Family socioeconomic status, financial difficulties, and children's cognitive outcomes: the role of inflammation

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Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work that has formed part of jointly authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 5 was previously published in *Brain, Behavior and Immunity* with the title, "Do upsetting life events explain the relationship between low socioeconomic status and systemic inflammation in childhood? Results from a longitudinal study", by me, Theodora Kokosi (author of this thesis and first author of that research article), Eirini Flouri (co-author and first supervisor) and Emily Midouhas (co-author and subsidiary supervisor). I carried out the preparation, investigation, validation and visualization of the data and the results, wrote up the manuscript draft and led on the editing of the article.

The work presented in Chapter 6 has been published in *Psychoneuroendocrinology* titled, "The role of inflammation in the association between poverty and working memory in childhood" (Kokosi, Flouri, & Midouhas, 2020). I carried out the preparation, investigation, validation and visualization of the data and the results, wrote up the manuscript draft and led on the editing of the article.

Finally, I declare that this research thesis adheres to the requirements of the ALSPAC study and has included an accurate description of the study numbers, the study details as stated in the manuals and the correct references to the cohort.

Abstract

Background: Family socioeconomic status and economic deprivation have been extensively associated with health and cognitive outcomes in children and adolescents. Children living under those conditions are also more likely to be exposed to stressful experiences which can cause significant increases in the inflammatory activity in the body. Several environmental and family mechanisms have previously explained part of those relationships, but no study has yet examined if inflammation is also an important mediator. This PhD thesis, therefore, will investigate the role of inflammation as an important biological pathway linking family SES and financial difficulties with cognitive outcomes in children and adolescents.

Methods: This thesis used secondary data from the Avon Longitudinal Study of Parents and Children to explore the associations between objective family SES and subjective parental financial difficulties, inflammation, and cognitive outcomes from early in life (0-3 years) and up to age 15 years. Structural Equation Modelling (SEM) was used with a latent SES variable and robust mediation analysis techniques to first estimate the path from objective SES to inflammation through childhood upsetting events and then the paths from objective SES and subjective financial difficulties to cognitive outcomes through inflammation in childhood and adolescence.

Results: Findings from the SEM models showed that upsetting childhood events explained part of the relationship between SES and childhood inflammation and that inflammation partly explained the relationship between financial difficulties and working memory, but there was no evidence for the mediating role of inflammation between SES and IQ.

Conclusions: Family SES and parents' financial difficulties were significant predictors of cognitive outcomes in children. Furthermore, it was shown that upsetting childhood events explained part of the relationship between SES and inflammation in childhood and that inflammation explained part of the effect of parental financial difficulties on children's working memory. Consequently, this project provided evidence indicating that socioeconomic and financial factors can directly and indirectly influence both physical health and cognitive functioning through psychosocial and biological mechanisms.

Impact Statement

Socioeconomic disadvantage has been consistently linked to lower cognitive ability and academic achievement in children and adolescents. Extensive research has underlined the impact of the disadvantage gap in education which has widened even more during the current pandemic, as students from disadvantaged backgrounds could now be around 7 months behind their less disadvantaged counterparts. In addition, it is now evident that families and children from lower socioeconomic backgrounds are more at risk of experiencing adversities and stressors that can bring about increased inflammation levels in the body and affect their physical health.

By using secondary data from the Avon Longitudinal Study of Parents and Children, this thesis aimed to explore how socioeconomic status (SES) is related to cognitive ability and executive functioning in childhood and adolescence and how the biological mechanism of inflammation could potentially explain this relationship. The pathway from SES to cognition through inflammation in childhood has never been studied before. Thus, findings may offer important benefits to both researchers inside and outside academia as well as to policymakers.

For academic researchers, this study paves the way for a more detailed exploration of the potential biological mechanisms that play a role in the relationship between the economic stressors associated with parents' low social position and children's cognitive functioning. It also makes it possible to understand the consequences of adversity on infection. This exploration is of great importance as understanding the risks to children's cognitive ability and executive functioning, especially that of working memory which is shown to be highly predictive of academic performance,

will help the development of early intervention and prevention of the effects of disadvantage and inflammation not only on short-term cognitive impairment but also long-term cognitive decline at older ages.

This study also has significant implications for policymakers and researchers outside academia who work closely with the government on developing programmes and relevant legislation to end child poverty. The findings provide further evidence for the impact of socioeconomic disadvantage on families and children and highlight the importance of relevant programmes that target and support children who are at greater risk of poor cognitive and educational outcomes from the early years. Evidence from longitudinal research, such as that presented in this thesis, provides further evidence for existing programmes in continuing to target those at risk, whilst suggesting the need to prioritise disadvantaged children in the development and/or application of new policies with the goal of closing gaps in educational achievement. Last, but certainly not least, this study provides evidence for the first time, that early socioeconomic disadvantage can trigger inflammation in childhood and thus, it is important for relevant policies to attempt to mitigate the impact of SES-related stressors on families and the consequences of inflammation on health. Such policies and interventions could be related to providing parents and children tools for managing stress at school and at home (e.g., practicing mindfulness, journaling to release their feelings and adopting healthy lifestyles) and learning how to cope with upsetting and stressful life situations that could affect their physical health and subsequently, their cognitive ability and mental health.

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List of abbreviations

ACE	Adverse childhood experience
ALSPAC	Avon Longitudinal Study of Parents and Children
APA	American Psychological Association
BMI	Body Mass Index
CFA	Confirmatory Factor analysis
CFI	Comparative Fit Index
CRP	C-reactive protein
CSE	Certificate of Secondary Education
EF	Executive Functioning
EFA	Exploratory Factor Analysis
ELSPAC	European Longitudinal Study of Pregnancy and Childhood
FIML	Full Maximum Likelihood
FoM1- FoM4	Follow-up clinic
GCSE	General Certificate of Secondary Education
GPA	Grade point average
HPA	Hypothalamic-Pituitary-Adrenal
IL-6	Interleukin 6
IPW	Inverse Probability Weighting
IQ	Intelligence Quotient
LCA	Latent Class Analysis
MAR	Missing at Random
MCAR	Missing Completely at Random
MCP-1	Monocyte Chemoattractant Protein-1
MI	Multiple Imputation
ML	Maximum Likelihood
MNAR	Missing Not at Random
OPCS	Office of Population Censuses and Surveys
OSA	Obstructive Sleep Apnea
RMSEA	Root Mean Square Error of Approximation
SEM	Structural Equation Modelling

SEP	Socioeconomic Position
SES	Socioeconomic Status
SRMR	Standardised Root Mean Square Residual
TLI	Tucker Lewis Index
TNF	Tumor Necrosis Factor
WASI	Wechsler Abbreviated Scale of Intelligence
WBC	White Blood Cell
WISC	Wechsler Intelligence Scale for Children
WLSMV	Weighted Least Squares Estimation
WM	Working memory

Chapter 1. Introduction

1.1 Context of this study

Socioeconomic status (SES) is a multidimensional concept that involves the compound of economic resources, such as material wealth and income, and other social and education-related characteristics such as prestige, power, education and social status (Adler et al., 1994; Adler & Rehkopf, 2008; Braveman et al., 2005; Duncan & Magnuson, 2003; Goodman et al., 2001; N. Krieger et al., 1997). SES is related to an extensive range of health, cognitive and socioemotional outcomes in children, with effects beginning prior to birth and continuing into adulthood. Previous evidence suggests that low SES is associated with lower cognitive ability and academic achievement scores in school-aged children (Gutman et al., 2003; Howse et al., 2003). Similarly, SES is associated with 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 (Finch & Obradović, 2017; Hackman & Farah, 2009; Noble et al., 2007; Obradovic et al., 2016).

Persistent economic deprivation, a key aspect of low SES, is found to have detrimental effects on children's cognitive development even after controlling for various confounders (Fagan & Holland, 2002; Schoon et al., 2012). Parental education and occupation, which are also considered significant indicators of SES, are linked with children's academic development (Walker et al., 2011). Nonetheless, SES is thought to also affect children's development indirectly through family and home environment pathways.

Numerous studies have shown the multiple pathways that account for the negative impact of low SES (or SES risks) on cognition and EF (Blair, 2010; Bradley & Corwyn, 2002; Evans & Schamberg, 2009). Children growing up in low SES families are exposed to many more stressors and physical health risks such as poor housing conditions, nutritional deficiencies, and toxins, which are all known as factors with detrimental effects on the brain and cognitive development (Brooks-Gunn & Duncan, 1997; Evans & Kantrowitz, 2002). Besides, parental conflict, poor parenting quality and lack of intellectual stimulation which are usually observed in low SES households may be responsible for impairments or delays in children's cognition (Blair & Raver, 2012; Hackman et al., 2010; Hoff, 2003; Raviv et al., 2004). These have been some of the most studied family- and environment-related mechanisms that mediate the associations between low SES and poor cognitive functioning.

However, recent literature suggests that biological mechanisms may also explain the link between SES and child cognitive functioning. Several mechanisms attempted to explain the above relationship. For one, high body mass index (BMI) and unhealthy lifestyle choices, which are related to disease, partially account for this association (Miller et al., 2011). More recent literature suggests that another, in many ways related, pathway may be inflammation. Inflammation is the body's primary response to physical injury or infection. The primary purpose of inflammation is to protect the nervous system, however, chronic exposure to inflammation becomes maladaptive and damages the brain and body due to the wear-and-tear of the body (McEwen & Gianaros, 2010). Inflammation has been strongly associated with low SES independent of individual characteristics (demographics), biomedical factors (e.g., longstanding illness) and health-related behaviours (e.g., smoking,

drinking, BMI, and stress) (Jousilahti et al., 2003; Lubbock et al., 2005; Owen et al., 2003; Panagiotakos et al., 2005; Prescott et al., 2007; Rosvall et al., 2006). Furthermore, stressful life experiences and psychosocial stressors, which may be more commonly experienced among people from lower SES backgrounds, can also trigger significant increases in inflammatory activity and get 'under the skin' (McDade et al., 2013; Slopen et al., 2013). These inflammatory processes are upregulated in response to the above stressful experiences, all of which are prevalent in lower SES populations. Thus, increased levels of inflammation may be a critical link between SES and health outcomes (Muscatell et al., 2020).

Inflammation is also found to be related to poor cognitive functioning where low-grade inflammatory processes of several pro-inflammatory markers such as Monocyte Chemoattractant Protein-1 (MCP-1), Interleukin 6 (IL-6), and C-reactive protein (CRP) are associated with poorer EF and poorer episodic memory in the adults. Some of the association can be present even after adjustments of demographic factors and health conditions (Lin et al., 2018; Stenfors et al., 2017; Teunissen et al., 2003; Todd, 2017). However, relevant literature in the child population is unexpectedly limited and results are mixed. For example, some studies reported associations between CRP and poorer cognitive functioning (Cullen et al., 2017) while other studies found no significant associations between this association (Jonker et al., 2014).

It seems that the separate links of SES and inflammation in children, and inflammation and cognitive functioning in children need further exploration. Furthermore, although the association between SES and cognitive functioning in children is well established, the biological mechanism of inflammation that may explain that link is not yet understood.

1.2 The rationale for this study

There is much evidence suggesting the significant relationship between SES and cognitive functioning as well as the relationship between SES and inflammation in adults, and inflammation and cognitive outcomes in adults. Many researchers attempted to disentangle the complexity of those three relationships separately in adults but the research on children and especially that on understanding the simultaneous links between all these three factors together in children is limited. In adult samples, there are several cross-sectional and longitudinal studies; however, most of the studies in children and adolescents are either experimental or in populations suffering from special health conditions, such as Obstructive Sleep Apnea (OSA) or have produced discrepant results.

The lack of evidence for the relationship between SES and inflammation in childhood is somewhat unexpected. Although there is much evidence for the association during infancy and adulthood, only a few studies were conducted in children and adolescents. One reason may be that it has historically been more difficult to measure biomarkers in children and adolescents. However, childhood and especially middle childhood is an important period of development and change due to the rapid brin development (Feldman, 2013) and, thus, it is important to explore how early stressful experiences affect children.

Similarly, evidence for the association in childhood between cognitive functioning and inflammation is needed. The existing literature from experimental studies and special child populations suggest that inflammation and neurocognitive functioning are connected and indeed, it has been shown that inflammation leads to cognitive impairments and not the reverse (Calderon-Garciduenas et al., 2004;

Gozal et al., 2007; Karlsson et al., 2010). Additionally, more recent findings from longitudinal studies in the general child population have produced mixed results though, as some of them reported significant associations between inflammation and IQ in childhood (Mackinnon et al., 2018), academic performance (Esteban-Cornejo et al., 2016) and poorer executive functioning (Cullen et al., 2017) whereas a couple of other longitudinal studies found no associations between inflammation and memory or executive function (Cohen-Manheim et al., 2015; Jonker et al., 2014).

Therefore, it is important to examine how children exposed to risks related low socioeconomic and financial factors develop their cognitive functioning and whether this can be explained by physiological mechanisms such as inflammation. The main goal of this longitudinal study is thus to further explore and create a clearer picture of the link between objective and subjective socioeconomic and financial factors, inflammation, and cognition in children.

1.3 The present study

To my knowledge, no large-scale representative studies have explored the association between SES, inflammation, and cognitive functioning in childhood. Consequently, the first aim of the thesis is to investigate whether family objective SES predicts higher levels of inflammation in childhood. This investigation will help to understand the direct and indirect mechanisms that connect low SES and childhood upsetting events to health outcomes in children. The second aim is to examine whether the association between subjectively measured parental financial difficulties and EF in children is explained by inflammation in childhood. Lastly, the third aim of this research project is to explore the direct and indirect longitudinal relationships between objectively measured early family SES and IQ in adolescence through

earlier and concurrent inflammation. In my dataset, inflammation was only measured in middle childhood (age 10 years) and adolescence (age 15 years), two important periods of development in children's lives.

In this thesis, SES was measured as a latent factor involving maternal education, paternal social class, housing tenure, overcrowding and perceived family financially difficulties, which have not been combined in previous research looking at those relationships together but have typically been examined separately. Furthermore, this study did not focus only on the relationships among objective family SES, financial difficulties, inflammation and cognitive ability and EF but also investigated another pathway, that of childhood upsetting events, which may explain the link between family SES and elevated inflammation in childhood. Lastly, this study also explored whether inflammation may lead to cognitive deficits measured by performance in a working memory task and IQ scores.

This project uses secondary analysis data from the Avon Longitudinal Study of Parents and Children (ALSPAC) which is an ongoing birth cohort study that recruited children and mothers in 1991 who have been followed since then. The sample 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.

1.4 Structure of the thesis

The structure of the thesis is as follows. **Chapter 2** reviews previous research on the associations between SES, inflammation, and cognitive functioning and focuses on the gaps that this thesis will try to address. **Chapter 3** describes the main source of data and how the independent and dependent variables were measured.

To be more specific, it describes how the latent factor for SES was created and how the rest of the variables were transformed and coded. **Chapter 4** describes the methods and analytic approaches that were followed in the thesis such as the models that were used, model estimators, model fit, missing data, confirmatory factor analysis and path analysis.

Subsequently, Chapters 5 to 7 comprise the three empirical chapters of the current thesis. **Chapter 5** explores whether objective family SES predicts inflammation in childhood through early life upsetting events and **Chapter 6** investigates whether the association between perceived family financial difficulties predict poorer working memory in children and whether inflammation explains that relationship. **Chapter 7** explores the longitudinal relationship between family SES and general intelligence (IQ) and whether this relationship is explained by earlier and concurrent inflammation. Lastly, **Chapter 8** discusses the overall findings, the significance of the research, its strengths and limitations, implications for future research and policy as well as concluding remarks.

Chapter 2. Literature Review

2.1 Socioeconomic Status and its Measurement

SES is a topic of great interest to those who conduct research around children's development. SES is a multidimensional concept that involves the compound of economic resources, such as material wealth and income, and other social and education-related characteristics such as prestige, power, education and social status (Adler et al., 1994; Adler & Rehkopf, 2008; Braveman et al., 2005; Duncan & Magnuson, 2003; Goodman et al., 2001; N. Krieger et al., 1997). Although children and adolescents have not yet been able to establish their own individual SES, their status is best measured by their parent's or caregiver's SES which can influence their development regardless of their own SES later.

Measuring SES has been at the centre of the research interest since very early (Davis & Havighurst, 1946; Sears et al., 1957). Although it can be measured using different composites, widely accepted definitions of SES are difficult to find. In fact, when SES is measured as a combination of different variables then the interpretation of research findings can be difficult (White, 1982) and it is still considered difficult to conceptualise it and use it as an empirical measurement in child and adolescent studies (Bornstein & Bradley, 2014). Looking back at the history of the definition of SES, the most frequent measures of SES in the past was the Index of Status Characteristics (Warner et al., 1949) and Hollingshead's Two-Factor Index of Social Position (Hollingshead & Redlich, 1958). The Index of Status Characteristics uses information about the family's a) occupation of principal breadwinner, b) source of income, c) quality of housing, and d) status of dwelling

area to arrive at a score that is converted to one of the five social classes.

Hollingshead's scale uses indices of occupation and educational attainment to

categorize families into one of five social classes. Previously, Chapin (1928) had

defined SES as "the position that an individual or family occupies with reference to

the prevailing average of standards of cultural possessions, effective income,

material possessions, and participation in a group activity in the community".

Similarly, the Michigan State Department of Education (1971) had previously created

their own definition of SES which comprised of three major factors: a) family income,

2) parents' educational level, and 3) parents' occupation. Until then, one could be

overwhelmed by the range of variables used to measure SES.

More recent research on the indicators of socioeconomic position has also

been conducted by UK-based researchers. Galobardes and colleagues developed a

glossary (Galobardes et al., 2006) which is a comprehensive list of indicators of

socioeconomic position used in health research. In that glossary, they discussed

how each indicator measure different but usually related aspects of socioeconomic

stratification and that each one of them is related to different health outcomes. The

choice of the SES indicators depends on the specific research question and the

proposed mechanisms linking SES to the outcomes, but it also depends on the

available measures at the time. The individual indicators that were identified were 1)

education, 2) housing tenure, housing conditions and housing amenities, 3) income,

4) occupation-based measures and 5) other proxy indicators such as the number of

siblings, infant and maternal mortality, maternal marital status, single parent, being

an orphan, illegitimacy, broken family and death of father or mother at an early age.

All the indicators have their strengths and limitations as well as interpretation and

different ways of measuring them. For instance, education is a frequently used

indicator in epidemiology and can be conceptualised within a life-course framework. Education captures the transition from parents' socioeconomic position (SEP) to adulthood (own SEP) and it is a significant predictor of future employment and income while it also determines the knowledge and skills gained that may affect one's cognitive development. Some of the strengths of measuring education are that it is convenient to measure in most studies through self-administered questionnaires; however, it is suggested that as the meaning of educational level varies across cohort studies, the results from studies that included participants from different birth cohorts may be biased if cohort effects are considered. In addition, housing tenure, conditions, and amenities have been frequently used in studies in both industrialised and non-industrialised countries. Housing tenure (whether housing is owned or occupied) is the most commonly used indicator in epidemiological research followed by household amenities and household conditions (e.g., presence of damp and condensation, overcrowding etc.) and all of them are thought to be markers of material circumstances. Although housing is an important and multifaceted indicator of SES sometimes it is difficult to interpret and might be specific to the temporal and geographical context where they were developed and thus comparison across studies could be difficult.

Furthermore, income is the indicator that directly measures the material resources of a person most directly and has an impact on several material circumstances that can affect health. Income is reported either as the absolute income of a person or participants can place themselves in predefined categories and is related to access to a wide range of resources (e.g., access to better quality resources and services) through which it can affect health. Although income has been arguably the best indicator of material living standards, one important

disadvantage when measuring it is the sensitive nature of asking this question to participants and that in every country income can be collected differently. Moreover, occupation is another important indicator of SES which holds from childhood by measuring parental occupation to adulthood. Occupation is also thought to be related to income and material resources that have a direct influence on health and notably, there are different occupational classification schemes. Occupational status can be routinely measured in many data sources; however, one setback is that people who are currently unemployed or have retired or are students or working in unpaid, informal, or even illegal jobs, cannot assign themselves into one category.

In the same report, researchers also discussed the use of composite measures to assess SEP at the individual level. It was acknowledged that several studies have used composite indices of SES depending on the data available in each particular dataset, however, they argued that using such indices is most appropriate when SEP is a confounding variable of the association of interest or when the specific mechanisms determining inequalities are not at the centre of interest of the study. More recent research contradicts the previous claims though as it has been suggested that multivariate scales of SES can be more reliable than single measures (Goosby & Walsemann, 2012; Walsemann et al., 2011; Yang et al., 2017). Single objective measures fail to capture the complex and multidimensional nature of socioeconomic well-being and its potential health impacts that can vary across the life course.

Studies on child development have placed significant attention on the role of SES in child outcomes due to the evidence that high SES families can afford their children material goods and services and provide them with social connections that would benefit them. Whereas low SES children lack access to those same

resources, thus, may be more prone to developmental problems (Brooks-Gunn & Duncan ,1997). Despite the discrepancies and the great variability in the experiences of children within every SES level, researchers continue to consider SES as a global concept, even though there has never been a consensus on precisely what it represents (Liberatos et al., 1988; McLoyd, 1997).

Looking at how family SES in relation to child outcomes has typically been modelled, family SES is measured using indicators such as occupation, education and income of the "householder" who is assumed to be the child's father or father figure (Hauser, 1994). Furthermore, it was possible to use the father's or mother's socioeconomic characteristics interchangeably when one of them was not present. However, substituting the occupational status of the mother or mother figure for that of the male provider can be problematic. Women had occupations that had relatively high prestige but would pay rather poorly (e.g., schoolteacher, librarian, social worker). Therefore, occupational prestige was considered a rather invalid indicator of financial resources for women (Entwislea & Astone, 1994). This traditional approach in studies had other limitations, too. For example, children in single-parent or stepparent families were more affected by the SES of the provider of the family they live in than by that of their biological parent if they live apart from them. In addition, some children in poorer stepfamilies would still have access to the earnings of an affluent biological father. Similarly, the traditional two-parent family could not apply to some cases of children from ethnic minority groups. Therefore, an alternative approach for measuring SES was suggested (Entwislea & Astone, 1994).

The alternative approach suggested by Entwisle and Astone (1994) was based on Coleman's (1988) idea that children growing up require three kinds of "capital" to facilitate optimal development. Coleman was the first to propose the idea

of capital which exemplifies the currently accepted definition of SES (Bornstein &
Bradley, 2014; Bradley & Corwyn, 2002). The idea of capital is categorised into three
groups: 1) the financial capital (material resources such as money to buy food,
clothes, and other things that they need), 2) the human capital (nonmaterial
resources from their parents that are indexed by parental education), and 3) social
capital (resources through social connection).

First, *financial capita*l can be measured by household income but also can be
a manifestation of occupational status. It is agreed though that a combination of both
provides a better approximation of financial capital (Duncan et al., 2002). Second,
social capital may be captured through one's occupational status as well as
measures of help and support from friends and family which may involve support in
terms of money, time or care to overcome difficult situations. Researchers have also
suggested that social capital might also be captured with the number of parents or
grandparents at home that offer support especially in households with many children
(Entwislea & Astone, 1994; Shavers, 2007). Finally, *human capital* can be best
measured by gathering information on parental education and now on parental
occupation as well. This is because well-educated parents, for example, can help
their children with their homework and language skills and they also tend to
encourage high educational aspirations (Entwislea & Astone, 1994). Mother's
education is always measured in surveys and it is also highly correlated with father's
education (Kalmijn, 1991). Therefore, it is suggested that mother's education is used
as the main indicator of human capital in the home.

Although there has still not been agreement on a) how to best combine the
indicators of SES, b) whether it is best to use a composite of the indicators of SES or
each one separately or c) how to best measure each component (N. Krieger et al.,

1997) several studies now seem to follow Duncan, Featherman, and Duncan's (1972) definition of SES that includes the three main indicators: 1) parental income, 2) parental education, and 3) parental occupation. Those three components were found to be positively related to each other but also considerably different to one another so they can be used either together or separately so that researchers can evaluate their unique, additive contributions to family characteristics and human development (Bollen et al., 2001; Conger et al., 2010; Conger & Donnellan, 2007).

In addition to those three main indicators, researchers have used measures of housing, a key correlate of socio-economic disadvantage, to capture the material circumstances surrounding those with lower SES positions linked to many health and life outcomes (Duncan et al., 2002). For instance, housing characteristics such as housing tenure, housing conditions and housing amenities measure material aspects of socioeconomic circumstances (Galobardes et al., 2007). The most commonly used characteristic is housing tenure – whether housing is owner-occupied (owned outright or being bought with mortgage) or rented from a private or social landlord, as described above. In addition, household conditions such as rooms in the dwelling and overcrowding are housing-related indicators of material resources. Residential crowding is typically measured by the ratio of people to the numbers of rooms available in the home (usually excluding kitchen and bathrooms) (Evans & Kantrowitz, 2002). Overcrowding is then defined as being above a specific threshold (most commonly two or more people per room) (Townsend et al., 1988). These indicators are mainly markers of material circumstances and are also related to income (Wardle et al., 2002). Housing is a multifaceted and extensively used indicator of SES and is generally the key component of most people's wealth.

A handful of studies using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a UK birth cohort study, utilised in the present thesis, have also measured family SES using several parental characteristics. For example, one study looked at SEP during pregnancy and used information on parental education and occupation during pregnancy (Alfano et al., 2019) where education was coded into three categories based on their educational achievement, i.e. low [Certificate of Secondary Education (CSE) or other vocational or education qualification obtained at age 16, intermediate (A-levels) and high (university degree) with occupation (manual and non-manual) measured by the UK Registrar General's classification (Office, 1991). Another study also used the indicators of parental occupation status, maternal educational level and household income to measure early SES (Tinner et al., 2020) and similarly, another one explored the effect of early SES on alcohol-related behaviours of adolescents using the three indicators of household income, maternal education and parental social class (Kendler et al., 2014).

The aforementioned indicators are *objective* measures of SES. Objective SES is the economic and social position of an individual in relation to others (Anderson et al., 2012; Kraus & Stephens, 2012). On the other hand, subjective SES refers to an individual's perception of their position compared with that of others. Subjective measures may not capture the full range of psychological processes and how individuals perceive their own position of SES based on what is most meaningful or relevant within their societal context (Tan et al., 2020). Furthermore, social comparisons of one's SES may be heightened and exacerbate socioeconomic disparities in important life outcomes. Subjective measures of SES can capture these comparisons in a more efficient way (Kraus et al., 2017; Pickett & Wilkinson, 2015). Both objective and subjective measures are traditionally measured in the area

of SES research in relation to health, emotional, and cognitive outcomes; however, by including subjective measures of SES, one can look beyond the objective markers and take into account individual perceptions of financial circumstances or of their relative position in the society. Subjective measures of SES have, in fact, been found to be consistently and strongly related to health outcomes even after controlling for objective SES assessments of income and education (Adler et al., 2000; Cohen et al., 2008; Cundiff & Matthews, 2017; Kraus et al., 2013). In some studies, objective and subjective SES seem to underlie the same phenomenon, as suggested by their intercorrelations and their similar correlations with outcome measures. In other studies, however, they seem to be indicating different underlying phenomena and to be related to different paths of influence (Ostrove et al., 1999). Although objective SES can be reasonably assumed to provide at least some basis for subjective SES (Demakakos et al., 2008), several studies have found their correlation only to be moderate (Adler et al., 2000; Gong et al., 2012; Huang et al., 2017; Ostrove et al., 2000). That means that they are different constructs that can operate individually but can also be combined to create a distinct measurement of SES, nonetheless.

In overview, the choice of how to measure SES remains open. This choice is partly determined by the hypotheses that are examined, the practical considerations with the acquisition of the data and partly by the population from whom the data are collected as theory and empirical findings suggest that SES indicators function differently across different cultural groups (Bornstein & Bradley, 2014; Bronfenbrenner, 1995). In the present thesis, I examined both objective and subjective indicators as both are deemed to be important aspects of socioeconomic experiences and as subjective indicators are explored less so in the literature.

2.2 Socioeconomic factors and cognitive functioning in children

2.2.1 Environmental pathways linking socioeconomic factors and cognitive functioning

In the literature, a key suggested reason for the association between SES and cognitive functioning in children is that high SES families can afford to buy their children a range of services, activities, and goods that can benefit their overall development. Low SES children, in contrast to high SES children, are resource- and experience-deprived (Brooks-Gunn & Duncan, 1997). Socioeconomic challenges typically indexed by lower levels of family income, parental education, and social status affect children's access to resources (Bradley & Corwyn, 2002; Duncan et al., 2014) and cognitively stimulating materials and learning experiences inside and outside of the home (Bassok et al., 2016; Espinosa et al., 2006; Hackman et al., 2015). Moreover, socioeconomic differences exist in access to high-quality school programmes which are known to benefit children's cognitive development (Bassok & Galdo, 2016; Loeb et al., 2007; Magnuson & Waldfogel, 2005) and all these account for socioeconomic differences in children cognitive development and executive functioning (EF).

Separately, economic deprivation can seriously affect parents' mental health, the quality of parenting and how much time a parent spends with their child as well as the parent-child interactions and the home environment (Choe et al., 2013; Heberle et al., 2015). Parents of low SES can be less supportive and warm as income deprivation and financial difficulty have affected their psychological health in a way that in turn affects their responsiveness towards the children. Previous and

recent studies have found that parents who had greater socioeconomic cumulative risks and experienced depressive symptoms were less able to provide stimulating caregiving. These symptoms, in turn, were associated with negative interactions in the family (Jeon et al., 2014), as parents were less emotionally healthy than other parents probably due to the exhaustion by the socioeconomic burden at home (Mistry et al., 2010).

In the literature there are two key models that attempt to explain the relationship between SES and child development including cognitive outcomes: the "Family Stress Model" and the "Family Investment Model".

The Family Stress Model

The Family Stress Model (see Fig.2-1), is a theoretical model that was first developed by Conger and Elder in 1994 and examines how relationships and interaction among family members are shaped under emotional distress, marital conflict and economic deprivation and how these difficulties affect children and adolescents' adjustment (Conger & Elder Jr, 1994). According to this model, economic hardship (i.e low income, unstable work, debt load, and decreasing income) produces inability to make ends meet which in turn generates conflict between the couple and expressions of harsh or neglectful parenting. Previous studies provide evidence of the disruptive effects of financial difficulties on parental behaviour, parent-child interactions and child development (Conger & Conger, 2002; Conger et al., 2010). Normally, a non-poor family can promote children's and adolescents' adjustment by providing them with a comfort zone when they go through life transitions (Simmons, 2017). However, when parents experience economic pressure which causes emotional distress, they then find themselves

unable to maintain an environment of safety and security for their children or they do not even have the emotional or physical strength to live up to their children's needs and expectations. Consequently, these children can end up displaying symptoms of depression and anxiety, substance use, lower academic attainment and other behavioural issues. Thus, the Family Stress model extends the research by proposing a direct effect of economic pressure on parental emotional distress and an indirect link between economic pressure and children's maladjustment through parental emotional distress, marital conflict and insufficient parenting. Finally, although the financial situation of the parents may affect the family dynamics and the development of their offspring, it seems that if parents can maintain their supportiveness and warmth towards their children, the latter will be more likely to have positive school experiences, academic achievement and good relationships with their peers as well as good self-esteem and less emotional problems (Conger & Conger, 2002; Conger & Donnellan, 2007). However, research has shown that highly educated and affluent adults can also experience stress, parental role overload, and mental health challenges (Luthar & Ciciolla, 2015; West et al., 1998) and can be perceived as emotionally unavailable (Luthar & Latendresse, 2005).

