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The role of inflammation in the association between poverty and working memory in childhood.

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Highlights

- We tested if financial difficulties predict child inflammation and working memory.
- We also tested if inflammation explains the difficulties-working memory link.
- Difficulties predicted increased IL-6, but not CRP, and poorer working memory.
- Higher levels of IL-6 and CRP were associated with poorer working memory.
- IL-6 partially mediated the link between financial difficulties and working memory.

Abstract:

Background: Family financial difficulties have been directly linked to poorer executive functioning in childhood. However, recent studies suggest that difficulties in affording basic items and other necessities may also indirectly affect children's executive functions through several psychological but also physiological paths. One of the latter may be inflammation, which has been related to both financial difficulties and executive functioning. In this study, we explored for the first time if the relationship between early family financial difficulties and working memory in middle childhood can be explained by inflammation.
Methods: Using data from 4,525 children of the Avon Longitudinal Study of Parents and Children, a general population birth cohort, we tested associations between parents' perceptions at ages 0-3 years of having difficulties in affording basic items for their children including food and clothing, and children's inflammation [measured by interleukin 6 (IL-6) and C-reactive protein (CRP)] at age 9 years and working memory performance at age 10 years. Confounders included socioeconomic status at ages 0-3 years, economic hardship between ages 3-9 years, BMI and gender.
Results: Using Structural Equation Modelling, we found that financial difficulties were associated with worse working memory (β=-0.076, 95% CI=-0.105, -0.043) even after adjusting for confounders. This association was partially explained by inflammation (β=-0.002, 95% CI=-0.005, -0.001) as measured by IL-6.
Conclusions: Children in families struggling to afford necessities early in life have higher levels of inflammation, in turn related to poorer executive functioning in middle childhood. These findings suggest that living under financial strain has a unique effect on children's cognitive development through inflammation in the general population.

Keywords: ALSPAC; childhood; IL-6; inflammation; SES; working memory

Declarations of interest: none

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Word count: 5100

1. Introduction

There is abundant evidence for the relationship between family socioeconomic status (SES) and children's executive functioning (EF), which indexes a range of cognitive processes such as attentional control, cognitive flexibility and working memory that facilitate control of behaviour and thoughts (Finch & Obradović, 2017; Hackman & Farah, 2009; Noble et al., 2007; Obradović et al., 2016). Among the several EF components, working memory is the one most studied. Working memory is the function needed to retain and manipulate information in order to perform a task or solve a problem (Baddeley, 2000). There is much research in its early development, especially in the preschool years, and its outcomes in primary school (Best et al., 2009). For example, it is now well established that it is significant for educational attainment (Best et al., 2011; Handley et al., 2004; Ostrosky-Solís et al., 2007) and is associated with good academic results in both language and mathematics (López, 2013). More recent research has shown that its development continues through adolescence, albeit there is evidence for stability too (Ahmed et al., 2019).

There is also much evidence that several complex mechanisms underlie the link between SES and EF in children (Blair, 2010; Evans & Schamberg, 2009). As one such mechanism may be stress, it is important to determine whether this relationship is produced by the key components of SES, such as parental education and social class, or is explained by the challenges typically associated with income deprivation or financial difficulties (Hughes et al., 2010; Kishiyama et al., 2009; Mezzacappa, 2004). One of the studies that tested the latter was conducted by Raver and colleagues (2013) and built on previous research that defined family financial difficulties as parents' perceptions of difficulties in affording basic items for their children such as food, clothing and other necessities (Burchinal et al., 2008; McLoyd, 1998). That study added to the literature by investigating the role of families' experiences of financial strain in children's EF and found that such experiences were uniquely predictive.

