trajectories

Having experienced 3 or more prenatal NLEs was associated with children following the high-level symptoms trajectory for total difficulties (OR [95 % CI] = 5.11 [1.76–14.8]), peer relationship problems

Table 1
Characteristics of EDEN cohort study participants by number of NLEs ($n = 1121$).

NLEs	Total n = 1121	0 $n = 759$	1 $n = 238$	2 $n = 92$	≥3 $n = 32$	p-Value
Variable	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	N (%) Mean (SD)	
Sociodemographic characteristics						
Migration background						0.212[a]
None	973 (86.8)	663 (87.4)	202 (85.1)	80 (88.9)	28 (93.3)	
First generation	99 (8.8)	68 (9.0)	23 (9.9)	7 (7.8)	1 (3.3)	
Second generation	25 (2.2)	11 (1.4)	10 (5.0)	3 (3.3)	1 (3.3)	
Missing data	24 (2.1)	17 (2.2)	3 (1.3)	2 (2.2)	2 (6.3)	
Mother's education (years)	14.1 (2.6)	14.1 (2.6)	14.1 (2.6)	14.1 (2.8)	14.2 (2.7)	0.831[b]
Missing data	3 (0.4)	1 (0.4)	0 (0)	0 (0)	4 (0.4)	
Low income (<1500 euros/month)	119 (10.5)	60 (7.9)	41 (18.0)	13 (14.1)	5 (15.6)	<0.001[a,**]
Missing data	6 (0.5)	5 (0.7)	1 (0.4)	0 (0)	0 (0)	
Mother unemployed and not studying (yes)	191 (16.9)	108 (14.4)	52 (22.2)	20 (21.7)	8 (25.0)	0.012[a,*]
Missing data	8 (0.7)	6 (0.8)	2 (0.8)	0 (0)	0 (0)	
Maternal characteristics						
Maternal age at birth (years)	30.6 (4.7)	30.9 (4.6)	30.1 (4.9)	30.5 (4.8)	31.1 (5.0)	0.467[b]
Missing data	23 (2.1)	17 (2.2)	3 (1.3)	1 (1.1)	2 (6.3)	
Primiparity (yes)	533 (47.0)	351 (46.2)	118 (49.6)	41 (44.6)	14 (43.8)	0.746[a]
Missing data	2 (0.2)	1 (0.1)	1 (0.4)	0 (0)	0 (0)	
Psychologist visit during pregnancy (yes)	151 (13.5)	74 (9.8)	37 (16.1)	28 (31.5)	10 (31.2)	<0.001[a,**]
Missing data	18 (1.6)	12 (1.6)	3 (1.3)	3 (3.3)	0 (0)	
Childhood behavioral problems of mother (yes)	65 (5.8)	30 (4.0)	16 (7.4)	8 (8.7)	9 (28.1)	<0.001[a,**]
Missing data	13 (1.2)	10 (1.3)	3 (1.3)	0 (0)	0 (0)	
Antidepressant use before pregnancy (yes)	171 (15.4)	101 (13.4)	42 (17.6)	18 (20.0)	8 (25.0)	0.072[b]
Missing data	24 (2.1)	15 (2.0)	7 (2.9)	2 (2.2)	0 (0)	
Any adverse childhood experiences (yes)	285 (25.5)	167 (22.6)	68 (30.0)	32 (35.6)	14 (43.8)	0.001[a,*]
Missing data	18 (1.6)	11 (1.4)	5 (2.1)	2 (2.2)	0 (0)	
Support indicators						
Mother cohabits with child's father (yes)	1091 (96.7)	744 (98.4)	224 (94.7)	81 (91.0)	28 (87.5)	<0.001[a,**]
Missing data	7 (0.6)	3 (0.4)	1 (0.4)	3 (3.3)	0 (0)	
Instrumental support from partner (yes)	1033 (91.9)	699 (92.6)	217 (92.6)	77 (87.5)	26 (83.9)	0.115[a]
Missing data	11 (1.0)	3 (0.4)	3 (1.3)	4 (4.3)	1 (3.1)	
Instrumental support from entourage (yes)	942 (83.1)	636 (84.1)	205 (86.1)	71 (78.0)	17 (53.1)	<0.001[a,**]
Missing data	5 (0.4)	3 (0.4)	1 (0.4)	1 (1.1)	0 (0)	
Emotional support from partner (yes)	1092 (97.4)	741 (98.2)	227 (96.7)	82 (94.3)	28 (90.3)	0.009[b,*]
Missing data	14 (1.2)	4 (0.5)	4 (1.7)	5 (5.4)	1 (3.1)	
Emotional support from entourage (yes)	1063 (94.2)	721 (95.4)	217 (91.4)	82 (90.1)	30 (93.8)	0.029[b]
Missing data	6 (0.5)	3 (0.4)	2 (0.8)	1 (1.1)	0 (0)	
Child characteristics						
Child's biological sex (masculine)	603 (53.1)	414 (54.5)	122 (51.0)	50 (54.3)	8 (25.0)	0.011[a,*]