FAMILY STRESS MODEL
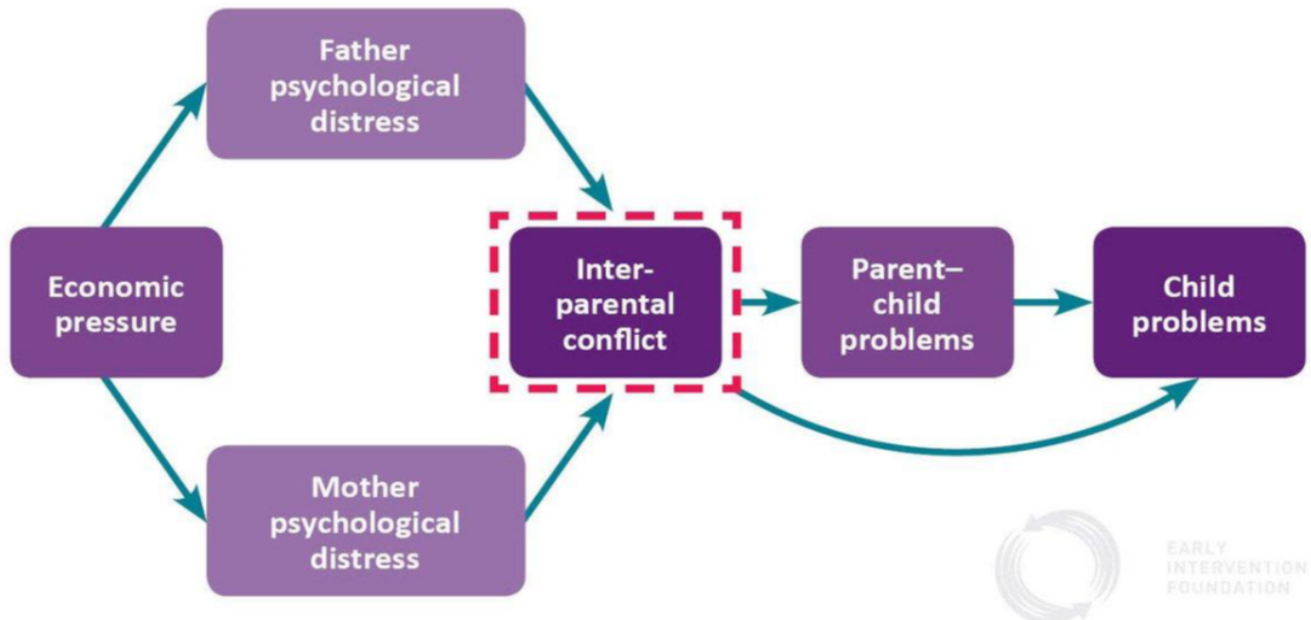
Figure 2-1. The Family Stress Model.

Source: Early Intervention Foundation (www.eif.org.uk). Resource provided as part of EIF Commissioner Guide: Reducing parental conflict.

The Family Investment Model

The Family Investment Model examines the effects of economic deprivation on children's resources. These resources could be about the money that parents can use to afford material goods, services and experiences for their children as well as other kinds of resources such as parental time, social capital and a good home environment. Numerous resource categories are under the Investment Model and families that experience multiple deficits are those who are most harmed. For example, income deprivation can reduce the number of stimulating toys and

resources children can have, resulting in fewer materials and poorer learning experiences (Conger & Elder Jr, 1994).

These children are less likely to go to museums or to activities that can provide important stimuli and enhance their cognitive skills (Conger et al., 2010; Yeung et al., 2002). Furthermore, the importance of the learning materials is evident through the opportunity of valuable interactions between the parents and the children as they can both be engaged and spend quality time together (Bradley & Corwyn, 2002). The time a parent spends with their children is of great importance, however, parental employment can be both positive and negative. It is positive because it provides parents with the amount of income that allows them to afford everything the family needs but is also negative because having a job is time-consuming and decreases the hours a parent spends with his or her child(Dearing et al., 2001). In fact, in a most recent study on income effects on the cognitive development of children from low SES families in Hong Kong, it was found that parental investment and parental stress mediated the relationship between income effects on children's cognitive and language abilities in the Asian context (Cheung & Wong, 2020).

Other family-related pathways

Social capital is also a pathway included in the Investment Model and refers to both the help and support from friends and family in terms of time and money (Boisjoly et al., 2016). Social capital offers parents who may face economic impoverishment and feel overwhelmed a sense of support to maintain their emotional health and prevents them from feeling isolated but rather relieved in times of economic hardship(Jackson et al., 2000). Furthermore, parental academic involvement has been consistently found to be positively associated with children's academic achievement in previous meta-analysis studies (Castro et al., 2015; Fan &

Chen, 2001; Jeynes, 2005) as well as in more recent studies (Zhang et al., 2020). According to the latter study in a sample of 815 fourth-to sixth-grade children in China that examined the relationships between family SES and academic achievement and explored the role of parental academic involvement as mediator and the role of parental subjective social mobility as moderator, it was found that both family SES and parental academic involvement were associated with children's Chinese and math achievement and that parental involvement mediated the relationships between SES and academic achievement. It was also found that parental subjective social mobility (i.e. the belief that one has the ability to move up to a position of higher class) (Huang et al., 2017; Kelley & Kelley, 1984) moderated the path from family SES to parental academic involvement as it was shown that the association between family SES and parental academic involvement was weak among children whose parents had high levels of subjective social mobility.

In addition, the physical home environment, child health and nutrition and living in poorer neighbourhoods are found to have effects on child development. Families living in poverty are more likely to reside in less safe and clean and more disorderly houses but also in poorer neighbourhoods. Children and babies growing in those families are also more likely to be malnourished and of low birth weight. All these adverse experiences are found to have negative effects on children's cognitive development, school attainment, physical health and developmental delays such as growth stunting (Bradley & Corwyn, 2002; Case et al., 2002; Kohen et al., 2008; Leventhal & Brooks-Gunn, 2000; McCoy et al., 2015).

These models are sharing potential environmental pathways through which socio-economic factors affect the family system and consequently child development. They provide adequate evidence of the impact of poverty on parental

mental health and the resulting implications on their behaviour as parents, their ability to make ends meet and children's development and adjustment. Thus, it seems that the link between SES and children's development can be partially explained by the link between family socioeconomic risk and disadvantage and parental psychological well-being.

2.2.2. Research findings on SES and cognitive functioning in children

Several decades of research have established the relationship between SES and cognitive development as well as academic attainment (Sirin, 2005). General cognitive ability comprises the adaptive mental processes of perception, reasoning, creativity, problem solving and intuition, typically measured by an intelligence quotient (IQ) measure (Al-Mekhlafi et al., 2011). Poor cognitive development and low IQ among children may result in poorer mental health (Emerson & Hatton, 2007), social development (Bellanti & Bierman, 2000) and overall quality of life in adulthood (Calvin et al., 2011).

Much literature provides evidence for the relationship between SES and cognitive ability beginning in infancy. It found that income has stronger links with measures of intelligence than with manifestations of emotional health in the childhood years (Brooks-Gunn & Duncan, 1997). For example, children living below the poverty threshold are more likely to score lower on standardized tests of IQ (Hanscombe et al., 2012; Turkheimer et al., 2003). Furthermore, in another recent study in Malaysian primary school children (age 5-12 years), it was found that those from disadvantaged backgrounds (from very low-income families and with parents who only received their primary education or lower) were more likely to have poorer non-verbal IQ (Poh et al., 2019). In the same study, children with severe obesity were also more likely to have scored lower in the IQ test, a finding that further

supports that nutritional status is an associated factor of SES (Babar et al., 2010; Kamiya, 2011) that can influence the cognitive performance of disadvantaged children. Differences in cognitive ability between poor and less poor children were found even after adjusting for significant confounders such as maternal age, marital status, education and ethnicity (Achenbach et al., 1990; Brooks-Gunn et al., 2003; Fagan & Holland, 2002; Strenze, 2007). However, the reasons given for differences across SES have varied. For example, Fagan and Holland (2002) found differences in the vocabulary scores between African American and Caucasian children even after controlling for demographic confounders. Cultural differences observed in cognitive tests performance might be due to the fact that concepts such as intelligence, for example, and the importance of each specific cognitive ability differs across various cultures (Fasfous et al., 2013). However, when they incorporated 40 novel words which children had to learn and then re-take the test, the differences in scores disappeared.

Other studies that focused on the effects of SEP- a term that is used interchangeably with SES in health research (Galobardes et al., 2006; Nancy Krieger et al., 1997) on cognitive function have also provided evidence for the above link. For instance, in a recent study by McElroy and colleagues (McElroy et al., 2021), they analysed data from three British cohort studies (the 1946 Survey of Health and Development, the 1958 National Child Development Study and the 1970 British Cohort Study) by using Structural Equation Modelling (SEM). In this study, they did not find evidence for a direct relationship between childhood SEP and mid-life cognitive function; however, they found indirect pathways from childhood SEP to mid-life cognitive ability via childhood cognitive ability, occupational status and

educational attainment. These three factors fully mediated the SEP-cognitive function link.

In addition, household income has a strong association with school achievement. It is known that cognitive development is of great importance for children as they prepare to enter the educational system (Welsh et al., 2010). Children in at-risk populations tend to have weaker academic performance than their privileged peers and this performance can consequently affect their long-term academic success (Howse et al., 2003). Recent studies suggested that among preschool and primary school children, family SES has been consistently predictive of academic performance (Hair et al., 2015; Hentges et al., 2019). Several systematic reviews in the past have shown that poor and low SES students, on average, are more likely to experience academic problems, i.e., from low grades and more detentions to fewer years of schooling (McLoyd, 1990, 1998). A study by Gutman, Sameroff and Eccles (2003) on African American teenage students found that students who scored lower in their grade point averages (GPAs), had more absences and had worse achievement scores if they were exposed to demographic and structural risk factors (e.g. poverty). Interestingly, higher IQ and better mental health did not function as protective factors for the students exposed to high risk. They were protective only for students exposed to no or low risk (Gutman et al., 2003).

SES disparities can also be seen in other cognitive outcomes. SES has a relationship with language development outcomes, evident even in the early years. For example, when children enter reception, possible language differences do exist between children of lower-SES families and children of higher-SES with the latter having more advanced language skills and coming from a more advantaged

environment (Ramey & Ramey, 2004) which predict later academic success. Fernald and colleagues (2013) wanted to investigate the processes of language development in terms of vocabulary learning in English-learning infants from families varying in SES. They followed longitudinally 48 English-learning infants from 18 to 24 months. They found that SES inequalities in verbal abilities are obvious in preschool-aged children and that these inequalities begin to develop in the first years of life, determining children's later academic success.

Parent's educational achievement and occupational status are also thought to be principal components of SES and have great effects on children's academic literacy skills as well as socio-emotional development (Walker et al., 2011). A wide range of conceptual frameworks (especially in the western countries) support that parental educational attainment and employment are associated with children's cognitive abilities, maths scores, school readiness, behavioural problems, executive functions and general intelligence (Blair & Raver, 2012; Jackson, 2003; Johnson et al., 2008; McGroder, 2000; Wolf & McCoy, 2019). These findings imply the importance of education as well-educated parents can create their children's future by providing them with a high-quality learning and educational environment which can lead to better future jobs (Yang & Gustafsson, 2010). In contrast, several studies have depicted that not only growing up in poverty but also having less educated and unemployed parents can lead to poorer IQ and school achievement in childhood (Davis-Kean, 2005; Duncan et al., 1994; Pianta et al., 1990).

Furthermore, low SES at the neighbourhood level has been linked to negative cognitive outcomes in children. For instance, in two studies it was found that neighbourhood concentrated disadvantage had a negative long-term effect on children's reading comprehension seven years later (Lloyd & Hertzman, 2010; Lloyd

et al., 2010). The relationship between disadvantaged neighbourhoods and negative child outcomes can be explained by the influence of the peers, limited resources in the neighbourhood, lack of monitoring (Froiland et al., 2013) and the lack of learning environments within the family (Dupere et al., 2010). However, neighbourhood-level SES has been shown to be less influential compared to that of the family, especially in the early years of development (Froiland et al., 2013; Vaden-Kiernan et al., 2010). This is due to the family playing a central role in a child's environment at that stage of development.

In line with the above, the relationship between family SES and children's EF, which indexes a range of cognitive processes such as attentional control, cognitive flexibility and working memory that facilitate control of behaviour (Finch & Obradović, 2017; Hackman & Farah, 2009; Noble et al., 2007; Obradovic et al., 2016) has also been extensively explored. In a meta-analysis by Hackman and Farah (2009), it was shown that SES predicts prominently neurocognitive performance especially that of language and executive function and that disparity in SES is found in neural processing even when performance levels are equal. In the adult population as well, SES differences in language are evident (Pakulak & Neville, 2010), suggesting an aggregate impact of childhood SES over time. John and colleagues (2019) used a systematic and nuanced approach to understand how SES relates to children's EF. They assessed children ages 4.5-.5.5 years, at a very important developmental stage as EF is no longer a unitary construct but rather components that can load on separate factors and index distinct aspects of EF. This study attempted to a) distinguish among EF factors rather than using composite accuracy measures to see whether SES is associated with global differences in EF accuracy, or if these differences are evident under certain circumstances, b) include reaction time

measures rather than accuracy only and, c) assess whether children's EF performance may change throughout a task and how SES may relate to this potential change in the performance. Children in this study completed a working memory task where their accuracy and reaction time, as well as inhibitory control and vigilance, were assessed and the findings suggested that for the majority of the EF domains, there were differences that were attributable to SES. Notably, no SES differences in performance for remembering two items and maintaining performance were found which suggests that, at that age, there are still skills that are emerging for children.

Some studies have reported independent effects of both maternal education and family income on children's EFs (Hackman et al., 2015; Raver et al., 2013), while other studies have stressed the importance of family financial resources (Piotrowski et al., 2013). Furthermore, parental income and education have been positively associated with children's EFs in families with different levels of income (Choe et al., 2013; Lengua et al., 2015; Obradovic et al., 2016; Raver et al., 2013). SES-related variances in EFs can be seen as early as in infancy (Clearfield & Niman, 2012). In this study, they assessed the children in 3 different time points, when they were 6, 9, and 12 months old and they looked at their shifting abilities. Results showed that infants from high-SES families followed the typical trajectories, however, those from low SES families displayed delays at each stage of testing. These differences were also apparent later in pre-school children (Noble et al., 2005). In a study by Raver and colleagues (2013), it was found that 4-year-old children from lower SES families showed significantly poorer performance in inhibition, shifting and updating abilities tasks. In line with these studies, other longitudinal studies also support the findings that SES inequalities have an impact on

EFs that persist throughout childhood (Hackman et al., 2014; Hughes et al., 2010; Lawson et al., 2018).

Although several studies have found an association between SES and EFs, other studies contradict these findings. In a study by Wiebe and colleagues (2008) where pre-school children had to carry out various EF tasks, researchers did not find any significant associations between SES and their performance. Similarly, in another study that measured children's ability to update, no links between SES and EF were found (Engel et al., 2008) and in another one on school-aged children (6 to 18 years of age), no differences in performance were found between low-SES and high-SES children (Waber et al., 2007). These contradictory results suggest that the relationship between SES and EFs may not be as robust as initially thought. However, there are some limitations of this body of research (Hackman et al., 2010). In some studies, researchers did not use a reliable measure of SES (Wiebe et al., 2008) while in other studies the exclusion criteria were so strict that the sample comprised only healthy and intellectually able children from low-SES families (Waber et al., 2007). Hence, the relationship between SES and EFs remains open, and therefore more research is warranted.

Furthermore, it is important to determine whether this relationship is produced by the key components of SES, such as parental education and social class or whether it 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 examined the relationship between financial difficulties and children EF performance was conducted by Raver and colleagues (2013) and built on previous studies 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). Families'

perceptions of financial strain and disadvantage, which are subjectively measured

socioeconomic and financial factors, can be part of a complex dynamic process as

they can affect parents' psychological health and reflect the challenges they may

face in meeting basic needs, both of which can lead to poorer child outcomes. Thus,

that study expanded the previously explored links between SES and EF by

investigating the role of families' experiences of financial strain in children's EF and

found that they were uniquely predictive of EF.

Taking all of this together, there are a few key gaps in the literature that this

study aims to address. Most of the aforementioned studies have only focused on

early childhood and have produced mixed results (Hackman et al., 2015). Middle

childhood is the period between early childhood and adolescence and is a significant

period of development where several cognitive changes in the brain occur (Feldman,

2013). Therefore, it is also important to explore the factors of influence for the link

between SES and cognitive ability in older children. Moreover, it is important to

understand the mechanisms of influence of cognitive development during that period

as experiences during middle childhood can maintain, magnify or reverse the

advantages and disadvantages children come across early in their lives (Huston &

Ripke, 2006). Changes during that period are proven to have a strong impact later in

adult life but are also found to exceed the effects of early life cognitive development

(Feinstein & Bynner, 2004) and thus, it is important to disentangle which

mechanisms play a role in the relationship between SES and cognitive development

in middle childhood. In addition, as some meta-analysis studies have reported that

the strength of the relationship between family SES and academic achievement

varies from weak to moderate (Kim et al., 2019; Liu et al., 2020; Sirin, 2005; White,

1982), it is necessary to explore further these possible mechanisms underlying this link to shed light on these discrepancies.

2.2.3 Potential biological pathways linking socioeconomic factors and cognitive functioning

As presented in sections 2.2.1-2.2.2, several studies have found that family SES and financial factors have indirect effects on children's cognitive skills through parental stimulation at home, parenting styles and parental mental health (Jeon et al., 2014; Kohen et al., 2008; McCoy et al., 2015).

In addition to parenting quality and the home environments, there are also other factors that may mediate the effects of SES on cognitive (neural) development. According to the "ecology of socioeconomic status" as discussed by Hackman and colleagues (2010), factors that might explain those effects include a) toxin exposure, i.e. low-SES children appear to have higher levels of lead in their blood (Evans, 2004) and lead is a neurotoxin that affects IQ (Surkan et al., 2007) and reading ability (Miranda et al., 2007), b) nutrition, i.e. low-SES families have less access to healthy foods and are more likely to experience nutritional deficiency (Evans, 2004), c) prenatal drug exposure, i.e. alcohol and drug use during pregnancy are related to SES; however, more research needs to be done on this topic as the effects are particularly small when factors such as the home environment is adjusted for (Frank et al., 2001), and d) stress, i.e. low-SES families experience more stress due to the inability to make ends meet and living in more dangerous neighbourhoods. These can lead to chronic stress which is associated with attentional control impairments (Liston et al., 2009; Liston et al., 2006) and it is also found that chronic stress mediates the relationship between childhood SES and working memory (WM) (Evans & Schamberg, 2009).

Regarding the latter, recent research has shifted the focus to the physiological effects of living in conditions associated with financial strain which will be discussed in the following sections. Children from families that experience such adversities have been found to develop different responses to stress that can impact their cognitive and executive function abilities, showing, for example, altered neuroendocrine stress response and compromised self-regulation (Arnsten & Li, 2005; Blair et al., 2005; Evans & Schamberg, 2009). Another 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 low SES and poor cognitive functioning in children, the main focus of the research for this thesis. To my knowledge, only a few studies have explored the mediating roles of upsetting childhood events and biological factors in the associations between family SES and child cognitive ability. Thus, the present study will examine the role of two key mechanisms proposed, but underexplored, in the literature for the relationship between parental economic and financial factors and aspects of child cognition: upsetting childhood experiences and the biological factor of inflammation.

2.3 Socioeconomic factors, inflammation, and cognitive outcomes

There is growing body of research in the physiological mechanisms through which environmental factors play an important part in determining behaviours and health. Over the last two decades, researchers have emphasized the immune system and specifically, inflammation which can be considered as a physiological connection through which a great variety of psychosocial, socioeconomic and nutritional factors exert their effects on the body (Ashley et al., 2012; Berk et al.,

2013). These factors do not cause the production of high-intensity inflammatory responses that are found in acute infections but are associated with long-term "low grade" activation of the same biochemical pathways (Fagundes & Way, 2014; Kuhlman et al., 2017; Miller et al., 2011; Minihane et al., 2015).

The present study examines the role of inflammation as an outcome of parental economic and financial factors as well as a mediator of the association between parental economic and financial factors and cognitive outcomes in children. To further understand the way that inflammation is altered due to early life socioeconomic circumstances, the present study also examines the role of childhood stressful life events in this pathway. The following defines inflammation including the two markers measured in the study, followed by a review of the literature on SES and inflammation, followed by the role of stressful life events as a mediator. Then it addresses the literature on inflammation as a mediator of parental financial and socioeconomic factors and cognitive outcomes.

2.3.1 Definition of inflammation and the two inflammatory markers of the study

Inflammation is a generalised response to actual or potential infections and a complex process involving dozens of molecules (Ashley et al., 2012; Baumeister et al., 2016; Fagundes & Way, 2014; Lochmiller & Deerenberg, 2000; Miller et al., 2011; Parkin & Cohen, 2001). Two biomarkers have been extensively examined in most of the behavioural studies to date: 1) the cytokine IL-6 and 2) the acute phase protein CRP. IL-6 is thought to be a pro-inflammatory cytokine and a reliable biomarker of inflammation which is released into circulation when inflammation is triggered. One of the main effects of IL-6 is to arouse the production of CRP, as well as other acute-phase proteins (e.g., fibrinogen, ferritin), in the liver and their release in the bloodstream (Libby et al., 2010; Lochmiller & Deerenberg, 2000; Parkin &

Cohen, 2001). Similarly, CRP which is produced as a response to IL-6 signalling increases in plasma during acute inflammation and begins to rise 4-6 hours after the start of infection and peak 1-2 days later (Schmit & Vincent, 2008). Both biomarkers are known to play an important role during inflammation as they contribute to somatic maintenance (the organism's investment in the integrity and functionality of the body) (Del Giudice & Gangestad, 2018; Roff, 2002) by their anti-inflammatory and pro-inflammatory effects and help in wound healing, tissue repair and clearance of damaged cells (McDade, 2003).

2.3.2 Research findings on the association between socioeconomic factors and Inflammation

Many studies in the health domain suggest that adults who were exposed to low SES as children are at higher risk of developing various chronic diseases later in life such as cardiovascular disease, diabetes and cancer, regardless of their adult SES (Hart et al., 1998; Kittleson et al., 2006; Ljung & Hallqvist, 2006) and it is shown that both objective and subjective measures of SES are strongly linked to health-related outcomes (Adler et al., 2000; Cundiff & Matthews, 2017; Kraus et al., 2013). Several mechanisms explain the relationship between SES and disease. For example, high BMI, which is more common amongst lower SES people, and unhealthy lifestyle choices partially account for this association (Miller et al., 2011). However, more recent literature suggests that another, in many ways related, pathway may be inflammation. The inflammatory response is an effort of the immune system to repair tissue and eliminate the risk of infection, but inflammation can become maladaptive if it remains after the infection is cleared.

SES in childhood has been extensively associated with chronic diseases (Adler & Rehkopf, 2008; Calixto & Anaya, 2014) and now with inflammation as well

(Carroll et al., 2011; Matthews et al., 2016; Nazmi et al., 2010) in adults. Several US and UK studies in the adult population showed negative correlations between SES and levels of CRP and IL-6 in the blood (Friedman & Herd, 2010; Koster et al., 2006; Stringhini et al., 2013). Similarly, in a study in the Brazilian elderly community, results showed that high SES has a strong inverse relationship with high levels of IL-6 (de Britto Rosa et al., 2011). Education, which is a significant SES indicator, is also negatively associated with levels of inflammation and prevalence of cardiovascular risk factors (Loucks et al., 2006; Steinvil et al., 2008). Parental education and individual educational attainment have also been found to be related inversely with CRP especially in middle-aged women, even after adjustment for lifestyle risk factors (Phillips et al., 2009). Furthermore, in a study where two cohorts, one from Switzerland and the other from Portugal, were compared, researchers found that in both cohorts, lower education and occupation were associated with higher inflammatory activity even when the underlying socioeconomic conditions of each country were dissimilar. Results were independent of demographic, behavioural and health confounders (Fraga et al., 2015). In one of the few longitudinal studies to date on SEP and inflammatory markers, using data from the Whitehall II study, researchers found that in a 12-year period, levels of CRP and IL-6 increased over time; however, results did not show any robust differential increase by SEP (Gimeno et al., 2007). Finally, in a recent meta-analysis by Liu and colleagues (2017), they found evidence about correlations between low SES in childhood and increased CRP levels later in adulthood.

It seems that several studies to date have examined the relationship between childhood SES and inflammation in adulthood. However, results are mixed partly due to the use of different measures of SES, inflammatory markers, methodological

approaches and life stages (Milaniak & Jaffee, 2019; Muscatell et al., 2020). In some studies, no significant relationships were found while in others the effect of low SES on inflammation remained even after controlling for demographic but also health-related characteristics such as BMI (Carroll et al., 2011; Park et al., 2005; Rexrode et al., 2003) and smoking (Malfertheiner & Schütte, 2006; Ohsawa et al., 2005). Finally, there are other cases where results were attenuated by mediating factors which may underestimate the effects of socioeconomic factors (Nazmi & Victora, 2007).

Evidence from the studies above suggests that, indeed, associations between SES and inflammation do exist. Most studies showed that early socioeconomic disadvantage as indexed by parental SES may determine inflammatory activity later in adulthood. Several studies though have now started providing evidence for the effects of SES on inflammation in childhood and adolescence.

With respect to studies on the child population, there are only a handful examining the relationship between SES and inflammation in childhood and adolescence. This is partly because inflammation in childhood was not of interest until recently and therefore typically not measured in childhood. A few studies with adolescents found that social disadvantage and especially parental education are associated with elevated inflammation, albeit results were attenuated in some cases by adiposity or lower levels of positive affect during daily life events in adverse socioeconomic circumstances (Chiang et al., 2015; Pietras & Goodman, 2013).

There are only a couple of studies that have examined the effects of low SES on increases in inflammation in early and mid-childhood; however, results are contradictory. In the first study that was conducted in the U.S child population, results showed that children whose parents were less educated and poor were more

likely to have low-grade inflammation, although these associations were reduced when they controlled for BMI (Schmeer & Yoon, 2016). In contrast, in an earlier study by Gimeno and colleagues (2007) researchers found that SES disparities did not result in CRP gradients in children, i.e., no strong evidence for the association between parental SES and CRP was found. These associations were found to be strong particularly in adulthood, as in most studies presented above. However, a more recent study that explored how early socioeconomic circumstances could impact inflammatory trajectories in childhood contradicts the previous evidence. In that study, they used data from a large birth cohort of children and examined relationships between their parents' SEP and CRP collected at ages four, seven, and ten years. Results showed that poor socioeconomic conditions were associated with higher levels of CRP throughout the first decade of life (Soares et al., 2020).

Since not all adults who lived in low SES conditions as children go on to develop inflammation and as health and lifestyle seem to explain only part of the association between childhood SES and adult inflammation, other mechanisms could be at play (Friedman & Herd, 2010; Loucks et al., 2010). The potential mechanisms of BMI and smoking for the link between SES and inflammation in adulthood are discussed in a meta-analysis by Muscatell and colleagues (2020). Using data from 43 papers (N= 111,156) that reported on SES and the two most common inflammatory markers, CRP and IL-6, they found that individuals with lower SES displayed higher levels of systemic inflammation of disease risk. As some of the results were explained partially by SES disparities in BMI and smoking, it is suggested that other pro-inflammatory pathways are possibly an important mechanism to understand how social inequalities may become health inequalities.

In overview, individuals can experience conditions of chronic inflammation where pro-inflammatory pathways stimulate low-grade levels of inflammatory response. Numerous sources can sustain this activity, such as persistent low-level infections and autoimmune conditions. In addition to this, chronic inflammation is extensively presented in the psychological literature as being related to exposure to stressors (e.g., psychosocial stress, low SES, traumatic life events and childhood adversity) (Baumeister et al., 2016; Fagundes & Way, 2014; Kuhlman et al., 2017; Miller et al., 2011) to psychiatric diseases such as depression and schizophrenia (Berk et al., 2013; Danesh et al., 2004; Fernandes et al., 2016; Howren et al., 2009; Miller & Raison, 2016), to cardiovascular diseases (Ridker et al., 2002), to poor lifestyle which involves poor dietary habits and lack of exercise (Minihane et al., 2015; Ruiz-Nunez et al., 2013) and to cognitive decline (Ravaglia et al., 2003).

Therefore, before we go on to investigate how inflammation operates as a potential pathway linking socioeconomic factors and several cognitive outcomes, it is important to first understand the mechanisms through which socioeconomic and financial factors might trigger increases of inflammation in the body. Given that the focus of this thesis is on the relationship between SES and inflammation in childhood, the next section discusses how adverse or stressful life experiences could be a potential pathway in the relationship between early life SES and inflammation in childhood.

2.3.2.1 Stressful life experiences as a potential pathway linking SES and inflammation and the biological embedding hypothesis

2.3.2.1.1 The biological embedding hypothesis and the role of the HPA axis

A large body of research has focused on the possible pro-inflammatory mechanisms or mediators linking SES and inflammation in childhood. It seems that the early socioeconomic environment may program immune phenotypes that contribute to disease risk and when adverse experiences and circumstances occur, the physiological response and biological interpretation of those experiences are negatively affected in a way that can change the long-term function of organ systems. This might contribute to widening socioeconomic differences in disease and mortality over time. Drawing on the Barker hypothesis about the foetal origins of adult disease (Barker, 1992), life-course epidemiology (Lynch & Smith, 2005), stress physiology (McEwen, 1998), and behavioural immunology (Coe & Lubach, 2005; Raison & Miller, 2003) the biological embedding model of early adversity (Miller et al., 2011) suggests that stressors and adversity experienced during early life, a critical and sensitive period of development, may become embedded within immune cells programmed to have a pro-inflammatory phenotype. According to this model, long-term exposure to stressful experiences, which may include financial strain and economic hardship, both of which are associated with lower socioeconomic position, can lead to chronic stimulation of the sympathetic nervous system and the progressive suppression of some anti-inflammatory pathways.

Stressors during early sensitive periods "activate" proinflammatory tendencies in cells which are intensified by behavioural patterns and hormonal dysregulation throughout life. Early exposure to stressors, for example, gives rise to behaviours that accentuate inflammation such as reading threat into situations, reacting with

anger, mistrusting others, and making poor life choices (Chen et al., 2004; Chen & Matthews, 2003; Kiecolt-Glaser, 2010; Pollak, 2005; Pollak et al., 2005; Yanbaeva et al., 2007).

Apart from the inflammatory arm of the immune system (Carpenter et al., 2010; Danese et al., 2011; Danese et al., 2007a; Taylor et al., 2006), there is also another peripheral biological system, the hypothalamic-pituitary-adrenal axis (HPA axis) (Gunnar & Quevedo, 2007; Heim & Nemeroff, 2001) which coordinates with the sympathetic nervous system (SNS), and the inflammatory arm of the immune system as a response to acute stress and help in development, survival, and well-being (Chrousos, 1995; Gunnar & Quevedo, 2007; Lopez-Duran, Hajal, et al., 2009; Lopez-Duran, Olson, et al., 2009). Both the HPA axis and the immune system are activated under circumstances of acute threat (Kuhlman et al., 2017).

The role of the HPA axis, specifically, is to maintain homeostasis and help in body adaptation (allostasis) to environmental stress through cortisol secretion (Hertzman, 1999; Shonkoff et al., 2009). This is because 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). When specific structures in the limbic system perceive a threat (e.g., pain, extreme temperatures, aggressor etc) the corticotropin releasing hormone (CRH) and vasopressin (AVP) secretion occurs from the paraventricular nucleus (PVN) of the hypothalamus to the anterior pituitary gland (Stratakis & Chrousos, 1995). In response, the pituitary secretes adrenocorticotropin hormone (ACTH) which stimulates the adrenal gland to increase production and release glucocorticoids (cortisol in humans) (Gunnar & Vazquez, 2006) which are responsible for maintenance, duration, and down-regulation of the stress response.

Several animal studies in rats (Meany, 1999), rhesus monkeys (Suomi, 1999) and free-ranging baboon populations (Sapolsky, 1995) have supported this theory by providing evidence for the role of HPA axis in general vulnerability and resistance to disease and it was overall observed, that when the HPA axis is overstimulated with daily stresses, an exaggerated cortisol response occurs. These studies in different species suggest that the life of HPA axis is concurrent to the determinants of health in human societies and that different social characteristics such as social stability and the place of the individuals can influence the response of the HPA axis.

Lastly, HPA axis also plays a crucial role in regulating inflammation as it is known that stress not only activates the HPA axis but also triggers the inflammatory activity. Glucocorticoids can affectively down-regulate inflammation and prevent its elevation in the blood (Stark et al., 2001). It is apparent that the HPA axis coordinates with inflammation as a response to stress and it important to understand how those two operate in order to better understand how stressors related to socioeconomic disadvantage and experiences of adversities can impact the immune system and physical health.

2.3.2.1.2 Research on SES, stressful life events, and inflammation

Low SES is linked to greater exposure to stressful life events throughout childhood and adolescence (Chandler et al., 1985; Gad & Johnson, 1980; Gillum et al., 1984). This is probably because children from disadvantaged families are more likely to grow up in environments that are uncontrollable and unpredictable (Evans, 2004). At the same time, childhood adversities have been already linked to psychopathology and other health-related conditions such as cardiometabolic disease (Baldwin & Danese, 2019; Danese & Baldwin, 2017).

