Prenatal and childhood adversity and inflammation in children: A population-based longitudinal study

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Abstract

Background: Stressful life events experienced during childhood and early prenatal development have been associated with inflammation during childhood. However, no study has considered these two exposures jointly, or has investigated the effect of their interaction. **Methods:** In the Avon Longitudinal Study of Parents and Children, a general-population birth cohort, we explored if inflammatory markers [serum C-reactive protein (CRP) and interleukin 6 (IL-6)] at age 9 years were related to early prenatal events (at 18 weeks pregnancy), childhood events (measured on seven occasions at ages 0-9 years) and their interaction (n=3,915). Latent growth curve modelling estimated trajectories of childhood events, and linear regression explored associations of prenatal and childhood events with inflammatory markers. Models controlled for ethnicity, socioeconomic status and body mass index, were stratified by gender and considered both unweighted and weighted (by impact) event exposures. **Results:** Even after adjustment for confounders and prenatal events, both the intercept and the slope of number of childhood events were associated with IL-6, but only in females. The significant effect of the slope held for both weighted (by impact) and unweighted event specifications. Prenatal events were not associated with either inflammatory marker when childhood events were controlled. There was no evidence for synergistic effects of prenatal and childhood events. **Conclusion:** Independently of prenatal adverse life events, the number and increase in number of adverse life events experienced in childhood were associated positively with plasma levels of inflammatory markers, such as IL-6, in girls. This gender specificity warrants further research.

Introduction

It is increasingly recognised that psychosocial stressors, such as adverse or stressful life events, can activate inflammatory responses both peripherally and in the brain (Danese *et al.* 2011). As a result of the increasing interest in epigenetics, for example, we know that as early as at the prenatal period adverse life events can establish pro-inflammatory tendencies in the foetus and persistently influence physiology after birth (Slopen *et al.* 2015). Stressors experienced after birth but still early in life can also result in similar 'programming' (Bale *et al.* 2010). In recent years, there has been much research into the role of early exposures to stressful life events in inflammatory responses in both adults (Slopen *et al.* 2015) and children (Hostinar *et al.* 2018, Slopen *et al.* 2012, Slopen *et al.* 2013). Intriguingly a recent meta-analysis underscored the importance of taking development into account when examining links between early exposure to stressors or adversity and circulating markers of inflammation (Kuhlman *et al.* 2019), such as C-reactive protein (CRP) and interleukin 6 (IL-6). Kuhlman et al. (2019) showed that the association between early life adversity and both CRP and IL-6 appears to be negligible across youth samples (Fisher's $z = 0.06$ for both; 95% confidence intervals, respectively, were [−0.01, 0.14] and [−0.17, 0.30]). By contrast, a meta-analysis investigating the association between childhood trauma exposure and circulating inflammatory markers in adulthood, published only 3 years earlier (Baumeister *et al.* 2016), showed small, yet significant, effect sizes overall; Fisher's $z = 0.10$ for CRP, $z = 0.08$ for IL-6, and $z = 0.23$ for tumor necrosis factor alpha (TNF-α), measured in too few studies with paediatric populations to make definitive conclusions. As Kuhlman et al. (2019) note, it is possible that in children upregulations in the HPA-axis may be masking the pro-inflammatory phenotype.

Some of the research into the role of early stressors in inflammation in adults has also shown evidence for the role of such early exposures in altering the stress response, for example by sensitizing neural responsiveness to stressful situations experienced in adult life (Levine *et al.* 2015, Nusslock and Miller 2016). To our knowledge, however, there is no research into such interactions for inflammation in childhood, a sensitive developmental window, and a period of great importance for adult health. For example, high inflammation in childhood has been linked to the presence of key preclinical indicators of adult disease risk, such as advanced atherosclerosis progression (Järvisalo *et al.* 2002).

Using longitudinal data from a large UK birth cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC), we carried out this study to explore, for the first time, both the independent and the synergistic effects of prenatal and childhood stressors on inflammatory marker levels in children. In attempting to address our specific research question, we took into account recent developments in the conceptualisation and measurement of stressors (Dohrenwend 2006, Park 2010) and investigated the role of stressful life events separately by number and perceived severity. We also explored if we could stratify our analyses by gender, in view of the evidence for sex differences in the effects of stressors on inflammation (Bourke *et al.* 2012, Derry *et al.* 2015, Baldwin *et al.* 2018), Substantively, we built on and extended previous findings about the role of stressful events in childhood inflammation, most notably by Slopen et al. (2013) who also used ALSPAC. However that study did not consider prenatal stressors at all and adopted a narrow view of childhood adversity (it considered five events out of the 14 available in ALSPAC). By contrast, our study modelled explicitly the effect of adversity prenatally as well as the effect of the interaction between prenatal and postnatal stressful life events.