Typically, such research is motivated by either the Family Stress Model or the Family Investment Model, two inter-related theoretical frameworks developed to explain how financial difficulties may shape relationships in the family and affect the health and development of children. According to the Family Stress Model (Conger & Elder Jr, 1994), economic hardship can lead to conflicts between the family members and harsh or neglectful parenting. Previous studies provide evidence of the disruptive effects of financial difficulties on parental behaviour, child-parent interactions, and child development (Conger & Conger, 2002; Conger et al., 2010). The Family Investment Model suggests that families who cannot afford basic material goods, food and experiences deny their children of essential stimuli that enhance their EF and their learning

experiences (Alaimo et al., 2001; Conger et al., 2010; Yeung et al., 2002). Central to both models is the acknowledgement that families' perceptions of financial strain and disadvantage can be part of a complex dynamic process as they can affect parents' psychological health and reflect the challenges they may face in meeting their children's basic needs, both of which predict child outcomes. However, recent research has shifted the focus to the physiological effects of living in conditions associated with financial strain. Children from families that experience such adversities have been found to develop different responses to stress that can impact their EF, showing, for example, altered neuroendocrine stress response and compromised self-regulation (Arnsten & Li, 2005; Blair et al., 2005; Evans & Schamberg, 2009). Another physiological response to stress is inflammation (Fagundes & Way, 2014; Kuhlman et al., 2017; Minihane et al., 2015), but this has yet to be explored as a possible explanation for the link between economic hardship and poor EF in children. According to the biological embedding hypothesis, long-term exposure to stressful experiences - such as, arguably, financial strain and economic hardship - can lead to chronic stimulation of the sympathetic nervous system and to the progressive suppression of some main anti-inflammatory pathways, such as the Hypothalamic-Pituitary-Adrenal (HPA) axis and the parasympathetic nervous system. Although the role of the HPA axis is to help in body adaptation (allostasis) through cortisol secretion (Hertzman, 1999; Shonkoff et al., 2009), chronic exposure to stress can lead to overstimulation and consequently to maladaptive wear-and-tear on the body and the brain (allostatic load) (McEwen & Gianaros, 2010). Most studies linking financial difficulties to cognitive ability via these pathways have focused on the role of cortisol for child EF (Blair et al., 2005; Blair et al., 2011; Obradović et al., 2016) or that of allostatic load for adult working memory (Evans & Schamberg, 2009). However, no study has tested whether the link between financial difficulties and EF in childhood can be explained by inflammation, a gap we aim to fill with this study. As we argue below, the link is plausible because inflammation has been linked to both poverty as its source and EF as its outcome.

The link between poverty and inflammation has been established in several studies, even after controlling for health-related confounders, such as BMI and smoking (Malfertheiner & Schütte, 2006; Park et al., 2005). In turn, inflammation has been directly implicated in impairing cognition and affecting brain development (Hagberg et al., 2012). Studies in middle-aged and older adults have shown that high concentrations of C-reactive protein (CRP) and interleukin 6 (IL-6), two of the most widely researched biomarkers of inflammation, were strong predictors of cognitive decline and dementia (Kuo et al., 2005; Schmidt et al., 2002; Teunissen et al., 2003; Yaffe et al., 2003). The association between inflammation and EF in children is less well studied. Although there is much evidence on the long-term effects of inflammation on the brain during the foetal and the neonatal period when inflammation plays a major role in determining the risk of a variety of neurological disorders

(Dammann et al., 2002; O'Shea et al., 2013), there is little evidence of a link between inflammation and EF in the general child population. In children, the studies that have examined the link are on special populations, such as children with obstructive sleep apnea (Huang et al., 2016) and sleep-disordered breathing (Gozal et al., 2008; Tauman et al., 2004). In adolescents, there have been studies examining the link in the general population, but these have produced mixed results. One study found that elevated salivary CRP was associated with poorer memory and EF (Cullen et al., 2017), while another (Jonker et al., 2014)(Jonker et al. (2014) found no association between CRP and memory or EF. Thus, our study, using data from a large general-population sample, the Avon Longitudinal Study of Parents and Children (ALSPAC), addresses limitations in the previous research into SES and child EF by looking specifically at whether SES-adjusted exposure to parent-reported financial strain or economic hardship is related to working memory in the general child population. It also investigates for the first time whether the relationship could be explained by inflammation.