In adult studies, the specific link between childhood adversities and chronic inflammation has been well documented thus far and it is known that such adverse life events or experiences in childhood are related to adult inflammation (Baldwin et al., 2018; Danese et al., 2007b; Iob et al., 2020; Slopen et al., 2015). In addition, a previous systematic review in 25 studies by Baumeister and colleagues (2016) and another more recent meta-analysis showed that traumatic experiences, in general, during childhood contribute to a pro-inflammatory state in adulthood (Milaniak & Jaffee, 2019). Last, a recent study by Lacey and colleagues (2020) addressed the association between childhood adverse experiences (ACEs) and adult inflammation using data from the 1958 British cohort. In this study, they went beyond exploring cumulative risk scores or individual adversities in their association with adult inflammation and tested the alternative approach of latent class analysis (LCA) which clustered adversities and identified specific patterns of ACEs that are important to health outcomes. Results from this study suggested that specific ACEs, such as family conflict, psychological and physical abuse, emotional neglect as well as witnessing abuse and ACE combinations, such as maltreatment and conflict and polyadversity were associated with mid-life inflammation.

In children and adolescent studies, evidence for the association between childhood adversities and inflammation during that period of development is constantly growing and suggests that early life adversities can have a more immediate impact even in childhood. For instance, studies have shown that adversities such as parental mental illness (O'Connor et al., 2020) and increasing exposure to upsetting events over time in childhood and prior to the age of 9 (Flouri, et al., 2020) as well as the number and increase in the number of adversities (Flouri et al., 2020) were all positively associated with plasma levels of CRP and IL-6 in

childhood and early adolescence. The latter two studies used data from the ALSPAC

study, and their findings are in line with other recent studies using the same data

from children of the ALSPAC study. More specifically, in a study by Lacey and

colleagues (2013), it was found that specific adversities such as parental

separation/divorce were associated with higher levels of IL-6 and that gender

differences do exist in these associations; however, other adversities such as

parental alcohol problems and mental health problems, parental convictions and

emotional abuse were linked to lower levels of IL-6 but there seems to be an

agreement in all three studies as no associations between adversities and CRP were

found. Notably, there is an older study using ALSPAC data that contradicts the

newest findings, as it was found that an ACE score and other specific ACEs were

associated not only with IL6 but also with CRP (Slopen et al., 2013). However, in this

study, they only focused on five specific adverse events and thus, it is pointed that

individual ACEs are particularly important in producing different inflammatory

responses (Lacey, Bartley, et al., 2020).

Looking at the link between early SES and adult inflammation through recent

life events there is one study John-Henderson and colleagues (2016) that discussed

the topic. In that study, participants had to give retrospective information on their

parents' as well as their own current (objective and subjective) SES. They also

provided information on current negative events such as divorce and financial loss.

The study showed that adults with low childhood SES and a high number of recent

negative events were more likely to develop inflammation. However, the role of

adverse life events in explaining the SES-inflammation link in children had not been

explored thus far. Among children, the association between SES and inflammation

(Dowd et al., 2010; Howe et al., 2010; Murasko, 2008; Pietras & Goodman, 2013;

Schmeer & Yoon, 2016), the association between poverty and ACEs clusters (Lacey, Howe, et al., 2020) as well as SEP and psychosocial adversity (Lawn et al., 2018) and the one between inflammation and SES-adjusted adverse life events (Flouri et al., 2019) have been investigated, but it is still uncertain if poverty and low SES bring about inflammation in children via increasing exposure to such psychosocial stressors.

To my knowledge, there are only a few prospective and longitudinal studies that attempted to elucidate the relationship between early exposure to socioeconomic risk and inflammation in childhood and adolescence and how exposure to adversities could explain that relationship. Two of the studies explored the above relationships in middle childhood/early adolescence when children were at age 11 years while the third one was conducted in adolescents between the ages 16 to 18 years. The first childhood study investigated the links between exposure to socioeconomic risk (household poverty and single-parent status) and psychosocial risks (family violence and caregiver depressive symptoms) and inflammation as measured by CRP, IL-6 and Tumor Necrosis Factor (TNF)-alpha as well as glucocorticoid receptor insensitivity (O'Connor et al., 2020). Results from that study indicate that risk exposure and more specifically caregiver depressive symptoms in early childhood predicted higher levels of CRP almost a decade later and that relationship remained even after controlling for multiple covariates. The second study used a nuanced measure of SES as indexed by maternal education, paternal social class, housing tenure, house overcrowding, and parental perceptions of financial difficulties to explore the link between early SES and inflammation in middle childhood but this time the researchers wanted to see how stressful experiences that children had personally experienced could explain that relationship (Kokosi et al.,

2020). Apart from early SES, in that study, they also used two indicators of stressful life events during early life taking into account several events that happened to the child up to three years of age and then up to age 9 years and two inflammatory markers as measured by CRP and IL-6. Contrary to the results of the first study, results from this study here showed that early low SES predicted higher levels of IL-6 but not CRP later in middle childhood even after controlling for covariates. It was also shown that upsetting life events explained part of the SES-inflammation link. Finally, the third study in adolescents used longitudinal data to investigate pathways between family adversity which was measured by three family-level dimensions: a) serious interpersonal conflict stress, b) serious financial stress, and c) maternal depressive symptoms) in infancy, depressive symptoms and BMI in childhood, and inflammation as measured by CRP in adolescence. Similar to the first study, this last study did not measure SES directly but interestingly, although depressive symptoms in childhood were not directly or indirectly associated with increases of CRP, greater exposure to adversity in infancy was indirectly associated with higher levels of CRP through higher BMI in childhood (Reid et al., 2019).

Overall, several studies in adults and now a few in child and adolescent samples attempted to elucidate the association between SES and inflammation through several potential mechanisms. In some studies results seem to agree while in other studies results are contradictory, suggesting that the mechanisms linking exposure to socioeconomic disadvantage and compromised physical health are quite complex and it might be that SES is a broad index which is also related to other several confounding risks (O'Connor et al., 2020). Nevertheless, adverse and stressful childhood experiences have been consistently and robustly linked to physical and mental illness and immune function (Kuhlman et al., 2017) and it is now

suggested that they might also operate as a pathway of risk that can exacerbate the effects of socioeconomic disadvantage on inflammation.

Following evidence on how inflammation can be an outcome to exposure to socioeconomic and financial disadvantage either directly or indirectly through several adverse and stressful life experiences, the next section describes how inflammation could also operate as a mediator in the relationship between socioeconomic factors and cognitive functioning including EF, the key proposed mechanism explored in this thesis.

2.3.3 Research findings on the association between inflammation and child cognitive functioning

Inflammation has been directly implicated in cognition. It can cause damages and central nervous system susceptibility through acute inflammation which can also be shifted to a lasting disease and can negatively affect the development of the brain (Hagberg et al., 2012). It is known that inflammation has longstanding effects and is thought of as moderating the risk of a variety of neurological disorders including autism spectrum disorders, cerebral palsy, schizophrenia, and Parkinson's disease (Godbout & Johnson, 2009; Schmidt et al., 2002b). Furthermore, studies have shown that inflammation through cytokines in the blood not only moderates the risk of the variability of several neurological disorders but also mediates illness-related behavioural changes and cognitive impairment.

In a systematic review by Kuo and colleagues (2005) , where the relationship between CRP, cardiovascular risk, cognitive impairment and depression were reviewed, it was revealed that high concentrations of CRP were related to increased risk of stroke and cognitive impairment. Six eligible studies were assessed, and it

was concluded that high concentrations of CRP were strong predictors of cognitive

decline and dementia. All studies were either cross-sectional or cohort studies that

followed elderly people who had given biochemical measures and had undertaken

cognitive tests. Overall, correlations and causal relationships between CRP and

cognitive decline were found, especially for participants at the highest tertile of CRP

or with CRP above 0.5 mg/dL (Ravaglia et al., 2003; Schmidt et al., 2002a;

Teunissen et al., 2003; Tilvis et al., 2004; Yaffe et al., 2003). However, in a study

where investigators used a prospective, nested case-control design and followed up

727 elderly individuals, no associations between increased CRP and development of

dementia was found (Engelhart et al., 2004). In a good number of studies, there

seems to be a pattern of evidence supporting the link between increasing levels of

CRP and cognitive decline and elevated risk of dementia. However, it is noted that

one should be cautious in interpreting the results as cognitive outcome measures

can be heterogeneous among studies and can sometimes lead to contradictory

results.

Furthermore, a couple of studies in the human middle-aged population

suggested that increased CRP and IL-6 levels were moderately associated with

lower cognitive status (Gimeno et al., 2008). In another study on Swedish young

men investigating the relationship between erythrocyte sedimentation rate (ESR),

which is a test that detects inflammation related to infections, tumours or

autoimmune diseases, and performance on a concurrent IQ-test in early adulthood,

Karlsson and colleagues (2010) found that low-grade inflammation was associated

with decreased cognitive ability in males at age 18-20. However, in a recent study in

overweight and normal-weight Chinese adults it was revealed that although

significant differences in the inflammatory levels between the two groups existed, an

association between elevated inflammation and lower cognitive scores was not found (Fan et al., 2019).

The association between inflammation and cognitive functioning in children and adolescents is less extensively studied. Although there is a lot of evidence for 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; Stoll et al., 2004), there is little evidence, and from certain child populations suffering from special health conditions, that supports the notion that inflammation and cognitive functioning are inter-related. In one of these studies, the researchers wanted to assess the magnitude of the systemic inflammatory response as measured by CRP serum levels in children with Obstructive Sleep Apnea (OSA) at higher vulnerability of cognitive deterioration. They found that levels of inflammation were higher in children with OSA and especially in those who develop cognitive impairments, suggesting that this sleep disorder can elicit inflammatory responses which are responsible for determining elevated risk for neurocognitive deficits (Gozal et al., 2007). However, it was highlighted that the above mechanism remains speculative due to the inability to directly test causality. That means that it is not clear whether OSA is causing increased CRP which in turn is causing cognitive impairments or the reverse. Hence, further evidence about the direction of the relationship is needed. Lastly, a study in refugee and non-refugee youth that explored trajectories of CRP, Epstein-Barr virus and cortisol and their association with stress, mental health and cognitive function found no association between trajectories of biomarkers and cognitive function (Panter-Brick et al., 2020).

In the general child population, the evidence for the direct association between inflammation and cognitive functioning is limited. A recent study in children using data from the ALSPAC study explored the association between childhood infection, inflammatory markers and IQ (Mackinnon et al., 2018). Findings from this study indicated that although earlier infections do not have an independent lasting effect on inflammation levels a few years later in childhood, higher levels of CRP, but not IL-6, were related to lower IQ suggesting that increased inflammation might be detrimental for intellectual function. From the results, it seemed that the association for IL-6 was attributable to socioeconomic factors (e.g., overcrowding and maternal occupation) as the effect was explained after they controlled for these variables; however, both inflammatory markers were associated with lower IQ scores prior to adjusting for potential confounders. There are also a handful of studies in adolescents, but these have produced mixed results. One study found that elevated salivary CRP was associated with poorer memory and executive function (Cullen et al., 2017), while a couple of other longitudinal studies found no association between CRP and memory or executive function (Cohen-Manheim et al., 2015; Jonker et al., 2014). Another study aimed to examine the relationship between inflammatory biomarkers and academic grades in children of the UP and DOWN study using an inflammatory index from these four inflammatory markers: CRP, IL-6, TNF-α and white blood cell (WBC) count (Esteban-Cornejo et al., 2016). The findings of this study suggested that the inflammatory index and all the inflammatory markers apart from TNF-α were negatively related to academic performance, independent of body fat percentage. Indeed, children and adolescents in the highest tertile of the inflammatory index had significantly lower scores in academic performance compared with those in the middle and the lowest tertile. A more recent study also

attempted to further elucidate the association between circulating inflammatory markers and academic performance in adolescence (Adelantado-Renau et al., 2020). In this study, they used data from 244 adolescents from the DADOS study and the measurements included the same four inflammatory markers [white blood cell (WBC), IL-6, TNF-α, and CRP) as in the previous study, and academic performance as assessed through academic grades and the Spanish version of the Science Research Associates Test of Educational Abilities. Contrary to the results of the previous study, these findings here indicated that only some of the inflammatory biomarkers (mainly TNF-α and WBC) were related to academic performance in adolescence.

The link between inflammation and cognition is complex due to different factors that may explain this relationship. For example, numerous studies in animals and elderly people have shown that elevated inflammatory response in the hippocampus had implications in cognitive tasks and memory impairments (e.g. worse performance on spatial tasks, verbal episodic memory and recognition memory tasks) suggesting that ageing explains the variance in neurobehavioural complexities which are linked to peripheral infections (Bettcher et al., 2012; Chen et al., 2008; Murray et al., 2012; Sartori et al., 2012). Similarly, findings from an experimental study by Reichenberg and colleagues (2001) showed that increases in cytokine secretion in the periphery and within the brain are related not only to infectious diseases but also with autoimmune diseases which are strongly comorbid with depression and anxiety as well as memory impairments that are especially obvious in a condition where central inflammatory processes are involved. In addition, there are other potential pathways related to psychopathology that connect inflammation to cognitive functioning. For example, findings from a study in

adolescents with depression suggest that inflammation is a marker of the disease process in adolescent depression and depressed adolescents with exposure to childhood trauma constitutes an exceptionally vulnerable group for cognitive dysfunction (Peters et al., 2019).

Concerning the direction of the relationship between inflammation and cognitive ability, there is some evidence suggesting the possibility of a reverse direction in the causal path between cognitive functioning and inflammation. Luciano and colleagues (2009) suggested that cognitive functioning in younger ages determines lifetime pro-inflammatory exposures and thus the risk for future cardiovascular disease and further cognitive decline at an older age. In support of these results, another study in young adults also showed that poor cognitive ability in early adulthood is associated with higher levels of inflammation in middle age (Phillips et al., 2009). The issue of the direction of the association between cognitive functioning and inflammation in children needs to be further examined and resolved. Most of the studies, however, seem to support the link from inflammation to cognition (not the reverse) according to which proinflammatory cytokines play a significant role in the cognitive processes in specific neurocognitive mechanisms responsible for promoting learning, memory and cognition under physiological conditions (McAfoose & Baune, 2009).

The current evidence suggests that there is a direct association between inflammation and cognitive functioning both in adults and in children although the mechanisms that connect those two are complex and need further investigation. Given the evidence provided in the previous sections for a direct association between socioeconomic and financial factors and inflammation and cognitive functioning separately as well inflammation and cognitive functioning, this thesis will

now attempt to explain how inflammation could operate as a potential pathway linking exposures to SES and financial factors with cognitive and EF.

To my knowledge, no study before has addressed child inflammation as a potential mechanism underlying socioeconomic disadvantage which can affect cognitive and EF in childhood. Therefore, to address the limitations in the existing literature, I conducted a study that explored the link between family financial strain and child EF via inflammation as measured by IL-6 (Kokosi et al., 2021). This study drew on previous research looking at the relationship between parental financial difficulties and children EF (Raver et al., 2013) and built on the idea that parental perceptions of financial difficulties in affording basic things for their children can be as detrimental for children's development as other objective measures of SES, such as education or social class (Burchinal et al., 2008; McLoyd, 1998). The results will be presented extensively in the next chapters; however, it is suggested that higher levels of IL-6 were associated with poorer working memory in children at age 10 years who had been exposed to economic hardship early in their lives. This a unique finding that supports inflammation in childhood as a biological pathway from socioeconomic disadvantage to children's working memory that has not been tested before in children.

2.4 Summary

As described, SES is a multidimensional concept that involves economic and social components, such as income, education, and social status. SES has great importance in the study of child development as socioeconomic circumstances predict a wide range of outcomes in children across various domains. For example, parents of high SES can afford necessary things for their children, and they also

have social connections and access to services that can benefit the overall development of their offspring. In contrast, low SES children lack access to the same resources and are more likely to display developmental problems. However, measuring SES is a complex process and theories around the different approaches go back a long way. Most researchers seem to agree on a definition of SES that includes three main indicators: parental income, parental education, and parental occupation. In addition to that, other indices of SES that are linked to main health and life outcomes are also used in research and have to do with household conditions, such as homeownership and overcrowding. It also seems that both objective and subjective measures of SES are frequently used in research with some subjective measures to be more robustly related to health outcomes due to the stronger impact individual's perceptions of their own social position and financial situation can sometimes have on their lives. Nevertheless, the choice of how to measure SES is still open and highly depends on the hypothesis, the data available and the population of each study.

SES has been directly implicated in children's cognitive development and EF. A plethora of studies suggests that low SES and poverty account for the variance in child cognitive outcomes. For example, children who live below the poverty threshold are more likely to score lower in various cognitive ability tests than their wealthier counterparts and other studies similarly reported lower academic achievement, lower IQ, and inequalities in language development. Specific components of SES such as parental education and occupation have also been implicated in children's cognitive abilities, school readiness, general intelligence and EF. Regarding the relationship between SES and EF, many studies provided evidence that children of low SES families had a poorer performance in inhibition, working memory, shifting and

updating abilities tasks. However, other studies contradict those findings as no significant associations between SES and executive function performance was found. These null findings could be attributed to small correlations combined with the chance error or systematic factors such as stringent exclusion criteria for health and cognitive ability that led to studies having analytic samples with extremely healthy and able participants from more affluent backgrounds (Hackman et al., 2010; Lawson et al., 2018). It is also worth mentioning that the period that EF performance was measured plays an important role because some EF skills have not emerged yet in younger ages, hence the lack of significant associations between SES and EF (John et al., 2019).

It is also important to examine whether this association is solely a product of the key component of objective SES, such as education and social class, or can be explained by challenges associated with income deprivation and financial difficulties. Some recent studies have now reported that parents' perception of financial difficulties in affording basic stuff for the children, which are subjective measures of SES, was uniquely predictive of executive function (Kokosi et al., 2021; Raver et al., 2013).

In an attempt to explain the mechanisms that connect SES to child cognitive functioning, researchers came up with two theoretical frameworks, the Family Stress Model and the Family Investment Model. These models were developed by Conger and Elder (1994) and examined how relationships and interaction among family members are shaped under economic deprivation, emotional distress and parental conflict. Parents who experience economic hardship are unable to make ends meet, are involved in conflicts with the other parent and the children and express more neglectful and harsh parenting. Besides, children from families who struggle

financially, do not have access to learning materials and stimulating toys or to other activities that are beneficial to their development. Consequently, these children are found to have worse cognitive outcomes.

Recent research has shifted focus to the physical pathways through which SES exerts its effects on cognitive functioning. As children from low SES families are more likely to experience adversities and stressful situations, they develop different responses to stress that can impact their cognitive and EF abilities. One of those mechanisms may be inflammation which is thought as the body's primary response to injury or infection and is a physiological connection between psychosocial, socioeconomic, and nutritional factors and the body which according to the biological embedding hypothesis described previously can in turn impact cognitive functioning. Thus, it is suggested that inflammation might be a biological pathway linking economic hardship with cognition. Two markers of inflammation have been extensively examined in most behavioural studies: the acute phase protein CRP and the cytokine IL-6. The initial role of inflammation is to protect the body and help in somatic maintenance, however, chronic exposure to inflammation becomes problematic and is associated with psychiatric disorders, cardiovascular diseases, poor lifestyle and cognitive decline. Several studies in the adult population have reported a significant association between SES and inflammation. Adults who were exposed to low SES and more stressors as children were at higher risk of developing ill-health later in life. As described previously, children from families of low SES may be exposed to more adversity which can affect the stress response in their body. This stress response can, in turn, impact their cognitive and executive function abilities by altered neuroendocrine stress response and compromised self-regulation (Arnsten & Li, 2005; Blair et al., 2005; Evans & Schamberg, 2009).

To understand how inflammation might operate as a biological pathway linking socioeconomic factors and cognitive outcomes, it is first important to understand the mechanisms through which exposure to lower SES is related to inflammation. One of the mechanisms proposed in this thesis that explains this relationship is based on the biological embedding hypothesis that exposure to stressful experiences, such as low SES and financial strain, can lead to chronic stimulation of the sympathetic nervous system and the progressive suppression of some main anti-inflammatory pathways, such as the HPA axis. These systems help in body adaptation, however, chronic exposure to stress can lead to overstimulation and eventually to maladaptive wear-and-tear of the body and the brain. In adults, many studies are supporting this association, however, results are mixed. In the child population, only a handful of studies from the pre-and neo-natal period and adolescence provide such evidence hence, it is important to address these association in middle childhood which a critical period of developmental change. From a limited number of studies though, it seems that children of low SES are more likely to develop higher levels of inflammation even at a younger age.

With regard to the association between inflammation and cognitive functioning, results are still not clear. Most studies were conducted in the adult population and support that inflammation in early life is associated with several cognitive impairments and cognitive decline in elder people. Several cross-sectional and longitudinal studies have found a significant association between elevated levels of both CRP and IL-6, and it seems that the same biological mechanisms that explain the association are at play. Once again though, the literature around inflammation in childhood and child cognitive functioning is extremely limited. Only a handful of studies but from children with special health conditions have found an

association between inflammation and neurocognitive deficits and a few others in the healthy child populations reported contradictory results, however, all findings seem to suggest that inflammation leads to cognitive dysfunction and not the reverse. Hence, it is of great importance to investigate those relationships in the general child population. Given the associations between socioeconomic and financial factors, inflammation, and cognitive functioning separately, it is now proposed that the biological mechanism of inflammation might operate as a pathway linking SES and other financial factors with cognitive outcomes. Figure 2 shows a conceptual model for the role of upsetting life events, inflammation, and BMI between socioeconomic factors (0-3 years) and executive functioning in middle childhood (10 years) and cognitive ability in adolescence (15 years). The final models tested will be presented in the empirical chapters 5, 6, and 7 that follow.

Consequently, this thesis sought to explore how objective measures of early life family SES and as well as subjective measures related to financial strain can affect child cognitive development and EF and whether this relationship can be explained by the biological mechanism of inflammation in middle childhood. The specific project aims and hypotheses are presented in the next section.
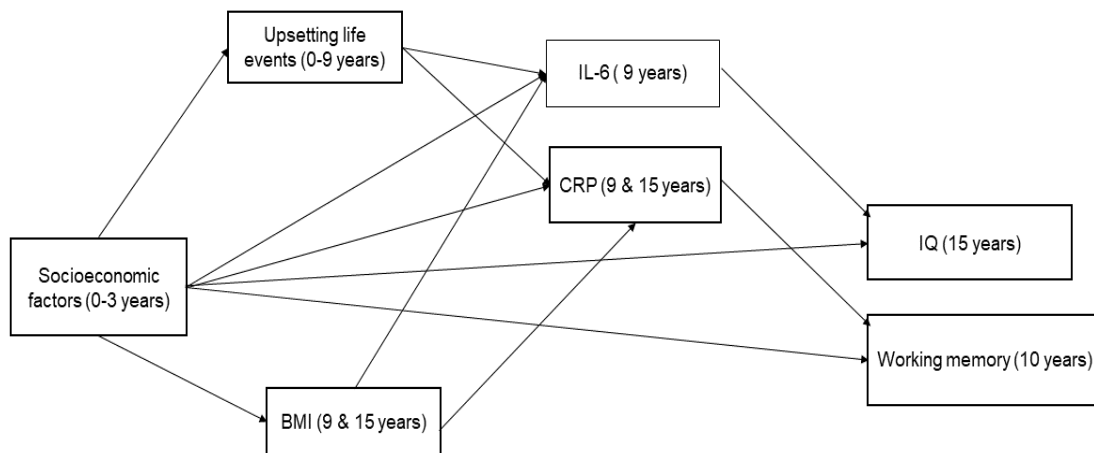
Figure 2-2. Conceptual model showing the role of upsetting life events, BMI and inflammation between socioeconomic factors, working memory, and IQ.

2.5 Project aims and hypotheses

The main purpose of this study is to investigate the relationships between objective and subjective measures of SES, inflammation, and cognitive functioning in children. This study will consist of three empirical chapters. Empirical chapter one explores the relationship between childhood objective family SES and childhood inflammation. It also tests the mediating role of upsetting childhood experiences in an attempt to explain how socioeconomic factors may be related to inflammation. Empirical chapter two examines the association between subjective SES, measured with parental perceptions of financial difficulties and EF as well as the mediating role of inflammation in childhood. Finally, in the third empirical chapter, the relationships among objective family SES, and child IQ via inflammation in childhood are

investigated. Both empirical chapters two and three aimed to explore the main proposed pathway in this thesis - from objective SES and subjective financial strain to child IQ and EF, covering comprehensively important exposures and outcomes in child development research.

The research aims of the first empirical chapter are:

1) To examine whether family early SES (age 0-3 years) is directly associated with the two inflammatory markers (CRP and IL-6) (age 9 years) in childhood that are available in my dataset.

2)   To further investigate whether the potential pathway of childhood upsetting events (age 3-9 years) may explain this relationship and which child and family confounders will also predict inflammation and whether SES remains a significant predictor even after adjusting for those.

My hypotheses, which are in line with the existing literature, is that objectively measured SES will be a significant predictor of both CRP and IL-6 irrespective of confounders and that childhood upsetting events will mediate the relationship between SES and inflammation in childhood.

In the second empirical chapter, the research aims are:

1)   To explore whether parents' financial difficulties (age 0-3 years) due to low SES are associated with poorer EF (age 10 years) in middle childhood irrespective of covariates.

2)   To further explore whether the relationship between parents' financial difficulties and children's working memory is explained by childhood inflammation (age 9 years).

I hypothesise that subjective financial difficulties as measured by parents' perceptions on financial difficulties will be associated with poorer EF in childhood independent of covariates and that inflammation will be a significant mediator in the association between financial difficulties and EF.

In the third empirical chapter, the research aims are:

1)   To examine the longitudinal associations between early family SES (age 0-3 years) and cognitive ability, as measured by IQ, in adolescence (age 15 years).

2)   To explore whether the above relationship is explained by earlier and concurrent inflammation at age 9 and 15 years, respectively.

I hypothesise that subjective family SES will be associated with IQ in adolescence and that earlier and concurrent inflammation would explain that relationship.

Chapter 3. Data

This research thesis is based on the secondary analysis of longitudinal data from the Avon Longitudinal Study of Children and Parents (ALSPAC). The ALSPAC study was established to understand how genetic and environmental characteristics influence health and development in parents and children and offers a large sample of young children from early in life. Therefore, ALSPAC is suitable for researching children's development. This chapter presents an overview of ALSPAC and describes how SES, inflammation, cognitive and EF and the key covariates were measured. Finally, the main strengths and weaknesses of the ALSPAC study are presented.

3.1 Research design

3.1.1 Longitudinal research with secondary data

The research in this thesis is based on a longitudinal design using secondary data from the ALSPAC study. To explore the effects of early SES on inflammation and cognitive functioning years later requires the use of large-scale longitudinal cohort data. In contrast to cross-sectional research which examines data from a point in time, longitudinal research examines data across time. Longitudinal research examines patterns of change and the direction and magnitude of proposed relationships (Menard, 2002). Thus, using secondary data collected in multiple timepoints allows one to get closer to identifying causal relationships over time and explore child development in depth.

3.1.2 The ALSPAC Study

In this project, data from the ALSPAC study were used. 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 concerning a similarly diverse range of health, social, and developmental outcomes (Boyd et al., 2013b).

3.1.3 Content and recruitment of participants

ALSPAC is a collaborating project of the broader European Longitudinal Study of Pregnancy and Childhood (ELSPAC) study. However, it was specifically designed to determine ways in which genotype and environmental characteristics influence health and development in both children and parents. Besides, it aims to identify pathways to optimal well-being for given environments or genotypes (Golding et al., 2001).

From its starting point, ALSPAC was envisaged as a study not just of the gene-environment relationships with child health and development but also of those of the parents. Substantial information on lifestyle, behaviours such as smoking, diet, physical activity, alcohol and use of illegal drugs have been collected repeatedly since pregnancy on mothers and their partners. Information on partners has been collected in two ways: either by responses from the mother about their partner's behaviour or by responses of the partners themselves when mothers have passed questionnaires on to their partners.

During the preparatory work, the questionnaire design for the entire ALSPAC study had gone through several different phases as part of the ELSPAC study. Questionnaires were first designed and pilot tested on about 100 parents at appropriate stages (prenatal and postnatal; mothers and partners).

The study eligibility criteria included being a female resident in Avon while pregnant with an expected date of delivery between 1 April 1991 and 31 December 1992.

Data were collected from early pregnancy using a variety of sources:

i. Self-completion questionnaires to mothers, their partners, and from age 5, the children;

ii. Medical, educational, and other records;

iii. Measurements of the environment of the sub-samples of homes, including levels of air pollutants, magnetic radiation and noise;

iv. Hands-on assessment at frequent intervals of a randomly selected 10% sample of the study from ages 4 months to 5 years – the Children in Focus[1];

v. In-depth interviews and examination of particular sub-groups and their controls;

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[1] A 10% sub-sample of children was identified from the ALSPAC births that occurred from June 1st to the end of December 1992. A standard number of children per week was chosen at random from the list of births within the study. The aim of the study was to examine these children in a way that could not be done using questionnaires up to age 7 when ALSPAC clinics for the whole cohort began. The sample provides both validation for certain aspects of the self-completion questionnaires and answers several important questions in regard to outcomes that cannot be identified easily from records or questionnaires. These are related to the prevalence and aetiology of childhood growth, anaemia, otitis media with effusion, visual defects, the development of intellectual competence, speech and language, as well as motor development.

vi.   Annual hands-on assessments of the whole study in a standardised environment from 7 years onwards; and

vii.   Biological samples from the mother, her partner and child.

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 of 12 months and have been followed up since then (Golding et al., 2001; Hardt & Rutter, 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, Macdonald-Wallis, Tilling, Boyd, Golding, Davey Smith, 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 clinical assessments at age 9 (62% of those invited), when inflammation was first measured in childhood.

3.1.4 ALSPAC sample

Participants who were recruited during the 1991 census, were used to compare the population of mothers with infants <1 year of age resident in Avon with those in the whole of Britain and to further compare participants in ALSPAC (using data collected ~8 months postnatal).

Mothers of infants in Avon were slightly more likely than those in Britain to live in owner-occupied accommodation and to have a car available at the household and less likely to have one or more persons per room and be non-White. Also, the proportion of women who were married was similar in Avon and Britain. Furthermore, ALSPAC participants at 8 months post-childbirth were more likely than mothers in Britain, and also those in Avon, to own their accommodation and have a car in their household and less likely to be non-White. ALSPAC mothers were more likely to be married than either the equivalent population of Avon or Britain. Interestingly, despite having higher socio-economic position indicators on average than equivalent women in both Avon and Britain, ALSPAC mothers were somewhat more likely to be living in overcrowded conditions (a higher proportion with on average more than one person per room) than either Avon or British women (Fraser et al., 2013). Table 3-1 shows the demographic characteristics of mothers in Great Britain and those who participated in ALSPAC.

Table 3-1. Socio-demographic characteristics of mothers of Great Britain, Avon, and those who participated in ALSPAC

Characteristics	Whole of Great Britain (%)	Avon (%)	ALSPAC participants (%)
Owner occupier	63.4	68.7	79.1
1+ person/room	30.8	26.0	33.5
Car in household	75.6	83.7	90.8
Married couple	71.8	71.7	79.4
Non-White mother	7.6	4.1	2.2

Note. Data for mothers in Great Britain and Avon from the 1991 census and based on women and infant <1 year of age. Data from ALSPAC based on questionnaire responses at ~8 months postnatal collected between 1992 and 1993; ~80% of the enrolled pregnancy cohort from ALSPAC completed this questionnaire. **Source:** Fraser et al., 2013. Cohort Profile: The Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort.

3.1.4.1 Predictors of missingness in the ALSPAC study

In 2008, all mothers still engaged with the study were invited to a follow-up clinic (FoM1). Of the 11624 eligible women, 4834 (43%) attended and provided valid data for the FoM 1 follow-up clinic. Comparative analysis showed the differences in characteristics between the 6430 women who were invited but did not attend FoM 1 and the 4834 who did attend. Fraser et al. (2013) found that in ALSPAC, attrition and non-response was higher among mothers who: did not attend were younger, from lower social class backgrounds and less likely to have a university degree and were more likely to have had two or more children prior to index pregnancy, compared with those who did attend. Moreover, those who did not attend had higher pre-pregnancy BMI and were more likely to experience hypertensive disorder of

pregnancy. However, mean gestational weight gain and the occurrence of gestational diabetes were similar in those attending and those not. Finally, another three further clinics were to follow (FoM2-FoM4) taking place between 2012 and 2016.