N (%) for categorical variables or mean (SD) for continuous variables; NLEs: negative life events. Cell counts may vary due to missing observations.
[a] Chi-2 test.
[b] Fisher's exact test.
[*] Statistical significance: $p < 0.05$.
[**] Statistical significance: $p < 0.01$.

(OR [95 % CI] = 5.69 [1.74–18.69]), emotional symptoms (OR [95 % CI] = 3.05 [1.08–8.63]), and conduct problems (OR [95 % CI] = 3.53 [1.20–10.42]) after adjustment. There was no evidence of an association between the experience of 2 or fewer NLEs and the membership to trajectories of high or intermediate symptoms for any of the SDQ subscales. For the total difficulties, the strength of the association increased with the number of NLEs, even though the effect for 1 and 2 NLEs were not statistically significant. Results from unadjusted and adjusted analyses can be found in Table 2.

3.3. Description of NLEs domains

In our study sample, death of a loved one was the most common type of event (11 %), followed by work related stressful events (7.7 %), health problems for the participant or for someone close to them (6.7 %), stress related to housing and living conditions (6 %), pregnancy related stressful events (3.5 %), stressful events related to the couple's relationship (3.2 %), stressful social events (3 %), legal issues (<1 %), and other events (<1 %).

3.4. Association between prenatal NLEs domains and child developmental trajectories

The children of mothers who reported NLEs related to housing, finances, or living condition problems presented a higher likelihood of belonging to the high-level symptom group for the total difficulties' trajectory (OR [95%CI] = 2.71 [1.26, 5.81]), compared to children whose mothers did not report this type of event. Results are shown in Fig. 1 and exact OR values can be found in Supplementary Table 4. The associations between reporting NLEs relative to the couple's relationship (which included intimate partner violence) or pregnancy related events, and the membership in the high-level symptom group for total difficulties were also moderate but failed to reach statistical significance ($p = 0.098$ and $p = 0.07$ respectively). The domains pertaining to legal issues and other events were not included in these analyses due to their very low prevalence (<1 %) in the sample.

4. Discussion

In this 11-year longitudinal study, data from >1000 mother-child dyads from a French community sample were used to analyze the relationship between prenatal maternal NLEs and emotional and behavioral problems in the child. Children whose mothers reported 3 or more prenatal NLEs had an increased likelihood of belonging to the high-level symptoms' trajectories for emotional symptoms, peer relationship problems, conduct problems, and total difficulties, when compared to children whose mothers reported no NLEs during pregnancy and after adjusting for confounders. Among the different domains of NLEs, death of a loved one was the most frequently reported event but only events related to housing, finance, and living conditions were significantly associated with high-level symptoms trajectories of total difficulties in the child.