2. Methods

2.1 Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing birth cohort study that recruited 14,541 pregnant women resident in Avon, UK, with expected delivery dates from April 1st 1991 to December 31st 1992 (http://www.bristol.ac.uk/alspac/researchers/our-data/ for details of all the data that is available). ALSPAC is a transgenerational prospective observational study that investigates influences on health and development across the life span. It takes into account multiple genetic, epigenetic, biological, psychological, social and other developmental exposures in relation to a similar diverse range of health, social, and developmental outcomes (Boyd et al., 2013). Assessments of the ALSPAC Cohort Profile showed that attrition and non-response was higher among mothers who were younger, were from lower socioeconomic backgrounds, did not have a university degree, had already two or more children, had higher pre-pregnancy BMI, and experienced hypertensive disorder of pregnancy. Ethical approval of the ALSPAC cohort was obtained from the ALSPAC Ethics and Law Committee and local research ethics committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time and no financial compensation was given (more details at www.alspac.bris.ac.uk). The study initially recruited 14,541 pregnant women which represented about 85% of the eligible population. Of those, there was a total of 14,676 foetuses, resulting in 14,062 live births, and 13,988 children were still alive at the age 12 months

and have been followed up since then (Golding & Team, 2004). Additional children were recruited using the original enrolment definition from the participating children's age 7 years onwards, allowing us to have available study data for 15,445 foetuses. Of those, 14,684 were alive at 1 year of age. In an attempt to bolster the initial sample size, new pregnancies have been enrolled since then resulting in additional children being enrolled as well. To date, the total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 foetuses. Of these 14,901 were alive at 1 year of age (Fraser et al., 2013). Children whose parents provided consent were eligible to continue and were invited to participate in the biological assessments. A total of 7,725 participated in the clinic assessments at age 9 (62% of those invited), when inflammation was measured in childhood. Our study's analytic sample (n = 4,525) comprised children who had valid data on inflammatory markers at age 9 years, were singletons or first-born twins, and did not have an infection at the time the blood samples were taken.

2.2 Measures

2.2.1 Inflammatory markers

In ALSPAC, inflammation in childhood was measured with CRP and IL-6 at age 9. Blood samples were collected using standard methods. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Concentration of CRP (mg/L) was measured by automated particle-enhanced immunoturbidimetric assay (Roche, UK). Concentration of high sensitivity IL-6 (pg/mL) was measured by enzyme-linked immunosorbent assay (R&D systems, Abingdon, UK). All interassay coefficients of variation were less than 5%. IL-6 and CRP were log-transformed first and then they were further transformed into quintiles for the regression analyses.

2.2.2 Financial difficulties

Our main exposure was financial difficulties. A summative score was first created using all available information in ALSPAC on financial strain early in the child's life. This was produced from the mother's responses to the following questions when the child was 8 months, 21 months, and 33 months old: "How difficult at the moment do you find it to afford these items?" a) food, b) clothing, c) heating, d) rent or mortgage, and e) things you need for the baby. Responses were recorded on a 4-point scale ranging from 1= "Very difficult" to 4="Not difficult". After reverse coding, the total score (ranging 0-15) was calculated for each timepoint. We then summed the three scores into a continuous variable ranging from

0 to 45. Following visual inspection of its distribution, we dummy-coded it to differentiate the bottom third (0=no or little difficulty affording items) from the top two-thirds (1=difficulty affording items).

2.2.3 Working memory

Children's working memory was assessed at age 10 years using the computer-based Counting Span Task which requires the simultaneous processing and storage of information (Case et al., 1982). The task is as follows: On the computer monitor, the child is presented with a number of red and blue dots on a white screen and is asked to point to and count the number of red dots out loud (the processing component). Children are shown: a) two practice sets of two screens, b) three sets of two screens, c) three sets of three screens, d) three sets of four screens, and finally, e) three sets of five screens. After each set, the child is asked to recall the number of red dots seen on each screen in the order they were presented within that set (the storage component). The tester inputs these numbers into the computer after each set. In ALSPAC, all children worked through all the sets regardless of their overall performance. A child's working memory span was calculated automatically by the computer programme, on the basis of the number of correctly recalled sets, weighted by the number of screens within each set. The maximum score a child could achieve was 5 (i.e., all correct). In this study, we used the span score which is the main outcome measure for this task.

