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ORIGINAL PAPER

Effects of early life adversity on immune function and cognitive performance: results from the ALSPAC cohort

Jessica F. Holland[1] · Golam M. Khandaker[2,3] · Maria R. Dauvermann[1] · Derek Morris[1] · Stanley Zammit[4,5,6] · Gary Donohoe[1]

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Abstract

Background Early life adversity (ELA) is a significant risk factor for mental health disorders. One hypothesised mechanism by which this occurs is via an effect on immune response. In this analysis of epidemiological data, we tested whether ELA was associated with cognitive performance, and if so, whether these effects were influenced by immune function.

Methods We investigated the longitudinal relationship between ELA, inflammatory markers, and cognition in data from Avon Longitudinal Study of Parents And Children (ALSPAC; $n \sim 5000$). ELA was defined in terms of physical/emotional abuse, harsh parenting, or domestic violence before 5 years. Social cognition was measured in terms of theory of mind, and general cognitive ability was measured using IQ. Inflammatory markers included serum C-reactive protein and interleukin-6 levels.

Results A significant association was observed between IQ and harsh parenting, whereby children who were physically disciplined had lower IQ scores (accounting for relevant social factors). Both immune markers were associated with variation in cognition, however, neither accounted for the effects of ELA on cognition.

Discussion This study highlights the impact of ELA on cognition. In the absence of evidence that these effects are explained by inflammation, other mechanisms by which the effects of ELA are mediated are discussed.

Keywords Cognition · ALSPAC · Adversity · Immune response

Introduction

Human cognitive development is an open system, where children are in constant interaction with their environment [1]. Although early life adversity (ELA) is known to widely impact developmental outcomes, the mechanism by which this occurs is only beginning to be elucidated, with many pathways to pathology still underexplored [2]. Negative impacts of ELA include disrupted cognitive [3] and neural [4] function during childhood, and increased risk for psychosis and other psychiatric disorders in adulthood [5, 6]. One mechanism by which this change in functioning may occur is via elevated immune response. A meta-analysis by Baumeister and colleagues suggests that ELA is associated with low-grade inflammation as reflected by increased levels of a number of circulating inflammatory markers, such as C-reactive protein (CRP) and interleukin 6 (IL-6), which are still apparent in adulthood [7]. As such, changes in immune response may represent at least one mechanism by which the negative effects of ELA on cognitive function (and psychiatric illness risk) is mediated.

✉ Gary Donohoe
gary.donohoe@nuigalway.ie

1 Cognitive Genetics and Cognitive Therapy Group, The Centre for Neuroimaging, Cognition and Genomics (NICOG), School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland

2 Department of Psychiatry, University of Cambridge, Cambridge Biomedical Campus, Herschel Smith Building for Brain & Mind Sciences, Cambridge, UK

3 Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

4 Centre for Academic Mental Health, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK

5 Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

6 National Institute for Health Research (NIHR) Biomedical Research Centre, University of Bristol, Bristol, UK

ELA and cognition

Studies during the last 30 years have consistently documented impaired cognitive abilities and poor academic achievement in maltreated young people [8]. Various traumas and ELAs have been studied in relation to receptive and expressive language skills [9], IQ [8, 10], and deficits in social cognition [11, 12]. Some studies have indicated that social cognition is specifically affected by exposure to severe physical adversity in childhood, i.e., physical abuse or domestic violence [11]. This could be because children who have experienced physical or emotional abuse are frequently reported to engage in general maladaptive thinking patterns and negative self-schema [13]. Studies of ELA and cognition have also reported that children who experienced physical abuse have deficits in verbal memory and general cognition [14] and that the degree of these effects may relate to adverse events occurring at particular developmental stages [15]. Studies recording retrospective abuse in individuals with depression as well as healthy controls also report an association between ELA and diminished memory function, as well as lower cognitive flexibility, irrespective of diagnosis [16]. Furthermore, 'polyvictimization' or non-specific multiple abusive experience has been associated with higher rates of mental illness later in development [3, 17].

Conversely, there may be alternative pathways to cognitive difficulties which involve genetic and environmental confounds, making certain children more susceptible to experiencing ELA [18]. When examining two large cohort studies of ELA and IQ, Danese et al. [18] observed that relationships between childhood victimization and IQ were largely accounted for when pre-existing cognitive ability (prior to ELA) was included in analysis. This finding challenges developmental programming theories that ELA causes later deficits in cognition, suggesting instead that lower cognitive function may be a risk factor for ELA.