4.1. Association between cumulative NLE score and child outcomes

Our findings are consistent with previous studies on prenatal life stress, showing an association between maternal exposure to multiple NLEs and child emotional and behavioral problems (MacKinnon et al., 2018; Robinson et al., 2011; Rudd et al., 2022). The study conducted by MacKinnon et al. (2018), also showed a relationship between prenatal stressful events and offspring trajectories of externalizing symptoms. In contrast to that study, our sample did not provide evidence of NLEs increasing the risk of hyperactivity and inattention problems. Additionally, we did not observe a clear dose-response relationship between the number of NLEs and emotional and behavioral problems. The differences in these findings could be attributed to the different methods of

Table 2
Unadjusted and adjusted multinomial regressions between child's SDQ trajectories and each of the NLEs categories according to the number of events (1, 2, ≥3) compared to the reference group (no experience of NLEs) ($n = 1135$).

Number of NLE		1				2				≥3			
SDQ subscales (outcome)		OR (95 % CI)	p-Value	aOR (95 % CI)	p-Value	OR (95 % CI)	p-Value	aOR (95 % CI)	p-Value	OR (95 % CI)	p-Value	aOR (95 % CI)	p-Value
Emotional symptoms	I	1.12 (0.81, 1.54)	0.42	1.03 (0.74, 1.44)	0.85	0.86 (0.54, 1.37)	0.50	0.78 (0.48, 1.28)	0.33	1.39 (0.59, 3.31)	0.41	1.18 (0.48, 2.91)	0.72
	H	**1.65 (1.05, 2.58)**	**0.02**	1.41 (0.88, 2.26)	0.15	1.35 (0.71, 2.57)	0.37	1.13 (0.57, 2.22)	0.73	**4.14 (1.60, 10.69)**	**0.003**	**3.05 (1.08, 8.63)**	**0.03**
Peer relationship problems	I	1.05 (0.75, 1.46)	0.79	0.93 (0.66, 1.31)	0.68	1.23 (0.76, 2.03)	0.39	1.09 (0.66, 1.84)	0.72	1.17 (0.76, 2.03)	0.67	1.12 (0.44, 2.83)	0.81
	H	1.36 (0.76, 2.41)	0.25	1.10 (0.60, 2.02)	0.75	1.29 (0.53, 3.15)	0.55	1.05 (0.41, 2.68)	0.92	**4.88 (1.69, 14.06)**	**0.002**	**5.69 (1.74, 18.69)**	**0.004**
Conduct problems	I	1.17 (0.83, 1.66)	0.31	1.14 (0.79, 1.62)	0.48	0.89 (0.54, 1.48)	0.67	0.86 (0.51, 1.46)	0.58	1.01 (0.41, 2.49)	0.99	0.98 (0.38, 2.55)	0.97
	H	1.00 (0.61, 1.66)	0.99	0.88 (0.52, 1.49)	0.64	1.42 (0.75, 2.67)	0.27	1.12 (0.55, 2.23)	0.77	2.64 (0.98, 7.08)	0.05	**3.53 (1.20, 10.42)**	**0.02**
Attention problems	I	1.15 (0.83, 1.59)	0.40	1.21 (0.86, 1.70)	0.27	1.06 (0.65, 1.72)	0.82	1.08 (0.65, 1.80)	0.76	1.39 (0.61, 3.14)	0.42	2.00 (0.83, 4.8)	0.12
	H	1.19 (0.75, 1.87)	0.45	1.17 (0.71, 1.91)	0.54	1.44 (0.77, 2.71)	0.25	1.34 (0.67, 2.68)	0.40	1.04 (0.31, 3.45)	0.94	1.45 (0.38, 5.52)	0.59
Prosocial behavior	L	1.25 (0.70, 2.23)	0.45	1.27 (0.69, 2.31)	0.43	1.44 (0.63, 3.31)	0.39	1.50 (0.62, 3.65)	0.37	1.54 (0.48, 4.94)	0.47	2.47 (0.67, 8.77)	0.16
	I	0.98 (0.72, 1.34)	0.89	0.96 (0.69, 1.33)	0.82	1.18 (0.73, 1.89)	0.49	1.23 (0.75, 2.00)	0.42	0.72 (0.33, 1.54)	0.39	0.91 (0.41, 2.01)	0.82
Total difficulties	I	1.15 (0.84, 1.56)	0.39	1.09 (0.79, 1.51)	0.58	0.89 (0.56, 1.42)	0.61	0.83 (0.51, 1.34)	0.45	1.21 (0.53, 2.69)	0.63	1.42 (0.62, 3.28)	0.41
	H	1.43 (0.84, 2.44)	0.16	1.23 (0.69, 2.15)	0.48	1.83 (0.93, 3.59)	0.08	1.44 (0.69, 3.01)	0.33	**4.12 (1.61, 10.52)**	**0.003**	**5.11 (1.76, 14.8)**	**0.002**