Furthermore, response rates in the ALSPAC cohort declined slightly between pregnancy and 33 months postnatal but remained constant at approximately 70% until 152 months (~12-13 years) postnatal. There was a decline after that, with response rates being between 50% and 60%. Similarly, response rates have dropped similarly for the children in the ALSPAC cohort probably due to "study fatigue" or the length of the questionnaires, which has been longer in recent years. The decline in child questionnaire responses over time somewhat exaggerates participation attrition as 11642 (82%) of mothers still remain engaged in the study and (Fraser et al., 2013).

3.1.5 Sample selection

The sample of this study was selected based on several criteria including valid data on the inflammatory markers at age 9 years, were singletons or first-born twins, and did not have an infection[2] at the time samples were taken. The study's inclusion criteria were not based on the main outcomes as it was important to include all those who participated in the clinic visits instead. At the beginning of each results section in the following empirical chapters five, six, and seven, the analytic strategy will be described and a bias analysis between the analytic and the non-analytic sample will be presented as well.

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[2] Infection at the time of the sample collection was assessed at the start of each session during the child clinics at age 9 years. The tester determined by asking the parent whether the child had recently or currently had an infection and if so, how long ago. Details were recorded as text (yes/no).

3.2 Main measures

This section describes how the key measures as well as the covariates were measured and analysed in the three empirical chapters of this thesis. In empirical chapter 5, SES was the main predictor, inflammation was the main outcome variable and upsetting childhood events was the mediator. In empirical chapter 6, the main predictor was parental perceptions of financial difficulties, the outcome measure was working memory, and the mediator was inflammation. Finally, in empirical chapter 7, SES was the main predictor, a measure of intelligence quotient (IQ) was the main outcome and inflammation was the mediator. The rationale to include different exposures and outcomes across the three empirical chapters was to facilitate investigation of underexplored pathways linking socioeconomic and financial factors with physical health and cognitive functioning in childhood. In this thesis, one pathway from objectively measured SES to inflammation in childhood through upsetting childhood events was explored to provide evidence on how objective family SES is associated with physical health outcomes. Following that evidence, in the next two empirical another pathway from subjective parental perceptions of financial difficulties to working memory (chapter 6) and another one from objective SES to child IQ (chapter 7) via childhood inflammation was explored. Previous studies have shown that both objective and subjective measures of SES are consistently and strongly related to health and cognitive outcomes (Adler et al., 2000; Cundiff & Matthews, 2017; Kraus et al., 2013) and in some cases, the subjective measures were even more robustly related to certain outcomes (Adler et al., 2000; Adler & Stewart, 2007; Cundiff & Matthews, 2017; Operario et al., 2004).

Thus, it was meaningful to not only look at the objective measures of SES but also at indicators of financial strain and psychological pressure that objective

measures cannot always capture. ALSPAC is a rich dataset that includes information on different socioeconomic and financial indicators measured in the early years which allowed exploitation and investigation of the role of different aspect of socioeconomic disadvantage. Similarly, each empirical chapter looked at different outcomes (i.e., inflammation in chapter 5, working memory in chapter 6, and IQ in chapter 7) as each empirical chapter aimed to answer a different research question in an attempt to disentangle complex biological pathways that may explain socioeconomic influences on children's cognitive development. Notably, both working memory and IQ are two important although distinct cognitive outcomes which are worth exploring separately.

3.2.1 Socioeconomic Status

SES was measured as a latent[3] variable using information from five observed variables during the first 3 years of the child's life: maternal education, paternal social class, overcrowding, housing tenure and financial difficulties. Examining the combination of these different aspects of SES is novel and has not been tested before. Thus, psychometric tools were used to establish validity and reliability of this new latent measure. First, a Principal Component Analysis was performed to check whether all variables can load onto a single latent factor. As the observed variables had different response scales, variables were recoded into binary variables prior to including them in the measurement models. Dichotomisation of each variable was based on standard approaches designated in the literature, apart from the variable for the financial difficulties which was measured slightly differently by previous studies (for example see Raver et al., 2013 and Lacey et al., 2020). Following that,

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[3] A latent variable is a variable that is not directly observed but rather inferred from other variables that are observed (directly measured). This is discussed in chapter 4.

the construct validity of the SES factor was tested by conducting a Confirmatory

Factor Analysis (CFA) in Mplus for the five categorical indicators. Mplus is a flexible

software that allows the use of estimators for categorical data (e.g., the weighted

least squares mean, and variance adjusted estimator) thus, enabling latent factors

based on binary items. Results indicated that a latent SES variable constructed by

binary indicators was an excellent fit to the data. However, it is acknowledged that

since this is a novel SES indicator, its validity and reliability as a measure needs to

be assessed in other samples as well.

Maternal education: Information was obtained on all the qualifications of the

mother, her partner, her mother and her father. A 6-point education scale was

derived for each of these individuals with the following categories: No qualifications,

No higher than CSE or GCSE (D, E, F or G), O-level or equivalent, A-level or

equivalent. Teaching or nursing qualification, University degree. This scale was

similar to that derived for the Child Health & Education Study (Osborn, 1984).

In the present research, maternal education was measured with the mother's

report of her highest educational qualification at 32 weeks of gestation. There were 5

categories: 1) CSE/none, 2) Vocational, 3) O level, 4) A level, and 5) Degree which

was then dichotomised into 1=Degree and 0=other [see also (Midouhas et al.,

2019)].

Paternal social class: Data were obtained on the current employment situation

of the mother and her partner together with information for both mother, partner, her

mother and her partner on the normal job, occupation, trade or profession with the

type of industry or service given. This will enable social class categorisations for the

mother, her partner, and her parents using the 1991 Office of Population Censuses

and Surveys (OPCS) classification (OPCS, 1991). In the present research, paternal social class was derived using information about the father's occupation, measured also at 32 weeks of gestation, using information on job codes from the OPCS. The categories were 6: 1=I, 2=II, 3=III(non-manual) and (manual), 4=IV, 5=V, 6=Armed forces. The variable was dichotomised into 1=non-manual (I,II,III) and 0=manual(IV,V) [see also(Marang-van de Mheen et al., 1999)].

Overcrowding: This was calculated using information obtained from the mother's questionnaire when the child was 33 months old (2.8 years). A crowding index was calculated by dividing the number of people living in the home by the number of rooms (including kitchen/diner) in the home, ranging 1 to 19. It was grouped as 1=<0.5, 2=0.5-0.75, 3=0.75-1.00, 4=1.00+ [see also (Flouri et al., 2014)]. The variable was then further dichotomised into 1=not overcrowded (groups 1,2,3) and 0=overcrowded (group 4).

Housing tenure: Homeownership status was reported by the mothers when they were 8 weeks pregnant. The question invited 7 possible answers: 0=Mortgaged, 1=Owned, 2=Council rented, 3=Rented from private landlord-furnished, 4=Rented from private landlord-unfurnished, 5=Rented from housing association, and 6=Other. A dichotomous variable was then created by combining the answers for the mortgaged and owned home ownership status as 1=owning the home vs. 0=not owning the home [see also (Galobardes et al., 2006)].

Financial difficulties: An index of financial difficulties was created using the following variables from the mother's questionnaire when the child was 8 months, 21 months, and 33 months old. Mothers were asked, "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: 1="Very difficult", 2="Fairly difficult", 3="Slightly difficult", and 4="Not difficult". Perceptions of family financial difficulties were also used as an individual predictor and is presented in chapter 6. After reverse coding, the total score (ranging from 0-15) was calculated for each timepoint. The three scores were then summed into a continuous variable ranging from 0 to 45. Following visual inspection of its distribution, it was dummy-coded to differentiate the bottom third (1=no or little difficulty affording items) from the top two-thirds (0=difficulty affording items). The purpose of this variable was to capture difficulties spanning many years and therefore, by dichotomising the variable as such indicates the financial strain that parents must have experienced at some point across the three timepoints and it expected that the distribution of this variable to be skewed in the general population.

3.2.2 Inflammation

Biological samples started being measured in children at age 9 years. A note was made for any infections, and treatments or medications being used at the time. Since taking blood from children for research purposes is very different from taking it from sick children where the sample is essential for their care these things were mandatory for this study:

- Obtain mother's or father's informed consents in writing before the sample was taken
- Have child's willingness to undergo the procedure
- Ask the parent(s) to say if they wanted the blood-taker to stop taking the blood at any time (this removed some of the anxiety from both parents and staff)
- Stop if the child asks blood-taker to do so, or if the child became distressed.

In ALSPAC, inflammation in childhood was measured with C-reactive protein (CRP) and Inerleukin-6 (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%.

3.2.3 Cognitive functioning

ALSPAC started measuring children's cognitive development as soon as 15 months of age. A child-specific questionnaire was administered to the mother or the partner. At age 15 months, mothers reported on their child's understanding, vocabulary, non-verbal communication and social development and at age 24 and 38 months also reported on their child's grammar and language skills. From age 7 years, children were tested on their reading and spelling abilities. At age 8 years and above children's cognitive functioning was measured with standardised tests. In this thesis, I used IQ as a measure of cognitive functioning and working memory as a measure of EF.

The Wechsler Intelligence Scale for Children (WISC-II[UK]) (Wechsler et al., 1992) was used to assess cognitive function. It is the most up-to-date version of the Weschler Intelligence Scale for Children, the most widely used individual ability test worldwide. The ten WISC subtests that were administered to children comprised five verbal subtests:

- Information (assessing the child's knowledge);

- Similarities (where similarities between things, e.g., *in what way are red and blue alike?* must be explained);

- Arithmetic (comprising mental arithmetic questions);

- Vocabulary (ascertaining the child's understanding of the meaning of different situations, e.g., *why are names in the telephone book in alphabetical order?)*

And five performance subtests:

- Picture completion (where the child must point out what is missing from each of a series of pictures);

- Coding (where shapes corresponding to different numbers must be copied as quickly as possible within a specified time limit);

- Picture arrangement (where pictures of specific patterns of blocks are copied with real blocks);

- Object assembly (which involves putting together puzzles).

The children were also given the forwards and backwards digit span task (a measure of short-term storage capacity), repeating lists of digits of differing lengths, firstly in the exact order, they were presented in and secondly, in reverse order.

To engage the children with the tasks, the tester explained to the children that they would be playing lots of games including looking at pictures, doing puzzles, making patterns and answering some questions. The children were told that they might find some of the tasks quite difficult but that they should not worry as they were the same things testers would ask older children to play. All children were encouraged to have a go at things, even if they thought they were just guessing.

Raw scores were calculated according to the items used in the alternate item form of the WISC. This was achieved by summing the individual items within each

subtest and multiplying by 2 for picture completion, information, arithmetic, vocabulary, comprehension and picture arrangement; multiplying by 5/3 for similarities, multiplying by 3/2 for object assembly and block design, thus, making the raw scores comparable to those that would have been obtained had the full test been administered (the raw score for the coding subtest was calculated in the standard way as the full subtest was administered). It is because of this multiplication that some of the scores do not follow a smooth distribution.

Total IQ at age 8 years: Using the Look-up tables provided in the WISC manual, age scaled scores were obtained from the raw scores and total scores were calculated for the Performance and Verbal scales. At this point, prorating was performed: If a child obtained a score for only four out of the five subtests on each of the performance or verbal scales, the total scores for each scale could still be calculated, by substituting the mean of the four available scaled scores in for the fifth score and summing in the usual way. This was done in accordance with WISC instructions. Although acceptable in WISC calculations, substituting the digit span score in place of an unobtained fifth verbal subtest was not done. Finally, a total score (ranging from 46 to 151) was derived and was used in this thesis.

Total IQ at age 15 years: To assess the cohort member's cognitive ability during the study's age 15.5 sweep (TeenFocus3), ALSPAC used the Wechsler Abbreviated Scale of Intelligence (WASI) (Wecshler, 1999). WASI is a measure of general cognitive ability designed for use in adults and older adolescents. It is a short-form measure that was developed in tangent with and designed to provide an estimate of the WISC scale. It is comprised of four subscales, two verbal and two performances (non-verbal). The two verbal subtests include 1) vocabulary and 2) similarities while the two performance subtests are: 1) block design and 2) matrix

reasoning. The WASI provides standard scores (M=100, SD=15) on verbal IQ, performance IQ and full-scale IQ. Raw scores were converted into age-adjusted standardized scores using tables provided in the WASI manual. It is noted that due to limitation at clinic time at this age, only the vocabulary and matrix reasoning subtests were administered. These were used to approximate the full IQ score which was also used in this thesis and ranged from 55 to 130.

Working memory- Span score at age 10 years: Working memory has been put forward as an important component of reading and arithmetic skills. It was tested using the Counting Span Task which requires the simultaneous processing and storage of information (Case et al., 1982). On the computer monitor, the child was presented with a number of red and blue dots on a white screen. The child was asked to point to and count the number of red dots out loud (the processing component). The children were 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 e) three sets of five screens. After each set, the child was 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 inputted these numbers into the computer after each set. 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, based on 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 and where higher scores indicate higher working memory.

3.3 Other measures

Other measures that were used in this thesis either as main measures or covariates were at the family- and the child-level. The family-level measures money problems/ perceived economic hardship (whether the parents had an income reduction or major financial difficulty) and the child-level measures were gender, age, upsetting events in childhood, and BMI.

3.3.1 Upsetting events in childhood

Mothers were asked at 7 timepoints in the child's life until age 9 years (18 months, 30 months, 42 months, 57 months, 69 months, 81 months and 103 months) whether and which 15 upsetting events had been experienced by the child since the previous timepoint, starting from when the child was 6 months old (e.g. child was taken into care, moved home, a pet died, was physically hurt by someone, was sexually abused, was separated from mother/or father for at least a week, acquired a new parent, changed carer). Each question was answered on a 5-point scale: 1=Yes, and child was very upset, 2=Yes, and child was quite upset, 3=Yes, and child was a bit upset, 4=Yes, but she wasn't upset, and 5=Did not happen. In this thesis, two indicators of upsetting events were created. The first captured the upsetting events that occurred from 3 to 9 years and was used as the mediator as described in chapter 5. The second captured the upsetting events that occurred in the early years (0-3 years) and at the period SES was measured in the study and was used as a covariate. Table 3-2 presents the full list of the events.

Table 3-2. List of events that might upset some children

List of events
1. Child was taken into care
2. A pet died
3. Child moved home
4. Child had a shock or fright
5. Child was physically hurt by someone
6. Child was sexually abused
7. Child was separated from her mother for at least a week
8. Child was separated from her father for at least a week
9. Child acquired a new parent
10. Child had a new brother or sister
11. Child was admitted to hospital
12. Child changed carer/caregiver
13. Child was separated from someone else
14. Child started creche or nursery or school
15. Something else

3.3.2 Covariates

Money problems: This was measured using two questions from 9 timepoints (18 weeks of pregnancy to 9 years of age) that were asked of the mothers: whether a) their income was reduced and b) they had a major financial problem since the previous timepoint. Answers were on a 5-point scale: 1="Affected a lot", 2="Fairly affected", 3="Mildly affected", 4="No effect at all" and, 5="Did not happen". Answers were then recoded into 1 = "happened" (irrespective

of impact) and 0 = "did not happen". A final variable was then created such that respondents who reported income reduction or major financial difficulties in any of the 9 timepoints would get a value of 1, indicating money problems since the previous timepoint. Those who reported, across all timepoints, that they did not have their income reduced or any major financial difficulty as well as those who had missing data in at least 6 out of the 9 timepoints would get a value of 0.

Perceived economic hardship: To create this variable, information using the same questions for the previous 'money problems' variable was gathered. Two questions to mothers at 4 timepoints (47 months, 61 months, 73 months, and 9 years of age) this time 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.

Body Mass Index (BMI) was measured using information from the clinic assessments at age 9 years and was calculated as weight (in kg) divided by height (in m) squared rounded to 1 decimal place. BMI at age 15 years was not calculated during the clinic assessments; however, for the purposes of the current study, this was calculated using the same information for adolescent's weight and height following the same approach they used in the clinic assessments.

3.4 Study strengths and weaknesses

ALSPAC study has several strengths but also limitations too. Some of the strengths are its large sample size and general population base, the breadth and frequency of data collection as well as the repeated measures available. Furthermore, the extensive biobank, the considerable size of genetic sampling and the ongoing support and commitment from the study families (Boyd et al., 2013a).

Another strength of the study is the relatively new statistical techniques for taking account of missing data which are being used increasingly (Steer et al., 2010).

ALSPAC has some limitations too. Although there is a variety of repeated measures collected across frequent time points, the early collection of data (up to 5 years) was limited to a 10% subsample. Collecting data from young people is extremely difficult and thus, response rates are expected to decrease over time. However, the data collected in early stages have been very informative in terms of early growth and development. ALSPAC is investing resources into collecting data from health and administrative records to address the drop-in response rates. Another weakness of the study is that incomplete recruitment and subsequent attrition have further reduced power and the availability of repeated measures across several timepoints which may have introduced bias in how some effects were estimated. Furthermore, the sample has an over-representation of more advantaged individuals and an under-representation of non-White minority ethnic groups compared with the national population. This is primarily due to the demographic profile of the catchment area populations and the effects of the differential attrition. This might have a bearing on the validity of some study findings based on prevalence, however, it should not negatively influence the longitudinal results.

Chapter 4. Data analysis

In this chapter, the type of analysis used in this research thesis is discussed. The main statistical approach used in this study is Structural Equation Modelling (SEM) and thus, this chapter describes what SEM is, the models fitted, estimation, model fit indicators as well as mediation analysis in SEM. Finally, it is discussed how missing data were handled in this thesis.

4.1 Types of analysis

4.1.1 Descriptives

The descriptive analysis including correlations, means, percentages and cross-tabulations as well as the bias analyses were performed in Stata 16.0 (Stata Corporation, College Station, TX, 1997).

4.1.2 Structural Equation Modelling

4.1.2.1 Introduction

Structural Equation Modelling (SEM) is "a collection of statistical techniques that allow examination of relationships between one or more independent variables (IV's) and one or more dependent variables (DV's)" (Tabachnick et al., 2007). It is an extension of the general linear model that enables a researcher to test a set of regression equations simultaneously (Byrne, 2013). SEM can test traditional models, but also other models that examine complex relationships and may be used as a more powerful alternative to multiple regression, path analysis, factor analysis, and time series analysis.

In simple terms, SEM can be thought of as regression models which contain casual relationships between latent variables as well as observed variables. These latent variables (also known as constructs or factors) are unobserved and often 'unmeasurable' variables which are measured by respective sets of observed variables (also known as indicators), e.g., family SES. Using latent variables or factors as opposed to using observed variables that are subject to measurement error, improves the reliability of our measures.

One of the advantages of SEM is that it takes a confirmatory approach to test hypotheses. There are two types of testing the relationships a priori: a) Exploratory Factor Analysis (EFA) and b) Confirmatory Factor Analysis (CFA). EFA is an exploratory procedure designed for model building and for describing relationships between variables. In EFA, we seek to identify which variables measure which underlying 'pure' factors or latent variables and interpret the meaning of these factors. Also, EFA is usually performed to derive one or more 'best' models for the relationships between the observed and the potential underlying factors. Such models are known as "measurement models" as they describe how observed variables (indicators) measure underlying concepts of interest. CFA is used to test how good such measurement models are, i.e., how well they fit the data, and it is always the first step in fitting an SEM. In CFA, the model is defined at the beginning of the process. This model likely emerges from a combination of preceding EFA, literature and the researcher's theories that are seeking to 'confirm' it (Brown & Moore, 2012). In this thesis, CFA preceded the SEM to construct the latent factor of SES which was used in the analysis for Chapters 5 and 7.

Furthermore, SEM provides explicit estimates of the error variance parameters which helps to avoid inaccurate results. As described previously, SEM

incorporates both latent and observed variables and multiple outcomes and can also test for mediating/moderating effects that may influence the relationships explored.

There are several steps when applying an SEM: model specification, model identification, parameter estimation, model fit, and model re-specification (Tanaka, 1993). The first step is the formation of a hypothesis based on theory and findings from previous studies. The second step is model identification which is about deriving a unique value for each unknown parameter in the model using a variance/covariance matrix of the measured variables that are known. When the degrees of freedom of the model is positive, i.e., there are more data points than the number of parameters to be estimated, then the model is identifiable. Subsequently, the parameter estimation follows and there are several estimators from which to choose. The most widely used one is Maximum Likelihood (ML). Other estimators are chosen based on sample size and normality of the data as well as the type of the data, i.e., continuous, categorical, multinomial etc. The estimators used in this thesis are discussed in section 4.1.2. The next step is examining the model fit which is about the degree to which the model fits the data examined. The most basic fit statistic for any path analysis model is the chi-square statistic, which is applied in a wide range of statistical test scenarios to test whether the "observed" (i.e., the actual data) departs from what is "expected" under the proposed model. If the chi-square statistic is significant, this indicates that the relationships between the variables in the model are significantly different from what we would have expected if the model was a true representation. However, when the sample is even moderately large, differences between the observed and expected covariance matrices that are small enough to be considered trivial can cause statistically significant chi-square statistics. However, if we relied purely on the chi-square statistic to determine model

fit in such situations, we would end up rejecting a lot of very good models. Hence, other indices have been developed to assess the fit of the models and it is discussed in section 4.1.3. Finally, the re-specification, which can be driven by theory, is another step to improve the model-data fit and involves removing statistically insignificant paths or adding paths to the model.

Considering all the information above, the most appropriate type of analysis for this thesis is therefore SEM. Using SEM was the optimal choice as it allowed to create and use of a latent variable (unobserved measures often created into latent constructs and used in psychology and social sciences) of SES while incorporating observed variables into the same model. Given that the ALSPAC study provided information on several separate indicators and proxies of SES (as described previously in chapter 3), a latent variable approach was necessary to construct this measurement of SES. To confirm the latent factor, a 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 of empirical Chapters 5 and 7. Finally, the latent construct used in this thesis were tested for model fit a discussed later in section 4.1.3. In addition, mediation models can also be fitted into the SEM and explore mediation effects. As the main purpose of this study was to explore the mediating effect of inflammation in the relationship between SES and child cognitive outcomes the choice of this type of analysis is therefore justified.

The statistical programme that was used to perform SEM in this thesis was Mplus version 8 (Muthén & Muthén, 2017). Mplus has many advantages in performing SEM compared to other statistical packages (Byrne, 2013). Mplus is incredibly flexible and it can fit models with even the most complex combinations of

observed and latent variables (e.g. in terms of type, distribution, data structure, sample weights, and subgroups). It also offers a vast range of fitting methods to do so. Additionally, Mplus can handle not only single-level models but also multilevel SEM, complex survey data and SEM using a Bayesian approach.

4.1.2 Types of Models

In this thesis, the main type of model that was used as a path model extended to SEM with continuous outcomes as described in Chapters 5, 6 and 7. Within the SEM, a mediation path was also added to test the indirect relationships between the predictors and the outcomes.

4.1.2.1 Path analysis

Path analysis encompasses any regression technique which enables the simultaneous modelling of several related regression relationships, including both direct and indirect effects (Menard, 2010). In the social sciences, path analysis has been widely used (most notably in areas of child or lifespan development or another longitudinal research). Path models are typically represented in the form of path diagrams but can also be modelled as a set of regression equations. A path model can include any number of independent (or exogenous) variables, any number of dependent (endogenous) variables, and any number of intermediate variables which are both dependent on some variables and predictive of others. When constructing any path analysis model, it is helpful to define a model both graphically and in terms of the equation making it up. For example, rectangles represent observed variables, ovals represent latent constructs, single-headed arrows represent causal relationships between variables and double-headed arrows represent correlations between variables.

4.1.2.2 SEM

SEM is an extension of path analysis, in which the paths of interest are typically among latent variables or factors, with an explicit measurement model linking factors to observed variables. The SEM models fitted in this thesis were conducted at one level, the individual level. In chapter 5, the relationship between family SES and inflammation was explored using an SEM model in which a mediation path was added to explore whether upsetting events in childhood explained the SES-inflammation link. In chapter 6, the same technique was used to investigate if family financial difficulties were related to working memory in childhood and another mediation path was included to test whether that relationship was explained by inflammation in childhood. Finally, in chapter 7, the relationship between SES and IQ was explored using an SEM model while it also tested whether earlier and concurrent inflammation could mediate that relationship.

4.1.2.3 Mediation

Mediation models are an attempt to explain why a relationship exists between predictor variables and outcomes (Baron & Kenny, 1986). In a mediation model, one hypothesizes that the effect of a predictor variable(s) upon an outcome operates, either fully or in part, through an intervening or mediator variable (MacKinnon, 2008). Full mediation is when the direct effects between the predictor and outcome are no longer significant when a mediator is introduced. For example, in a hypothetical study where they wanted to test whether maternal educational level (X) would predict child behavioural problems (Y) and if those were influenced by mother's depression (M), a full mediation would assume that child behaviour problems are present only due to depression and that depression is only associated with maternal education. On the other hand, partial mediation is when the direct effect between the predictor

and outcome is still present but reduced when a mediator variable is introduced. For one, a hypothetical example of a partial mediation would be whether childhood poverty (X) lead to emotional problems (Y) through the home environment (M). A partial mediation would then assume that childhood poverty can predict emotional problems but that is also influenced by a third variable, the home environment.

Mediation is considered as causal since it shows the direction of influence. However, causal conclusions should not be drawn unless the research is experimental. Using longitudinal data such as in this thesis allows for temporal models that specify time-based sequence of events rather than a causal sequence of events. This would be difficult to be achieved with cross-sectional data as the level of inference between variables is restricted.

The effects of mediation analysis are called 'indirect' effects and there are several ways to calculate indirect effects in SEM. The default is what is known as the delta method of estimation, which is equivalent to a Sobel's test which assumes that the indirect effect has a normal distribution. However, this is often not the case. Hence, another more robust way of assessing whether indirect effects differ from zero is preferred. MacKinnon (2008) and Hayes (2013, 2017) advised to calculated bootstrapped bias-corrected confidence intervals for each parameter tested. Bootstrapped confidence intervals do not rely on any distributional assumptions. Instead, they use estimates from many samples of the data, 'collected' by repeatedly sampling with replacement from the sample and calculate the statistics of interest (i.e., indirect effects) for each of them. They then line these estimates up from the lowest to the highest and use the percentiles of these estimates as the confidence intervals. In this thesis, bootstrapping was used in all mediation models as the mediator variables used were not normally distributed. Specifically, the variable for

upsetting childhood events in chapter five was not normally distributed and the inflammatory markers used as mediator in chapters six and seven were not normally distributing either although they were log-transformed for that reason.

4.1.3 Model estimators

Estimators are used in the SEM analysis to solve model equations and produce parameter values. In Mplus, there are different estimators depending on the type of the analysis and the measurement scale of the outcome (dependent) variable. Not all estimators are available for all models. Two of the most common estimators are Maximum likelihood (ML) - used when all dependent variables in the model are treated as continuous - and weighted least squares estimation (WLSMV), used when one or more dependent variables are defined as categorical.

Consequently, these two estimators were used in the analysis for this thesis. To construct the latent SES variable during the CFA, the WLSMV estimator was used as all the variables were categorical. WLSMV estimates parameters using a diagonal weight matrix with standard errors and a mean- and variance- adjusted chi-square test statistic that uses a full weight matrix. For the SEM analysis in chapters 5, 6, and 7, the ML estimator was used as the main outcomes were continuous variable (inflammation as measure by CRP and IL-6 in chapter 5, working memory in chapter 6, and IQ in chapter 7). ML estimates conventional standard errors and the chi-square test statistic (Muthén & Muthén, 1998-2017).

4.1.4 Model fit

In SEM, it is important to assess how well the model fits the data. The most basic fit statistic for any path analysis model is the chi-square statistic which is applied in a wide range of statistical test scenarios to test whether the "observed"

departs from what is "expected" under the proposed model. However, as discussed previously, we cannot rely purely on the chi-square statistic to determine model fit and thus, other indices have been developed to assess the fit of the data. These fit indices use a variety of methods (e.g., comparison against the independence model - "baseline" or "null" model - and assessing residual errors) and can be classified into two distinct types: a) Absolute Fit Indices and b) Incremental Fit Indices. Absolute fit indices are simply derived from the fit of observed and expected covariance matrices and the ML minimization function. Incremental fit indices make weighted or unweighted comparisons between the chi-square statistic for the model being tested and the chi-square statistic from the independence model (Xia & Yang, 2019).

In this thesis, various measures of goodness of fit of the model to the data were used. These were the Chi-Square test of Model Fit, the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Standardised Root Mean Square Residual (SRMR). The chi-square statistic is commonly used; however, it is sensitive to large samples as the sample in this thesis. The RMSEA and the SRMR indices are absolute fit indices. The RMSEA is a predictive fit index (Steiger, 1990). It determines how well the hypothesized model fits the sample data and is sensitive to the complexity of the model (Byrne, 2013). The CFI belongs to the increment fit indices and measure the proportionate improvement in model fit between the hypothesized model and a less restricted baseline model. Hu and Bentler (1999) examined various cut-offs for many of these measures under different conditions (varying sample size, model complexity, etc.). For RMSEA, a value of zero indicates a perfect fit and a value of less than .05 a good fit (Steiger, 1990). For CFI, the values are restricted from zero to 1.00 with values close to 1.00 being consider a very well-fitted model and values greater than

.90 are considered a reasonable model fit. SRMR also ranges from zero to 1.00 with values closer to zero indicating a very good fit. The recommended cut-offs are CFI (≥ 0.95), SRMR (≤ 0.08), and RMSEA (≤ 0.06). As it will be described in the following empirical chapters under the analytic strategy section of each chapter, all the SEM models appeared to have a very good fit.

4.2 Treatment of missing data

Missing data is common in longitudinal data not only due to non-response in a given wave but to attrition of participants across waves. Research should always take this into account during the analysis to avoid mistakes and draw valid conclusions. There are three main missing data mechanisms: 1) missing completely at random (MCAR), 2) missing at random (MAR), and 3) missing not at random (MNAR).

Missing completely at random (MCAR) implies that the probability of being missing is the same for all cases and that the causes of missing data are unrelated to the data. MCAR also implies that there are no systematic differences between the missing values and the observed values. However, this never holds in longitudinal analysis and MCAR is relatively rare because dropouts usually occur due to different causes and some of them may depend on responses. An example of MCAR is when we take a random sample of population where each member has the same chance of being included in the sample and thus, the data of people that were not included in the sample are MCAR.

The probability of being MAR is when there are systematic differences between the missing values and the observed values and can be explained by the observed data. MAR is not as restrictive as the MCAR and provides a more flexible

perspective for handling missing data as it allows missing observations to depend on observable outcome values. One example of MAR is when we take a sample from a population where the probability to be included depends on a (or several) characteristic, such as owning a property for instance. MAR is more general and more realistic than MCAR and it is more likely that in modern research, the missing methods start at the MAR assumption.

MNAR is when neither the MCAR or MAR assumption stands, and it implies that the probability of being missing is due to reason that are unknown to us. In fact, MNAR is also when differences between the missing values and the observed values remain even after accounting for all observed information. An example of MNAR would be the case when measuring public opinion responses, those with weaker opinions were found to responded less.

In empirical analysis, the most frequently used and most realistic assumption on the missing-data mechanism is MAR. A straightforward model with the MAR assumption has been found to predict actual outcomes more accurately than a standard nonignorable model or other ad-hoc method, allowing nonresponse to depend on outcomes (David et al., 1986; Rubin et al., 1995). In contrast, MNAR should be assumed in some special situations in which missing data depend directly on missing values.

There are several statistical methods of dealing with missing data including handling MCAR, MAR, and MNAR mechanisms. The simplest and most direct method is listwise deletion (also known as complete case analysis) which involves the removal of all cases with missing values and is the default in most statistical packages such as SPSS and Stata. If the data are MCAR then listwise deletion

produces unbiased estimates of means, variances and regression weights. Another

alternative approach to the complete case analysis is the pairwise deletion method

where a case is deleted only when the missing items is in direct use in the analysis

of a specific relationship. In addition, the pairwise deletion attempts to correct the

problem of data loss by listwise deletion as it calculates the means and

(co)variances on all observed data. Another simple and quick fix approach for the

missing data is mean substitution which involves substituting a sample mean for the

missing value of a given item. Although convenient, mean substitution as well as

listwise and pairwise deletion is not valid if missing data are not MCAR as the

estimates produced are very likely to be biased. Furthermore, even if the data being

MCAR, methods like complete-case analysis will ignore valuable information in

incomplete cases which can be detrimental when an important covariate in the

model is the main missing variable. Therefore, applying those methods can be

detrimental to the quality of the longitudinal data analysis (Liu & Pang, 2016)

especially when the amount of missing data is high.