Inflammatory markers and cognitive performance

C-reactive protein (CRP), an acute-phase reactant, and interluekin-6 (IL6), a pro-inflammatory cytokine, have been examined in many studies as hallmarks of systemic inflammation [19]. Population-based longitudinal studies have reported an association between elevated levels of IL-6 and CRP in childhood and increased risks of symptoms/diagnosis of schizophrenia and depression in adulthood [20, 21]. While the relationship between elevated levels of childhood CRP and IL6 and mental health outcomes in adulthood has received some attention [22, 23], the longitudinal effects of elevated IL6 and CRP on cognition during childhood development remain unexplored [8, 24–26]. Abnormal levels of CRP, elevated above 3 mg/l in adults was found to be associated with lower IQ scores in a large sample of patients with schizophrenia [27]. Higher IL6 blood concentrations were also found to be negatively associated with performance on a range of memory tests in a study of 151 patients with schizophrenia [28]. These findings suggest that low-grade inflammation could be a precursor to illness [22, 23, 29]. The mechanism by which inflammatory response may affect cognition remains to be elucidated, and this may shed light on the association with psychotic disorders.

The present study

The aim of this study was to examine the relationship between ELA and social cognitive ability, while exploring whether any observed relationship was accounted for by variation in inflammatory markers. Based on available variables from ALSPAC, we defined ELA in terms of a range of negative early parenting experiences, including physical discipline by a parent ('harsh parenting'), physical abuse by a parent, emotional abuse by a parent, and/or presence of domestic violence between parents before the age of 5 years. In ALSPAC literature, this is considered 'preschool' age [30], thus accounting for ELA in the home and not including factors outside the home like bullying or later adversities. Immune response was measured using CRP and IL-6 levels taken from peripheral blood at 9 years. Social cognition was measured using a computerized Theory of Mind task administered at age 13 years. General cognitive ability was assessed in terms of IQ at age 8 years, used in secondary analysis. Based on these data, we tested the following hypotheses: (1) that ELA at the age of 5 years was associated with poorer performance in and social cognition (theory of mind) at 13 years, and second with general cognitive ability (IQ) at 8 years; (2) that a relationship exists between elevated levels of immune response and cognitive function; and (3) that the relationship between immune response (IL-6 and CRP) and cognition partially accounts for variation in cognition that is explained by ELA.

Methods

Participants

The current sample was drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC), a birth cohort based on a recruited 14,541 pregnant women residing in the

county of Avon, with expected delivery dates between April 1991 and December 1992. Fourteen thousand, five hundred and forty-one is the initial number of pregnancies for which the mother enrolled in the ALSPAC study and had either returned at least one questionnaire or attended a "Children in Focus" clinic by 19/07/99 (http://www.alspac.bris.ac.uk). Parents completed regular postage questionnaires about many aspects of their child's development and health since birth. This resource includes a wide range of phenotypic and environmental measures in addition to biological samples. The area of Avon includes both urban and rural areas, with the population representative of all children in the UK [31]. Please note that the study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/).

The current study is based on up to 5000 participants with information regarding adverse childhood events up to age 5 years, and relevant experiential and cognitive assessments completed at ages 8.5 years or 13 years. Sample sizes vary for each analysis depending on availability of data. Choice of variables was driven by availability of data. Ethical approval for the study was obtained from ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Childhood adversity

1. Domestic violence

   Mothers reported via a series of postal questionnaires on a range of victimization experiences that they and their children had been exposed to since birth. At interview timepoints of 8 months, 1.5, 2.5, 4, and 5 years, mothers were asked whether they experienced emotional or physical abuse from their partner: "Your husband/partner was physically cruel to you" and "Your husband/partner was emotionally cruel to you." This measure was then split into binary terms—a positive response to either of these two questions at any of the timepoints was considered to be evidence of domestic violence (see [32]). Use of a binary domestic violence measure has been reported on previously as part of a composite victimization score [33].
2. Physical cruelty

   Physical cruelty was assessed based on mother's self-report at interview timepoints of when the child was ages 8 months, 1.75 years, 2.75 years, 4 years, and 5 years. Again, a binary yes/no variable was calculated to reflect the presence or absence of any daily/weekly physical cruelty up to age 5 was considered a 'yes' and recorded [33].
3. Emotional cruelty

