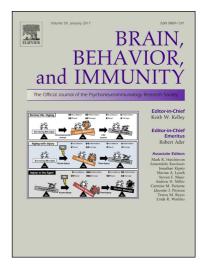# Accepted Manuscript

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Stressful life events, inflammation and emotional and behavioural problems in children: A population-based study

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Short/running title: adversity, inflammation & problem behaviour in children

Keywords: ALSPAC, externalising, inflammation, internalising, life events

Abstract

Objective: To test the hypothesis that higher plasma levels of inflammatory markers due to exposure to adverse life events may lead to internalising and externalising symptoms in children. **Method:** Using data from 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 explain the longitudinal association between adverse life events (at ages 1-9 and 9-11 years) and internalising and externalising symptoms (at ages 9 and 11 years). Data (n=4,583) were analysed using cross-lagged panel modelling to take into account reciprocal associations and reverse causality, and path analyses to test for mediation. Gender, ethnicity, body mass index, maternal education, paternal social class and maternal depression were used as potential confounders.

Results: CRP was not associated with adverse life events. There was evidence for partial mediation by IL-6 such that exposure to adverse life events was associated with increased levels of IL-6 later, in turn associated with later internalising symptoms. These associations were robust to adjustment for confounders. IL-6 did not explain part of the opposite association, that of earlier internalising symptoms and later life events, nor did it explain either direction of the association between life events and externalising symptoms.

Conclusion: Our findings suggest a pathway that may connect early psychosocial adversity and childhood internalising symptoms via higher plasma levels of inflammatory markers such as IL-6.

1. Introduction

Adverse life events are associated with emotional (internalising) and behavioural (externalising) problems in children but the mechanisms explaining this association are not clear. Most models of developmental psychopathology postulate that exposure to these psychosocial stressors can initiate biological processes that increase risk for both types of problems in children but, to our knowledge, no study has yet examined inflammation as the biological process that mediates this association. Inflammation is typically thought of as the body's primary response to physical injury or infection. However, there is now substantial evidence that psychosocial stressors can also trigger significant increases in inflammatory activity in children and 'get under the skin'.[1-4] In fact, it appears that psychosocial adversity in childhood may alter the long-term predisposition to inflammation. For example, a recent meta-analysis showed that childhood trauma is associated with dysregulation of the inflammatory system in adulthood, highlighting the long-term role of early stressful events in the modification of the inflammatory immune system.[5] Increases in inflammatory marker levels can in turn elicit profound changes in cognition and behaviour, which include the initiation of symptoms such as sad mood, anhedonia, fatigue and social and behavioural withdrawal in both children[1-4] and adults. For example, several studies with adults have demonstrated a significant association between higher levels of inflammatory markers and the development of psychiatric diseases such as depression and psychosis.[6, 8, 9]

One can hypothesise therefore that adverse life events may be associated with internalising and externalising symptoms in children via inflammation. Among children however, there is also evidence that some adverse life events may be both the cause and the consequence of internalising and externalising symptoms,[10, 11] and that higher levels of inflammatory markers can also result from internalising or externalising symptoms.[12] Internalising and externalising

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symptoms may affect social and personal life and therefore could increase risk for problems in social relationships or for some types of life events.[11, 13, 14] For example, children who are extremely sad or anxious (therefore exhibiting internalising symptoms) may have more problems socialising with other children or building a good relationship with their parents or teachers which may lead to a series of negative events or adverse experiences such as school withdrawal, financial problems due to medical expenses or an increase in parents' arguments. Moreover internalising and externalising symptoms have been associated with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis [15, 16] and with higher levels of inflammatory markers.[12] Importantly, although elevated inflammatory markers have been linked to previous exposures to psychosocial stressors, they can also reflect selection into them. That is, as an indicator of poor health[17] or cognition, [18] elevated plasma levels of inflammatory markers can arguably function also as a selective mechanism into stressors such as adverse life events. Together, these findings suggest not only that psychosocial stressors and internalising and externalising symptoms can be reciprocally related in children but also that higher levels of inflammatory markers could explain either direction of their relationship.[19]

We carried out this study to explore this. Using longitudinal data from a large UK birth cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC), we tested for the first time if higher levels of inflammatory markers due to adverse life events may play a role in internalising and externalising symptoms in children while considering that, as discussed above, causal associations between these variables may be complex. Although we expected life events to cause these symptoms rather than the reverse, by measuring life events longitudinally we were also able to test for reverse causality. This in turn enabled us to test which effect inflammatory markers would mediate (that is, the effect of life events on

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symptoms or that of symptoms on life events). To our knowledge, no study has yet tested the mediating role of inflammatory markers in these two frequently competing hypotheses about the direction of the association between psychosocial stressors and internalising/externalising symptoms in children.