Method

Study design and participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing transgenerational longitudinal cohort study that enrolled 14,541 pregnant women in the Bristol area of the UK between April 1991 and December 1992 (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Its goal was to investigate social, biological, and environmental impacts on pregnancy outcomes and child mental and physical health (Boyd *et al.* 2013). Additional children were recruited using the original enrolment definition from the participating children's age 7 years onwards, increasing the number to 15,445 foetuses (Fraser *et al.* 2013). Parents completed questionnaires regularly during the pregnancy period and beyond. Starting at children's age 7 years, the sample was invited for biannual clinic visits which included face-to-face interviews and physical tests. Ethics approval was received from the ALSPAC Ethics and Law Committee and local research ethics committees. All participants provided written informed consent and there was no financial compensation (more details at www.alspac.bris.ac.uk). Our analytic sample included 3,915 children (singletons and first-born multiples) who met the following inclusion criteria: had data on (mother-reported) adverse life events at 18 weeks pregnancy; had data on inflammatory markers at age 9 years (measured in ALSPAC with CRP and IL-6); and did not report an infection at the time of blood collection or during the preceding week.

Measures

Inflammation

In ALSPAC, inflammation in childhood was measured with CRP and IL-6 at age 9 years, during a clinic visit. Blood samples were collected from nonfasting participants and were immediately spun and frozen at −80°C. Inflammatory markers were assayed in 2008 after a

median of 7.5 years in storage with no previous freeze-thaw cycles during this period. IL-6 (pg/mL) was measured by enzyme-linked immunosorbent assay (R&D Systems) and high-sensitivity CRP (mg/L) was measured by automated particle-enhanced immunoturbidimetric assay (Roche). All inter-assay coefficients of variation were less than 5%. In the total ALSPAC sample, IL-6 (n=5,072) values ranged from 0.007 to 20.051 pg/mL, while CRP (n=5,082) values ranged from 0.01 to 67.44 mg/L (60 children had CRP values over 10 mg/L).

Life events

In ALSPAC, stressful life events until the time of measurement of inflammation in childhood were measured with two different life events inventories (Supplementary Table S1, available online), both completed by the mother: a 41-item one in pregnancy, covering mother-reported events since the beginning of the pregnancy (Dorrington *et al.* 2014), and a 14-item one, covering upsetting events for the children since their first year of life. Both inventories were derived from other life events checklists (Barnett *et al.* 1983, Brown *et al.* 1973, Brown *et al.* 2009, Honnor *et al.* 1994). In our study, mothers' events were measured at 18 weeks pregnancy (covering events since the beginning of pregnancy) and children's upsetting events were measured at the following time-points: 18 months (covering events since the child was 6 months), 30 months (for events since 18 months), 42 months (for events since 30 months), 57 months (for events since 42 months), 69 months (for events since 57 months), 81 months (for events since 69 months), and 103 months (for events since 81 months). At each time-point and for each of these events there was information about whether the event occurred or not and how severe the impact was (0=No, did not happen, 1=Yes, but was not upset to 4=Yes, and very upset). In our analyses, we considered both the unweighted and the weighted by

mother-rated impact number of the events. Unfortunately, test-retest reliability of the children's events inventory was not tested at the time.

Covariates

We adjusted for a number of covariates known to be associated with both inflammation and exposure to life events among children. These included ethnicity (white, non-white), parental socioeconomic status, which we approximated by maternal education (below O-level, O-level only, A-level only, university degree), and body mass index (BMI). BMI (weight (kg)/height $(m)^2$) was measured during the clinic visit at age 9 years (Lobstein *et al.* 2004).