   A measure of emotional cruelty was calculated by asking mothers to assess whether they had been emotionally cruel to their child at ages 8 month, 1.75 year, 2.75 year, 4 year, and 5 year interview timepoints. Again, a binary yes/no variable was computed in which any indication of emotional cruelty up to age 5 was considered a 'yes', and recorded, similar to emotional abuse measures calculated elsewhere [33].
4. Harsh parenting

   Harsh parenting was measured based on responses made by mothers to the question "When you are at home with your child how often do you slap him' or 'do you smack your child when they are naughty?' at the interview timepoints for when the child was aged 2 or 3.5 years. The answer of 'daily' or 'weekly' was coded as indicating the presence of Harsh parenting, with answers of 'once a month', 'never', or 'rarely' coded as absence of Harsh parenting. In secondary analysis, the same group was divided into a scaled score based on frequency of hitting. Measures of maternal maladaptive parenting in ALSPAC have been reported on previously using these measures as part of composite scores on victimization [34, 32].
5. Poly-victimization

   Poly-victimization has been operationalized as the total number of victimization types that a child experiences [11]. Our poly-victimization variable was derived by summing all ELA experiences that each child experienced on a regular basis prior to the age of 5. The score ranged from 0 to 4, with four representing presence of all the above ELAs. As some victimization measures correlated, this poly-victimization score is used for primary analysis of effects. Secondary analysis will include individual ELAs.

Measure of social cognition

The 'triangles' social cognition assessment was completed at the age 13.5 year visit [mean subject age: 13.75 years (SD = 71 days)]. This test involves the use of computerized abstract animations to measure the participant's ability to attribute an emotional mental state to non-human animate entities. The animations are used to test the participant's ability to use motion cues, such as speed and trajectory of movement, and movement in relation to others, to infer emotions [35]. Participants are shown 5-s animations of a circle and a triangle on a computer screen. In some of the animations, the triangle moves in a self-propelled manner designed to evoke a particular emotion: angry, happy, sad, or scared. In the other animations, it moves in a manner designed to make it appear "non-living." Participants are asked (a) whether the triangle is living, and if so, how living (measured on a Likert scale 0–5), or (b) whether the triangle has a particular emotion (happy, sad, angry, or scared). We calculated the total score by adding the score for all the

emotional items. To avoid negative scores, we added 40 to the total score, giving the score a range from 0 to 80, similar to other studies of triangles data [36].

Measure of general cognition

IQ assessment was completed during the age 8 years visit (mean subject age: 8 years, 8 months SD = 3.1 months), using a shortened version of the WISC 3rd UK Edition, administered by trained psychologists. Use of the shortened version reduced the length of assessment, so the children were less likely to fatigue [37]. IQ data obtained using this method have been shown to be valid [38], shown robust correlations with neurodevelopmental disorders, and correlates with other concurrent neurocognitive measures such as short-term memory, working memory, and socio-economic factors [2, 29]. While IQ was measured in the year prior to serum inflammatory markers, this measure shows robust test–retest reliability during childhood (6–13 years), and was considered unlikely to have changed during this period [38]. For the purposes of this analysis, total IQ scores were used.

Potential confounders

Maternal education at pregnancy was found to be the highest predictor of children's educational attainment at ages 16 and 18 years in previous studies of ALSPAC [39], even when accounting for children's cognitive ability. This variable has been strongly and robustly linked to multiple later life outcomes [8], and is likely to represent an important environmental confound. Therefore, maternal educational attainment was examined as a possible confounder in the analysis of the relationship between ELA and IQ. Gender, BMI, and maternal education were entered as covariates in analysis, as these factors have been found to impact on immune response and/or cognition in previous ALSPAC studies [29]. Finally, paternal social class and ethnicity were included as potential confounders [40].