2. **Materials and Methods**

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.bristol.ac.uk/alspac/researchers/our-data/). Its goal was to investigate social, biological, and environmental impacts on pregnancy outcomes and child mental and physical health.[20] Additional children were recruited using the original enrolment definition from the participating children's age 7 years onwards, increasing the number to 15,445 pregnancies to date.[21] 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 Law and Ethics 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 study's analytic sample included children who had data on inflammation at age 9 years [measured in ALSPAC with C-reactive protein (CRP) and interleukin-6 (IL-6)] and who did not report an infection at the time of blood collection or during the preceding week (n=4,583). We measured adverse life events at two time periods, at ages 1-9 years and 9-11 years, and internalising and externalising symptoms at ages 9 and 11 years.

2.1. Measures

2.1.1 Inflammation, age 9 years

In ALSPAC, inflammation in childhood was measured with CRP and IL-6 at age 9, 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%.

2.1.2 Life events, ages 1-9 and 9-11 years

We used a mother-reported inventory of 43 common and rare life events (full list of events in Table S1 in the Supplementary Material), included in other life events checklists.[22-25] This inventory was administered at several time-points after the child's birth, including 21 months (covering events since the child was 8 months), 33 months (covering events since the child was 18 months), 47 months (covering events since the child was 33 months), 61 months (covering events since the child was 47 months), 73 months (covering events since the child was 61 months), 110 months (covering events since the child was 73 months) and 134 months (covering events since the child was 110 months). At each time-point, a score of 0 was assigned if the event did not occur and a score of 1 if it did. For our analysis, we derived a life events score at ages 1-9 (see eMethods in the Supplementary Material) by calculating whether each of the 43 events ever occurred between 8 and 110 months. In order to make the level of exposure to events comparable between the two time periods we divided the total score of life events at each time period by the number of months each covered (102 months for our first time period and 24 months for our second).

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2.1.3 Internalising and externalising symptoms*, ages 9 and 11 years*

Internalising and externalising symptoms were assessed using the mother-rated Strengths and Difficulties Questionnaire (SDQ) at ages 9 and 11 years. The SDQ is a valid and reliable tool for measuring such difficulties in children. [26] It includes 20 items related to children's difficulties (in the past 6 months) scored on a 3-point scale with 0 = 'not true', 1 = 'somewhat true' and 2 = 'certainly true'. Items can be summed to form four scales (emotional symptoms, conduct problems, hyperactivity, and peer problems), or two (internalising problems, the sum of the scores on the emotional and peer problems items, and externalising problems, the sum of the scores on the conduct problems and hyperactivity items). [27]

2.1.4 Covariates

We adjusted for a number of covariates known to be associated with children's level of inflammatory markers, internalising and externalising symptoms and exposure to life events. These included gender, ethnicity (white, non-white), maternal depression, which in ALSPAC was assessed with the Edinburgh Postnatal Depression Scale (EDPS) at 32 weeks of pregnancy, parental socio-economic status at the same time-point, which we approximated by maternal education (university degree or not) and paternal social class (I, II, III (non-manual), III (manual), IV, V), and obesity status (body mass index (BMI) above the 95th percentile for children of the same age). [28] BMI (weight (kg)/height (m)^2) was measured during the clinic visit at age 9. Consistent with previous literature, we used antenatal maternal depression, rather than measuring maternal depression closer to our assessment points, because antenatal maternal depression is not on any causal pathway and is associated with both inflammation and development of mental problems in the offspring during childhood and adulthood. [29,30]

2.2. Statistical analysis

Analyses were performed in STATA 15.0 (Stata Corporation, College Station, TX, 1997).