Given that it is very unlikely for the data in longitudinal studies to be MCAR,

the MAR and MNAR assumptions are generally more likely to hold in epidemiological

studies (Perkins et al., 2018) like this thesis. Hence, the aforementioned approaches

of treating missing data should be avoided to eliminate the risk of introducing biased

estimates. When data are MAR, there are other methods to deal with the

missingness which depends on the nature of non-response in those studies. Some

of those principled methods are multiple imputation (MI), inverse probability

weighting (IPW) and full maximum likelihood (FIML) and they all rely on the

assumption that the data are MAR. The MI method attempts to produce unbiased

and efficient estimates for the population parameters of interest. What MI essentially

does is that it creates several complete versions of the data by replacing the missing values with other possible data values. These possible data values are estimated from a distribution that is modelled specifically for each missing entry. Multiple versions of the imputed data are created which result into a determined number of imputed datasets. Consequently, estimates of the parameters of interest from each imputed dataset are calculated and finally, these parameter estimates from the imputed datasets are pooled into one final estimate which under the appropriate conditions is unbiased. On the other hand, the IPW method attempts to build a logistic regression model to estimate the probability of the exposure observed for a person and uses the predicted probability as a weight in any subsequent analysis. IPW is useful when accounting for attrition-related missingness in follow-up studies (Klebanoff & Cole, 2008).

FIML is a method that instead of imputing the values of missing data, it attempts to estimate the value of some population parameter by determining the value that maximizes the likelihood function based on the sample data that are available. What FIML essentially does is that it employs data from partially completed cases which contribute to the estimation of parameters that involve the missing portion of data. This approach is probably the most practical way of estimating missing data in Structural Equation Modelling which has been shown to produce unbiased parameter estimates and standard errors under MAR and MCAR (Enders & Bandalos, 2001). FIML requires that missing values to be at least MAR and produces probable implied values for the missing data by the relationship between the observed values of other variables in the dataset with the missing data (Schafer & Graham, 2002). With missing data, the FIML fit function (Arbuckle et al., 1996) is computed for each set of cases with the same unique pattern of missing

values. What FIML also does, is that instead of following the typical approach to calculate chi-square, it estimates two models, the H_0 and the H_1 model. The H1 model is the "unrestricted" model, which means that all the variables are correlated whereas the H0 models is the specified model. The difference between the two log-likelihoods is used to derive the chi-square (Muthén & Muthén, 1998-2017) and this process allows to use all the available information in the variables.

The approach that was employed to handle missing data in this thesis, was FIML. As explained previously, FIML is one of the most useful ways of treating missing data in SEM while producing unbiased parameter estimates and standard errors as opposed to listwise deletion or older imputation approaches. In addition, the main statistical package used for the analysis in this thesis was MPlus which allows to specify the type of information matrix used in the FIML estimation. Even if the mechanism is not MCAR or MAR (i.e., data are MNAR), modern missing data mechanisms such as FIML is still preferable for its convenience to implement. Below in Table 4-1, the amount of missingness in the study variables is presented:

Table 4-1. Amount of missingness in the variables of the study (N=4525)

	N	% of missingness
IL-6 (pg/mL) **(age 9)**	4,525	<5.0[4]
CRP (mg/L) **(age 9)**	4,525	<5.0[4]
CRP (mg/L) **(age 15)**	2,210	51.2
Upsetting events (early)	3,776	16.6
Upsetting events (later)	3,050	32.6
BMI (age 9)	4,474	<5
BMI (age 15)	2,966	34.5
Gender	4,521	<5
Maternal education	4,157	8.1
Paternal social class	3,831	15.3
Overcrowding	3,721	17.8
Housing tenure	4,168	7.9
Financial difficulties	4,525	<5.0[4]
Money problems	4,278	5.5
Working memory	3,817	15.7
IQ (age 8)	3,888	14.1
IQ (age 15)	2,771	38.8

Note. IL-6=interleukin 6; CRP=C-reactive protein; Upsetting events (early)=measured

at 0-3 years; Upsetting events (later)=measured at 3-9 years; BMI=Body Mass Index.

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[4] This many include zero.

Chapter 5. Do upsetting life events explain the relationship between low SES and systemic inflammation in childhood?

5.1 Introduction

This chapter examines if SES is related to inflammation in childhood and whether this relationship can be explained by upsetting life events during early to middle childhood. Other individual- and family-level predictors of inflammation were also examined including gender, economic hardship and BMI. This chapter outlines the aims of the research followed by a description of the methodology of the study, the results and a summary of the findings and conclusions.

5.1.1 Study aims

SES in childhood has been associated with a variety of health outcomes in the adult population (Adler & Rehkopf, 2008; Calixto & Anaya, 2014). Several mechanisms account for the relationship between SES and disease in adulthood, such as BMI and unhealthy lifestyle choices (Miller et al., 2011). More recently, inflammation has been proposed as the biological pathway through which SES may exert its effects on the body. Previous studies have linked SES and inflammation in adulthood, however, results were mixed (Milaniak & Jaffee, 2019; Muscatell et al., 2018). The pathways that were tested to explore the above relationship were health-related characteristics such as BMI (Carroll et al., 2011) and smoking (Malfertheiner & Schütte, 2006) but could only partly explain that relationship. Consequently, there might be other mechanisms that play a mediating role between SES and inflammation.

One proposed pathway is through stressful or upsetting life events in childhood as children from lower SES are more likely to be exposed to these throughout childhood and adolescence. According to the biological embedding hypothesis (Miller et al., 2011), early exposure stressors, which may be associated with lower socioeconomic position, activate proinflammatory tendencies in the body. Studies in adults have investigated the link between early SES and adult inflammation through recent life events (John-Henderson et al., 2016). However, the link between SES and inflammation in childhood is less explored and the role of early upsetting events in this association has not been examined yet.

Therefore, the **first aim** of this chapter was to examine if SES early in life (at ages 0-3 years) is associated with inflammation at age 9 years. The study predicted that higher SES would be related to lower levels of inflammation as measured by CRP and IL-6. I also expected that other individual- and family-level covariates would be directly related to elevated inflammation. Furthermore, I predicted that early upsetting life events (at ages 0-3 years) would also be related to higher inflammation in middle childhood. The **second aim** of this chapter was to explore whether the relationship between early SES and inflammation is explained through upsetting life events. It was expected that SES would not only be directly related to inflammation but also indirectly through upsetting events.

5.2 Method

5.2.1 Participants

In this study, data from the Avon Longitudinal Study of Parents and Children (ALSPAC) were used. As discussed in chapter 3, ALSPAC is an ongoing birth cohort study that recruited 14,541 pregnant women residents in Avon, UK, with expected

delivery dates from April 1st 1991 to December 31st 1992. These women 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 of 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 15,454 pregnancies, resulting in 15,589 foetuses. Of these, 14,901 were alive at 1 year of age (Fraser, Macdonald-Wallis, Tilling, Boyd, Golding, Smith, 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 clinical assessments at age 9 (62% of those invited). Assessments of the ALSPAC Cohort Profile showed that attrition and non-response were higher among younger mothers, 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. The study's analytic sample (n=4525) 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.

5.2.2 Measures

5.2.2.1 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%. Both CRP and IL-6 were log-transformed for the regression analyses.

5.2.2.2 Socioeconomic status

SES was measured as a latent variable using information from five observed variables during the first 3 years of the child's life: maternal education, paternal social class, overcrowding, housing tenure and financial difficulties. As the observed variables were measured on different scales, they were recoded into binary variables prior to including them in the measurement model as follows:

Maternal education: Children's mothers reported their highest educational qualification at 32 weeks of gestation. There were 5 categories (1=CSE/none to 5=Degree) and a binary variable was then created as 1=degree, 0=otherwise.

Paternal social class: This was derived using information about the father's occupation, measured also at 32 weeks of gestation, using information on job codes from the OPCS. The initial categories were 6 [1=I to 6=V (Armed forces)]. 'Armed forces' was considered missing, and the paternal social class variable was then recoded into 1=non-manual, 0=manual.

Overcrowding: This was calculated using information obtained from the mother's questionnaire when the child was 33 months old (2.8 years). A crowding index was calculated by dividing the number of people living in the home by the number of rooms (including kitchen/diner) in the home, ranging from 1 to 19. The index was then recoded into a binary variable using the <1 cut-off to define the less crowded homes (1=non-crowded, 0=overcrowded).

Housing tenure: Homeownership status was reported by the mothers when they were 8 weeks pregnant. The question invited 7 possible answers (0=mortgaged to 6=other), then recoded into 1=owns the home, 0=does not own the home.

Financial difficulties: An index of financial difficulties was created using the following variables from the mother's questionnaire when the child was 8 months, 21 months, and 33 months old. Mothers were asked, "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 from 0-15) was calculated for each timepoint. The three scores were then summed into a continuous variable ranging from 0 to 45. Following visual inspection of its distribution, it was dummy-coded to differentiate the bottom third (1=no or little difficulty affording items) from the top two-thirds (0=difficulty affording items).

5.2.2.3 Upsetting events

Mothers were asked at 7 timepoints in the child's life until age 9 years (18 months, 30 months, 42 months, 57 months, 69 months, 81 months and 103 months) whether a list of 15 upsetting events had been experienced by the child since the

previous timepoint, starting from when the child was 6 months old (e.g. child was

taken into care, moved home, a pet died, was physically hurt by someone, was

sexually abused, was separated from mother/or father for at least a week, acquired a

new parent, changed carer) (Full list of events in Table 3-2 described in Chapter 3).

Each question was answered on a 5-point scale (1=event happened and child was

very upset to 5=event did not happen). First, the responses were reverse-coded and

then a within-timepoint upsetting events score was calculated for each of the 7

timepoints by summing the items at each timepoint together. Participants with

missing values on all 15 items were considered as missing (around 10-19% of

missingness across the 7 timepoints). Then, a total (across-timepoint) upsetting

events score was calculated by summing the 7 (within-timepoint) scores. For

analysis purposes, two indicators of upsetting events were created. The first

captured the upsetting events that occurred from 3 to 9 years and was used as the

mediator of the study. The second captured the upsetting events that occurred in the

early years (0-3 years) and at the period SES was measured in the study and was

used as a covariate.

5.2.2.4 Covariates

In the study, several individual and family covariates that are known to be

associated with the predictor and the outcome of the study, including early upsetting

events (as described above), gender, money problems, and BMI were used. Money

problems[5] was measured using two questions from 9 timepoints (18 weeks of

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[5] The study used 'money problems' as an additional covariate in the analysis because it captures

subjective financial difficulties from the prenatal period until age 9 years, when inflammation was

measured. Although this variable is conceptually similar to the 'financial difficulties' variable that was

used to create the latent construct of early SES, it was not included in the calculation of the latent

pregnancy to 9 years of age) that were asked of the mothers: whether a) their

income was reduced and b) they had a major financial problem since the previous

timepoint. Answers were on a 5-point scale from "Affected a lot" to "Did not happen".

Answers were subsequently recoded into 1="happened" (irrespective of impact) and

0="did not happen". A final variable was then created such that respondents who

reported income reduction or major financial difficulties in any of the 9 timepoints

would get a value of 1, indicating money problems since the previous timepoint.

Those who reported, across all timepoints, that they did not have their income

reduced or any major financial difficulty as well as those who had missing data in at

least 6 out of the 9 timepoints would get a value of 0. BMI (weight (kg)/height (m)2)

was measured using information from the clinic assessments at age 9 years.

5.2.3 Analytic strategy and hypotheses

Analyses were performed in STATA 15.0 (Stata Corporation, College Station,

TX, 1997) and Mplus statistical package (version 8) (Muthén & Muthén, 2017). To

create the latent SES factor, first, a principal components analysis was conducted

which showed that all five SES indices loaded onto a single factor. Then the

construct validity of the SES factor was tested by conducting a Confirmatory Factor

Analysis (CFA) in Mplus for the five categorical indicators. The CFA was performed

using the weighted least squares mean and variance adjusted estimator for

categorical variables and, again, one factor was extracted (factor loadings in Table

5-1. The following indices of fit were used: 1) Comparative Fit Index (CFI), 2)

Standardized Root Mean squared Residual (SRMR) and 3) Root Mean Square Error

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SES construct as the study wanted to measure 'objective' early SES. Furthermore, its addition to the

confirmatory factor analysis (see section 5.3.3.1) worsened model fit.

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 excellent (CFI=0.95, SRMR=0.06, RMSEA=0.05, 90% CI=0.000, 0.000). Factor scores were then saved and used as a continuous variable in the analysis.

Following this, a Structural Equation Model (SEM) extended to a path analytic model was conducted to test the relationships between early SES, upsetting childhood events and inflammation at age 9 years. Two longitudinal models were run using a total upsetting events score as a mediator for the relationship between SES and inflammation as measured by IL-6 and CRP. The models also adjusted for covariates (gender, BMI, money problems and early upsetting events) and examined the extent to which the association between SES and inflammation in childhood were mediated by life upsetting events. Each inflammatory marker was tested separately to avoid multicollinearity (the hypothesised model is shown in Figure 5-1 as fitted). To assess model fit, the following indices of fit were used: 1) CFI, 2) SRMR and 3) 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 perfect (CFI=1.00, SRMR=0.00, RMSEA=0.00, 90% CI=0.00, 0.00).

To conduct mediation analysis using SEM techniques in a path analysis framework such as the one provided by Mplus, an explicit test for the indirect effect of the predictor (financial difficulties) via the mediating variable (inflammatory marker) was fitted into the SEM 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. Robust methods to estimate the indirect effects were used by calculating bootstrapped bias-corrected confidence

intervals for each parameter tested, as advised by MacKinnon (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. Residual covariances among predictors were also included and produced the study's estimates using full information maximum likelihood.

Finally, two sensitivity analysis was also carried out to explore 1) if results change when participants with CRP>10 mg/L (N=32) were excluded, as those CRP levels likely indicate infection 2) if results are different for children who were not taking medication (N=4,057).

5.3 Results

5.3.1 Confirmatory factor analysis

The study assessed the construct validity of the SES factor by conducting a CFA. Model fit was excellent as all fit indices were within the recommended cut-offs as described previously in section 5.2.3. All factor loadings were satisfactory ($\geq$ 0.40), as shown in Table 5-1.

Table 5-1. Factor loadings and standard errors of the confirmatory factor analysis for SES measured at age 0-3 years

	Standardized factor loadings	S.E.	p-value
SES			
Maternal education	0.68	0.03	0.000
Parental social class	0.68	0.03	0.000
Overcrowding	0.49	0.04	0.000
Housing tenure	0.55	0.03	0.000
Financial difficulties	0.54	0.03	0.000

Model fit: CFI=0.95; RMSEA=0.06; SRMR=0.05.

5.3.2 Descriptive statistics

Table 5-2 shows the descriptive statistics of the study. As can be seen, children in the analytic sample had low levels of IL-6 and CRP and average BMI. The impact of upsetting events was approximately the same for both early and later measurements (1.40 and 1.04, respectively[6]). 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

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[6] The early and later upsetting events specifications capture time periods of different length. Hence, to make mean scores comparable the sum of the events was divided for each period by the months each period covered.

outright or were buying with a mortgage (83%) and which were not overcrowded (94%). Finally, around 85% of the mothers reported that they had not experienced income reduction or had a major financial problem. However, 73% of them reported that at some point they had difficulties affording items such as food, clothing, or things for the baby.

Also, a bias analysis (see Table 5-3) was conducted 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 IL6 and CRP, had experienced fewer upsetting events between ages 3 and 9 and had lower BMI. Furthermore, their parents were more likely to have a university degree, be from higher socioeconomic backgrounds, live in less overcrowded places, own their home, and have fewer difficulties in affording things.

Table 5-2. Descriptive statistics of the main variables of the study (N=4525)

	Continuous	
	n	M(SD)
IL-6 (pg/mL) **at age 9**	4,525	1.21(1.48)
CRP (mg/L) **at age 9**	4,525	0.63 (1.94)
Upsetting events (early)	3,776	33.71(3.95)
Upsetting events (later)	3,050	91.16 (7.80)
BMI at age 9	4,474	17.58 (2.77)
	Categorical	
	N	**%**
Gender		
Male	2,296	50.79
Female	2,225	49.21
Money problems		
No money problems	3,639	85.06
Money problems	639	14.94
SES at ages 0-3		
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
Financial difficulties		
No difficulties affording things	1,211	26.76
Difficulties affording things	3,314	73.24

Note. IL-6=interleukin 6; CRP=C-reactive protein; Upsetting events (early)=measured at 0-3 years; Upsetting events

(later)=measured at 3-9 years, BMI=Body Mass Index.

Table 5-3. Bias analysis of study variables between the analytic and the non-analytic sample

	Analytic sample (n=4525)		Non-analytic sample (n=10920)		Test
		Continuous			
	n	M(SD)	n	M(SD)	T
IL-6 (pg/mL) **at age 9**	4,525	1.21(1.48)	547	1.94(2.22)	10.17***
CRP (mg/L) **at age 9**	4,525	0.63 (1.94)	557	2.22(5.90)	13.34***
Upsetting events (early)	3,776	33.71(3.95)	5,925	33.78(3.88)	0.87
Upsetting events (later)	3,050	91.16 (7.80)	3,239	91.81(8.96)	3.03**
BMI at age 9	4,474	17.58 (2.77)	3,161	17.91(3.09)	4.80***
		Categorical			
	N	%	N	%	
Gender					0.98
Male	2,296	50.79	5,339	51.67	
Female	2,225	49.21	4,994	48.33	
Money problems					3.16
No money problems	3,639	85.06	7,070	83.85	
Money problems	639	14.94	1,362	16.15	

SES at ages 0-3

Maternal education					90.27***
Degree	703	16.91	906	10.87	
Other	3,454	83.09	7,430	89.13	
Paternal social class					76.92***
Non-manual	2,358	61.55	3,797	52.84	
Manual	1,473	38.45	3,389	47.16	
Overcrowding					20.33***
Not overcrowded	3,489	93.77	5,272	91.23	
Overcrowded	232	6.23	507	8.77	
Housing tenure					315.67***
Owning the home	3,474	83.35	6,411	68.69	
Not owning the home	694	16.65	2,922	31.31	
Financial difficulties					320.27***
No difficulties affording things	1,211	26.76	1,591	14.57	
Difficulties affording things	3,314	73.24	9,329	85.43	

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

Note. IL-6=interleukin 6; CRP=C-reactive protein; Upsetting events (early)=measured at 0-3 years; Upsetting events (later)=measured at 3-9 years; BMI=Body Mass Index.

5.3.3 Correlations of main study variables

The correlations among the main study variables are shown in Table 5-4. Early lower SES was related to higher levels IL-6 and CRP. Similarly, lower SES was also related to later upsetting events at ages 0-3 years. Furthermore, the two inflammatory markers were moderately related to each other and additionally, they were both positively associated with later upsetting events although relationships were weak.

Regarding the associations between the covariates and SES, upsetting events and inflammation, it was shown that early and later upsetting events were moderately related to each other. However, having experienced upsetting events early in life was not related to either the predictor (SES) or the main outcomes (inflammation). Furthermore, having higher BMI was negatively related to SES and positively related to higher levels of IL-6 and CRP. Similarly, having money problems was related to lower SES and increased levels of IL-6 but not CRP. Finally, being female was associated with higher IL-6 and CRP; however, there was no association between female gender and SES.

Table 5-4. Correlations of the main variables of the study

	1.	2.	3.	4.	5.	6.	7.	8.
1. IL6 at age 9	1							
2. CRP at age 9	0.44***	1						
3. SES at ages 0-3	-0.06***	-0.04*	1					
4. Early upsetting events (ages 0-3)	-0.00	-0.01	0.03	1				
5. Later upsetting events (ages 3-9)	0.07***	0.04*	-0.05*	0.29***	1			
6. BMI	0.24***	0.43***	-0.07***	-0.00	0.04*	1		
7. Money problems	0.05**	-0.02	-0.15***	0.11***	0.14***	0.02	1	
8. Female	0.14***	0.20***	-0.01	-0.01	0.05*	0.09***	-0.01	1

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

5.3.4 SEM and path models

5.3.4.1 Longitudinal models for the direct effects of early SES and later upsetting events between ages 3-9 on inflammation at age 9 years.

5.3.4.1.1 Longitudinal SEM model testing later upsetting events as a mediator of the link between SES and IL-6 at age 9 years.

Results from the SEM (Table 5-5) showed that in the unadjusted model, SES at ages 0-3 was a significant predictor of IL-6 but not of CRP at age 9 years. It was also shown that direct paths from SES to later upsetting events at ages 3-9 years and later upsetting events to IL-6 at age 9 years were also significant.

The same associations were observed in the fully adjusted models and although the relationship between the exposures, the mediator and the outcome remained significant, the strength of the regression coefficients of the direct path from the main exposure to the outcome became smaller after adjusting for covariates. Specifically, the size of regression coefficients for the direct relationship between SES and IL-6 was reduced mostly after controlling for BMI primarily and then for money problems. Given that BMI and money problems are related to both SES (exposure) and IL-6 (outcome), this indicates that BMI and money problems might have a played a confounding role in the above relationship. On the other hand, the regression coefficient for the direct path from the exposure (SES) to the mediator (later upsetting events) became larger after controlling for earlier upsetting events, indicating that the effects of SES are greater if upsetting events at an earlier age occurred prior to later events measure; however, there is no confounding in this

relationship as earlier upsetting events was only related to later upsetting events and not SES.

Results from the fully adjusted model showed that SES was significantly related to IL-6 (β=-0.03, *SE*=0.015), independently of other covariates. SES was also related to upsetting life events at ages 3-9 years(β=-0.05, *SE*=0.017). Additionally, upsetting life events at ages 3-9 years were positively associated with levels of IL-6 at age 9 years (β=0.05, *SE*=0.018).

Regarding the other covariates (BMI, female gender, earlier upsetting events, and money problems) and their relationship to the main outcome, being female and having a higher BMI were related to higher levels of IL-6 (β =0.11, SE=0.014, β=0.22, *SE*=0.013, respectively). However, earlier upsetting life events at ages 0-3 years or income reduction/financial problems (money problems) were not significant predictors of IL-6 at age 9.

We also adjusted for the impact of early upsetting events on later upsetting events to estimate the net effect of SES on subsequent events independently of its continuation. Results revealed that early upsetting events predicted later upsetting events (β=0.32, *SE*=0.026).

As discussed, CRP was not related to SES but, for completeness, the model results for CRP are presented in Table 5-6.

5.3.5 Mediation analysis

Later upsetting events mediated part of the effect of early SES on later levels of IL-6 (indirect effect: b=-0.005, SE=0.002, p<0.05, 95% CI=-0.011, -0.001, β=-0.003; total effect: b=-0.068, SE=0.028, p<0.05, 95% CI=-0.123, -0.015, β=-0.036;

direct effect: b=-0.063, SE=0.028, p<0.05, 95% CI=-0.063, -0.005, β=-0.034). Figure 5-1 shows all paths in this final model tested.

Regarding the results for later upsetting events as mediator of the relationship between early SES and CRP, it was shown that upsetting childhood events did not mediate the effect of SES on CRP in childhood (indirect effect: b=-0.002, SE=0.003, p>0.05, 95% CI=-0.003, 0.001, β=-0.001; total effect: b=0.013, SE=0.032, p>0.05, 95% CI=-0.021, 0.029 , β=0.005; direct effect: b=0.015, SE=0.032, p>0.05, 95% CI=-0.020, 0.030, β=0.006).

Table 5-5. Results of longitudinal SEM model testing later upsetting events between ages 3-9 years as a mediator of the link between early SES and for IL-6 at age 9 years (N=4525)

	Unadjusted model			Adjusted model		
	b	SE	95% CI	b	SE	95% CI
Direct paths						
1. SES at ages 0-3 -> IL-6 at age 9	-0.10***	0.03	-0.153, 0.044	-0.06*	0.03	-0.118, -0.010
2.SES at ages 0-3 -> Later upsetting events at ages 3-9	-0.81**	0.32	1.423, -0.190	-0.94**	0.30	-1.520, -0.358
3.Later upsetting events at ages 3-9 -> IL-6 at age 9	0.01***	0.00	0.004, 0.011	0.01**	0.00	0.002, 0.009
4.Early upsetting events at ages 0-3 -> IL-6 at age 9				-0.00	0.00	-0.009, 0.005
5. Money problems at ages 0-9 -> IL-6 at age 9				0.06	0.04	-0.014, 0.125
6. BMI at age 9 -> IL-6 at age 9				0.07***	0.00	0.061, 0.076
7. Female -> IL-6 at age 9				0.19***	0.03	0.138, 0.234

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; IL-6=Interleukin 6; BMI=Body Mass Index

Table 5-6. Results of longitudinal SEM model testing later upsetting events between ages 3-9 years as a mediator of the link between early SES and for CRP at age 9 years (N=4525)

	Unadjusted model			Fully adjusted model		
	b	SE	95% CI	b	SE	95% CI
Direct paths						
1. SES at ages 0-3 -> CRP at age 9	-0.06	0.04	-0.133, 0.011	0.02	0.03	-0.050, 0.076
2.SES at ages 0-3 -> Later upsetting events at ages 3-9	-0.80**	0.32	-1.411, -0.181	-0.94**	0.30	-1.513, -0.350
3.Later upsetting events -> CRP at age 9	0.01	0.00	-0.001, 0.011	0.00	0.00	-0.003, 0.007
4.Early upsetting events at ages 0-3 -> CRP at age 9				-0.00	0.00	-0.011, 0.005
5. Money problems at ages 0-9 -> CRP at age 9				-0.04	0.04	-0.127, 0.045
6. BMI at age 9 -> CRP at age 9				0.17***	0.01	0.163, 0.186
7. Female -> CRP at age 9				0.37***	0.03	0.312, 0.428

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; CRP=C-reactive protein; BMI=Body Mass Index

5.3.6 Sensitivity analysis

The initial SEM model showed that SES was not a significant predictor of CRP. Only having a higher BMI (β=0.42, *SE*=0.014) and being female (β=0.16, *SE*=0.013) were associated with higher levels of CRP. Although in our analyses throughout children with a reported infection at the time the blood measures were taken were excluded, a sensitivity analysis was also carried out where the SEM refitted for CRP after participants with CRP>10 mg/L (N=32) were excluded. Results of the fully adjusted model from the sensitivity analysis showed no differences before and after excluding those participants. SES was still not significantly associated with CRP and having a higher BMI and being female remained significant predictors of higher levels of CRP (b=0.43, SE=0.015, β=0.17, *SE*=0.013, respectively).

With regard to the second sensitivity analysis that was carried out to see if results are different for children who were not taking medication, findings from that analysis revealed that there were no differences in the results between the main and the sensitivity analysis for both IL-6 and CRP. In the fully adjusted model for IL-6, SES was related to IL-6 (*β*=-0.04, *SE*=0.015) and later childhood upsetting events (*β*=-0.06, *SE*=0.02). Later upsetting events also predicted higher levels of IL-6 (*β*=0.05, *SE*=0.02). Similar results for CRP were also observed. Early SES was not related to CRP in childhood (*β*=0.01, *SE*=0.013) but it was associated with later upsetting childhood experiences (*β*=-0.01, *SE*=0.02).
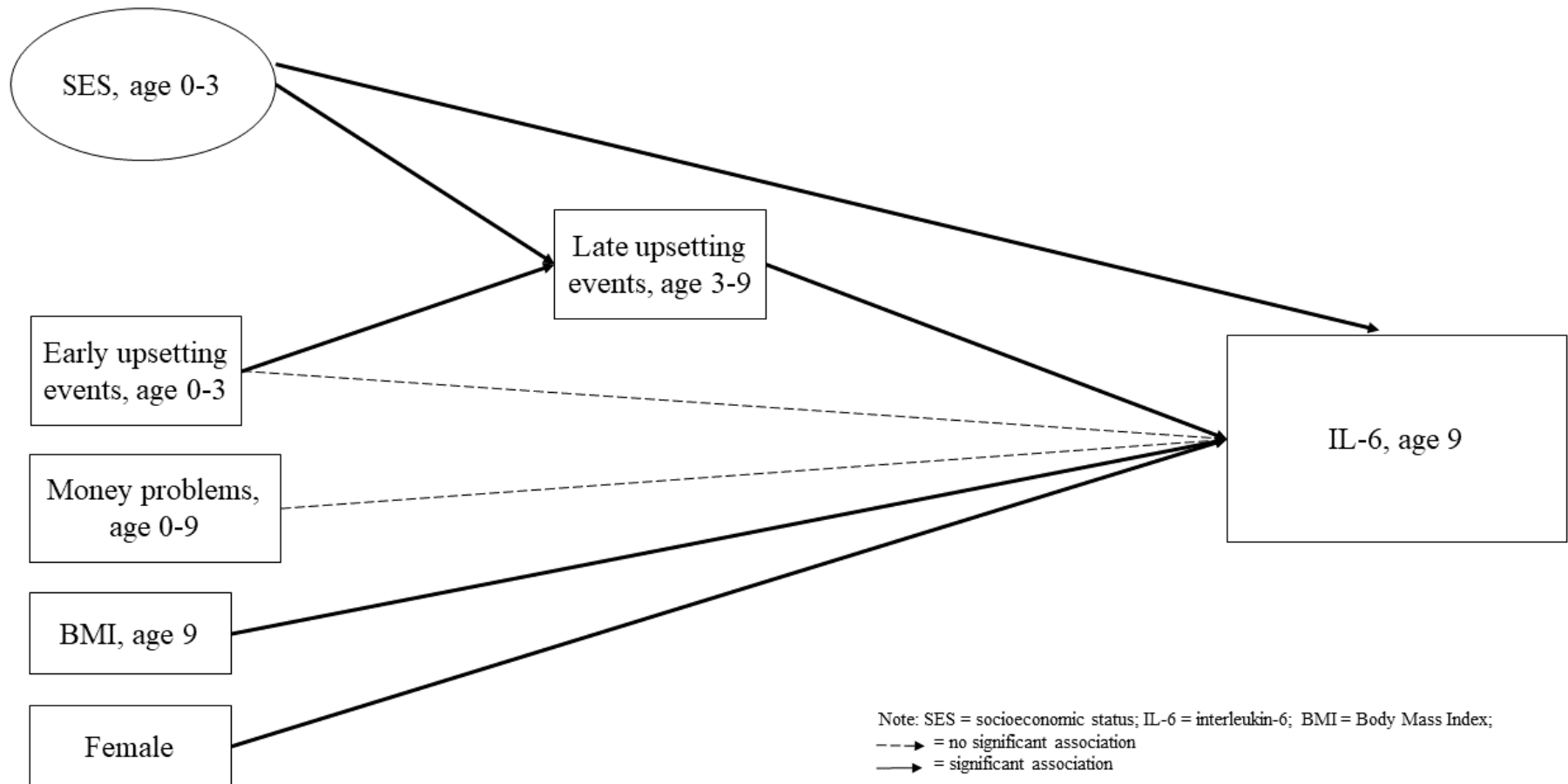
Figure 5-1. Results of final SEM and path analysis model for IL-6 at age 9 years as tested in this thesis

5.4 Conclusions

This study investigated the relationship between early socioeconomic disadvantage and inflammation in childhood and it also explored the relationship between low SES and upsetting events in childhood which in turn, may have an effect on increased levels of inflammation a few years later. The study explored the direct pathways from low SES to inflammation and the indirect pathway via upsetting childhood events while adjusting for early upsetting childhood events, BMI, gender and family economic hardship.

Two longitudinal models were conducted to explore the relationship between SES and inflammation through childhood upsetting events. As hypothesized, lower SES early in life was related to higher levels of inflammation (as measured by IL-6) in middle childhood (age 9 years). However, this study did not find SES to be related to CRP, the other inflammatory marker available in the dataset. In this study, the effect of SES on IL-6 was small, however, this was in line with previous literature (Kuhlman et al., 2020) suggesting that the association between early-life disadvantage and both the inflammatory markers, CRP and IL-6, across childhood was very modest with particularly small effects sizes especially for middle childhood, compared to infancy and adolescence. In addition, the hypothesis of the upsetting childhood events being related to higher inflammation was also confirmed but only in the case of IL-6 with significant albeit small effects.

Finally, with regard to the second aim of the study which was to explore indirect effects from SES to inflammation via childhood upsetting events, this study found that upsetting childhood events partially mediated the effect of SES on IL-6 but not CRP.

Chapter 6. The role of inflammation in the association between poverty and working memory in childhood.