Measurement of IL6 and CRP

Serum Interleukin-6 (IL-6) and C-reactive protein (CRP) levels measured at 9 years were examined in the current study (mean age 119.0 months; SD 3.9 months). At this study visit, non-fasting blood samples were collected via venepuncture from participants, with informed consent signed by a guardian. In total, IL-6 and CRP concentrations were measured from 5076 individuals. No other inflammatory markers were measured. Blood samples were immediately centrifuged and serum samples were frozen at − 80 °C in 1 mL aliquots for an average of 7.5 years without freeze–thaw cycles [29]. Although the samples were frozen for an extensive period and this could influence the quality of ELISA [41], it has been previously shown in ALSPAC studies that immune markers can be reliably measured [29]. Studies assessing reliability of measures have found that IL-6 and CRP stored at temperatures of − 80° have been found to remain stable over time (without freeze–thaw cycles) [42, 43]. An enzyme-linked immunosorbent assay (ELISA) was used to measure IL-6 levels (R&D systems, Abingdon, UK), and CRP was measured by automated particle-enhanced immuno turbidimetric assay (Roche UK, Welwyn Garden City, UK). Inter-assay coefficients of variation for both cytokines were < 5% reflecting low variation. The minimum detection limit for IL-6 was 0.1 pg/ml, with IL-6 values ranging from 0.1 to 20.1 pg/ml. The minimum detection limit for CRP was 0.03 mg/l. Of all included participants, 29 samples (0.6% of the sample) were below this limit, and were assigned values of 0.01 pg/ml ($n = 16$) and 0.02 mg/l ($n = 13$); these were included in the analysis. In summary, CRP values ranged from 0.01 to 45.17 mg/l (32 subjects over 10 mg/l). Of these, 431 children reported an infection in the 7 days preceding blood collection and were excluded from the cohort due to infection as a confounding factor. Furthermore, all those with measures of zero for IL6 or CRP values were also removed from analysis. The total number of individuals with IL6 or CRP values was ~ 4150 individuals, with numbers varying in analysis depending on availability of other variables in the model. Mahalanobis distances were calculated for variables in each analysis to detect multivariate outliers, and using this calculation for each analysis, no multivariate outliers were detected. Univariate analysis identified outliers which were defined by three standard deviations from the mean for both cytokines and were winsorised to the nearest value within normal range (IL6: highest value = 5.63, $N = 111$ samples; CRP: highest value = 6.40, $N = 52$ samples).

Analysis

Primary analysis: poly-victimization score

To test the associations between childhood victimization (independent variable) and cognition (dependent variable), linear regressions were carried out in SPSS (version 24). Covariates were included in the first step of regression analysis prior to inclusion of independent variables. 'Triangles Score', a factor created using a combination score of four triangle task subtests, was used as the outcome variable. Second, full-scale IQ was analysed as potentially effected by ELA. Poly-victimization score was used as the predictor in this model, ranging from 0 to 4. Therefore, two analyses are run in the primary: one for poly-victimization and social cognition and subsequently an analysis of poly-victimization and General Cognition (IQ).

Secondary analysis: differential impact of specific ELAs

We looked at each ELA separately as predictors of cognitive deficits (social cognition at 13 years and IQ at 8 years). This allowed us to take advantage of the richness of the data set, and extra participants available in different measures of ELA. The aim of secondary analysis is to identify specific associations in the data which may be differential depending on the type of adversity experienced. These effects would have been diluted if a composite score of adversity was to be used only. Gender was entered as a possible confounder of results in each analysis, along with maternal education.

Are ELAs associated with CRP/IL-6?

Linear regressions were analysed to test the relationship between elevated levels of IL6 or CRP and cognition. Values of IL-6 and CRP were used as the dependent variables in analysis, with ELA as the predictor variable. All those with infection at the time of blood draw were removed from analysis. Covariates of age, gender, BMI and maternal education were added to the model, as these have been found to predict immune response in the previous studies [20, 29, 37, 45, 46].

Does the association between CRP/IL-6 and cognition partly explain the relationship between ELA and cognition: regression analysis

As a mediating role of IL6 and CRP cannot be observed due to temporality of variables examined, IL6 and CRP, respectively, were added as covariates in a regression model, to test whether inclusion of inflammatory markers in the model changes the relationship between ELA and cognition. Interaction terms representing the combined effect of inflammatory markers and ELA were also tested as predicting cognition. Gender, age, BMI, maternal education, ethnicity, and paternal class were entered as covariates in the model [20, 29, 40].

Results

Descriptive information for all variables analysed is presented in Table 1. For each regression analysis, assumptions of linear regression were checked using P–P plots and scatter plots. Multi-collinearity was not observed between independent variables, with all predictor variables yielding a variance inflation factor (VIF) of < 1.15. Correlations between ELA measurements were either low or non-significant (Pearsons R less than 0.3).