First, we explored the differences between the analytic sample (n=4,583) and the non-analytic

sample (n=10,862) in the study variables (Table 1). In our analytic sample, only

inflammatory markers (IL-6 and CRP) had complete data. Among exposures and outcomes,

missingness ranged between 14·6% (internalising and externalising symptoms at 9 years) and

30·3% (adverse life events at 1-9 years). The percentage of missingness in the confounding

variables varied from 0·1% (gender) to 15·2% (paternal social class) (further details in

eMethods in the Supplementary Material). To deal with missingess, we imputed missing data

(20 imputed datasets) using multiple imputation by chained equations (MICE)[31]. We assumed

that missingness was dependent on observed data (missing at random). To predict missing

data, we used all variables selected for analysis models. We imputed up to the sample with

complete data on inflammation.

To test if life events predict symptoms and vice versa, we estimated a cross-lagged model

(Model 1) using the imputed data. Next, in path analyses, we explored if CRP and IL-6 levels

mediate any direction of the longitudinal relationship between events and symptoms (Model

2). We then adjusted for all covariates (Model 3). We also carried out a sensitivity analysis,

in which we refitted all models in a restricted sample of children with no psychiatric

disorders. By measuring pre-clinical outcome in this sensitivity analysis, we were thus able to

examine the role of CRP and IL-6 levels in the (possible) progression to psychiatric disorder.

We were also able to elucidate the association between CRP and IL-6 levels and risk of

psychiatric disorders without the confounding burden of psychiatric comorbidities.

Eliminating this confound is an important strength. Findings from adults suggest that

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examining proinflammatory markers as putative biomarkers and using anti-inflammatory medications as putative treatments may be more fruitful among those younger and/or earlier in their course of illness. In ALSPAC, psychiatric disorders in childhood were assessed at ages 7 and 10 years using the parent version of the Development and Well-Being Assessment (DAWBA) and were coded, according to DSM-IV criteria, by two experienced psychiatrists. The DAWBA assesses the presence of emotional, behavioural, and hyperactivity disorders in children. Finally, we carried out a second sensitivity analysis to explore the association of specific life events with both inflammatory markers and internalising and externalising symptoms.

3. Results

3.1 Bias and descriptive analyses

Among the 14,689 ALSPAC children alive at age 1, 7,722 attended the clinic visit at age 9. CRP and IL-6 data at age 9 were available for 5,072 children, 489 of whom reported an infection at the time of the blood collection or during the preceding week and were therefore excluded from the analysis. Thus, our analytic sample was 4,583 children.

Table 1 shows the descriptive statistics and the differences between the analytic and non-analytic samples. The non-analytic sample had higher internalising and externalising symptom scores at both time-points, higher CRP and IL-6 values, mothers with more depressive symptoms and fathers in lower-prestige occupations. The two samples did not differ in the number of events at 9-11 years, however, or gender distribution (girls represented 49% of the analytic sample and 48·4% of the non-analytic sample). The analytic sample was exposed to more adverse life events at 1-9 years and had higher proportions of white children, non-obese children and university-educated mothers.

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As expected, internalising and externalising symptoms measured at ages 9 and 11 years were positively correlated with life events at both periods (ages 1-9 and 9-11 years) (Table 2). Although IL-6 and CRP were correlated, only IL-6 was positively related with both life events and symptoms. CRP was not related to life events and although, like IL-6, it was associated only with internalising symptoms, its associations with them were weaker. We therefore decided to exclude CRP from all further analyses and focus on IL-6.

3.2 Cross-lagged models

3.2.1 Models 1a and 1b

The internalising symptoms model (Model 1a) showed that the number of life events experienced until age 9 was positively associated with an increase in the level of internalising symptoms at age 11 (Figure 1 and Figure S1 in the Supplementary Material). Additionally, internalising symptoms at age 9 were positively associated with an increase in the number of events experienced from then until age 11. A Wald test revealed that the effect of events on symptoms was larger than that of symptoms on events (chi-square=33·36, df=1, $p<0·001$). The externalising symptoms model (Model 1b) showed a different pattern (Figure 1 and Figure S2 in the Supplementary Material). Again, both cross-lagged paths were significant, showing a reciprocal association between life events and externalising symptoms, but the effect of symptoms on events was larger than the reverse (chi-square=18·85, df=1, $p<0·001$).