Unadjusted and adjusted multinomial regressions (95 % CI) for each SDQ subscale. Adjustment variables include maternal age, migrant status, primiparity, maternal employment status, maternal education, low revenues, mother cohabits with the father of the child, partner support, social support, antidepressant use before pregnancy, maternal ACEs, maternal childhood behavioral problems.
H, high-level symptoms; I, intermediate-level symptoms; L, low-level symptoms; SDQ, Strengths and Difficulties Questionnaire; NLE, negative life events. Significant associations in bold.

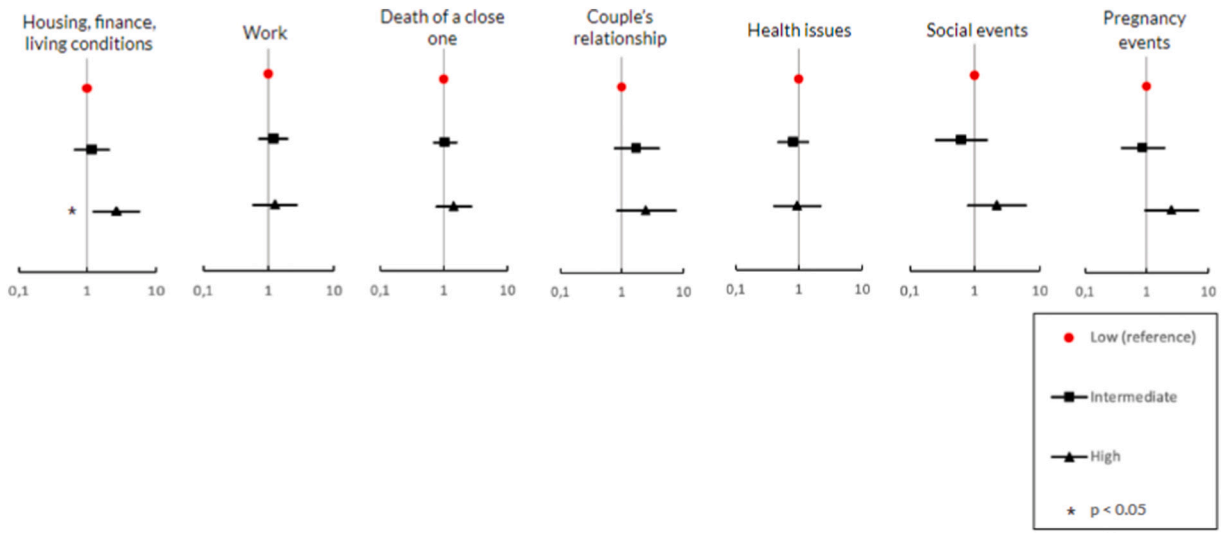

Fig. 1. Adjusted multinomial regressions (95 % CI) between child's SDQ total difficulties trajectories and each of the NLEs domains compared to the reference group (no experience of NLEs), presented in the log scale (n = 1135).