2.2.4 Covariates

We included several individual and family covariates including SES, gender and BMI. *SES* was measured as a latent construct using information from four binary observed variables during the first 3 years of the child's life: maternal education (degree or not), paternal social class (manual or non-manual), overcrowding (yes, no) and housing tenure (homeownership or not). *BMI (*weight (kg)/height $(m)^2$) was measured using information from the clinic assessment at age 9 years. We also adjusted for *perceived economic hardship,* measured by two questions to mothers at 4 timepoints (47 months, 61 months, 73 months, and 9 years of age) about whether they had experienced, since the previous timepoint: a) an income reduction and b) a major financial difficulty. Responses were on a 5-point scale from 1 (*Affected a lot*) to 5 (*Did not happen*). Responses were reverse-coded so that higher scores indicated greater economic hardship. Then, for each question, a longitudinal summative score was calculated from all the 4 timepoints. A total score was then created by adding these two summative scores. The economic hardship variable therefore covered the period from 3 to 9 years, ranging from 0 to 35.

2.2.5 Analytic strategy

All analyses were performed in STATA 15.0 (Stata Corporation, College Station, TX, 1997) and Mplus (version 8) (Muthén & Muthén, 2017). First, we conducted a Confirmatory Factor Analysis (CFA) in Mplus to create a latent SES factor. The CFA was performed using the weighted least squares mean and variance adjusted estimator for categorical variables and one factor was extracted. Factor scores were saved and used as a continuous variable in the analysis. Following this, we conducted a Structural Equation Model (SEM) to test the relationship between financial difficulties and working memory. We specified a path of financial difficulties on working memory, along with a direct path from SES to financial difficulties - to control for differences in type of financial difficulties by socioeconomic position. We also adjusted for covariates and examined the extent to which the observed associations between financial difficulties and working memory were mediated by inflammation. Each inflammatory marker was tested separately to avoid multicollinearity. (For illustration, Figure 1 shows the SEM testing mediation by IL-6 as fitted.) To assess model fit, we used the following indices of fit: 1) Comparative Fit Index (CFI), 2) Standardized Root Mean squared Residual (SRMR) and 3) Root Mean Square Error of Approximation (RMSEA). According to the recommended cut-offs of CFI (≥ 0.95), SRMR (≤ 0.08), and RMSEA (≤ 0.06) (Hu & Bentler, 1999), the fit to the data was very good (CFI=0.93, SRMR=0.02, RMSEA=0.04, 90% CI=0.030, 0.047). To conduct mediation analysis using SEM techniques in a path analysis framework such as the one provided by Mplus, we fitted the SEM adding an explicit test for the indirect effect of the predictor (financial difficulties) via the mediating variable (inflammatory marker) using the subcommand 'MODEL INDIRECT' within the main model command. This subcommand tests and displays results for all possible specific indirect effects between predictors and outcomes, along with total indirect effects, direct effects and total effects. We used robust methods to estimate the indirect effects by calculating bootstrapped bias-corrected confidence intervals for each parameter tested, as advised by McKinnon (2008) and Hayes (2017). Bootstrapped confidence intervals do not rely on any distributional assumptions and instead use estimates for many samples of the data, 'collected' by repeatedly sampling with replacement from the sample available and calculating the statistics of interest. We included residual covariances among predictors, and produced our estimates using full information maximum likelihood. Finally, we carried out a sensitivity analysis to explore if results change when we exclude participants with CRP>10 mg/L (N=32), as it is likely that those CRP levels indicate infection.

3. Results

3.1 Descriptive analysis

Table 1 shows the descriptive statistics. As can be seen, children in the analytic sample had average BMI, low levels of IL-6 and CRP and scored relatively high in the working memory test. Although economic hardship as reported by the mothers at child ages 3-9 years was low, 73% of them had reported at child ages 0-3 years that they had difficulties affording items such as food, clothing, or necessities for the baby at some point. Regarding the observed SES variables, most of the mothers in the analytic sample did not have a university degree (83%). More than half of the fathers belonged to non-manual social classes (62%), and the majority of the children lived in homes which their parents owned outright or were buying with a mortgage (83%) and which were not overcrowded (94%). We then ran a bias analysis (Supplementary Table S1) to explore any differences in the study variables for those in and out of the analytic sample. Those in the analytic sample had lower levels of IL-6 and CRP and lower BMI but their parents had experienced more financial problems at some point in their lives. Furthermore, their parents were more likely to have a university degree, be from higher socioeconomic backgrounds, live in less overcrowded homes, own their home, and have fewer difficulties in affording basic items. However, there were no differences in working memory between samples.