6.1 Introduction

This chapter investigates if parents' financial difficulties early in life (age 0-3 years) are related to poorer working memory in childhood and whether this relationship can be explained by inflammation during middle childhood. Several individual- and family-level predictors of EF were also examined including gender, economic hardship, and BMI.

First, the chapter summarizes the research aims of the study followed by a description of the methodology of the study, the results and a summary of the findings and finally the conclusions.

6.1.1 Study aims

Previous studies have explored the role of families' experience of financial strain on children's EF and found that those experiences were associated with poorer EF outcomes (Hackman et al., 2015; Lawson et al., 2018; Raver et al., 2013). However, there have also been studies that contradicted these findings as they suggested that no associations between SES and EF were found (Engel et al., 2008; Waber et al. 2007; Wiebe et al., 2008).

Several theoretical frameworks on family dynamics associated with financial strain and their role in child development tried to explain that relationship. For instance, a previous study explored the mediating role of parental involvement in the relationship between SES and EFs (Deng et al., 2016; Pendleton, 2018; Zhang et

al., 2020) and another one explored how the role of children's affective state and stress could explain that relationship (He & Yin, 2016). However, as the focus has now shifted to the role of the physiological effects of living under economic disadvantage, it is proposed that inflammation – a physiological response to stress-may explain some of the effects of financial strain on children's EF.

The **first aim** of the study was to investigate if early financial difficulties (age 0-3 years) were associated with worse working memory at age 10 years. The study predicted that financial difficulties, defined as parents' perceptions of difficulties in affording basic items for their children, would be associated with poorer working memory as shown in previous studies (Raver et al., 2013). Furthermore, it was also expected that several individual- and family-level covariates would be directly related to worse performance in the working memory task. Finally, the study predicted that higher inflammation as measured by IL-6 and CRP at age 9 years would also be associated with poorer working memory one year later, at age 10 years.

The **second aim** of the study was to examine whether the relationship between financial difficulties and working memory is explained by inflammation. The study predicted that financial difficulties would not only be directly related to poorer working memory in children but also indirectly through inflammation - a physiological mechanism that has already been linked with poverty as the exposure and EF as the outcome.

6.2 Method

6.2.1 Participants

Information on the participants and the ALSPAC study has been previously described in chapter 3. Also described in the previous empirical chapter of the thesis

(see chapter five), the 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.

6.2.2 Measures

6.2.2.1 Inflammatory markers

In this study, inflammation in childhood was measured with CRP and IL-6 at

age 9 years. Details about the collection of the blood samples are described in

chapter 3.

6.2.2.2 Financial difficulties

The study's 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 from 0-15) was calculated for each timepoint.

The three scores were then summed into a continuous variable ranging from 0 to 45.

Following visual inspection of its distribution, the variable was dummy-coded to

differentiate the bottom third (0=no or little difficulty affording items) from the top two-

thirds (1=difficulty affording items).

6.2.2.3 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, the span score was used which is the main outcome measure for this task.

6.2.2.4 Covariates

Several individual and family covariates including SES at ages 0-3, gender, BMI at age 9 years and economic hardship at ages 3-9 were included in the analysis. Details on the covariates and how they were measured can be found in Chapter 3, section 3.3.3.1.

6.2.3 Analytic strategy and hypotheses

All analyses were performed in STATA 15.0 (Stata Corporation, College Station, TX, 1997) and Mplus (version 8) (Muthén & Muthén, 2017). First, a Confirmatory Factor Analysis (CFA) in Mplus was conducted 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 (see factor

loadings in Table 5-1 in previous chapter 5). Factor scores were saved and used as a continuous variable in the analysis. (The indices of fit for the CFA model are described in chapter five, section 5.2.3)

Following this, an SEM extended to a path analytic model was conducted to test the relationship between financial difficulties and working memory. Two longitudinal models were run which used IL-6 and CRP respectively at age 9 years as mediators for the relationship between financial difficulties and working memory. In both models, a path of financial difficulties on working memory was specified, along with a direct path from SES to financial difficulties - to control for differences in the type of financial difficulties by socioeconomic position. The models also adjusted for covariates (gender, BMI, and economic hardship) 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 6-1 shows the SEM testing mediation by IL-6 as fitted.) To assess model fit, the following indices of fit were used: 1) CFI, 2) SRMR and 3) 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, an explicit test for the indirect effect of the predictor (financial difficulties) via the mediating variable (inflammatory marker) was fitted into the SEM 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. Robust methods to estimate the

indirect effects were used by calculating bootstrapped bias-corrected confidence intervals for each parameter tested, as advised by MacKinnon (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. Residual covariances among predictors were also included and produced the study's estimates using full information maximum likelihood. Finally, two sensitivity analysis were carried out to explore: a) if results change when participants with CRP>10 mg/L (N=32) are excluded, as it is likely that those CRP levels indicate infection and b) if results are different for children who were not taking medication (N=4057) (see Table 6-6).

6.3 Results

6.3.1 Descriptives

Table 6-1 shows the descriptive statistics of the study. 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%).

A bias analysis was also conducted (see Table 6-2) 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 the working memory between samples.

Table 6-1. **Descriptive statistics of the main variables of the study (N=4525)**

	Continuous	
	n	M(SD)
IL-6 (pg/mL) **at age 9**	4,525	1.21(1.48)
CRP (mg/L) **at age 9**	4,525	0.63 (1.94)
Working memory at age 10	3,817	3.43(0.86)
Economic hardship at ages 3-9	4,525	9.98(5.11)
BMI at age 9	4,474	17.58 (2.77)
	Categorical	
	N	%
Financial difficulties at ages 0-3		
No difficulties	1,211	26.76
Difficulties	3,314	73.24
Gender		
Male	2,296	50.79
Female	2,225	49.21
SES at ages 0-3		
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; BMI=Body Mass Index.

Table 6-2. Bias analysis of the study variables between the analytic and the non-analytic sample

	Analytic sample (n=4525)		Non-analytic sample (n=10920)		Test
	Continuous				
	N	**M(SD)**	**n**	**M(SD)**	**T**
IL-6 (pg/mL) **at age 9**	4,525	1.21(1.48)	547	1.94(2.22)	10.17***
CRP (mg/L) **at age 9**	4,525	0.63 (1.94)	557	2.22(5.90)	13.34***
Working memory at age 10	3,817	3.43(0.86)	3,190	3.40(0.83)	-1.35
Economic hardship at ages 0-3	4,525	9.98(5.11)	10,920	5.64(5.85)	-43.48***
BMI at age 9	4,474	17.58 (2.77)	3,161	17.91(3.09)	4.80***
	Categorical				
	N	**%**	**N**	**%**	
Financial difficulties at ages 0-3					320.27***
No difficulties affording things	1,211	26.76	1,591	14.57	
Difficulties affording things	3,314	73.24	9,329	85.43	
Gender					0.98
Male	2,296	50.79	5,339	51.67	
Female	2,225	49.21	4,994	48.33	

SES at ages 0-3

Maternal education					90.27***
Degree	703	16.91	906	10.87	
Other	3,454	83.09	7,430	89.13	
Paternal social class					76.92***
Non-manual	2,358	61.55	3,797	52.84	
Manual	1,473	38.45	3,389	47.16	
Overcrowding					20.33***
Not overcrowded	3,489	93.77	5,272	91.23	
Overcrowded	232	6.23	507	8.77	
Housing tenure					315.67***
Owning the home	3,474	83.35	6,411	68.69	
Not owning the home	694	16.65	2,922	31.31	

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

Note. IL-6=interleukin 6; CRP=C-reactive protein; BMI=Body Mass Index.

6.3.2 Correlations of main study variables

The correlations among the main study variables are shown in Table 6-3. Financial difficulties were associated with higher levels of IL-6 (but not CRP) and worse working memory. Furthermore, higher IL-6 was related to worse working memory and similarly, higher CRP was negatively related to working memory. The two inflammatory markers were moderately related to each other.

Regarding the relationships among the covariates, financial difficulties, inflammation and working memory, higher BMI was associated with increased levels of inflammation (IL-6 and CRP) and economic hardship was related to having financial difficulties. Additionally, higher SES was related to not having financial difficulties, lower levels of IL-6, better working memory and lower BMI. Finally, female gender was associated with increased levels of IL-6 and CRP and with higher BMI.

Finally, regarding the associations from the covariate (gender) to the main outcome (working memory) and the mediator (IL-6), it was found that being female is associated with better working memory (β=0.05, SE=0.017) but also with higher levels of IL-6 (β=0.13, SE=0.015). As for the other covariates (BMI and economic hardship) and their relationship with the mediator (IL-6), results showed that only having a higher BMI was associated with higher levels of IL-6 (β=0.26, SE=0.014).

Table 6-3. Correlations among the main variables of the study

	1.	2.	3.	4.	5.	6.	7.	8.
1.Financial difficulties at ages 0-3	1							
2.IL-6 at age 9	0.04[*]	1						
3.CRP at age 9	-0.00	0.40[***]	1					
4.Working memory at age 10	-0.08[***]	-0.06[***]	-0.05[**]	1				
5.BMI at age 9	0.02	0.26[***]	0.42[***]	-0.02	1			
6.Economic hardship at ages 3-9	0.08[***]	-0.00	-0.01	-0.01	0.02	1		
7.(Higher) SES at ages 0-3	-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

6.3.3 SEM and path models

6.3.3.1 Longitudinal models for the direct effects of financial difficulties and inflammation at age 9 years on working memory at age 10 years.

6.3.3.1.1 Longitudinal SEM model testing IL-6 at age 9 as mediator of the link between financial difficulties and working memory

Results from the SEM (Table 6-4) showed that in the unadjusted model, financial difficulties at ages 0-3 were related to worse working memory at age 10 years. In addition, the direct paths from financial difficulties to IL-6 and IL-6 to working memory were also significant.

In the fully adjusted models, the associations remained the same even after adjusting for covariates although the effect of the regression coefficient from financial difficulties to IL-6 became slightly smaller. From the covariates that were controlled for in that path (BMI, gender, economic hardship), none of them were associated with both the exposure (financial difficulties) and the exposure (in that case IL-6) and thus, the reduction in the effect size was only due to the adjustments made.

As mentioned previously, financial difficulties were SES-adjusted in our model. Financial difficulties at ages 0-3 years predicted worse performance in the working memory task at age 10 years (β=-0.08, SE=0.016), independently of early SES but also the other covariates. Furthermore, financial difficulties early in life were associated with higher IL-6 six years later at age 9 years (β=0.04, SE=0.014). Higher levels of IL-6 in childhood were also negatively related to working memory (β=-0.06, SE=0.016).

Concerning the paths from covariates (gender) to the main outcome (working memory), female gender was associated with better working memory (β=0.04, *SE*=0.016). As for the paths from covariates (BMI, economic hardship, gender) to the mediator, it was found that higher BMI and being female was related to higher IL-6 (β=0.26, *SE*=0.013; β=0.13, *SE*=0.014, respectively). However, parental perceptions of economic hardship between ages 3 to 9 years were not related to IL-6 at age 9 years.

Finally, a regression path from financial difficulties at ages 0-3 to economic hardship at age 3-9 years was fitted. Results showed that effects did not change. In fact, it was shown that early financial difficulties did not predict later economic hardship (β=0.00, *SE*=0.012).

6.3.3.1.2 Longitudinal SEM model testing CRP at age 9 as a mediator of the link between financial difficulties and working memory

With respect to the SEM model testing CRP as a mediator (see Table 6-5), results from the unadjusted model showed that financial difficulties at ages 0-3 years were associated with working memory at age 10 years. At the same time, higher levels of CRP at age 9 years were also associated with worse working memory performance although the association was weak. However, the direct path from financial difficulties to CRP was not significant.

In the fully adjusted model, results remained the same. Financial difficulties at ages 0-3 years predicted worse working memory at age 10 years (β=-0.08, *SE*=0.016). However, financial difficulties were not related to CRP at age 9 years. Additionally, higher levels of CRP predicted worse performance in the working memory task (β=-0.06, *SE*=0.016).

Regarding the relationship among the covariate (gender) that was adjusted for in the model and the main outcome, it was shown that being female was associated with better working memory (β=0.04, SE=0.016). Finally, analysis on the relationships between the other covariates (BMI, economic hardship, and gender) and the mediator showed that having a higher BMI and being female were related to increased levels of CRP (β=0.41, SE=0.012; β=0.18, SE=0.013, respectively).

6.3.4 Mediation analysis

IL-6 at age 9 years mediated part of the effect of early financial difficulties (age 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.

Table 6-4. Results of longitudinal SEM model testing IL-6 at age 9 years as a mediator of the link between financial difficulties and working memory at age 10 years (N=4525)

	Unadjusted model			Fully adjusted model		
	b	SE	95% CI	b	SE	95% CI
Direct paths[7] to working memory (WM) at age 10						
1. Financial difficulties at ages 0-3 -> WM	-0.15***	0.03	-0.204, -0.084	-0.15***	0.03	-0.204, -0.084
2. IL-6 at age 9-> WM	-0.03***	0.01	-0.052, -0.014	-0.04***	0.01	-0.055, -0.017
3.Female -> WM				0.07*	0.03	0.012, 0.121
Paths to IL-6 at age 9						
1. Financial difficulties at ages 0-3 ->IL-6	0.16***	0.05	0.066, 0.253	0.13**	0.05	0.045, 0.222,
2. BMI at age 9->IL-6				0.13***	0.01	0.119, 0.144
3.Economic hardship at ages 3-9 -> 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; BMI=Body Mass Index

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[7]Not shown in the table is the path from SES to financial difficulties, also modelled as explained int the fully adjusted model. SES was negatively related to financial difficulties (*b*=-.270, *SE*=0.014, *p*<.001, *β*=-.027).

Table 6-5. Results of longitudinal SEM model testing CRP at age 9 years as a mediation of the link between financial difficulties and working memory at age 10 years (N=4525)

	Unadjusted model			Fully adjusted model		
	b	SE	95% CI	b	SE	95% CI
Direct paths[8] to working memory (WM) at age 10						
1. Financial difficulties at ages 0-3 -> WM	-0.15***	0.031	-0.209, -0.088	0.15***	0.03	-0.209, -0.089
2. CRP at age 9 -> WM	-0.03***	0.01	-0.049, -0.012	-0.04***	0.01	-0.054, -0.017
3.Female -> WM				0.07	0.03	0.017, 0.127
Paths to CRP at age 9						
1. Financial difficulties at ages 0-3 -> CRP	0.03	0.05	-0.070, 0.119	-0.01	0.04	-0.095, 0.072
2. BMI at age 9-> CRP				0.22***	0.01	0.203, 0.228
3.Economic hardship at ages 3-9 -> CRP				0.00	0.00	-0.007, 0.008
4.Female -> CRP				0.52***	0.04	0.448, 0.599

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; CRP=C-reactive protein; BMI=Body Mass Index

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[8] As mentioned in the previous footnote, a path from SES to financial difficulties (not showing in the table) was also fitted in the fully adjusted models. Results showed that higher SES is negatively related to financial difficulties (*b*=-.0270, *SE*=0.014, p<.001, *β*=-.027)

6.3.5 Sensitivity analysis

Throughout the analysis, children with a reported infection at the time the blood samples were taken were excluded, however, a sensitivity analysis was also carried out where the SEM (fully adjusted model) for CRP was refitted after participants with CRP>10 mg/L (N=32) were excluded. Results did not change as early financial difficulties still predicted worse working memory (b=-0.15, SE=0.031, p<.001, β=-0.08); however, those 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)

Regarding the second sensitivity analysis (see Table 6-6) on data without children who were taking any medication, it was found that results did not change. Financial difficulties predicted worse working memory (β=-0.07, SE=0.017) and higher levels of IL-6 (β=0.04, SE=0.015). Higher levels of IL-6 also predicted worse performance in the working memory task (β=-0.06, SE=0.017). Concerning the results for CRP, those did not change in the model using the analytic sample without children who were taking medication. Financial difficulties early in life did not predict CRP in childhood (β=-0.01, SE=0.014) but they predicted worse working memory (β=-0.07, SE=0.017) again in childhood. Finally, higher levels of CRP were associated with worse working memory (β=-0.05, SE=0.017).
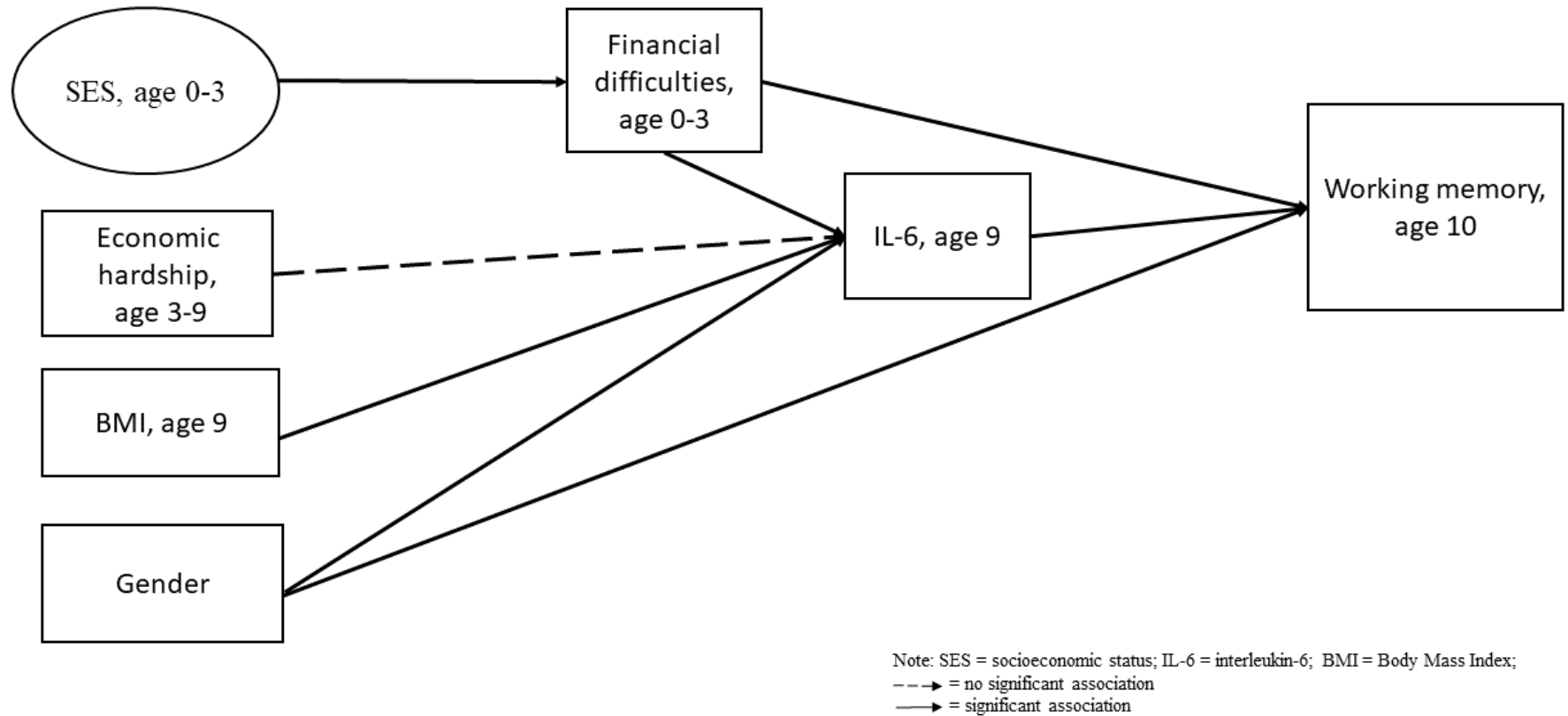
Figure 6-1. Results of final SEM and path analysis model for IL-6 at age 9 years as tested in this thesis

Table 6-6. Sensitivity analysis on data without children who were taking medication (N=4057). Results for IL-6 (fully adjusted model).

	b	SE	95% CI
Direct paths[9] to working memory (WM) at age 10			
1. Financial difficulties at ages 0-3-> WM	-0.14***	0.032	-0.197, -0.081
2. IL-6 at age 9-> WM	-0.04***	0.01	-0.057, -0.016
3.Female -> WM	0.08**	0.03	0.023, 0.138
Paths to IL-6 at age 9			
1. Financial difficulties at ages 0-3 ->IL-6	0.13**	0.05	0.036, 0.222
2. BMI at age 9 ->IL-6	0.13***	0.01	0.118, 0.145
3.Economic hardship at ages 3-9-> IL-6	-0.00	0.00	-0.010, 0.006
4.Female -> IL-6	0.36***	0.04	0.278, 0.449

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; IL-6=Interleukin 6 (in quintiles); BMI=body mass index

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[9] 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*=-0.269, *SE*=0.015, *p*<.001, *β*=-0.27).

6.4 Conclusions

This study examined if early financial difficulties (ages 0-3 years) are associated with poorer EF in childhood as measured by a working memory task. It also explored whether experiences of financial strain are associated with inflammation during childhood which in turn, might have an effect on working memory one year later. The study explored the direct pathways from financial difficulties to working memory and the indirect pathway from financial difficulties to working memory via inflammation while adjusting for several individual- and family-level covariates such as gender, BMI, and economic hardship.

Two longitudinal models were carried out to explore the association between financial difficulties and working memory through inflammation (IL-6 and CRP). Results showed that early financial difficulties predicted poorer working memory in childhood. Furthermore, having financial difficulties early in life was associated with higher levels of IL-6 in childhood; however, no association was found between financial difficulties and CRP. As for the association between the inflammatory markers and the main outcome, both IL-6 and CRP were negatively related to working memory. These results support the first aim of the study and confirm the initial hypotheses that there would be an association between early financial difficulties and EF in childhood and also an association between inflammation and EF at the same age.

With respect to the second study aim, as hypothesized, inflammation, as measured by IL-6, mediated part of the relationship between SES-adjusted financial difficulties early in life and poorer working memory in childhood. This is an important

finding despite the small effect sizes as research on this particular topic in the

general child population is very limited. However, no mediation by CRP was found.

Although the data analysis did not allow to clarify whether higher levels of

inflammation lead to impaired cognition or the reverse and as no assumptions can

be made for a causal link between these findings are important the two, it is certainly

concluded that there is a relationship between inflammation and EF.

Chapter 7. Longitudinal associations between early life SES and adolescent IQ and whether this is explained by earlier and concurrent inflammation.

7.1 Introduction

This chapter explores if SES early in life (age 0-3 years) is related to lower IQ in adolescence and whether this relationship can be explained by earlier (age 9 years) and concurrent (age 15 years) inflammation. In the models presented, several individual- and family-level predictors of IQ and inflammation were also examined including gender, BMI, and an earlier measure of intelligence at age 8 years.

This chapter begins by summarising the research aims of the study followed by the description of the methodology, the results section, and the conclusions.

7.1.1 Study aims

Previous literature has shown that SES accounts for much of the variance in cognitive outcomes. For example, some studies show that children from families with lower SES have been shown to score lower on various standardised tests of IQ (Hanscombe et al., 2012; Turkheimer et al., 2003; Von Stumm & Plomin, 2015). Furthermore, increased inflammation levels measured with CRP were associated with lower IQ in childhood (Mackinnon et al., 2018) and lower verbal ability in adolescence (Adelantado-Renau et al., 2020). Several potential family and home environment pathways such as parental involvement behaviours (Guo & Harris, 2000; Wolf & McCoy, 2019; Zhang et al., 2020), family relationships (Conger et al., 2010) and the home atmosphere (Seidler & Ritchie, 2018) may account for the

association between SES and cognitive development but this is the first study to explore if the biological mechanism of inflammation could explain the relationship between SES and IQ in youth.

The first aim of the study was to investigate the longitudinal associations between early family SES (ages 0-3), inflammation (IL-6 and CRP) at age 9 years and IQ at age 15 years after adjusting for key confounding variables. It was hypothesized that higher family SES would be associated with higher performance on an intelligence test in adolescence as shown in previous studies (Feinstein & Bynner, 2004; Von Stumm & Plomin, 2015). It was also hypothesized that SES would be related to both IL-6 and CRP at age 9 years and that IL-6 and CRP at age 9 years would in turn be related to IQ at age 15. These associations were also tested with inflammation (CRP) being measured at age 15 apart from age 9 years.

The second aim of the study was to explore whether the relationship between early SES and IQ in adolescence is *mediated* by earlier (IL-6 and CRP at age 9) and/or concurrent (CRP at age 15) inflammation. As described above, it was hypothesized that early SES would be directly associated with IQ in adolescents irrespective of adjustments and also indirectly through inflammation – a physiological pathway through which SES may exert its effect on cognition.

7.2 Method

7.2.1 Participants

Information on the participants and the ALSPAC study has been described in chapter 3. Also described in the previous studies of this thesis (see chapters five and six), the 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.

7.2.2 Measures

7.2.2.1 Inflammatory markers

In this study, inflammation in childhood and adolescence was measured with IL-6 and CRP at age 9 years and CRP at age 15 years. Details about the collection of the blood samples are described in chapter 3.

7.2.2.2 Socioeconomic status

SES was measured as a latent variable using information from five observed variables during the first 3 years of the child's life: maternal education, paternal social class, overcrowding, housing tenure and financial difficulties. Information on how these were recoded and manipulated can be found in chapter 3, section 3.2.1.

7.2.2.3 IQ (intelligence quotient)

This study used two measures of total IQ: 1) IQ at age 8 as a covariate and 2) IQ at age 15 as the main outcome. Details on the measures can be found in chapter 3, section 3.3.3. Both measures were continuous variables ranging from 46 to 151 (age 8) and from 55 to 130 (age 15).

7.2.2.4 Covariates

The covariates of the study consisted of several individual- and family- level variables including gender, BMI at ages 9 and 15 and IQ at age 8 years, as described above. Information on the covariates and how they were measured can be found in chapter 3, section 3.3.3.1.

7.2.3 Analytic strategy and hypotheses

All analyses were performed in Stata 16.1 (Stata Corporation, College Station, TX, 1997) and Mplus (version 8) (Muthén & Muthén, 2017). First, a CFA in Mplus was conducted 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 (see factor loadings in Table 5-1 in previous chapter 5). Factor scores were saved and used as a continuous variable in the analysis. (The indices of fit for the CFA model are described in chapter five, section 5.2.3)

Following this, several SEMs extended to path analytic models were conducted to test the relationship between early SES, inflammation, and IQ at age 15 years. Three models in total were run: two longitudinal models using IL-6 and CRP respectively at age 9 years as mediators and one cross-sectional model using CRP at age 15 years as the mediator. In all models, a path of SES on IQ was specified, along with a direct path from IQ at age 8 years on IQ at age 15 years to account for differences in intelligence scores by age. The models also controlled for covariates (BMI and gender) and investigated the extent to which each of the observed associations between SES and IQ in adolescence were mediated by inflammation. Each inflammatory marker was tested separately to avoid multicollinearity (For illustration, Figures 7-1 to 7-3 shows the SEM testing mediation by IL-6 and CRP at both timepoints as fitted). To assess model fit, the following indices of fit were used: 1) CFI, 2) SRMR and 3) 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 for all 3 models(CFI=1.00, SRMR=0.01, RMSEA=0.01, 90% CI=0.000, 0.031, for IL-6; CFI=1.00, SRMR=0.01,

RMSEA=0.04, 90% CI=0.018, 0.054, for CRP at age 9 years ; CFI=1.00, SRMR=0.01, RMSEA=0.01, 90% CI=0.000, 0.035 for CRP at age 15 years).

To conduct mediation analysis using SEM techniques in a path analysis framework such as the one provided by Mplus, an explicit test for the indirect effect of the predictor (SES) via the mediating variable (an inflammatory marker) was fitted into the SEM 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. Robust methods to estimate the indirect effects were used by calculating bootstrapped bias-corrected confidence intervals for each parameter tested, as advised by MacKinnon (2008) and Hayes (2013, 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. Residual covariances among predictors were also included and produced the study's estimates using full information maximum likelihood. Also, two sensitivity analysis were carried out to explore: a) if results change when participants with CRP>10 mg/L (N=32 at age 9 and N=38 at age 15 years) are excluded as it is likely that those CRP levels indicate infection and b) if results are different for children who were not taking medication (N=4057).

7.3 Results

7.3.1 Descriptives

The descriptive statistics of the study are shown in Table 7-1. As can be seen, children in the analytic sample had low levels of IL-6 and CRP at age 9 years as well

as age 15 years and had an average BMI and IQ between ages 8 and 15 years. Regarding the observed SES variables, the majority of the mothers in the analytic sample did not have a university degree (83%); however, more than half of the fathers belonged to the non-manual social classes (61%). Furthermore, although 73% of the mothers reported that they had difficulties in affording basic items for their babies like food, heating, and clothing, most of them lived in houses that they owned outright or with a mortgage (83%) and which were not overcrowded (94%). Then, a bias analysis was also conducted (Table 7-2) to investigate the differences between the analytic and the non-analytic sample. Results showed that children in the analytic sample had significantly lower levels of IL-6 and CRP at both ages 9 years but there was not a difference for the levels of CRP at age 15 years between the two samples. Furthermore, the children in the analytic sample had lower BMI and had scored higher in the IQ test at both ages than those in the non-analytic sample. Regarding the SES of the two samples, the parents in the analytic sample were more likely to have a university degree, belong to higher social classes, live in less overcrowded places, and own their home. Finally, parents in the analytic sample had fewer difficulties affording basic items for their children compared to the parents not in the analytic sample.

Table 7-1. Descriptive statistics of the main variables of the study (N=4525)

	Continuous	
	n	M(SD)
IL-6 (pg/mL) **at age 9**	4,525	1.21(1.48)
CRP (mg/L) **at age 9**	4,525	0.63(1.94)
CRP 15 (mg/L) **at age**	2,210	1.22(3.78)
IQ at age 15	2,771	92.49(12.91)
IQ at age 8	3,888	105.20(16.15)
BMI at age 9	4,474	17.58(2.77)
BMI at age 15	2,996	21.23(3.35)
	Categorical	
	N	%
Gender		
Male	2,296	50.79
Female	2,225	49.21
SES at ages 0-3		
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
Financial difficulties		
No difficulties	1,211	26.76
Difficulties	3,314	73.24

Note. IL-6=interleukin 6; CRP=C-reactive protein; BMI=Body Mass Index.

Table 7-2. Bias analysis of study variables between the analytic and the non-analytic sample

	Analytic sample (n=4525)		Non-analytic sample (n=10920)		Test
	Continuous				
	N	**M(SD)**	**n**	**M(SD)**	**T**
IL-6 (pg/mL) **at age 9**	4,525	1.21(1.48)	547	1.94(2.22)	10.17***
CRP (mg/L) **at age 9**	4,525	0.63 (1.94)	557	2.22(5.90)	13.34***
CRP 15(mg/L) **at age**	2,210	1.22(3.78)	1,278	1.27(3.80)	0.43
IQ at age 8	3,888	105.20(16.15)	3,460	102.60(16.85)	-6.74***
IQ at age 15	2,771	92.49(12.91)	2,184	91.29(13.10)	-3.23***
BMI at age 9	4,474	17.58 (2.77)	3,161	17.91(3.09)	4.80***
BMI at age 15	2,996	21.23(3.35)	2,450	21.72(3.81)	5.10***
	Categorical				
	N	**%**	**N**	**%**	
Gender					0.98
Male	2,296	50.79	5,339	51.67	
Female	2,225	49.21	4,994	48.33	
SES at ages 0-3					
Maternal education					90.27***
Degree	703	16.91	906	10.87	
Other	3,454	83.09	7,430	89.13	

Paternal social class					76.92***
Non-manual	2,358	61.55	3,797	52.84	
Manual	1,473	38.45	3,389	47.16	
Overcrowding					20.33***
Not overcrowded	3,489	93.77	5,272	91.23	
Overcrowded	232	6.23	507	8.77	
Housing tenure					315.67***
Owning the home	3,474	83.35	6,411	68.69	
Not owning the home	694	16.65	2,922	31.31	
Financial difficulties					320.27***
No difficulties affording things	1,211	26.76	1,591	14.57	
Difficulties affording things	3,314	73.24	9,329	85.43	

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

Note. IL-6=interleukin 6; CRP=C-reactive protein; BMI=Body Mass Index.

7.3.2 Correlations of main study variables

The correlations among the main study variables are shown in Table 7-3.
Higher SES was related to lower levels of IL-6 at age 9 years and CRP at age 15
years but not to CRP at age 9 years. Furthermore, higher SES was associated with
higher IQ in adolescence (age 15 years). Additionally, higher early SES was
associated with higher IQ in childhood (age 8 years).