Table 1 Demographic information and descriptive statistics for variables used in analysis

	Age	ELA	*N*	*M*	SD
Domestic abuse	Up to 5 years	+	654		
		−	2068		
Physical cruelty	Up to 5 years	+	107		
		−	2630		
Emotional cruelty	Up to 5 years	+	290		
		−	2431		
Harsh parenting	Up to 3 years	+	2108		
		−	2558		
Polyvictimization	Up to 5 years	+	1594		
		−	1074		
IL6 level	9.8 years		4143	1.26	1.55
CRP levels	9.8 years		4152	0.76	2.55
IQ score	8.5 years		5787	105.27	16.31
Triangles task	13.75 years		5220	48.40	3.74

Table 2 Linear regression models for early life adversity (total [polyvictimization] score, harsh parenting, domestic abuse, physical abuse, physical abuse and emotional abuse) and theory of mind (triangles total) scores

ELA score	*N*	*B*	B1	*p*	R^2 change
Poly-victimization	2192	−0.020	−0.012	0.585	<0.001
Domestic abuse	2612	−0.039	−0.017	0.386	<0.001
Physical abuse	2626	0.148	0.029	0.138	0.001
Emotional abuse	2609	0.121	0.038	0.051	0.001
Harsh parenting	4679	−0.031	−0.016	0.289	<0.001

Analysis adjusted for covariates of age, gender and maternal education

B unstandardized beta value, *B1* standardized beta value

Association between ELA score and social cognition (measured by triangles score)

To test for an association between cognition and 'polyvictimization', linear regression was used based on the three models described in the methods section. No association between effects of ELA 'poly-victimization' was observed using the 'Triangles' theory of mind task scores (Table 2). Similarly, when examining each ELA separately, no relationship between ELA and social cognition was observed (Table 3).

Table 3 Linear regression models for early life adversity (total [poly-victimization] scores, harsh parenting, domestic abuse, physical abuse, physical abuse and emotional abuse) and general cognitive ability (full scale IQ scores)

ELA score	Model 1				Model 2				Model 3			
	B	B1	*p*	R^2 change	*B*	B1	*p*	R^2 change	*B*	B1	*p*	R^2 change
Poly-victimization												
n = 2147												
1	**−1.9**	**−0.068**	**0.002**	**0.005**	−1.92	−0.069	0.001	< 0.001	−1.093	−0.039	0.057	0.003
2					−0.346	−0.011	0.617		−0.466	−0.015	0.478	
3									4.47	0.318	2.06E−51	
Domestic abuse												
n = 2533												
1	0.453	0.012	0.552	< 0.001	0.455	0.012	0.55	< 0.001	0.166	0.004	0.816	0.119
2					0.14	0.004	0.829		0.019	0.001	0.975	
3									4.759	0.346	< 0.001	
Physical abuse												
n = 2548												
1	2.817	0.034	0.085	0.001	2.809	0.034	0.086	< 0.001	1.947	0.024	0.206	0.117
2					0.118	0.004	0.855		0.016	0	0.979	
3									4.713	0.343	< 0.001	
Emotional abuse												
n = 2531												
1	1.288	0.024	0.22	0.001	1.292	0.024	0.218	< 0.001	1.311	0.025	0.183	0.119
2					0.178	0.005	0.784		0.036	0.001	0.953	
3									4.742	0.345	< 0.001	
Harsh parenting												
n = 4607												
1	**−3.378**	**−0.105**	**1.07E−12**	**0.011**	**−3.45**	**−0.107**	**4.29E−13**	**0.001**	**−1.913**	**−0.059**	**0.000024**	**0.109**
2					−0.829	−0.026	0.08		−0.694	−0.022	0.12	
3									4.612	0.333	< 0.001	

Model 1: analysis unadjusted for other variables; Model 2: gender included as a covariate; Model 3: gender and maternal education included as covariates

Statistically significant findings are highlighted in bold

B unstandardized coefficients, *B1* standardized coefficients

Association between ELA score and cognition (measured by IQ)

An association was observed between poly-victimization scores and lower general IQ at 8 years (Table 3). When the effects of adversity variables were considered separately, a significant association between 'harsh parenting' and full-scale IQ was observed that survived correction for multiple testing (Bonferroni; four ELA types, $p = 0.0125$). Furthermore, while maternal education was, as expected, strongly associated with child IQ ($b = 4.612$; $p = 7.22\text{E}-117$), the association between 'Harsh Parenting' and IQ remained significant after covarying for this and all other variables of interest (see Table 3).