The correlations among the main study variables are shown in Table 2. Not having financial difficulties was associated with lower levels of IL-6, better working memory, less economic hardship and higher SES. The two inflammatory markers were moderately related to each other. Higher IL-6 was related to worse working memory, higher BMI, lower SES and female gender but was not associated with economic hardship. On the other hand, CRP was negatively related to working memory and positively related to BMI and female gender only. From the covariates, working memory was only associated with higher SES.

Table 1. Descriptive statistics of the main variables of the study (N=4,525)

Continuous		
	n	**M(SD)**
IL-6 (pg/mL)	4,525	1.21(1.48)
CRP (mg/L)	4,525	0.63 (1.94)
Working memory	3,817	3.43(0.86)
Economic hardship	4,525	9.98(5.11)
BMI	4,474	17.58 (2.77)
Categorical		
	N	**%**
Financial difficulties		
No difficulties	1,211	26.76
Difficulties	3,314	73.24
Gender		
Male	2,296	50.79
Female	2,225	49.21
Maternal education		
Degree	703	16.91
Other	3,454	83.09
Paternal social class		
Non-manual	2,358	61.55
Manual	1,473	38.45
Overcrowding		
Not overcrowded	3,489	93.77
Overcrowded	232	6.23

Housing tenure		
Owning the home	3,474	83.35
Not owning the home	694	16.65

Note. IL-6=interleukin 6; CRP=C-reactive protein

Table 2. Correlations of the main variables of the study

	1.	2.	3.	4.	5.	6.	7.	8.
1.Financial difficulties	1							
2.IL-6	0.04*	1						
3.CRP	-0.00	0.40***	1					
4.Working memory	-0.08***	-0.06***	-0.05**	1				
5.BMI	0.02	0.26***	0.42***	-0.02	1			
6.Economic hardship	0.08***	-0.00	-0.01	-0.01	0.02	1		
7.(Higher) SES	-0.28***	-0.07***	-0.02	0.15***	-0.06***	-0.03	1	
8.Female	0.00	0.14***	0.21***	0.03	0.08***	-0.02	-0.01	1

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note. IL-6=interleukin 6 (log-transformed); CRP=C-reactive protein (log-transformed); BMI=body mass index; SES=socioeconomic status

3.2 SEM

As explained, financial difficulties were SES-adjusted in our model. Results from the SEM (Table 3) showed that financial difficulties at ages 0-3 years predicted poorer performance in the working memory task at age 10 years (*b*=-0.15, *SE*=0.031, *p*<.001, *β*=-0.08), independently of early SES but also the other covariates. IL-6 at age 9 years was negatively related to working memory (*b*=-0.036, *SE*=0.010, *p*<.001, *β*=-0.06), and girls had better working memory (*b*=0.07, *SE*=0.028, *p*<.05, *β*=0.04). With respect to the paths from covariates to mediators, financial difficulties early in life were associated with higher levels of IL-6 several years later at age 9 years (*b*=0.13, *SE*=0.045, *p*<.001, *β*=0.04), as were higher BMI (*b*=0.13, *SE*=0.006, *p*<.001, *β*=0.26) and being female (*b*=0.36, *SE*=0.040, *p*<.001, *β*=0.13). However, parental perceptions of economic hardship between ages 3 to 9 years were not related to IL-6 at age 9 years. With respect to the role of CRP as a mediator, financial difficulties at ages 0-3 years were not related to CRP at age 9 years. However, higher levels of CRP predicted worse performance in the working memory task (*b*=-0.04, *SE*=0.009, *p*<.001, *β*=-0.06) (See table S2 in the Supplementary Material for more details on the model with CRP as mediator).