Higher CRP (but not IL-6) at age 9 was associated with lower IQ at age 15
although the relationship was weak. Both CRP and IL-6 at age 9 were related to
lower IQ at age 8. Interestingly, there was not a significant association between CRP
and IQ at the same age (15).

Regarding the associations among the covariates and SES, inflammation and
IQ, higher BMI at both timepoints was associated with lower IQ at age 8 and 15 and
higher inflammation (CRP and IL-6) at both ages. Being female was not associated
with SES. It was related to more inflammation (CRP and IL-6) at age 9 but not at age
15 and to lower IQ at age 15 but not age 9.

Table 7-3. Correlations of the main variables of the study

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1.SES at ages 0-3	1								
2.IL-6 at age 9	-.06***	1							
3.CRP at age 9	-.03	.45***	1						
4. CRP at age 15	-.07**	.10***	.30***	1					
5.IQ at age 8	.35***	-.05**	-.07***	-.05*	1				
6.IQ at age 15	.35***	-.03	-.04*	-.04	.60***	1			
7. BMI at age 9	-.07***	.24**	.44***	.27***	-.06***	-.05*	1		
8. BMI at age 15	-.07***	.19***	.32***	.31***	-.08***	-.09***	.79***	1	
9.Female	-.02	.13***	.20***	-.03	-.01	-.05**	.08***	.12***	1

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

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

7.3.3 SEM and path models

7.3.3.1 Longitudinal and cross-sectional SEM models for the direct effects of early SES and inflammation at age 9 and 15 years on IQ at age 15 years

7.3.3.1.1 Longitudinal SEM model testing IL-6 at age 9 as mediator of the link between SES and IQ at age 15

As can be seen in Table 7-4, results in the unadjusted model showed that higher SES at ages 0-3 years was related to higher IQ at age 15 years. SES was also related to IL-9 at age 9 years; however, the direct path from IL-6 to IQ was not significant.

In the fully adjusted model, results remained the same, although the size of the regression coefficients of the paths from the exposure to the outcome (SES-IQ link) and from the exposure to the mediator (SES-IL-6 link) became smaller. For the direct path from SES to IQ at age 15 years, the size of regression coefficient was reduced greatly after controlling for earlier IQ at age 8 years which is both related to SES and later IQ indicating that it might have played a confounding role in that relationship. As for the association between SES and IL-6 this was partly explained by BMI which was related to both SES and IL-6 and might have played a confounding role. In more detail, higher SES at ages 0-3 predicted higher IQ at age 15 years (β=0.15, *SE*=0.016), independently of other covariates. Higher SES was also associated with lower levels of IL-6 (β=-0.04, *SE*=0.014). However, IL-6 at age 9 was not related to IQ at age 15.

Regarding the paths from the covariates (IQ at age 8, BMI at age 9 and female gender) to the main outcome (IQ at age 15), it was found that higher IQ at

age 8 predicted higher IQ at age 15 (β=0.55, *SE*=0.016) and being female was

negatively related to IQ (β=-0.04, *SE*=0.015). Moreover, higher BMI and being

female were related to higher levels of IL-6 (β=0.23, *SE*=0.013; β=0.11, *SE*=0.015,

respectively).

7.3.3.1.2 Longitudinal SEM model testing CRP at age 9 as a mediator of the link between SES and IQ at age 15

As shown in Table 7-5 and similar to the previous model, results in the

unadjusted model showed that higher SES at ages 0-3 years was related to higher

IQ at age 15 years, however, the direct paths from SES to CRP at age 9 years and

from CRP to IQ were not significant.

In the fully adjusted model, the results were unchanged although the effect

size of the SES-IQ association became smaller due to adjusting for earlier IQ at age

8 years which might have played a confounding role, as also explained in the

previous model. Specifically, higher SES at ages 0-3 years predicted higher IQ at

age 15 years (β=0.15, *SE*=0.016). However, contrary to that found for IL-6, early

SES was not related to CRP. Similar to the results for IL-6, CRP at age 9 years did

not predict IQ at age 15 years. Furthermore, higher IQ at age 8 years was positively

related to higher IQ six years later (β=0.55, *SE*=0.014) and being female was

negatively related to IQ (β=-0.04, *SE*=0.015).

Concerning the paths from the covariates (BMI at age 9 and female gender)

to CRP, having a higher BMI and being female were related to higher levels of CRP

in childhood (=0.42, *SE*=0.014; β=0.16, *SE*=0.013, respectively).

7.3.3.1.3 Cross-sectional SEM model testing CRP at age 15 as a mediator of the link between SES and IQ at age 15

As shown in Table 7-6, results from the unadjusted model showed that SES at ages 0-3 years was related to IQ at age 15 years. Furthermore, early SES was also related to CRP at age 15 years however, CRP was not related to IQ at the same age.

In the fully adjusted model, results remained unchanged as in the previously tested models, although the regression coefficient of the direct path from SES to IQ and from SES to CRP became smaller after adjusted for covariates. Similar to the previous models, the effect size for the relationship between SES and IQ at age 15 years was reduced greatly after adjusting for earlier IQ at age 8 years and as IQ in childhood was related to both early SES and IQ in adolescence, this indicates a potential confounding role of early IQ in the above link. As for the early SES-CRP at age 15 years link, the regression coefficient of that link was partly explained after adjusting for BMI and gender. In more detail, higher SES predicted higher IQ in adolescence (β=0.15, SE=0.016). As for the direct path from concurrent CRP and IQ, results showed that there was not any association between the two. In contrast to the findings for CRP in childhood, higher SES at ages 0-3 was significantly negatively related to CRP in adolescence (β=-0.04, SE=0.020).

Furthermore, age 8 IQ predicted age 15 IQ (β=0.55, SE=0.014) and being female was negatively related to higher IQ (β=-0.04, SE=0.015).

Regarding the paths from the covariates (BMI at age 15, female gender) to the mediator (CRP at age 15), higher BMI was related to higher CRP at the same

age (β=0.32, *SE*=0.021) and being female was negatively related to elevated levels of CRP (β=-0.07, *SE*=0.020).

7.3.4 Mediation analysis

Results from the mediation analysis showed that neither of the inflammatory markers at either age 9 years or age 15 years mediated the relationship between early SES and IQ in adolescence. In the longitudinal models there was no mediation by IL-6 in childhood (indirect effect: *b*=-0.010, *SE*=0.017, *p*>0.05, *95% CI*=-0.052, 0.018, β=0.00; total effect: *b*=4.355, *SE*=0.451, *p*<0.001, *95% CI*=3.476, 5.231, β=0.15; direct effect: *b*=4.365, *SE*=0.452, *p*<0.001, *95% CI*=3.487, 5.254, β=0.15). Similarly, there was no mediation by CRP at age 9 years (indirect effect: *b*=0.001, *SE*=0.007, *p*>0.05, *95% CI*=-0.006, 0.025, β=0.00; total effect: *b*=4.351, *SE*=0.450, *p*<0.001, *95% CI*=3.469, 5.222, β=0.15; direct effect: *b*=4.350, *SE*=0.450, *p*<0.001, *95% CI*=3.463, 5.222, β=0.15).

Regarding the cross-section model, there was no mediation by concurrent CRP at age 15 years either (indirect effect: *b*=0.009, *SE*=0.023, *p*>0.05, *95% CI*=-0.031, 0.068, β=0.00; total effect: *b*=4.349, *SE*=0.451, *p*<0.001, *95% CI*=3.457, 5.219, β=0.15; direct effect: *b*=4.340, *SE*=0.451, *p*<0.001, *95% CI*=3.446, 5.205, β=0.15).

Table 7- 4. **Results of longitudinal mediation model testing IL-6 at age 9 years as mediator of the link between SES and IQ at age 15 years (N=4525)**

	Unadjusted model			Fully adjusted model		
	b	SE	95% CI	b	SE	95% CI
Direct paths to IQ at age 15						
1. SES at ages 0-3 -> IQ	9.73***	0.50	8.785, 10.736	4.37***	0.45	3.487, 5.254
2. IL-6 at age 9 -> IQ	-0.07	0.26	-0.569, 0.438	0.14	0.22	-0.288, 0.562
3. IQ at age 8 -> IQ				0.44***	0.01	0.417, 0.467
4.Female -> IQ				-0.98**	0.39	-1.725, -0.173
Paths to IL-6 at age 9						
1. SES at ages 0-3 -> IL-6	-0.11***	0.03	-0.160, -0.053	-0.07**	0.03	-0.127, -0.023
2. BMI at age 9 -> IL-6				0.07***	0.00	0.062, 0.077
3.Female -> IL-6				0.19***	0.00	0.140, 0.238

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; IL-6=Interleukin 6; BMI=Body Mass Index

Table 7-5. Results of longitudinal mediation model testing CRP at age 9 years as mediator of the link between SES and IQ at age 15 years (N=4525)

	Unadjusted model			Fully adjusted model		
	b	SE	95% CI	b	SE	95% CI
Direct paths to IQ at age 15						
1. SES at ages 0-3 -> IQ	9.71***	0.50	8.780, 10.719	4.35***	0.45	3.463, 5.222
2. CRP at age 9 -> IQ	-0.36	0.20	-0.762, 0.018	0.08	0.17	-0.271, 0.405
3. IQ at age 8 -> IQ				0.44***	0.01	0.417, 0.467
4. Female -> IQ				-0.97**	0.40	-1.725, -0.174
Paths to CRP at age 9						
1. SES at ages 0-3 -> CRP	-0.06	0.04	-0.136, 0.007	0.02	0.03	-0.047, 0.079
2. BMI at age 9-> CRP				0.17***	0.01	0.163, 0.185
3. Female -> CRP				0.37***	0.03	0.311, 0.428

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; IL-6=Interleukin 6; BMI=Body Mass Index

Table 7-6. Results of cross-sectional mediation model testing CRP at age 15 years as mediator of the link between SES and IQ at age 15 years (N=4525)

	Unadjusted model			Fully adjusted model		
	b	**SE**	**95% CI**	**b**	**SE**	**95% CI**
Direct paths to IQ at age 15						
1. SES at ages 0-3 -> IQ	9.702***	0.49	8.738, 10.645	4.34***	0.45	3.446, 5.205
2. CRP at age 15 -> IQ	-0.239	0.24	-0.719, 0.215	-0.09	0.20	-0.470, 0.324
3. IQ at age 8 -> IQ				0.44***	0.01	0.417, 0.467
4.Female -> IQ				-0.95*	0.40	-1.768, -0.179
Paths to CRP at age 15						
1. SES at ages 0-3 -> CRP	-0.16**	0.05	-0.253, -0.056	-0.10*	0.05	-0.198, -0.008
2. BMI at age 15 -> CRP				0.10***	0.01	0.091, 0.117
3.Female -> CRP				-0.16***	0.05	-0.248, -0.071

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

Note. b=Unstandardised regression coefficient; SE=Standard error; CI=Confidence interval; IL-6=Interleukin 6; BMI=Body Mass Index
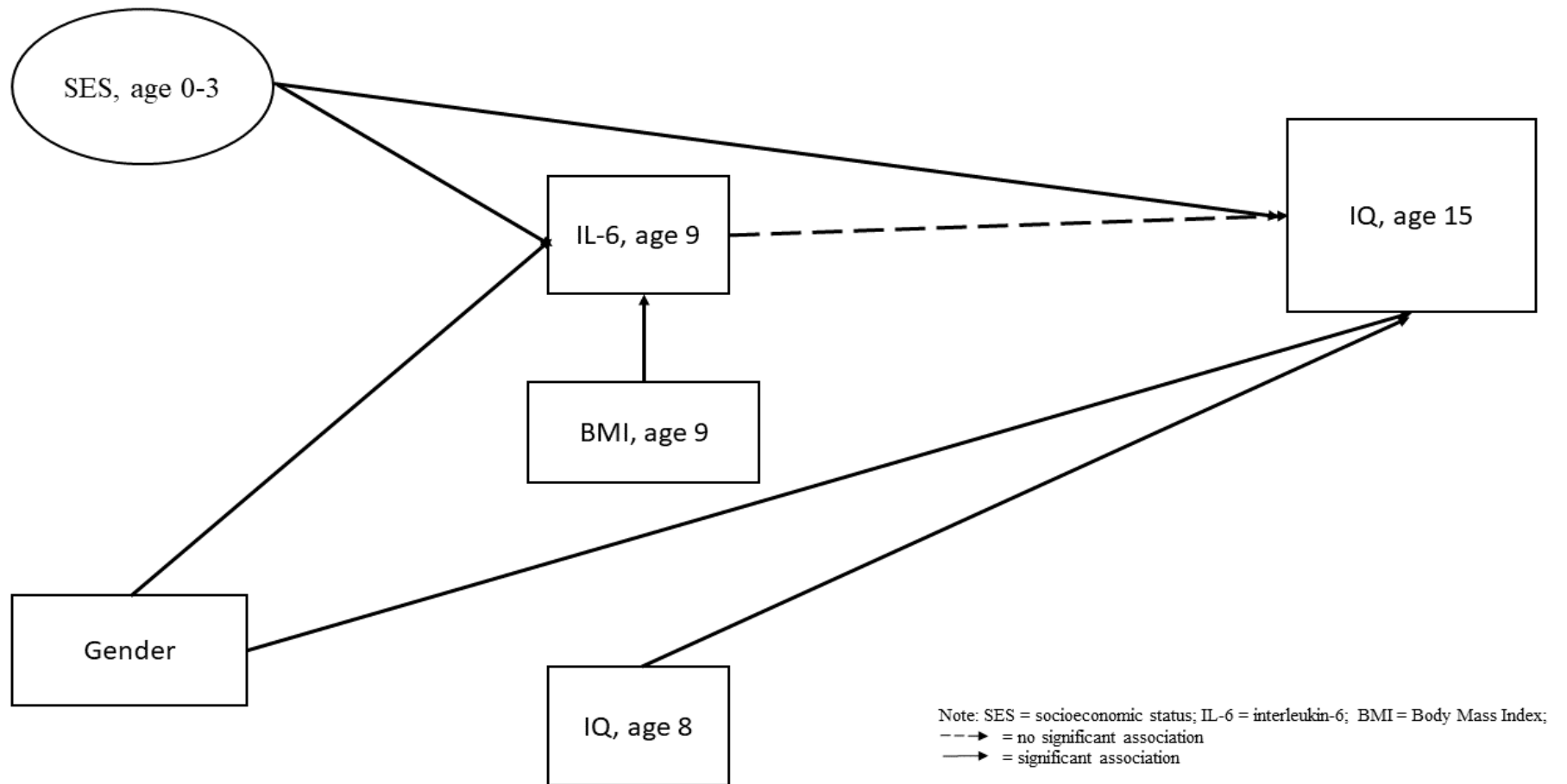
Figure 7-1. Results of final SEM and path analysis model for IL-6 at age 9 years as tested in this thesis
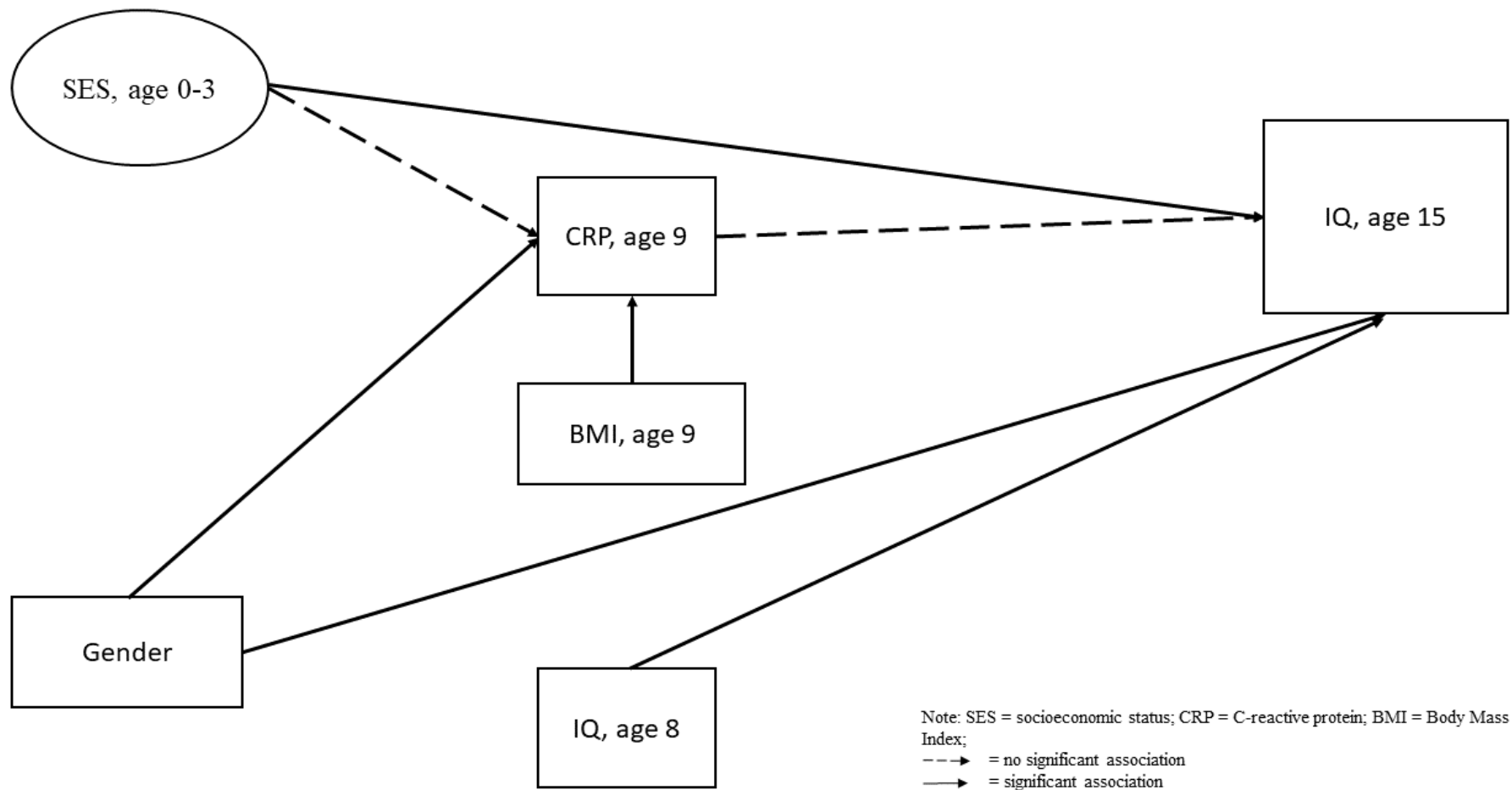
Figure 7-2. Results of final SEM and path analysis model for CRP at age 9 years as tested in this thesis
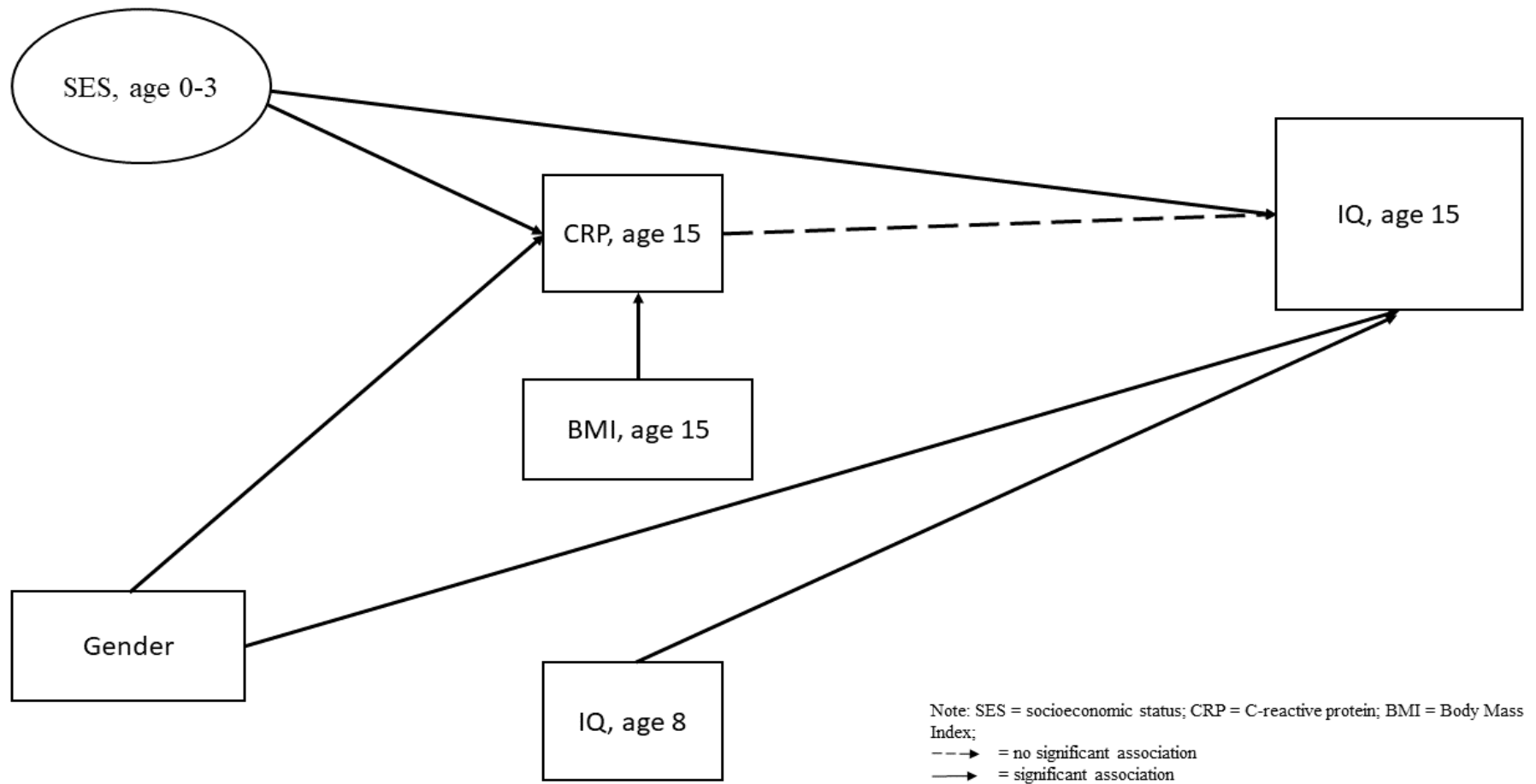
Figure 7-3. Results of final SEM and path analysis model for CRP at age 15 years as tested in this thesis

7.3.5 Sensitivity analysis

Two additional sensitivity analyses were conducted excluding from the sample a) participants with reported CRP>10 mg/L (N=32 for age 9 years and N=38 for age 15 years), as this is likely to indicate infection and b) participants who were taking any medication at age 9 years (N=438 resulting to an analytic sample of N=4,057) even though children with a reported infection at the time the blood samples were taken were excluded.

For the first sensitivity analysis, results did not change in the fully adjusted longitudinal model for CRP at age 9 years after excluding those with CRP>10 mg/L. Higher SES predicted higher IQ at age 15 years (b=4.35, SE=0.45, p<.001, β=0.15). However, CRP in childhood was not related to IQ in adolescence and the relationship between early SES and IQ at age 15 years was not mediated by CRP at age 9 years.

Findings from the fully adjusted cross-sectional model for CRP at age 15 years showed that although results remained the same as in the main analysis with higher SES predicting higher IQ (b=4.34, SE=0.45, p<.001, β=0.15), this was not true for the SES- CRP link at age 15 years. It was found that after excluding those with CRP levels above 10 mg/L, the effect of SES on CRP in adolescence was explained. Also, as shown in the main analysis, there was no mediation by CRP in the cross-sectional model either.

Regarding the results from the sensitivity analysis on data without children who were taking any medication, it was shown that findings in the fully adjusted model remained unchanged in both the longitudinal and cross-sectional models. In the longitudinal model testing IL-6 as a mediator, it was shown that higher SES

predicted higher IQ at age 15 years (b=4.26, SE=0.47, p<.001, β=0.15) and also that SES was negatively related to IL-6 (b=-0.08, SE=0.03, p<.001, β=-0.04). However, IL-6 did not predict IQ and there was no mediation by IL-6.

In the other fully adjusted model testing CRP as a mediator, it was shown that once again, higher SES was associated with higher IQ (b=4.24, SE=0.47, p<.001, β=0.15), however, SES was not related to CRP and in turn, CRP did not predict IQ in adolescence either. Consequently, there was no mediation by CRP.

Finally, results from the fully adjusted cross-sectional model testing CRP at age 15 years as mediator showed that higher SES predicted higher IQ (b=4.24, SE=0.47, p<.001, β=0.15) and also that higher SES still predicted lower CRP in adolescence (b=-0.11, SE=0.05, p<.001, β=-0.05). Furthermore, consistent with the results in the main analysis, CRP was not related to IQ at the same age and it was not found to explain the relationship between SES and IQ either.

7.4 Conclusions

This study explored if early SES (age 0-3 years) is associated with inflammation in childhood (and adolescence) and IQ in adolescence. In addition, for the first time, it tested whether inflammation could explain the relationship between SES and IQ. The study investigated the direct pathways from early SES to IQ and the indirect pathways from SES to IQ through inflammation in both longitudinal and cross-sectional models, while adjusting for covariates including BMI, gender, and an earlier measure of IQ at age 8 years.

Two longitudinal models were conducted for the association between SES and IQ through inflammation as measured by IL-6 and CRP at age 9 years. As expected, higher early SES was associated with higher IQ scores in adolescence

irrespective of the covariates. Consistent with findings from previous research discussed in chapter 5, it was also shown that higher SES was inversely related to IL-6 but it was not related to CRP in childhood. In contrast to the initial hypothesis, earlier IL-6 and CRP did not predict later IQ in adolescence.

In the cross-sectional model that tested the association between SES and IQ through concurrent inflammation as measured by CRP at age 15 years, it was also found that higher SES was directly related to higher IQ scores. However, CRP did not predict IQ at the same age. Interestingly though, early SES was directly related to CRP in adolescence even after adjusting for BMI at the same age (age 15 years). This is a new finding considering the non-significant association found between SES and CRP at an earlier age.

Concerning the second aim of the study which was to explore whether early SES is related to IQ through early and concurrent inflammation (ages 9 and 15, respectively), it was found that there was no mediation by childhood IL-6 and CRP nor by concurrent adolescent CRP. Although it was hypothesized that there would be significant mediation by inflammation at either age, these findings are in line with a recent study where it was suggested that inflammation by IL-6 and CRP was unlikely to explain the variation between IQ explained by early life adversity (Holland et al., 2020). Similarly, inflammation was not able to explain the variation in IQ explained by SES in this study, suggesting that there might be other biological and cognitive pathways that explain the relationship between SES and IQ.

Chapter 8. Discussion & conclusions

In this chapter, three main components are discussed. In the first part, a summary and a discussion of the key findings of this research are presented. In the second part, the strengths and limitations of the study are discussed and, finally, in the third part, the recommendations for future work and policy implications are considered.

8.1 Summary and discussion of key findings

The present study aimed to examine the role of inflammation as an important biological pathway linking family SES, measured objectively and subjectively, and cognitive outcomes in children and adolescents within a large longitudinal community sample. The findings of this research suggest early SES including experiencing multiple low SES-related factors may influence children's health by triggering the elevation of inflammation levels in the blood. They also indicate that financial difficulties, one indicator of SES, may affect children's EF (especially working memory), not only directly, but also indirectly, by raising levels of inflammation in the body. These pathways had not been tested before in the child general population until now and thus, this research highlights the importance of understanding the mechanisms that underlie the effect of socioeconomic disadvantage on childhood health and cognition, which have implications in both theory and policy (Hertzman et al., 1999). The first empirical study (Chapter 5) sought to explore whether early family SES was associated with higher inflammation in childhood and subsequently, whether upsetting childhood experiences could explain that relationship. Investigating this allowed for the identification of the direct and indirect mechanisms that link SES and childhood upsetting events to health outcomes in children.

Findings revealed that early SES, the main predictor of the study, was related to

higher levels of inflammation in middle childhood (age 9 years) as measured by IL-6.

Despite much evidence for the association between SES and inflammation in

adulthood (Muscatell et al, 2018), this thesis adds to the existing literature as only a

handful of studies have examined the effect of SES on inflammation in childhood

(Dowd et al., 2010; Howe et al., 2010; Kuhlman et al., 2019; Murasko, 2008; Pietras

& Goodman, 2013; Schmeer & Yoon, 2016). Although the effect of SES on IL-6 was

small, this is in line with evidence from a recent meta-analysis by Kuhlman and

colleagues (2019). They found that the association between early-life disadvantage

and both CRP and IL-6 across childhood was very modest, with particularly small

effect sizes for links in middle childhood compared to during infancy and

adolescence. In this study, no similar effects were found for CRP, the other

inflammatory marker of the study. But, according to more recent studies on the topic,

the results that were produced were mixed. For example, the lack of evidence for the

association between parental SES and CRP in childhood has been previously

supported by studies that found that SES disparities did not relate to CRP gradients

in children (Gimeno et al., 2007). However, a recent study found that poorer

socioeconomic conditions were associated with higher CRP throughout the first

decade of life (Soares et al., 2020).

Looking at the indirect pathway that was explored in the same chapter, early

SES was associated with childhood upsetting events which in turn predicted

childhood inflammation. Low SES has been linked to greater exposure to stressful

life events throughout childhood and adolescence in previous studies (Chandler et

al., 1985; Gad & Johnson, 1980; Gillum et al., 1984) and this is probably due to

children from disadvantaged families being more likely to grow up in environments

that are uncontrollable and unpredictable (Evans, 2004). It has also been evident that chronic exposure to such experiences leads to an elevation in inflammation levels due to chronic stimulation of the sympathetic nervous system, as well as progressive down-regulation of key anti-inflammatory pathways, such as the Hypothalamic-Pituitary-Adrenal (HPA) axis and the parasympathetic nervous system. Moreover, the HPA axis plays a major role in the perception of and response to adverse experiences (Hertzman, 1999; Shonkoff et al., 2009). This thesis drew on Miller et al.'s (2011) biological embedding model for early adversity which suggests that stress during childhood activate proinflammatory tendencies and showed that upsetting events from early to middle childhood can have a more immediate short-term effect on children's health. Previous studies that explored the effects of low SES on inflammation through adverse life events in childhood have been conducted mainly on the adult population (John-Henderson et al., 2016). Thus, this thesis makes an original contribution to the literature of child health as it links socioeconomic SES and childhood upsetting events with childhood inflammation.

The second empirical chapter (Chapter 6) of this thesis had another two research aims which were: (1) to explore whether family financial difficulties early in life predict poorer EF in childhood and (2) to examine whether this relationship was mediated by inflammation in childhood. The hypothesis was that family financial difficulties due to low SES would be related to inflammation in childhood which, in turn, would be related to EF in childhood.

First, it was found that early family financial difficulties as defined by parents' perception of difficulties in affording basic items for their children such as food, clothing, and other necessities (Burchinal et al., 2008; McLoyd, 1998) were related to working memory, a core component of EF. The current study built on previous

research by Raver and colleagues (2013) which found that financial strain was uniquely predictive of children's EF and the findings of this thesis also remained consistent with other studies that supported the association between financial strain and EF in children (Dickerson & Popli, 2018; Hackman & Farah, 2009). Also, it was found that financial difficulties were also predictive of higher inflammation at age 9 years which in turn, predicted worse working memory performance one year later, at age 10 years. Studies that explored the pathways that might explain the poverty-inflammation link have focused mainly on linking financial difficulties and child EF through cortisol (Blair et al., 2005, 2011; Obradovic et al., 2016) or allostatic load for adults working memory (Evans & Schamberg, 2009).

Hence, exploring the indirect pathway from financial difficulties to working memory through inflammation provided evidence for another important association that has not been tested before. These findings are of great importance as research on the particular topic at this stage in life is very limited. Thus, this study added to the existing literature by exploring the severe strain of worrying about having enough food to survive or being able to access basic life necessities as measured by parents' perceptions of financial strain in relation to children's working memory. This study also went beyond testing direct effects and explored whether inflammation could explain that relationship and it is the first study to provide evidence that children born to families struggling to make ends meet show subsequent deficits in working memory, via increased inflammation in the blood. In addition, this study addressed a central empirical question in the literature of child development regarding whether parents' perception of financial strain is uniquely related to children's EF even after adjusting for SES (Raver et al., 2013). Given the importance of the length and timing of the family exposure to economic hardship for child

cognitive outcomes (Bradley & Corwyn, 2002; Hackman et al, 2015; McLoyd, 1998), this study also accounted for exposures to economic hardship from the age of 3 to the time of measurement of inflammation at age 9 years.