As a post hoc analysis, when harsh parenting was re-classified according to frequency—'never', 'sometimes' (less than once per week), or 'often' (more than once per week), a dose–response effect was observed: children who were disciplined frequently had significantly lower IQ scores than those disciplined less frequently (Tukey HSD = −4.10, $p = 3.08 \times 10^{-7}$), and those hit less frequently had lower scores than those never hit (Tukey HSD = −2.37; $p = 0.00001$).

Relationship between immune markers, ELAs and cognition

To test for significant associations between ELA and either IL6 or CRP levels at age 9, linear regression was carried out with each ELA as the independent variable and IL6 or CRP as the dependent variable. Based on these analyses, no significant association between any ELA and levels of either IL6 or CRP levels was observed (see Table 4).

Table 4 Linear regression models for ELA (domestic violence, physical abuse, physical abuse, emotional abuse, and harsh parenting) predicting immune activation (measured by CRP and IL6 levels)

	IL6				CRP			
	N	*B*	B1	*p*	*N*	*B*	B1	*p*
Poly-victimization	1580	0.008	0.004	0.877	1582	−0.041	−0.025	0.303
Domestic abuse	1920	0.023	0.009	0.389	1922	−0.030	-0.013	0.540
Physical abuse	1930	−0.045	−0.008	0.728	1932	−0.138	−0.028	0.192
Emotional abuse	1916	−0.098	−0.027	0.227	1918	−0.051	−0.016	0.447
Harsh parenting	3441	0.028	0.012	0.463	3449	0.015	0.008	0.636

Analysis adjusted for covariates of age, gender, BMI and maternal education

B unstandardized beta value, *B1* standardized beta value

Table 5 Linear regression models for Immune activation (measured by CRP and IL6 levels) and general cognitive function (measured by full scale IQ)

Model	Variable	IL6				CRP			
		N	*B*	B1	*p*	*N*	*B*	B1	*p*
1	IQ	**3940**	**−0.576**	**−0.039**	**0.014**	**3948**	**−1.109**	**−0.065**	**0.00005**
2	IQ	3372	−0.161	−0.011	0.494	3380	−0.465	−0.027	0.113
	Gender		0.208	0.007	0.684		0.221	0.007	0.666
	Age		−0.012	−0.08	< 0.001		−0.012	−0.083	< 0.001
	BMI		−0.093	−0.016	0.338		−0.058	−0.01	0.563
	Mother's education		4.667	0.339	< 0.001		4.654	0.339	< 0.001
	Paternal class		−0.694	−0.108	< 0.001		−0.693	−0.108	< 0.001
	Ethnicity		0.305	0.012	0.446		0.3	0.012	0.453

Model 1: analysis unadjusted for other variables; Model 2: gender, age, maternal education, BMI, ethnicity and paternal class included as covariates

Statistically significant findings are highlighted in bold

B unstandardized beta value, *B1* standardized beta value, R^2 change per model

As Table 5 indicates, significant negative relationships between both IL-6 or CRP and IQ were observed, such that higher inflammatory response (measured using either marker) was associated with lower IQ scores. With the inclusion of BMI, maternal education, paternal class, and ethnicity in the model, the significance of these results was diminished (see Table 5). Finally, no association between either IL6 or CRP, and 'Triangles' task scores was observed.

Does immune response partly account for the variance in cognitive performance explained by ELA?

Given the association between IL6, CRP, and IQ, an analysis was carried out in which IQ was the dependent variable, Harsh Parenting was the independent variable, and each of IL6 or CRP (taken in turn) were tested as covariates. This analysis examined whether the variation in IQ explained by Harsh parenting was reduced (hence, partially accounted for) when immune function was considered. Neither immune marker (IL6 or CRP) was observed to explain the relationship between harsh parenting and IQ; after immune response was covaried for, Harsh Parenting continued to explain a comparable percentage of variation in IQ when either marker was included in the analysis (IL6: $b = -3.209$, $p = 2.4356\text{E}-9$; CRP: $b = 3.204$, $p = 2.5535\text{E}-9$). To further rule out an interaction between immune markers and ELA, interaction terms were created using mean centered values for IL6 and CRP multiplied by scores of Harsh Parenting. These interaction terms were tested for association with IQ in linear regression. When added to the model, neither interaction term predicted IQ scores (IL6 × harsh parenting: $b = -0.462$, $p = 0.392$; CRP × Harsh Parenting $b = 0.158$, $p = 0.443$).