Table 3. Fully-adjusted mediation model for working memory through IL-6 (N=4,525)

	b	SE	95% CI
Direct paths[1] to working memory (WM)			
1. Financial difficulties -> WM	-0.15***	0.03	-0.204, -0.084
2. IL-6-> WM	-0.04***	0.01	-0.055, -0.017
3.Female -> WM	0.07*	0.03	0.012, 0.121
Paths to IL-6			
1. Financial difficulties ->IL-6	0.13**	0.05	0.045, 0.222,
2. BMI ->IL-6	0.13***	0.01	0.119, 0.144
3.Economic hardship -> IL-6	-0.00	0.00	-0.010, 0.005
4.Female -> IL-6	0.36***	0.04	0.282, 0.440

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Note: b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; IL-6=Interleukin 6 (in quintiles)

[1] Not shown in the table is the path from SES to financial difficulties, also modelled as explained. SES was negatively related to financial difficulties (*b*=-0.270, *SE*=0.014, *p*<.001, *β*=-0.27).

3.2.1 Mediation analysis

IL-6 at age 9 years mediated part of the effect of early financial difficulties (0-3 years) on working memory at age 10 years (indirect effect: *b*=-0.005, *SE*=0.002, *p*<0.05, *95% CI*=-0.010, -0.002, *β*=-0.002 ; total effect: *b*=-0.151, *SE*=0.031, *p*<0.05, *95% CI*=-0.209, -0.089, *β*=-0.078; direct effect: *b*=-0.146, *SE*=0.031, *p*<0.05, *95% CI*=-0.204, -0.084, *β*=0.076). Figure 1 shows all paths that were tested in this final model. There was no mediation by CRP.

3.3 Sensitivity analysis

Although in our analyses throughout we excluded children with a reported infection at the time the blood samples were taken, we also carried out a sensitivity analysis where we refitted our SEM for CRP after we excluded participants with CRP>10 mg/L (N=32). Results did not change as early financial difficulties (ages 0-3 years) were not related to CRP at age 9 years. Also similar to the main analysis, elevated CRP predicted worse working memory performance (*b*=-0.03, *SE*=0.010, *p*<.001, *β*=-0.05).