Statistical analysis

All analyses were performed in STATA 15.0 (StataCorp 2017). Using the SEM command we fitted latent growth curve models to estimate longitudinal trajectories of childhood events, measured with the 14-item upsetting events checklist from ages 18 to 103 months (collected at one-year intervals from 18 to 81 months and almost a two-year interval from 81 to 103 months, as shown above). This command models the intercept and slope of trajectories as latent variables. The individual predicted values of the intercept (set at baseline, 18 months) and the slope (rate of annual change) were then used as predictors of level of inflammation (log-transformed CRP and IL-6 at age 9 years) in a linear regression model. Using the predict command in STATA we generated predictions for the out-of-sample cases, i.e., the cases that were not used in the original estimation. (This command creates predicted values, both in-sample and out-of-sample. Thus, even if a child out of the 3,915 children in our sample had a missing events score on any of the 7 occasions then by this method they would still receive an intercept value and a slope value.) In this way we were able to estimate the intercept and the slope for childhood events in our whole analytic sample (n=3,915). In our linear

regression models therefore, both outcomes (CRP and IL-6) and exposures (prenatal and childhood events) had complete data. In line with our study aims, we examined the effect of the interaction between prenatal events and the intercept and slope of childhood events (and, in all cases, we considered the number and the impact of events in separate models). Events variables were centred before their interaction terms were calculated. Missingness among the confounders ranged from 1.1% (BMI) to 5.3% (maternal education). Confounders were then imputed (20 imputed datasets) using multiple imputation by chained equations. We assumed that missingness was dependent on observed data (missing at random). To predict missing data, we used all variables selected for the analysis models. We imputed up to the analytic sample. With respect to gender differences, there were significant sex by events interactions on inflammation as expected. The significant interactions were sex*adverse life events (ALE) slope on IL-6 and CRP (b=2.72, p<.05, b=2.89, p<.05, respectively); sex*ALE intercept on IL-6 and CRP (b=.21, p<.01, b=.31, p<.01, respectively), and sex*ALE (weighted by impact) intercept on IL-6 and CRP (b=.08, p<.05, b=.12, p<.01, respectively). (There were no significant sex*prenatal adversity interactions on either inflammatory marker.) Thus, we stratified by gender throughout (although, for completeness, we also reported the full sample results in all regression analyses).

Results

Descriptive analyses

A total of 7,722 children attended the clinic visit at age 9. Of these, 5,072 had available information on CRP and IL-6. Of these, 489 reported an infection at the time of the blood collection or during the preceding week and for 668 there was no information about life events at 18 weeks pregnancy. Our final sample was therefore 3,915 children. Table 1 shows descriptive statistics and gender differences in the study variables. As shown, males

experienced a higher number of life events at 18 and 57 months but females were more affected by events at 81 and 103 months. Mothers of males experienced a lower number of events in early pregnancy. At age 9 years, females had higher BMI and higher levels of CRP and IL-6.

Correlations between the study variables are shown in Supplementary Table S2. As expected, weighted and unweighted event specifications were highly inter-related within time-point. IL-6 was positively related to mother's events at 18 weeks pregnancy, childhood events at 81 and 103 months and BMI, while it was negatively associated with maternal education. Even though IL-6 and CRP were correlated, CRP did not correlate with events at any time-point. As expected, and like IL-6, it was associated positively with BMI and negatively with maternal education. As also expected, our analytic sample had experienced less adversity overall (the differences and similarities between the analytic and the non-analytic samples in all study variables are shown in Supplementary Table S3).

Regression models

Below we discuss the results from all four models fitted, and in Supplementary Table S5 we report the results on the sample excluding children with CRP values over 10 mg/L.

Model 1. Number of events in pregnancy and number of events during childhood

In our first linear regression model, we tested, separately for males and females, whether the number of events experienced by the mother in early pregnancy and the number of events experienced by the child in childhood (and their interaction) were associated with IL-6 and CRP at 9 years. We found, in females but not males, that both the intercept and the slope of

childhood events were associated with IL-6, even after adjusting for confounding (Table 2; Supplementary Table S4 for complete cases). By contrast, there was no effect of childhood events on CRP in either males or females, and no association between prenatal events and either inflammatory marker in either gender (although the interaction between prenatal events and the intercept of childhood events was significant in females).

Model 2. Number of events in pregnancy and impact of events during childhood

In this model, we investigated the roles of the number of events experienced during early pregnancy, the perceived impact of childhood events, and their interaction, in IL-6 and CRP levels. We did not find any associations with CRP in either males or females, and the only significant effect on IL-6 was that of the slope of the impact of childhood events in females (Table 2; Supplementary Table S4 for complete cases).