data collection on NLEs. In their study, women were asked to rate the severity of the impact of stressful events from 1 to 4, while we did not have information on the subjective ratings in the included events. Due to the small number of observations after stratification of the NLE score, we could not perform separate subgroup analyses based on biological sex. The lack of association between NLEs and hyperactivity/inattention may be due to this limitation. Previous studies investigating prenatal subjective stress have indicated that there may be a varying impact of prenatal stress on ADHD symptoms depending on the child's sex, with boys being at a higher risk than girls (Shao et al., 2020). Neurobiological changes in the child related to prenatal stress, which may be influenced by the child's sex, may also explain these findings. One study demonstrated that prenatal stress is associated with enlarged amygdala volumes in girls, which may be linked to emotional symptoms and total difficulties (Acosta et al., 2019). However, Jones et al. (2019) showed that boys born to mothers who experienced prenatal stress had larger amygdala volumes, which were associated with externalizing symptoms. These inconsistent findings support the need for additional research in this field.

Similar to our results, Robinson et al. (2011) found no significant increase in emotional and behavioral difficulties when women reported 1 or 2 NLEs compared to 0 NLEs. These findings suggest that the impact of exposure to NLEs cannot be solely determined by their mere presence or absence. Rather, it is the presence of a higher number of events, specifically 3 or more in our case, compared to the absence of events, that seems to have significance. This could be attributed to the repetitive adaptations' individuals undergo when faced with multiple stressful events. This leads to multi-system responses (e.g. neuroendocrine, metabolic) and to the depletion of coping resources, resulting in an accumulation of physiological and psychological "wear-and-tear" on body systems, known as allostatic load (Premji et al., 2022).

Our results support the fetal programming hypothesis for child emotional and behavioral problems, in which bioregulatory mechanisms might be affected by early life exposure to stress. Being highly exposed to stress in early life might increase the predisposition to a more sensitive response system to stressful events after birth. One of these mechanisms is the alteration of the fetal hypothalamic-pituitary-adrenal (HPA) axis and cortisol dysregulation. During high levels of prenatal stress, the fetus can be exposed to increased concentrations of glucocorticoids, which can alter the fetal brain development (Mairesse et al., 2007). Other mechanisms that might explain the fetal programming hypothesis involve inflammatory markers (Andersson et al., 2016), testosterone (Sarkar et al., 2008), dopamine (Pastor et al., 2017), serotonin (Bondarenko et al., 2022), and catecholamines (Wroble-Biglan et al., 2009). However, biological mechanisms alone do not account for the link between NLEs and child neurodevelopment. In fact, not all children exposed to stress in utero develop emotional and behavioral problems. The postnatal environment and the quality of mother-child interactions are significant factors in shaping this relationship. Several postnatal parental factors such as postpartum depression and maltreatment might act as mediators between prenatal stress and child outcomes (Hartman et al., 2020; Sebők-Welker et al., 2023). Furthermore, recent research has explored the role of factors that may mitigate the effects of prenatal stress, including adequate parental involvement (Clayborne et al., 2023; Nolvi et al., 2023), positive maternal mental health (Clayborne et al., 2022), and access to psychiatric care (Kallas et al., 2023); all of which have been shown to act as protective factors.

4.2. Description of NLE domains and their association with child outcomes

The most frequently reported NLEs were death of a loved one, work related events, and health related events. Women in our study sample come from households with an overall higher income and education than the national average. This might explain why there was a rather low prevalence of traumatic experiences related to legal problems. In contrast to studies conducted in the United States, NLEs associated with financial issues were not the most frequent events during pregnancy (Burns et al., 2015). Moreover, with the inclusion of the answers to the open-ended questions, we were able to identify domains of pregnancy-related and social-related events, which were not part of the initial questionnaire.