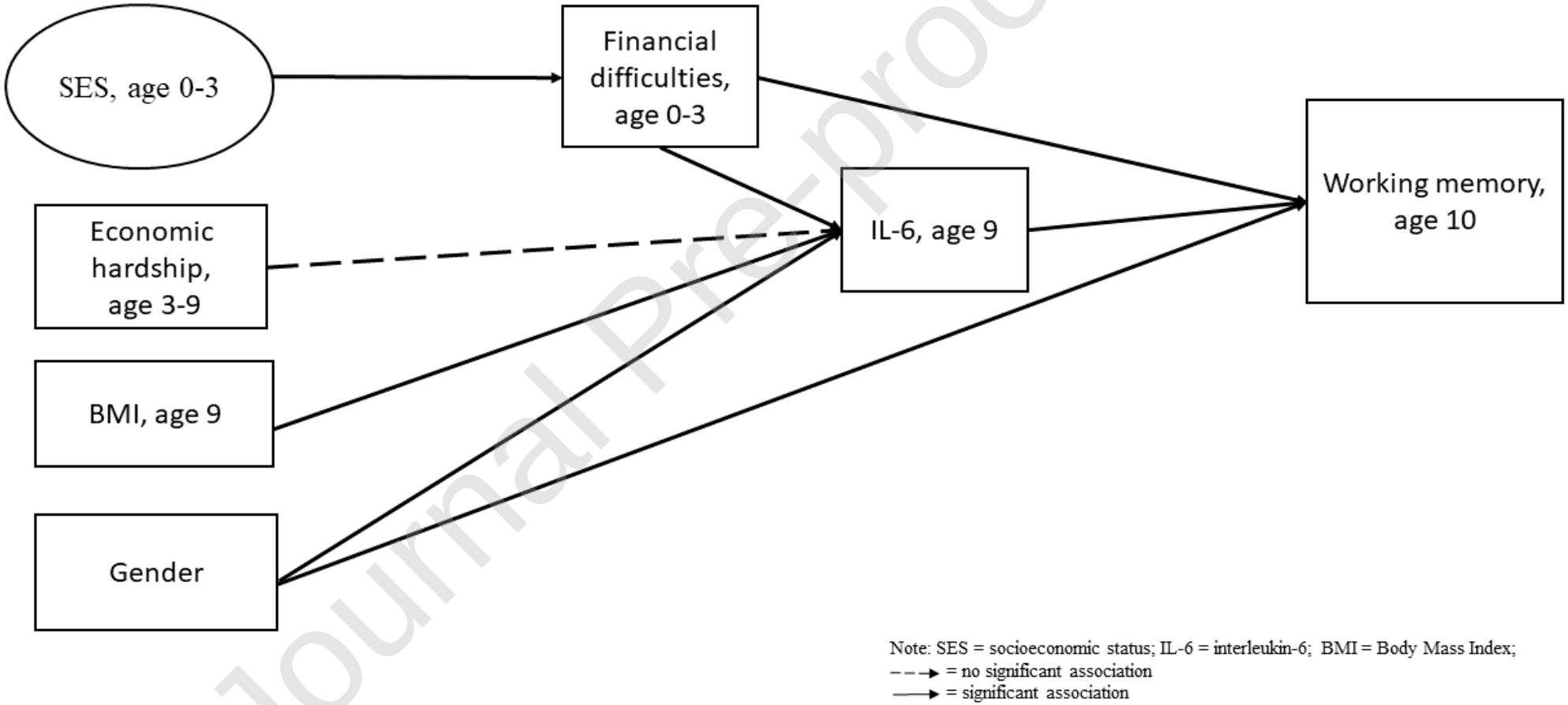

Figure 1. SEM and path analysis results.

4. Discussion

To our knowledge, this is the first general-population study to examine the relationship between family financial difficulties and working memory in middle childhood and whether it can be explained by inflammation as measured by IL-6 and CRP. The results suggest that financial difficulties in early childhood (at ages 0-3 years) predict worse performance in a working memory task years later (at age 10 years) even after stringent adjustment for SES and subsequent economic hardship. This finding is in line with previous research (Dickerson & Popli, 2018; Hackman & Farah, 2009) suggesting that financial strain is associated with lower EF in children. At the same time, we also found that a higher level of IL-6 in middle childhood (age 9 years) was associated with poorer working memory at age 10 years. In line with a recent study in adolescents showing links between CRP and cognition (Cullen et al., 2017), we found that elevated CRP at age 9 years was also associated with poorer working memory at age 10 years.

Despite the small effect sizes, these are important findings. Research on these particular relationships at this stage of life is very limited. In addition, previous studies have mainly focused on the role of 'objectively-measured' poverty or SES in children's EF. However, the severe strain of worrying about having enough food to survive or being able to access basic life necessities is a serious practical and psychological challenge with likely direct effects on children, but one that has been very rarely examined in the research linking family SES and child EF (Hughes et al., 2010; Kishiyama et al., 2009; McLoyd, 1998; Raver et al., 2013). Our study adds to the existing evidence on this link but also expands it by taking into consideration parents' perceptions of financial strain and testing the effect of SES-adjusted financial strain on children's EF. As for the link between inflammation and EF in childhood, the research on this to date has been conducted with special child populations or produced mixed results (Cullen et al., 2017; Huang et al., 2016; Jonker et al., 2014; Tauman et al., 2004). Our study, using a large general-population child sample, adds to this research as well.

However, our study went beyond testing direct effects by exploring whether inflammation could explain the relationship between financial difficulties and child working memory. Results showed that inflammation as measured by IL-6 partially explained that relationship, an important finding. Ours is the first study to provide evidence that children born to families struggling to make ends meet show subsequent deficits in working memory, a core component of EF, via elevated inflammation in the blood. Another strength of the study is that we addressed a crucial empirical question in the literature of child development: whether parents' perceptions of financial difficulties are uniquely related to children's EF even after adjusting for SES (Raver et al., 2013). We were able to directly explore the SES-adjusted effect of economic stressors early

in life (ages 0-3 years) on children's EF and we provided evidence for that relationship. Finally, given the importance of the length and timing of family exposure to economic hardship for child cognitive outcomes (Bradley & Corwyn, 2002; Hackman et al., 2015; McLoyd, 1998), we also accounted in our analyses for exposures to economic hardship from age 3 years to the time of measurement of inflammation at age 9 years.