Model 3. Impact of events in early pregnancy and impact of events during childhood

In the third model, we explored the roles of the impact of maternal events in early pregnancy, the impact of childhood events, and their interaction. As in model 2, we did not find any associations with CRP in either males or females, and the only significant effect on IL-6 was that of the slope of the impact of childhood events in females (Table 2; Supplementary Table S4 for complete cases).

Model 4. Impact of events in early pregnancy and number of events during childhood

In the final model, we tested whether the impact of maternal events in early pregnancy, the number of events during childhood and their interaction were associated with inflammatory marker levels at age 9 years. As in model 1, we found, in females but not males, that both the intercept and the slope of childhood events were associated with IL-6, even after adjusting for confounding (Table 2; Supplementary Table S4 for complete cases). By contrast, there was no effect of childhood events on CRP in either males or females, and no association between

the impact of prenatal events and either inflammatory marker in either gender (although the interaction between the impact of prenatal events and the intercept of childhood events was significant in females).

Supplementary analysis

Although our approach to testing interactions follows logically from our approach to testing main effects, we repeated our analysis using the average number of childhood stressors instead of the intercept and slope of their average trajectory (Supplementary Table S6). The interaction between prenatal and childhood stressors was again nonsignificant. This analysis therefore complements our finding that in children prenatal stressors do not affect how the trajectory of stressful life events in childhood is associated with inflammation.

Discussion

Despite much interest in the hypothesis that inflammation can result from maternal exposures to prenatal stressors that sensitize, due to the resulting placental inflammation, to the effect of stressors experienced later, no study has tested it in children. Our study, on a large general-population longitudinal sample with data on plasma levels of inflammatory markers (IL-6 and CRP) at age 9 years, did not show support for this hypothesis. Mother's exposure to stressful life events in early pregnancy (18 weeks) was not associated with inflammatory marker levels when child's exposures to adverse events in childhood were taken into account, nor did it generally sensitize to the long-term effect of stressors experienced by the child after birth on inflammatory marker levels. Rather, child's own initial level of adversity and increase in level of adversity over time across the first decade of life were positively associated with level of IL-6, but only in females. The significant effect of the longitudinal change in adversity held for both weighted and unweighted event specifications. Thus, longitudinal

increases in events, irrespective of their impact, experienced in childhood are associated with IL-6 level in girls.

Our null results about the long-term impact of prenatal adversity on inflammation in the offspring seem to be inconsistent with findings of studies demonstrating that exposures to adversity during gestation have lasting effects on the development of the immune system. For example, in a recent study with adults Slopen et al. 2015 found that when prenatal and childhood adversity were considered together, only prenatal adversity was significantly associated with CRP. It is important to note however that in that study prenatal adversity was a composite score of socioeconomic disadvantage (by using information about family structure, parental education, parental occupation, and family income) based on the expectant mothers' reports, and that not only socially-patterned exposures can have effects on immune function. In our study, we both included a large number of prenatal events, not only those risks that accompany socioeconomic disadvantage or result from it, and added separate controls for socioeconomic disadvantage (Jensen *et al.* 2017).

It is important, however, to note that our measurement of prenatal events did not include maternal depression or maternal history of maltreatment, which have been associated with both inflammation and psychopathology in the offspring. For example, Plant *et al. (*2017), also using ALSPAC, found that maternal history of childhood maltreatment was associated with higher levels of offspring internalising and externalising symptoms in adolescence. Earlier, they had found that maternal prenatal depression was associated with elevated CRP levels (Plant *et al.* 2016) and higher risk of depression (Plant *et al.* 2015) in the offspring at age 25 years.

It is also important to reflect on the inconsistent patterns of association found for our two inflammatory markers, IL-6 and CRP. In our study, no event specification had a significant main effect on CRP. This may reflect the different functions of these two markers, as well as their sources of production (Lockwood *et al.* 2016). As IL-6 is a precursor of CRP (Kerr *et al.* 2001), stressor-evoked IL-6 responses may cause subsequent increases in CRP. In vitro models show that IL-6 can stimulate phasic production of CRP from human hepatocytes within hours (Castell *et al.* 1990). It is not yet known how long it would take for increases in IL-6 to cause increases in systemic levels of CRP in humans in vivo. In our epidemiological sample, IL-6 and CRP were measured at the same time.