3.3 Mediation models

3.3.1 Model 2a (Adverse life events to internalising or externalising symptoms)

This model showed that IL-6 mediated part of the effect of early life events on later internalising symptoms (indirect effect: $β=0·01$, $p<0·05$, 95% CI=0·000-0·005; total effect:

β=0·17, p<0·01, 95% CI=0·138-0·211; direct effect: β=0·17, p<0·01, 95% CI=0·136-

0·208[1]). There was no mediation by IL-6 in the externalising symptoms model (Figure 1).

3.3.2 Model 2b (Internalising or externalising symptoms to adverse life events)

In this model IL-6 did not mediate either the association between early internalising

symptoms and later number of life events or the one between early externalising symptoms

and later number of life events (Figure 1).

3.3.3 Model 3

This model tested if the path from early life events to later internalising symptoms via IL-6

(Model 2a) was robust to adjustment for confounders. Table 3 shows all the regression

coefficients (both in the imputed sample and in the complete cases sample) of this model. As

can be seen, the path from life events at ages 1-9 to internalising symptoms at age 11 via IL-6

at age 9 was significant even after adjustment (indirect effect: β=0·01, p<0·05, 95%

CI=0·000-0·004; total effect: β=0·14, p<0·01, 95% CI=0·103-0·177; direct effect: β=0·13,

p<0·01, 95% CI=0·100-0·175[2]) (Figure 1).

3.4 Sensitivity analyses

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[1] Using unstandardised regression coefficients, direct effect: b=9·58, SE=1·07; indirect effect:
b=0·17, SE=0·06; total effect: b=9·75, SE=1·07.

[2] Using unstandardised regression coefficients, direct effect: b=7·57, SE=1·06; indirect effect:

b=0·12, SE=0·06; total effect: b=7·69, SE=1·06.

[3] Using unstandardised regression coefficients, direct effect: b=6·95, SE=1·03; indirect effect: b=0·12,

SE=0·05; total effect: b=7·07, SE=1·03.

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Given the significant effects only on internalising symptoms, we carried out a sensitivity

analysis in which we excluded those children with any emotional disorder diagnosis, assessed

with the DAWBA, at ages 7 or 10 years (142 children) and replicated our analyses in this

restricted sample (n=4,441). Our findings did not change. That is, both the reciprocal

association between life events and internalising symptoms remained, and IL-6 mediated the

effect of early life events on later internalising symptoms, even after adjustment for

confounders (indirect effect: β=0·01, p<0·05, 95% CI=0·000-0·004; total effect: β=0·13,

p<0·01, 95% CI=0·098-0·173; direct effect: β=0·12, p<0·01, 95% CI=0·096-0·171[3]).

We also considered examining the effects of specific events, in line with much evidence,

including from ALSPAC as well [36], showing differential associations of psychiatric outcomes

by event type. However, an exploratory factor analysis we performed extracted different

factors for the two time-points. More importantly, at both time-points the full scale of events

correlated more strongly with both internalising symptoms and IL-6 than did any of the

specific factors (see eMethods and Table S2 in the Supplementary Material for full details).

4. Discussion

Despite much interest in the hypothesis that elevated plasma levels of inflammatory markers

due to psychosocial stressors, such as adverse life events, cause mental health problems,[7] no

study, to our knowledge, has tested it in children while allowing for reciprocal associations

between stressors and mental health problems and reverse causality. Until we carried out this

study, it was also unknown if elevated inflammatory markers explain the opposite effect, also

much discussed, that of mental health problems causing adverse life events, [10] in children.

Our study, measuring longitudinally life events and children's mental health problems

(internalising and externalising symptoms) in the first decade of life, showed clear support for

the first hypothesis. Exposure to mother-reported family stressors was associated with later higher IL-6 levels, in turn associated with later internalising symptoms, even after adjustment for confounders. Levels of inflammatory markers did not explain the opposite association, that of earlier internalising symptoms and later life events, nor did it explain either direction of the association between life events and externalising symptoms. Importantly, it partially mediated the dominant association in the internalising symptoms model, that of adverse life events on symptoms rather than the reverse. As such, our study breaks new ground while adding to the existing evidence of an association between childhood levels of inflammatory markers and later psychiatric symptoms. [6]