However, our study has weaknesses too. First, we had only one measurement of inflammatory markers in childhood (at age 9 years) and although we could see the short-term effect of inflammation on child working memory (measured at age 10 years), we could not test for this relationship longitudinally. Thus, we note that given the very short time interval between inflammation and EF, and the absence of repeated measures of inflammation and working memory, it is not possible to conclude that either IL-6 or CRP might have a causal effect on EF in children. In addition, our analysis did not allow us to clarify whether high levels of inflammation lead to later impaired cognition or whether there is a possibility of reverse causality. Evidence from previous experimental studies in older adults (Reichenberg et al., 2001) and rodents (Chen et al., 2008) suggests that there is a causal link between cognitive functioning and inflammation, with acute systemic inflammation directly impairing cognitive functions such as working memory. Conversely, a more recent longitudinal study argued that early cognitive functioning (at age 11 years) determined lifetime pro-inflammatory exposures which consequently led to cognitive decline at an older age (Luciano et al., 2009). Subsequently, from the longitudinal analysis of our observed data, we can only assume that there is certainly a relationship between inflammation and executive functioning in middle childhood, however, we are not able to draw any conclusions about causality or whether a reverse causal mechanism exists. More longitudinal studies are required in the future. Second, whilst high levels of CRP were associated with poorer working memory performance in our study, CRP was not a significant mediator of the relationship between financial difficulties and working memory. Unlike IL-6, it was not related to financial difficulties. In addition, as only a very small proportion of the variance in working memory could be explained by inflammation, other potential influences are more important. Previous studies have pointed to environmental inputs (Jeon et al., 2014; McCoy et al., 2015) but also genetic influences. Another limitation is that we were not able to control for health conditions such as allergies and diabetes as well as physical activity which may confound inflammation. Furthermore, the financial difficulties questionnaire was completed by the mothers and thus may not reflect well the financial situation of the family or indeed other household members' perceptions. We should also note a seemingly odd finding that many mothers reported financial difficulties and yet had a high social status and owned their home. This can be explained by the well-established finding that self-reported financial distress reflects both economic resources and the demands that are made on them and does not necessarily imply low or lower income or lower

SES (Clark et al., 2019). Also, not being able to use a measure of weight for age percentiles for children instead of BMI is another limitation of the study. Finally, we must acknowledge that our analytic sample is somewhat selective. In comparison to the ALSPAC families not included in our study, our sample was more socio-economically advantaged. Interestingly however there were no differences in children's working memory performance between the two samples. Despite these limitations, our study has significant strengths and contributes a great amount to the literature. Understanding the potential mechanisms that play a role in the relationship between the economic stressors associated with parents' low social position and children's cognitive functioning is important for the development of early intervention and prevention. Future research should focus on further explaining the associations we explored. For example, it would be important to test for associations longitudinally by including repeated measures of both EF and inflammation as well as understand how inflammation due to financial stressors may affect the cognitive development of children.

4.1 Conclusions

Our findings suggest that inflammation, as measured by IL-6, partly mediates the relationship between SES-adjusted financial difficulties early in life and working memory in middle childhood. The novelty of our study lies in delineating a physiological mechanism that explains, at least in part, the relationship between SES (and the economic stressors associated with low social position) and EF that had not been tested before in children. Future research with children in the general population should explore why inflammation due to early exposure to financial hardship affects cognition and what other mechanisms may be at play.

AUTHOR DECLARATION

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that neither the entire paper nor any of its content has been submitted, published, or accepted by another journal. The paper will not be submitted elsewhere if accepted for publication in the Journal.

Theodora Kokosi

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). She is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author and which has been configured to accept email from dora.kokosi.15@ucl.ac.uk

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