Our study has some more important weaknesses, however. First, inflammation was assessed only once. Second, given the observational design, we are not able to conclude definitively that the associations found are causal. Third, mothers reported both on events they themselves experienced and on those experienced by their child, which may introduce issues related to shared method variance and potential reporter bias. Fourth, as with all prospective cohort studies, in ALSPAC the number of participants declines over time, and this sample attrition is non-random (Fraser *et al.* 2013). In turn, selection bias can influence observed associations (Munafò *et al.* 2017). These limitations notwithstanding, our study makes a unique contribution by suggesting an aetiological pathway that may connect plasma levels of IL-6 in childhood with prenatal and childhood adversity, even among the general population. A significant strength of our study is that it was unique in taking a broad view of adversity; it considered both conditions or experiences marked by misfortune (either relative or absolute) (Slopen *et al.* 2013) and stressors that are arguably developmental or universal challenges most families or children encounter, while also allowing individual differences in how both types of stressors were perceived. Our findings clearly suggest that increases in the number of

stressors encountered in childhood, irrespective of their perceived severity, are associated with inflammation in girls. This gender specificity warrants further research.

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Table 1. Descriptive statistics of study variables by gender in the analytic sample (n=3,915), complete cases								
Continuous variables								
	Females (n=1,885)			**Males (2,030)**			**Kruskal-Wallis Test**	**Median test**
	n	**M (SD)**	**Mode [Median] (Range)**	**n**	**M (SD)**	**Mode [Median] (Range)**	χ^2	χ^2
Number of ALE, 18 weeks pregnancy	1,885	3.51 (2.42)	2 [3] (0-16)	2,030	3.44 (2.43)	2 [3] (0-15)	1.18	**0.04***
Number of ALE, 18 months	1,782	0.88 (1.07)	0 [1] (0-14)	1,929	0.92 (1.04)	0 [1] (0-6)	2.52	**5.27***
Number of ALE, 30 months	1,700	1.32 (1.24)	1 [1] (0-8)	1,854	1.33 (1.27)	0 [1] (0-14)	0.00	1.57
Number of ALE, 42 months	1,706	1.55 (1.22)	1 [1] (0-12)	1,868	1.56 (1.23)	1 [1] (0-7)	0.05	0.16
Number of ALE, 57 months	1,668	1.74 (1.08)	1 [1] (0-7)	1,825	1.81 (1.12)	2 [2] (0-6)	3.47	**4.71***
Number of ALE, 69 months	1,611	1.31 (1.22)	1 [1] (0-10)	1,769	1.29 (1.12)	1 [1] (0-7)	0.13	1.13
Number of ALE, 81 months	1,701	1.27 (1.11)	1 [1] (0-9)	1,847	1.22 (1.11)	0 [1] (0-9)	1.58	2.85
Number of ALE, 103 months	1,617	1.15 (1.16)	1 [1] (0-9)	1,728	1.07 (1.10)	1 [1] (0-7)	2.42	1.31
Number (weighted by impact) of ALE, 18 weeks pregnancy	1,885	8.00 (7.04)	4 [6] (0-51)	2,030	7.62 (6.76)	4 [6] (0-46)	3.02	1.65

Number (weighted by impact) of ALE, 18 months	1,782	1.45 (2.24)	0 [1] (0-50)	1,929	1.50 (1.93)	0 [1] (0-12)	1.80	2.67
Number (weighted by impact) of ALE, 30 months	1,700	2.21 (2.43)	0 [2] (0-24)	1,854	2.26 (2.76)	0 [2] (0-56)	-0.00	1.40
Number (weighted by impact) of ALE, 42 months	1,706	2.53 (2.42)	1 [2] (0-18)	1,868	2.52 (2.40)	1 [2] (0-16)	0.03	0.05
Number (weighted by impact) of ALE, 57 months	1,667	2.52 (2.59)	0 [2] (0-25)	1,824	2.56 (2.59)	1 [2] (0-16)	0.43	1.24
Number (weighted by impact) of ALE, 69 months	1,611	2.24 (2.54)	0 [1] (0-24)	1,769	2.10 (2.21)	0 [2] (0-16)	0.33	0.04
Number (weighted by impact) of ALE, 81 months	1,610	1.92 (2.40)	0 [1] (0-21)	1,759	1.68 (2.27)	0 [1] (0-18)	**8.53****	**9.35****
Number (weighted by impact) of ALE, 103 months	1,617	2.44 (2.74)	0 [2] (0-31)	1,728	2.22 (2.65)	0 [2] (0-26)	**5.66***	**5.47***
IL-6	1,885	1.28 (1.44)	0.43 [0.88] (0.01-13.90)	2,030	1.11 (1.48)	0.51 [0.68] (0.01-20.05)	**83.10****	**66.77****
CRP	1,885	0.70 (1.92)	0.11 [0.26] (0.01-41.04)	2,030	0.52 (1.80)	0.08 [0.16] (0.01-45.17)	**195.11****	**165.96****