Our study has some weaknesses, too. First, it is limited by only one assessment of inflammatory markers. Second, given the observational design, we are not able to conclude definitively that the associations found are causal. It is important to also consider genetic mechanisms, which offer an alternative, noncausal interpretation of the associations [32] we found between exposure to psychosocial stressors, elevated IL-6 and increased internalising symptoms in children. For example, genetic pathways related to the immune system predict risk for several psychiatric diagnoses including depression.[33] In turn, early expressions of liability to these conditions might increase the risk of exposure to psychosocial stressors, in line with a stress generation explanation.[34] According to this, in adults but also children,[35] depression or depressogenic vulnerabilities can increase susceptibility to stressful events that are at least in part influenced by the individual. Third, our events checklist did not cover specifically events experienced by the child, and so our analyses may have underestimated the relative importance of events for both inflammatory marker levels and internalising/externalising symptoms. Fourth, mothers reported on both events and internalising and externalising symptoms, which may introduce issues related to shared

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method variance or raise concerns about potential reporter bias. Whilst shared method variance is important to acknowledge, we note that we controlled for maternal depression and thus likely reduced reporter bias substantially. Finally, the mediation effect found is small which underlines the strong direct impact of adverse life events on internalising symptoms.

4.1 Conclusions

These limitations notwithstanding, our study makes a unique contribution by suggesting an aetiological pathway that may connect early psychosocial adversity and childhood internalising symptoms via IL-6 levels. Current investigations of the role of psychosocial adversity in mental health problems via inflammatory markers focus on clinical diagnoses and almost exclusively on adults. Our study shows that even within healthy children variation in inflammatory marker levels correlates with psychosocial stressors and internalising symptoms, an important finding. Our results however go beyond this. They show that exposure to adverse life events was positively related to elevated inflammatory markers, in turn associated with internalising symptoms. Importantly, the design of our study allowed us to test for reverse causality in the association between events and symptoms, which in turn enabled us to test which effect inflammatory markers would mediate (that is, the effect of events on symptoms or that of symptoms on events). To our knowledge, no study has yet tested the mediating role of inflammatory markers in these two directional hypotheses linking psychosocial stressors and internalising/externalising symptoms in children. Our study showed that the association between events and symptoms was, as expected, reciprocal for both types of symptoms although the dominance of the association differed by symptom type, with life events having a larger effect on internalising symptoms than the reverse, and externalising symptoms having a larger effect on events than the reverse. Our findings suggest that, in childhood, the plasma level of inflammatory markers explains, albeit partly,

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the stronger path of the reciprocal relationship between adverse life events and internalising

symptoms.

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	Analytic sample (N=4,583)		Non-analytic sample (N=10,106)		
	N	M (SD)	N	M (SD)	p value
Internalising symptoms (9 years)	3,913	2·46 (2·62)	4,113	2·82 (2·83)	0·00
Externalising symptoms (9 years)	3,911	4·08 (3·12)	4,115	4·38 (3·23)	0·00
Internalising symptoms (11 years)	3,631	2·38 (2·57)	3,696	2·75 (2·87)	0·00
Externalising symptoms (11 years)	3,628	3·86 (3·13)	3,693	4·09 (3·20)	0·00
Adverse life events (1-9 years)	3,196	13·13 (4·65)	4,309	12·62 (5·05)	0·00
Adverse life events (9-11 years)	3,741	3·89 (2·90)	3,905	3·96 (3·06)	0·25
IL-6, 9 years	4,583	1·21 (1·47)	489	2·02 (2·30)	0·00
CRP, 9 years	4,583	0·62 (1·93)	499	2·43 (6·19)	0·00
Paternal social class (I to V)	3,883	2·95 (2·37)	7,162	3·32 (3·81)	0·00
Maternal depression	4,141	6·70 (4·86)	8,059	7·28 (5·19)	0·00
	n	%	n	%	
Obesity, 9 years	185	4·08	196	6·31	0·00
Mother is university-educated	711	17·46	898	11·74	0·00
Female	2,244	49·02	4,975	48·41	0·49
Non-white	167	4·02	446	5·58	0·00

Note. IL-6=Interleukin-6; CRP=C-reactive protein. Number of events is not weighted by time period, for illustrative purposes, in this table