Discussion

This paper sought to characterise the effects of ELA on cognitive ability in children, and to examine whether any observed effects were partly accounted for by immune response. We hypothesised that ELA would negatively impact on children's cognitive development, specially disrupting social cognition. Unfortunately, a relationship was not observed between poly-victimization and social cognition at 13 years. Following a nominal association between total number of ELAs experienced (poly-victimization score) and general cognitive ability (IQ) at age 8, we observed a

significant association between 'Harsh Parenting' before age 5 (measured in terms of maternal physical discipline) and IQ at age 8 years in secondary analysis. This association survived correction and remained strongly significant after accounting for other relevant covariates, including maternal education and gender. Finally, although elevated levels of IL-6 and CRP were significantly associated with lower IQ scores, these inflammatory markers were not observed to account for the association between ELA and IQ.

Harsh parenting and cognition

Our analyses support the view that 'harsh parenting' in early childhood is associated with lower general cognitive ability in middle childhood. Specifically, the experience of harsh parenting prior to the age of 5 was associated with an average reduction of three scaled score IQ points compared to children without this experience. In a post hoc analysis, we further observed a dose–response in this relationship, such that increased frequency of harsh parenting was associated with larger effects on IQ. Furthermore, covarying for maternal educational attainment in the analysis, as a proxy for maternal IQ, did not appear to explain this relationship. This association may reflect a causal relationship, or alternatively the combined effect of other biological and/or environmental factors jointly affecting both parenting and general cognitive ability. The suggestion of a causal relationship is supported by the temporality of variables, as ELA was measured before age 5 and IQ measured later at age 8. However, in a large study of ELA and IQ, cognitive deficits in victimized individuals were largely explained by cognitive deficits that predated childhood victimization and by confounding genetic and environmental risks [18]. As there was only one timepoint for IQ available for the current analysis, an alternative explanation is that those with lower IQ may be more susceptible to harsh parenting.

Harsh parenting, lower IQ, and inflammatory response

Our hypothesis that the effects of ELA (such as harsh parenting) on cognition might be partially explained by inflammatory response was not supported. While elevated levels of inflammatory markers IL-6 and CRP were both found to be negatively correlated with IQ scores, neither IL-6 nor CRP significantly accounted for variation in IQ explained by ELA. A recent meta-analysis of ELA and inflammatory response found that physical abuse was associated with higher IL6 scores, but not CRP, emotional abuse was not associated with either marker, while Tumour Necrosis Factor a (TNFa) was strongly influenced by early trauma [7]. The unavailability of additional immune markers, such as TNFa, precludes us from drawing firm conclusions about the potential effects of these markers on the relationship between ELA and IQ in this data set.

Alternative explanations for the relationship between ELA and cognition

As an alternative to immune-based accounts for the effects of ELA on cognition and social cognition, cognitive developmental accounts of ELA focus on how a child's representation of the world is thwarted due to past experiences in a 'cascade of increasingly deviant development' [47]. If children are deprived of consistent, sensitive caregiving, and a responsive loving exchange early in life, it has been argued that this can have a profound effect on cognitive development [9, 10]. Prior to developing coping strategies for stress, children withdraw and isolate themselves following ELA, as their understanding of the world is biased due to perceived threat at home [9]. Avoiding adult social interactions slows down the process of social learning which might otherwise take place—for example, learning language, appropriate behaviours, and communication of ideas [47, 48]. The relevance of parent–child interactions to cognitive development has already been supported by Chong et al. [49] in a previous study of the ALSPAC data set. In this study, differences in IQ at age 8 were associated with 'parental warmth' and 'parental control', measured up to 47 months. They found that higher parental control was associated with lower IQ scores [49]. While physical reprimanding was not assessed in the Chong et al. study [49], and parenting styles were not a subject of the current study, it is not difficult to imagine that these variables may be correlated. Future research should investigate whether and how these variables are related regarding cognitive development.