Analyzing NLE domains can help identify the most impactful stressors, which is valuable for tailoring prevention and health promotion strategies. For instance, our findings revealed that NLEs related to housing, finances, and living conditions were associated with high-level symptoms in the total SDQ difficulties trajectory. Pregnancy can bring about significant life changes that can affect household finances (Taylor et al., 2021). When such events occur, they may add to a financial burden women are already experiencing, leading to increased worry about future financial difficulties during pregnancy and after childbirth. Furthermore, alterations to housing conditions, such as relocating during pregnancy, may affect other areas of life. For instance, it could disturb social support or interrupt healthcare (Bond et al., 2019).

5. Strengths and limitations

Our study possesses several notable strengths. The use of longitudinal data on emotional and behavioral problems experienced by the child spanning from early to late childhood allows for a more precise assessment of developmental patterns and potential long-term effects. Likewise, the measurement of several family characteristics and psychosocial risk factors allowed for adjustment on multiple potential confounders. The decision to employ an objective measure for prenatal stress, rather than relying solely on indicators such as depression, anxiety, or perceived stress, helps evaluate the impact of stress independently from the mother's coping ability and includes subclinical levels of stress (MacKinnon et al., 2018). Additionally, a recent study supports the validity and reliability of utilizing life event-based stress measures in prenatal stress research and demonstrated the suitability of stress measures based on life events during pregnancy to assess their impact on emotional and behavioral difficulties in the offspring (Štěpáníková et al., 2020).

However, our results should be considered within certain limitations. First, the participants in the EDEN cohort have higher levels of education and come from households with higher incomes compared to the average French population. Therefore, they may not be fully representative of the national population, and as a result, our findings may not be generalizable to more vulnerable populations. Second, emotional and behavioral problems were only parent reported. However, both parent and teacher reported versions of the SDQ have previously been validated (Stone et al., 2010) and exhibited a better inter-rater agreement compared to other child psychopathology measures. Third, the instrument used to measure NLEs in this study is not a validated questionnaire but rather draws from other widely used tools in life-stress research. Nevertheless, the incorporation of the answers from the open-ended question enabled us to include additional information pertaining to NLEs. Fourth, the group of participants with the highest level of exposure ($\geq$3 NLEs) represents a small proportion of the sample, which explains the wide confidence intervals in the regression models. Finally, there is a potential attrition bias due to a higher dropout rate for children experiencing early indications of emotional and behavioral difficulties. The mothers of these children were less educated and more unemployed than those who did not drop out.

6. Research implications

Studies evaluating potential interventions to mitigate the effects of prenatal stress on child outcomes are needed to further advance research. Strategies for stress management in pregnant women that have been shown to be effective (e.g., yoga, mindfulness) (Min et al., 2023; Ng et al., 2019) could be explored as factors that may reduce the potential negative effects of prenatal stress. In addition, multidimensional interventions in prenatal care, such as referrals to professionals who can identify resources to alleviate financial burdens, may also be beneficial, and their potential effects should be studied (Liu and Tronick, 2013). Public policies can also make a difference for expecting mothers. For example, a recent study found that receiving cash transfers from pregnancy, rather than only after birth, had an effect on reducing low birth weight, which may be associated with reduction in prenatal stress (Reader, 2023). Future research could explore the long-term effects of such interventions on child mental health outcomes.

7. Conclusion

Reporting multiple NLEs during pregnancy and events related to housing, finances, and living conditions predicted an increased likelihood for persistent high child emotional and behavioral trajectories. These results align with previous research and provide further evidence supporting the fetal programming hypothesis and the impact of prenatal stress on long-term child emotional and behavioral development. Our findings underscore the importance of identifying high-risk pregnant women through a possible assessment of prenatal NLEs in order to provide appropriate multidisciplinary care.

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CRediT authorship contribution statement

Sara Avendano: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Simi Moirangthem:** Writing – review & editing, Data curation. **Muriel Taflet:** Data curation. **Barbara Heude:** Writing – review & editing, Funding acquisition. **Muriel Koehl:** Writing – review & editing, Funding acquisition. **Judith van der Waerden:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. **Naomi Downes:** Writing – review & editing, Writing – original draft, Supervision, Methodology.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

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