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	Internalising symptoms, Age 9	Internalising symptoms, Age 11	Externalising symptoms, Age 9	Externalising symptoms, Age 11	Adverse life events, Ages 1-9	Adverse life events, Ages 9-11	IL-6, Age 9	CRP, Age 9
Internalising symptoms, Age 9	1							
Internalising symptoms, Age 11	0·589**	1						
Externalising symptoms, Age 9	0·373**	0·317**	1					
Externalising symptoms, Age 11	0·301**	0·393**	0·730**	1				
Adverse life events, Ages 1-9	0·154**	0·175**	0·170**	0·180**	1			
Adverse life events, Ages 9-11	0·138**	0·166**	0·129**	0·154**	0·432**	1		
IL-6, Age 9	0·069**	0·054**	0·027	-0·000	0·059**	0·029	1	
CRP, Age 9	0·065**	0·047**	-0·003	-0·025	0·017	-0·011	0·451**	1
Female	0·046**	0·029	-0·136**	-0·133**	0·026	0·021	0·130**	0·197**
Obesity, Age 9	0·060**	0·062**	0·017	-0·004	0·002	-0·012	0·171**	0·299**

Table 2. Pearson's correlations of the study variables in the analytic sample (N=4,583)

Mother is university educated	0·000	-0·004	-0·079**	-0·074**	0·014	0·029	-0·017	-0·025
Non-white	0·016	0·023	0·028	0·021	0·052**	0·029	0·026	-0·003
Paternal social class (low)	0·014	0·013	0·096**	0·093**	-0·005	-0·036*	0·051**	0·006
Maternal depression	0·182**	0·200**	0·188**	0·176**	0·203**	0·128**	0·021	0·017

Note. IL-6=Interleukin-6 (log-transformed); CRP=C-reactive protein (log-transformed)

* p<.05   ** p<.01

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Table 3. Fully-adjusted mediation model (Model 3) of internalising symptoms

Direct paths (Adverse life events to internalising symptoms)	Imputed Sample (n=4,583)			Complete Cases Sample (n=2,466)		
	b	SE	95% CI	B	SE	95% CI
IL-6[1] (age 9) → internalising symptoms (age 11)	0·11*	0·04	0·02-0·21	0·08	0·05	-0·03-0·19
Adverse life events (ages 1-9) → internalising symptoms (age 11)	7·57**	1·06	5·45-9·68	7·65**	1·16	5·38-9·93
Obesity (age 9) → internalising symptoms (age 11)	0·52**	0·19	0·14-0·90	0·26	0·25	-0·23-0·76
Non-white → internalising symptoms (age 11)	0·02	0·21	-0·39-0·44	0·24	0·28	-0·30-0·79
Maternal education → internalising symptoms (age 11)	0·00	0·11	-0·22 -0·22	0·11	0·13	-0·13 -0·37
Female → internalising symptoms (age 11)	0·05	0·07	-0·10-0·21	0·14	0·10	-0·05-0·33
Paternal social class (low) → internalising symptoms (age 11)	0·00	0·03	-0·06-0·08	-0·01	0·04	-0·09-0·06
Maternal depression → internalising symptoms (age 11)	0·09**	0·00	0·07-0·10	0·08**	0·01	0·06-0·11
Adverse life events (ages 1-9) → IL-6 (age 9)	1·04**	0·30	0·44-1·63	1·34**	0·39	0·57-2·11
Obesity (age 9) → IL-6 (age 9)	0·63**	0·05	0·52-0·74	0·61**	0·08	0·44-0·78
Non-white → IL-6 (age 9)	0·07	0·06	-0·05-0·20	0·14	0·09	-0·04-0·33
Maternal education → IL-6 (age 9)	-0·00	0·03	-0·06 -0·08	-0·00	0·04	-0·08 - 0·08
Female → IL-6 (age 9)	0·20**	0·02	0·15-0·25	0·22**	0·03	0·16-0·29
Paternal social class (low) → IL-6 (age 9)	0·02**	0·01	0·00-0·05	0·02*	0·01	0·00-0·05
Maternal depression → IL-6 (age 9)	0·00	0·00	-0·00-0·00	0·00	0·00	-0·00-0·00
Direct paths (Internalising symptoms to adverse life events)	Imputed Sample (n=4,583)			Complete Cases Sample (n=2,930)		
	b	SE	95% CI	B	SE	95% CI
IL-6[1] (age 9) → adverse life events (ages 9-11)	0·00	0·00	-0·00-0·00	0·00	0·00	-0·00-0·00
Internalising symptoms (ages 9) → adverse life events (ages 9-11)	0·01**	0·00	0·00-0·00	0·01**	0·00	0·00-0·00
Obesity (age 9) → adverse life events (ages 9-11)	-0·01	0·00	-0·03-0·00	-0·01	0·01	-0·03-0·00
Non-white → adverse life events (ages 9-11)	0·01	0·01	-0·00-0·03	0·02	0·01	0·00-0·04
Maternal education → adverse life events (ages 9-11)	0·00	0·00	-0·00-0·01	0·00	0·00	-0·00-0·01
Female → adverse life events (ages 9-11)	0·00	0·00	-0·00-0·01	0·00	0·00	-0·00-0·01
Paternal social class (low) → adverse life events (ages 9-11)	-0·00*	0·00	-0·00 - -0·00	-0·00*	0·00	-0·00 - -0·00
Maternal depression → adverse life events (ages 9-11)	0·00**	0·00	0·00-0·00	0·00**	0·00	0·00-0·00
Internalising symptoms (ages 9) → IL-6 (age 9)	0·01**	0·00	0·00-0·02	0·01**	0·00	0·00-0·03
Obesity (age 9) → IL-6 (age 9)	0·62**	0·05	0·51-0·73	0·63**	0·07	0·47-0·78
Non-white → IL-6 (age 9)	0·08	0·06	-0·04-0·21	0·11	0·08	-0·05-0·28
Maternal education → IL-6 (age 9)	0·01	0·03	-0·06-0·08	0·01	0·04	-0·06-0·09
Female → IL-6 (age 9)	0·20**	0·02	0·15-0·25	0·21**	0·03	0·15-0·27
Paternal social class (low) → IL-6 (age 9)	0·02**	0·01	0·00-0·04	0·02**	0·01	0·00-0·05