Strengths and limitations

A strength of the study was availability of a large epidemiological data set consisting of longitudinal data, where the effects of ELA could be associated with later cognitive function. Often, in psychiatric studies, ELA is assessed retrospectively considering a diagnosis, whereas here, ELA data were collected contemporaneously on a year-to-year basis. Another strength of this study was the availability of IL6 and CRP blood markers for analysis in longitudinal data. A limitation of the study, however, is the unavailability of other markers of immune response: it is possible that a measure of TNFa may have been more relevant to ELA analysis [7]. Similarly, the fact that these measures were taken on average 1 year after assessment of IQ precluded a more direct analysis of the mediating role of inflammatory response between ELA and IQ.

A limitation to this study is that there is a substantial amount of missing data in ALSPAC that is said to be systematic, and not random [31]. Some studies use methods such as multiple imputation to estimate values for cases with missing data, requiring detailed modelling and specialist statistical advice if it is to enhance study validity [50]. In order for multiple imputation to be appropriate, data should be assumed to be missing completely at random, or missing at random after taking into account the background factors known to be related to missing ness [51]. It is not appropriate to make such an assumption in this case; it is highly likely that there are unrecorded reasons for mothers to drop out of the study, or not respond to questionnaires that are related to the variables for ELA included in analysis. In addition, assumptions for multiple imputation are harder to justify, where more than 20% of the data are missing [51]. In studies of ALSPAC attrition, there is a direct relationship between socioeconomic status and the number of questionnaires returned [31]. Therefore, it was not possible to account for missing data using imputation techniques. Missingness may represent a bias in the data, as many of those in abusive homes may not attend follow-up visits, and so the data available may be based on more functional homes.

A further limitation is the lack of clear-cut, well-validated ELA definitions in the field. While we studied here the presence or absence of individual ELAs, other ALSPAC-based studies have used a cumulative score of childhood adverse events not specific to parent–child relationship [33]. Sexual Abuse was not discussed in the current study, as there was only a small number of children with experience of this ELA ($n = 27$), making the analysis low powered in comparison with others. The 'harsh parenting' variable is based on timepoints of 2 and 3.5 years, thus captures a more representative sample than other measures of ELA. This score was derived from composite ELA measures in previous ALSPAC research [33]. A limitation of the use of this variable is a lack of corroborative evidence from witnesses of ELA, such as evidence from a partner or the child themselves. Finally, each ELA measure is based on mother's self-report, without input from fathers or male caregivers. As fathers can also be victims of domestic violence, the incidence of domestic violence is likely to be underreported in this sample, making this a potential confounding issue [52, 53].

Finally, no family and child medical history was used in this analysis, nor were medications used as covariates. From the previous studies of the ALSPAC data, it is clear that various atopic disorders can impact on inflammatory markers [44], as can various medications and conditions. Furthermore, the impact on freezing and storage on immune markers could be seen as a further limitation, although the stability of these measures is said to be reliable at − 80° without free–thaw cycles, which follows the storage outlined in ALSPAC methods [29, 41–44]. Finally, environmental factors such as sibling number, birth difficulties, and genetics could also be included to further understand developmental context and inflammatory response to stress. Although beyond the scope of the current study, further data on depression scores or evidence of psychotic disorders at later timepoints could have been included in analysis, especially as these have already been cited as impacting cognition and immune response in ALSPAC [20, 29]. Strategies for coping including internalizing and externalizing indicators could also be taken into consideration in analysis on childhood development, whereby an underlying vulnerability can predict psychological and cognitive outcomes [54]. Emotional regulation, which was not included in this analysis, may be integral to understanding cognitive outcomes, as distress has been cited as a key factor in cognitive development [55].

Conclusion

This study, based on a longitudinal epidemiological cohort, provides evidence that harsh parenting during the early years of development is associated with lower cognitive performance in middle childhood by comparison with children who have not had this experience. This study also suggested a dose–response in this relationship, whereby more frequent smacking/slapping was associated with lower cognitive performance than less frequent physical discipline. These findings may have implications for public health interventions aimed at supporting caregivers, particularly in emphasising the importance of adopting alternative parental disciplining methods. Finally, our study suggested that altered immune function, as measured by IL6 and CRP, is unlikely to explain a large proportion of the variation in IQ explained by ELA. While other immune markers remain to be examined, our study highlights the need to consider alternative biological and cognitive pathways for explaining the relationship between ELA and cognition.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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