BMI	1,857	17.81 (2.87)	16 [17.24] (12.64-34.25)	2,013	17.32 (2.55)	16 [16.73] (12.46-29.49)	**28.50****	**28.51****
Maternal education	1,782	3.36 (1.15)	3 [3] (1-5)	1,992	3.32 (1.17)	3 [3] (1-5)	0.75	0.63
Categorical variables								
	n	**%**		**n**	**%**		χ^2	χ^2
Non-white	1,824	3.84	-----	1,957	4.09	----	0.01	0.15

Note: ALE=Adverse life events; IL-6=Interleukin 6; CRP=C-reactive protein; BMI=Body Mass Index
* p<.05 **p<.01

Table 2. Associations between prenatal and childhood (0-9 years) exposures to adverse life events and inflammation at age 9

	IL-6[1]						CRP[1]					
	Males (n=2,030)		Females (n=1,885)		Total Sample (n=3,915)		Males (n=2,030)		Females (n=1,885)		Total Sample (n=3,915)	
	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE
Model 1: Number of adverse life events (ALE) at 18 weeks pregnancy and intercept and slope of number of ALE in childhood												
Unadjusted												
ALE slope	0.29	1.23	**2.11****	0.55	**1.64****	0.54	-0.50	1.58	1.68	0.75	1.25	0.72
ALE intercept	0.00	0.07	**0.13***	0.05	**0.08***	0.04	-0.09	0.09	0.11	0.07	0.02	0.05
ALE pregnancy	0.00	0.00	0.01	0.00	0.01	0.00	-0.01	0.01	-0.00	0.01	-0.00	0.00
ALE slope * ALE pregnancy	0-.00	0.46	0.00	0.20	0.08	0.20	-0.41	0.59	0.12	0.27	0.08	0.26
ALE intercept * ALE pregnancy	-0.01	0.02	0.01	0.01	0.00	0.01	-0.04	0.03	**0.05***	0.02	0.01	0.01
Fully adjusted												
ALE slope	-0.05	1.20	**1.67****	0.53	**1.09***	0.52	-1.25	1.45	0.58	0.68	-0.07	0.64
ALE intercept	0.00	0.06	**0.12***	0.05	**0.07***	0.03	-0.13	0.08	0.08	0.06	-0.01	0.04
ALE pregnancy	0.00	0.00	0.01	0.00	0.00	0.00	-0.01	0.00	-0.00	0.01	-0.01	0.00
ALE slope * ALE pregnancy	0.11	0.45	0.01	0.19	0.08	0.19	-0.08	0.54	0.13	0.24	0.10	0.24
ALE intercept * ALE pregnancy	0-.00	0.02	0.01	0.01	0.00	0.01	-0.02	0.02	**0.05***	0.02	0.01	0.01
Model 2: Number of ALE at 18 weeks pregnancy and intercept and slope of (weighted by impact) number of ALE in childhood												
Unadjusted												
ALE slope	0.40	0.34	**0.51****	0.13	**0.49****	0.13	0.14	0.44	0.31	0.19	0.32	0.18
ALE intercept	0.00	0.02	0.04	0.02	0.02	0.02	-0.04	0.03	0.03	0.04	-0.00	0.02
ALE pregnancy	0.00	0.00	0.01	0.00	0.00	0.00	-0.01	0.01	-0.00	0.01	-0.00	0.00
ALE slope * ALE pregnancy	0.01	0.13	0.02	0.04	0.02	0.05	-0.02	0.16	0.09	0.06	0.07	0.06
ALE intercept * ALE pregnancy	-0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.01	0.02	0.01	0.00	0.00

Table 2. Associations between prenatal and childhood (0-9 years) exposures to adverse life events and inflammation at age 9