Maternal depression → IL-6 (age 9)	0·00	0·00	-0·00-0·00	0·00	0·00	-0·00-0·00

Note: b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence Interval; IL-6=Interleukin-6;

[1] Log-transformed
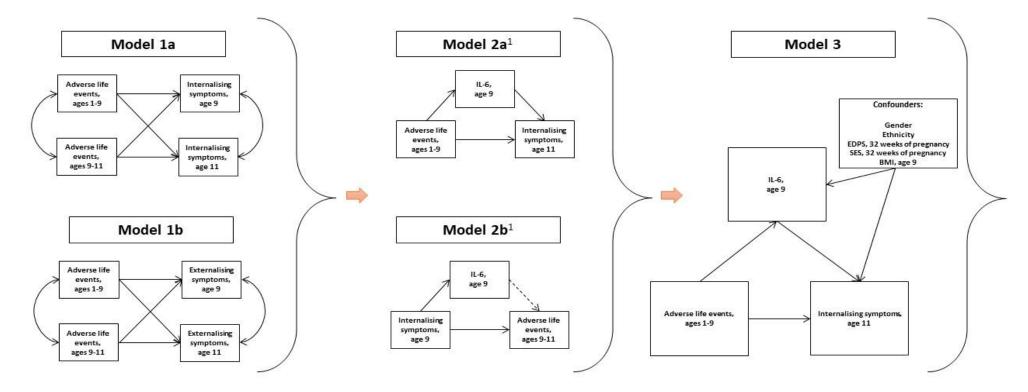
[*]p<0.05 [**]p<0.01

Figure 1: Models tested in our analysis.

Note: IL-6 = Interleukin 6; BMI= Body Mass Index; SES = Socio-Economic Status, approximated by paternal social class and maternal education; EDPS = Edinburgh Postnatal Depression Scale.
[1] These models have also been tested with externalising symptoms.

----> = Non significant path

——> = Significant path

Highlights

1. We test if inflammatory markers (IL-6, CRP) explain the link between adverse life events and child mental health
2. Only IL-6 is associated with adverse life events
3. IL-6 explains part of the path from events to later internalising symptoms
4. IL-6 does not explain the opposite association (from internalising symptoms to later events)
5. IL-6 does not explain either direction of the link between events and externalising problems