	IL-6[1]						CRP[1]					
	Males (n=2,030)		Females (n=1,885)		Total Sample (n=3,915)		Males (n=2,030)		Females (n=1,885)		Total Sample (n=3,915)	
	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE
Fully adjusted												
ALE slope	0.18	0.33	**0.40****	0.13	**0.30***	0.13	-0.35	0.40	0.03	0.17	-0.013	0.16
ALE intercept	-0.00	0.02	0.04	0.02	0.02	0.01	-0.05	0.03	0.03	0.03	-0.01	0.02
ALE pregnancy	0.00	0.00	0.01	0.00	0.00	0.00	-0.01	0.00	-0.00	0.01	-0.01	0.00
ALE slope * ALE pregnancy	0.04	0.12	0.02	0.04	0.03	0.04	0.04	0.15	0.09	0.06	0.08	0.05
ALE intercept * ALE pregnancy	-0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.01	0.01	0.01	0.00	0.00
Model 3: (Weighted by impact) number of ALE at 18 weeks pregnancy and intercept and slope of (weighted by impact) number of ALE in childhood												
Unadjusted												
ALE slope	0.37	0.34	**0.52****	0.13	**0.49****	0.13	0.13	0.44	0.32	0.19	0.32	0.18
ALE intercept	-0.00	0.02	0.04	0.02	0.01	0.01	-0.04	0.03	0.03	0.03	-0.01	0.02
ALE pregnancy	0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.00	-0.00	0.00	-0.00	0.00
ALE slope * ALE pregnancy	0.01	0.04	0.00	0.01	0.00	0.01	0.00	0.05	0.03	0.02	0.02	0.02
ALE intercept * ALE pregnancy	-0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.00	0.00	0.00	0.00	0.00
Fully adjusted												
ALE slope	0.15	0.34	**0.41****	0.13	**0.29***	0.13	-0.36	0.40	0.03	0.17	-0.14	0.16
ALE intercept	-0.00	0.02	0.04	0.02	0.02	0.01	-0.05	0.03	0.03	0.03	-0.01	0.02
ALE pregnancy	0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.00	-0.00	0.00	-0.00	0.00
ALE slope * ALE pregnancy	0.02	0.04	0.00	0.01	0.00	0.01	0.02	0.05	0.03	0.01	0.03	0.02
ALE intercept * ALE pregnancy	-0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.00	0.00	0.00	0.00	0.00
Model 4: (Weighted by impact) number of ALE at 18 weeks pregnancy and intercept and slope of number of ALE in childhood												

Table 2. Associations between prenatal and childhood (0-9 years) exposures to adverse life events and inflammation at age 9

	IL-6[1]						CRP[1]					
	Males (n=2,030)		Females (n=1,885)		Total Sample (n=3,915)		Males (n=2,030)		Females (n=1,885)		Total Sample (n=3,915)	
	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE	Coef.	SE
Unadjusted												
ALE slope	0.24	1.23	**2.14****	0.55	**1.64****	0.54	-0.51	1.58	**1.71***	0.75	1.26	0.72
ALE intercept	-0.00	0.07	**0.13****	0.05	**0.08***	0.04	-0.10	0.09	0.11	0.07	0.02	0.05
ALE pregnancy	0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.00	-0.00	0.00	-0.00	0.00
ALE slope * ALE pregnancy	0.02	0.16	-0.03	0.06	0.00	0.06	-0.10	0.21	0.04	0.09	0.02	0.09
ALE intercept * ALE pregnancy	-0.00	0.00	0.00	0.00	0.00	0.00	-0.01	0.01	**0.01***	0.00	0.00	0.00
Fully adjusted												
ALE slope	-0.10	1.20	**1.70****	0.53	**1.09***	0.52	-1.26	1.45	0.60	0.67	-0.07	0.64
ALE intercept	-0.00	0.06	**0.13***	0.05	0.07	0.03	-0.13	0.08	0.09	0.06	-0.01	0.04
ALE pregnancy	0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.00	-0.00	0.00	-0.00	0.00
ALE slope * ALE pregnancy	0.07	0.16	-0.02	0.06	0.01	0.06	0.02	0.19	0.05	0.08	0.05	0.08
ALE intercept * ALE pregnancy	0.00	0.00	0.00	0.00	0.00	0.00	-0.00	0.01	**0.01***	0.00	0.00	0.00

Notes: IL-6=Interleukin 6; CRP=C-reactive protein; ALE=Adverse life events. The fully-adjusted models controlled for all confounders (BMI, SES, ethnicity). The total sample results are adjusted for gender.

[1]Log-transformed

* p<.05 ** p<.01