In the third empirical chapter (Chapter 7), the last two research aims of this research were explored. The first was to: 1) explore the direct relationship between early SES at ages 0-3 years and IQ in adolescence at age 15 years and 2) further explore whether these are related via earlier (age 9 years) and concurrent (age 15 years) inflammation. The hypothesis was that early SES would be related to IQ in adolescence via inflammation.

Findings also supported previous evidence that SES is related to cognitive ability as measured by IQ. A direct path from early SES to IQ in adolescence in cross-sectional and longitudinal models was found, which is in line with previous literature that has provided evidence for the association between low SES and lower IQ (Hanscombe et al., 2012; Turkheimer et al., 2003; von Stumm & Plomin, 2015). The findings from this study made an additional contribution by providing evidence for an association between early SES and CRP in adolescence (age 15 years) even after adjusting for BMI at the same age. This is a new and important finding considering the previous non-significant results for the association between early SES and CRP at an earlier age (Kokosi et al., 2020). Although SES has been consistently found to be associated with IL-6 but not CRP in childhood in this thesis, it now seems that the magnitude of this relationship for CRP becomes larger and more apparent at an older age (Lam et al., 2021; Yang et al., 2017). This could be attributed to the different functions that each inflammatory marker has in the inflammation process. As discussed in a paper by Flouri and colleagues (2020), increased IL-6 initiates acute inflammatory effects directly on the brain whereas CRP

levels might take days or even weeks to elevate after an inflammatory stimulus. In fact, a continuous increase in IL-6 levels is required for circulating CRP levels to rise. Therefore, it is speculated that the significant effect of SES on CRP, which was observed in adolescence but not in childhood, might be due to the fact that CRP is a marker of chronic, long-term inflammatory response while IL-6 is a better marker of acute inflammation in the brain where effects are shown more immediately.

Another recent study also showed that poor socioeconomic conditions were associated with higher levels of CRP throughout the first decade of life, at ages 4, 7, and 10 years (Soares et al., 2020). This discrepancy in findings could be partly attributable to how SES was measured as well as the age biomarkers were collected. As differences in the associations between SES and inflammation do arguably exist though, it is important to further investigate the mechanisms of influence for the association between SES and inflammation in children.

Furthermore, contrary to the initial hypothesis that early IL-6 and CRP would predict later IQ, it was found that neither of them was associated with IQ in the longitudinal models. Similarly, in the cross-sectional model, CRP at age 15 years did not seem to predict IQ at the same age. Consequently, these inflammatory markers were not observed to account for the association between SES IQ. While this finding is consistent with the results from a recent study where neither IL-6 nor CRP at age 9 predicted IQ at age 8 (Holland et al., 2020), it also contradicts findings from another study where elevated CRP at age 9, but not IL-6, was found to be associated with lower IQ at age 8 even after controlling for potential confounders (Mackinnon et al., 2018). Although there is evidence that elevated inflammatory markers may be deleterious for intellectual development, the discrepancy in findings makes it difficult to interpret the lack of associations between inflammation and IQ in

adolescence in this thesis. First, the different time in IQ measurements among this current study and previous studies might be one possible explanation of the null findings. As discussed previously, IL-6 and CRP function differently during the inflammatory process and as IL-6 has more immediate effects on the brain, these effects couldn't be observed six years after the initial measurement. It is also worth mentioning that other studies that found no association between IL-6 and academic performance (Adelantado-Renau et al., 2020; Borsini et al., 2015) suggested that IL-6 does not affect proliferation and gliogenesis, which in turn might not influence cognition or academic performance. On the other hand, CRP does not cross the blood-brain barrier and consequently, does not affect neurobiology. Thus, it could be somewhat expected for CRP not to be related to IQ as it could be more directly associated with behavioural and physiological aspects such as changes in body weight, diet, physical activity, and sleep. Second, the inflammatory markers at physiological levels can act both anti- and pro-inflammatory effects (Sartori et al., 2012), indicating that for a relationship between inflammation and IQ to be observed, higher levels of inflammation, probably above the clinical cut-off which likely indicates infection, should be considered in the analysis. However, CRP levels above that cut-off were excluded throughout the analysis of the present thesis. Third, it is suggested that these divergent results could be attributed to the matrix (whole blood, serum or plasma, saliva) in which inflammatory biomarkers were measured (Adelantado-Renau et al., 2020; Cullen et al., 2017) as well as to the different techniques of analysis implemented in each study.

Despite the lack of evidence for the indirect pathway of SES to IQ in adolescence via inflammation in childhood and adolescence, this is the first study that explored the association between SES and IQ through inflammation in childhood

and adolescence using data from the general child population. Previous studies explored similar pathways linking childhood infection and intelligence through inflammation (Mackinnon et al., 2018) or early life adversity and cognitive performance through inflammation. Finally, this study provides additional evidence for the direct relationship between SES and cognitive function in childhood which is of other modifiable risk factors.

In this thesis, both objective and subjective measures of family socioeconomic and financial factors were explored across the three empirical chapters. Inflammation, the key mediator of the study, was investigated both as an outcome of family socioeconomic factors as well as a mediator of the association between family socioeconomic factors and cognitive outcomes in children. The rationale to include multiple exposures and child outcomes across the three empirical chapters was to facilitate investigation of underexplored pathways linking socioeconomic and financial factors with physical health and cognitive functioning in childhood and adolescence. By exploring the pathway from a latent measure of family SES (captured with objective indicators) to inflammation in childhood via upsetting childhood events, this thesis provided evidence on how broad family socioeconomic disadvantage may be associated with inflammation. The next two empirical chapters looked at inflammation as a pathway from subjective and objective measures of family socioeconomic factors to childhood executive functioning, as measured by working memory performance in middle childhood and to cognition, measured by IQ in adolescence. Using data from the ALSPAC study, this thesis had a unique opportunity to shed light into the complex biological mechanism of inflammation as a pathway that may explain socioeconomic influences on cognitive development in the general child population. Thus, using multiple exposures and outcomes across the

chapters enabled a more comprehensive investigation of the above relationships. Despite the importance of using multiple exposures and outcomes in this thesis, there are also some limitations to doing so. This is mostly associated with not being able to consistently interpret results across the chapters had the same exposures and outcomes been explored. Further discussion on the specific strengths and limitations of the study will follow in the next sections.

8.1.1 Summary of pathways supported by the present findings

As discussed previously, three main pathways linking objectively measured SES and subjective financial difficulties with inflammation, cognitive ability and executive functioning were examined. Figure 8-1 depicts a conceptual representation of all the pathways tested in this thesis.
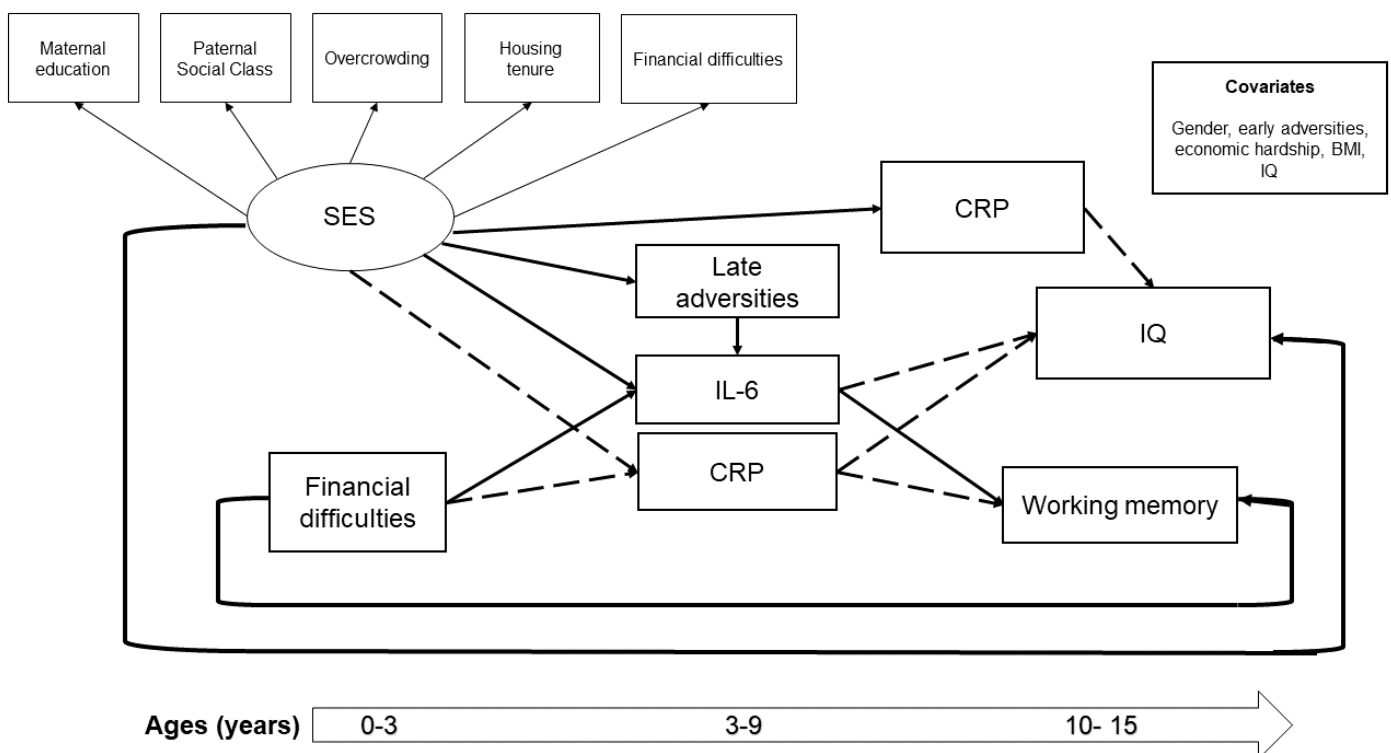

Figure 8-1. Conceptual representation of all the pathways tested in this thesis Arrows represent significant relationships whereas dashes represent non-significant relationships. Covariates were adjusted for in all the models on the mediators and the main outcomes.

Considering the findings of previous research and the results from this thesis together, two pathways were supported by the three empirical studies conducted:

1. For childhood inflammation, a pathway from objective family SES to IL-6 via childhood adversities.

2. For EF in childhood, a pathway from subjective financial difficulties to working memory via inflammation.

To summarise, SES and financial difficulties were significant predictors of working memory in childhood and IQ in adolescence. Albeit the weak associations between the main exposures, the mediators and the outcomes, the pathways presented are important and supported a theoretical framework that has not been tested before in children. This work showed that there is a relationship between i) SES and inflammation through upsetting childhood events and ii) financial difficulties and EF in children through inflammation even after controlling for important covariates of inflammation and EF.

8.2 Strengths and limitations of the study

8.2.1 Strengths

One of the main strengths of the study is the use of the Avon Longitudinal Study of Parents and Children (ALSPAC). Data for the analysis of this thesis were obtained from a large longitudinal sample of children in the general population. As mentioned in the previous chapters, ALSPAC is a transgenerational prospective observational study that takes into account multiple genetic, epigenetic, biological, psychosocial, social and other developmental exposures in relation to a similarly diverse range of health, social, and developmental outcomes (Boyd et al., 2013). Thus, the availability of a wide range of detailed family background characteristics as

well as various aspects of child development allows for the exploration of various theoretical frameworks as well as generalisation of the findings to the general child population. Specifically, ALSPAC had available data on children and mothers since pregnancy and allowed me to explore longitudinal associations beginning early in life and up to adolescence at age 15 years. For example, the longitudinal models included exposures (i.e., early SES and financial difficulties) measured between ages 0 and 3 years - a very sensitive period in children's development - two key mediators which was measured between ages 3 and 9 years (i.e., upsetting life events) and at age 9 years (inflammation) which covered a long time after exposure to risks associated with lower socioeconomic and financial factors. Finally, it included two main cognitive outcomes measured in middle childhood at age 10 years (working memory) and adolescence at age 15 years (IQ). Therefore, using ALSPAC data was a great choice as it provided a unique opportunity to answer to specific research questions of this thesis that another cohort study might have not been able to cover and it also allowed for exploration of conceptual pathways linking socioeconomic and financial factors with physical health and cognitive outcomes that have not been tested before in the general child population.

Linked to this, the second most important asset of the study was that the data available allowed me to create a latent factor of parental SES that took into account several related but distinct aspects of SES including education, social position, income, and housing conditions. This study went beyond using only the three main indicators of SES, which are parental income, parental education and parental occupation and exploited available data on additional proxies of SES that are considered important determinants of health and life outcomes (Duncan et al., 2002). Those were two housing characteristics - housing tenure and overcrowding - both of

which are linked to SES and are key components of material circumstances and wealth (Galobardes et al., 2006). Previous important work on the indicators of socioeconomic position in epidemiological research has argued that using composite measures of SES would be efficient in the case when SES is measured as a confounding factor and not as the main variable of interest (Galobardes et al., 2006); however, more recent research now suggests the opposite, i.e. it is better using SES as a scale rather than single measures (Goosby & Walsemann, 2012; Walsemann et al., 2011; Yang et al., 2017). Following the latter, this study chose to create a latent factor of SES that seemed to be a reliable and effective measure given the results of the factor analysis and the associations found between SES, the inflammatory markers and the cognitive outcomes. In addition, it is important to note that the use of blood-derived inflammatory biomarkers and standardized measures of cognitive ability and EF is another advantage of the study.

Another strong point of this thesis was the application of statistical techniques that allowed for the simultaneous modelling of a latent variable with observed variables while testing for indirect effects. Structural Equation Modelling (SEM) is a more powerful alternative to multiple regression, path analysis, factor analysis, and time series analysis (Tabachnick, 2007). Given that the models in this thesis involved exogenous, endogenous and intervening variables, conducting SEM has contributed to producing meaningful and robust results while also appropriately accounting for measurement error in latent variables (Schofield, 2015) such as the latent factor of SES that was constructed in this thesis.

Lastly, given the richness of the data that were measured across different timepoints, I was able to look at the prospective relationships tested in this project both longitudinally and cross-sectionally. This will also allow for findings to be

compared across different samples and studies and to be examined for their robustness.

8.2.2 Limitations

Despite its significant strengths, this study has limitations, too. First, it must be acknowledged that the ALSPAC study is homogeneous in the sense that participants were more likely to be White and more advantaged compared to the national population as discussed in Chapter 3. More specifically, participants in the study's analytic sample were significantly more advantaged in terms of socioeconomic characteristics compared to the ALSPAC families that were not included in the study. consequently, the analytic sample is somewhat selective; Also, given that most of the sample was socioeconomically advantaged, it is then acknowledged that the ALSPAC data might not be the most accurate representation of socioeconomic differences in the general population; however, it is noted that this is primarily due to the demographic profile of the catchment area populations and the effects of the differential attrition. Hence, a bias analysis was conducted in all empirical chapters to investigate the differences between the analytic sample and those outside that sample.

Results from the bias analysis in chapters five, six and seven showed that the two samples, apart from being distinctly different in SES, also had significant differences in their inflammation levels, with those outside the analytic sample reporting slightly higher levels of inflammation. Furthermore, there were differences in IQ scores between the children of the analytic sample and those who were not included in the sample with children in the analytic sample scoring significantly higher in the IQ test at both ages 8 and 15. However, no differences in the working memory performance between the samples were inspected. It should also be noted

that it was not meaningful to include ethnicity in the analysis due to the non-White participants comprising only 4% of the sample and thus, the study did not account for those. Having only 4% of non-White people in the sample, meant that there was not a sufficient number of individuals from non-White ethnic backgrounds to allow for statistically robust comparisons by ethnic background.

Related to the ALSPAC data, it must be noted that although creating a novel composite variable for socioeconomic factors has been a great strength of this study, it also has its limitations. For one, as this variable has never been used before as a composite using those specific indicators and although several validity checks were carried out, the robustness of this latent variable is yet to be confirmed by further research using the same indicators and the same techniques to construct the composite SES factor. Furthermore, by creating a composite variable, this thesis was not able to test which of the individual indicators – objective or subjective – were more important for a given outcome or most strongly related to cognitive ability (IQ) and working memory (EF). In addition, as described in chapter 3 and all three empirical chapters, a specific procedure was followed to construct the final latent SES variable which might pose some limitations. Specifically, as all SES indicators were measured on different scales, those were first dichotomized before conducting a Principal Component Analysis. Although this dichotomisation was according to previous literature, it must be acknowledged that this might have resulted in lost information on the socioeconomic situation of the participants. For example, the variable that indicated parents' difficulties in affording staff for their baby was grouped after visual inspection of its distribution and the bottom third (no difficulties in affording items) was differentiated from the top two thirds (having difficulties in affording items) and this crude way of grouping might not be a good representation

of the financial difficulties of the sample. However, it has been consistently mentioned throughout the thesis that this dichotomisation indicates the financial strain that parents must have experienced at some point across the three timepoints and it was expected that the distribution of this variable was skewed in the general population. Similarly, given that the proportion of the 'low SES' group in the other indicators varies, this might indicate that the composite SES did not capture exactly those socioeconomic differences in the sample which would have been observed if the original variables were used to construct the latent factor. It should be noted though that the construct validity of the latent SES factor has been established based on Principal Component Analysis and Confirmatory Factor Analysis. These analyses indicated that the binary variables loaded into one single factor and the model also was a great fit to the data.

Another weakness of the study is that only one measurement of inflammatory marker in childhood (at age 9 years) was available. This did not allow me to test for the associations at younger ages in chapters five and six. In fact, in chapter six, although there was evidence for the short-term effects of inflammation (age 9) on child working memory (measured at age 10 years), this could not be tested longitudinally. Thus, it is important to note that given the very short interval between inflammation and child EF and the absence of repeated measures of inflammation and working memory, is it impossible to imply that either IL-6 or CRP would have a causal effect on EF in children. It must be acknowledged though that a study like this can't determine causality as it is not experimental, nor it manipulates variables. Having longer intervals and repeated measures this study could perhaps get closer to establishing temporal ordering of these factors and get closer to determining causality.

Furthermore, the lack of repeated measures did not allow me to clarify whether high levels of inflammation predicted impaired cognition or whether there was a possibility of bidirectionality. Previous experimental studies in older adults (Reichenberg et al., 2001) and rodents (Chen et al., 2008) have provided evidence for the causal link between cognitive functioning and inflammation where acute systemic inflammation directly impaired cognitive functions including working memory. On the contrary, results from another longitudinal study supported a model of reverse causation because apart from the finding that the inflammatory markers in that study were related to cognitive decline at the same time, at age 70 years, it was also found that childhood IQ at age 11 years also predicted late-life inflammation (Luciano et al., 2009). Given the current data and the type of analysis of the study, it can be assumed that there is certainly a relationship between inflammation and executive and cognitive functioning in middle childhood and adolescence. However, no conclusions can be drawn about causality or the existence of reverse causality. Several studies have found that inflammation is associated with greater cognitive impairments, particularly in memory and other executive function domains among older adults (Dickerson et al., 2013; Frydecka et al., 2015; Johnsen et al., 2016; Noble et al., 2010; Teunissen et al., 2003). However, studies in children and adolescents have produced mixed results and, thus, the relationship between inflammation and working memory performance in children needs further exploration. The available data of the study also did not allow me to test for earlier or other measures of EF which would be meaningful. However, focusing on working memory exclusively, which is a core component of EF, allowed me to demonstrate a relationship between inflammation and memory performance.

Furthermore, the findings from empirical chapters revealed that the indirect effects of SES on inflammation and those of inflammation on EF and IQ were small but statistically significant or not statistically significant. For example, in chapter five, it was shown that the effects of SES on IL-6 in children via upsetting events were small but significant and results for CRP were not significant. Similarly, in chapter six, the effect of financial difficulties on working memory through IL-6 was small but significant, too, and CRP was not a significant mediator of the above relationship. In chapter seven, mediation by inflammation of the relationship between SES and IQ in adolescence was not found either. Given that only a small proportion of the variance in inflammation could be explained by upsetting events and, similarly, only a small proportion of variance in cognitive performance could be explained by inflammation, other important mechanisms might be at play. These mechanisms could be related to psychopathology and childhood trauma (Peters et al., 2019) as well as body composition (Esteban-Cornejo et al., 2015; Poh et al., 2019) and exposure to air pollution (Brockmeyer & D'Angiulli, 2016; Calderon-Garciduenas et al., 2016). Finally, the lack of findings for CRP in all empirical chapters is something common in studies in middle childhood (Flouri et al., 2019). Effects of such exposure on CRP are shown either in infancy or in adolescence, suggesting that the period of development may play an important role (Kuhlman et al., 2019).

Another limitation of the study is that it did not adjust for cortisol which seems to play a role in the relationship between SES and inflammation. Cortisol is one of the end products of the HPA axis activation by stressful life events, but it was not accounted for in the models. The role of cortisol is to inhibit the production of inflammatory cytokines by binding to glucocorticoid receptors in healthy immune cells. Therefore, these increases of the HPA axis activity could possibly conceal the

proinflammatory phenotype in children as measured by circulating cytokines due to cortisol secretion. As a result, children exposed to adversity may show lower levels of inflammation which is carefully regulated throughout childhood and adolescence and accumulates with age through biological ageing and via other behavioural, psychosocial and environmental pathways. Consequently, it is likely that the association between inflammation and SES-related stressors does not emerge before adulthood or may be masked by regulatory processes (Franceschi & Campisi, 2014; Miller et al., 2011). It also acknowledged that it would be useful for the study to have tested for other biomarkers too; however, IL-6 and CRP are arguably two of the most frequently assessed biomarkers in epidemiological datasets like the one of this study which facilitates comparison of results with other studies. Those were the only biomarkers measured during childhood in ALSPAC.

Furthermore, there are a few other issues with the mothers' reports that need to be addressed. The first one is regarding the upsetting events checklist (see Chapters 3 and 5) which was completed by the mothers who may have over-or under-estimated the impact these events had on their children. However, this was not possible in this study given the very young age of the children in the sample. Related to this, it is also acknowledged that this study, apart from the item indicating that the child has been sexually abused, it did not include the typically used items in the literature on adverse childhood experiences (ACEs) such as abuse (psychological, physical) and household dysfunction (living with a household member with substance abuse problems, mental illness or who had ever been to prison, and mother was treated violently) as well as parental separation/divorce, and emotional and physical neglect (Anda et al., 1999; Dong et al., 2004; Lacey & Minnis, 2020). These items along with some additional adversities including poverty

and parenting styles and more recently bullying, war, and parental death (WHO, 2018) have been linked to several health outcomes such as cardiovascular risk factors (Appleton et al., 2017) and inflammation (Lacey et al., 2020). Consequently, the lack of using a universal measure of adversity, as the literature on ACEs suggests, does not allow comparisons across studies exploring the adversities-inflammation link in childhood (for example, Lacey et al., 2020). However, the upsetting childhood events checklist was used as an alternative to an ACE measure and covered a range of different constructs of stressful life events in childhood that varied in severity (e.g., from child having a pet die, starting a new school to being taken into care/separated from parents, being sexually abused, being physically hurt by someone). In fact, some of these items have also been used in the literature on adversities including sexual abuse and being physically hurt. The measure was shown to be significantly associated with inflammation and SES not only in this thesis but in other recent studies using ALSPAC data as well (Flouri et al., 2020a; 2020b) despite the weak associations which might be attributable to the choice of events or who reported the events. Finally, another limitation related to the upsetting childhood events is that in this thesis, no moderation by gender was explored. Previous studies have reported significant sex differences in patterns of childhood stressors (Haahr-Pedersen et al., 2021); however, there was another study that contradicted these findings as it showed no differences in groups of adversities by gender (Lacey et al., 2020). These associations depend on the types of adversities, the approach that was followed to measure them as well as the person who reports those adversities (e.g., parent-focused ACEs or parent–child ACEs). Thus, it would have been meaningful to also explore the interaction between gender and upsetting childhood events in this thesis and provide further evidence.

The second issue is regarding the financial difficulties scale which was completed only by the mothers and therefore it may not reflect well the family's financial situation or other household's members' perceptions. Furthermore, it should be noted that the finding concerning many mothers having reported financial difficulties while having a social status or owning their home should is seemingly contradictory. It would be expected that most of the participants would not report financial difficulties considering the analysis from ALSPAC demographics (Russell et al., 2018) which shows that the majority of the mothers in the study are more advantaged than the mothers in the rest of the country. However, in this study, the main interest was to capture difficulties spanning many years. Therefore, most of the parents would have had at least some difficulties at some point across the three timepoints when this variable was measured regardless of their overall socioeconomic background. Previous research has also supported that self-reported economic hardship is a better indicator of financial insecurity than income itself (Jeanne Leininger & Kalil, 2014; Pradhan & Ravallion, 2000). Financial distress reflects both on economic resources and the demands that are made on individuals and do not necessarily imply a lower income or SES (Clark et al., 2019). In the same vein, it is acknowledged that the variable of financial difficulties (or poverty as mentioned interchangeably in empirical chapter 6), was grouped as 1/3 of the sample having difficulties in affording items for the baby and 2/3 of the sample as not having difficulties. This might not be a true indicator of poverty as poverty is measured objectively by living below a certain income threshold (in the UK, this is 60% of the median income) in other studies. This may have led to losing information on participants' financial situation which in turn might have resulted in weaker associations among the exposure, the mediator, and the outcome in the models

tested. However, the approach that was followed in this thesis does capture the experience of financial difficulties in the early years, the distribution of which is expected to be skewed in the general population and especially in the analytic sample of this research where most of the parents were socioeconomically more advantaged that those in the non-analytic sample. It also worth mentioning that the term "poverty" has been used previously for describing socioeconomic disadvantage (Flouri et al., 2014) or economic hardship (Lacey et al., 2020), nonetheless.

Another weakness of this study is that it was not possible to control for medication and health conditions such as allergies (Yoshimura et al., 2012) and diabetes (Garcia et al., 2010) as well as diet (Minihane et al., 2015) and physical activity (Abramson & Vaccarino, 2002; Ertek & Cicero, 2012; Ford, 2002) which are well-established confounders of inflammation. Physical activity in ALSPAC was objectively measured and was not available until the age of 11 when it was measured for the first time. Likewise, the lack of using a measure of weight for age percentiles for children instead of BMI is another limitation of the study. It is acknowledged that BMI is not a diagnostic tool and is interpreted differently for children and teens compared to adults due to changes in weight and height with age, as well as differences in the relation of BMI to body fatness. However, given that BMI was used as a covariate in the models rather than a main independent or a dependent variable, it is argued that this is not unduly problematic, especially because using BMI is what several other ALSPAC studies on child inflammation have also done.

Finally, the use of BMI as a covariate in the fully adjusted models and not as a potential mediator as shown in previous studies linking SES with disease (Miller et al., 2011) or SES and family poverty with inflammation (Carroll et al., 2011; Muscatell

et al., 2020; Rexrode et al., 2003; Schmeer & Yoon, 2016) may have led to different results observed in this thesis. Although modelling BMI as a mediator has been shown to account for part of these relationships, the choice of not including BMI as such in this current thesis was due to the focus on inflammation as the key biological pathway linking socioeconomic and financial factors to cognitive outcomes. However, it is acknowledged that having modelled BMI as mediator rather than a covariate might have resulted in different outcomes. The effect sizes of the relationships observed could have also been further reduced or explained in the presence of another mediator given that the associations between different exposures and outcomes with inflammation as a mediator have already been weak in this thesis.

8.3 Recommendations for future work and policy

8.3.1 Future research

This study provided evidence of the association between family early SES, child cognitive outcomes and inflammation in childhood. The pathways modelled produced significant indirect associations, however, since the magnitude of the associations were weak or non-significant in some cases, it is suggested that other pathways should be also tested, and that further research is needed to elucidate those relationships. For one, regarding the association between SES and inflammation via upsetting events, other mechanisms related to the type of family and area environments to which children in poverty are exposed might be of greater influence (Evans, 2004). Factors such as poor nutrition and lack of exercise as well as other environmental factors including exposure to air pollution and "wear and tear" of the immune system caused by extended cortisol elevation (Danese & McEwen, 2012; Janicki-Deverts et al., 2009; Juster & McEwen, 2015) have been linked with

both low SES and inflammation. Furthermore, different types of adversity can affect psychoneuroimmune development differently (Kuhlman et al., 2017). Hence, it is important to investigate the different types of adversity, their timing and chronicity.

For example, it is important to explore one of the main relationships in this study, that of socioeconomic disadvantage and inflammation, using different measures of adversity. Given that in current research thesis significant, albeit weak, associations between childhood upsetting events cumulative scores and inflammation in childhood were reported, it is recommended that other approaches such as single adversities or clustering ACEs in the above association using the commonly used items of ACEs as described in the literature on adversities should be further examined following the example of previous studies (Lacey et al., 2020; Lacey et al., 2020). This would allow shedding more light on how specific adversities and combinations of them affect early life inflammation and would also allow for comparisons across studies which would also benefit clinicians, practitioners, patients and the public (Lacey & Minnis, 2020). Furthermore, the upsetting events checklist was completed by the parents. A self-completion checklist by the children in the next sweeps of ALSPAC when they are older would capture the perceived impact of these events and would also enable the same checklist to be used in further research and establish an additional measurement of life events. Finally, it is suggested that future studies using similar measurements should examine whether the association between upsetting childhood events and inflammation is moderated by sex, as shown in previous studies (Haahr-Pedersen et al., 2021; Lacey et al., 2020).

Moreover, in light of the evidence that individuals with moderately elevated IL-6 and/or CRP do not necessarily suffer from chronic low-grade inflammation (Del &

Gangestad, 2018), a clear understanding of the complex biological systems is needed before interpreting causal processes involving biomarkers. The finding that the effects of SES on CRP at age 15 years vanished after those with higher CRP were excluded is also related to the previous suggestion and needs more attention. It is also important for future models to account for the role of cortisol especially in such processes in childhood.

With regard to the association between SES and EF as well as SES and IQ via the specific pathway of inflammation, since inflammation only accounted for a small variance in the cognitive outcomes, it is suggested that other environmental inputs and genetic influences which might explain the variation in cognitive outcomes by SES are taken into account (Holland et al., 2020; Jeon et al., 2014; McCoy et al., 2015).

Furthermore, in this study no repeated measures of working memory at an earlier age were available and thus, it would be useful for future research to include earlier and/ or repeated measures of EF in the model for the SES-inflammation-EF link to account for the differences in EF performance by age. Additional longitudinal associations between other measures of cognitive functioning such as literacy, language, mathematical reasoning, participant's key stage scores as well as EF components with later measures of inflammation could be tested to understand the influence of inflammation due to financial stressors on the different aspects of cognitive development in children.

Finally, future research should also explore reciprocal associations using cross-lagged models to determine the direction of the relationship between inflammation and cognitive functioning at ages 9 and 15 using the ALSPAC data.

Subsequently, considering the results from the cross-lagged models, growth curve models could then be applied to estimate how inflammation may explain the effect of SES on the development of cognitive functioning over time.

8.3.2 Policy implications

The findings of this study identified important mechanisms that underly the SES effect on inflammation and cognitive development in children which are important for both theory and policy (Hertzman, 1999). First, the current results from a large sample of children and adolescents suggested that early life SES was associated with inflammation in childhood independently of covariates. Identifying how socioeconomic disadvantage can bring about increases in the inflammation levels in the body plays an important in helping to mitigate the consequences inflammation has on health across life (Mackinnon et al., 2018). In addition, relevant policies and interventions should be created with the aim to improve the socioeconomic conditions of children from disadvantaged backgrounds for the SES disparities in health across the lifespan to be reduced (Yang et al., 2017). These interventions could be relevant to educating, training, and helping low SES parents to gain job skills and job security which will directly improve the health of their children and set them on an SES trajectory that will benefit them for the rest of their lives.

As this study also explored childhood adversity as one of the key mediators of the link between SES and inflammation, it makes it possible to understand the consequences of adversity on infection. By detecting the determinants of inflammation, it will allow the development of early interventions which will have much public health benefit (Kuhlman et al., 2019; McEwen & Gianaros, 2010). For example, by identifying the consequences of SES-related stressors and adversities

have on physical health, relevant programmes that aim to provide parents and children tools for managing stress at school and at home should continue to develop. For example, practicing mindfulness, journaling to release their feelings and adopting healthy lifestyles are some of the proposed techniques that may help children to learn how to cope with the stresses and strains of life.

Second, the study paves the way for a more detailed exploration of 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. This exploration would play a significant role in the development of early intervention and prevention as understanding risks especially to children's working memory is of great importance. For example, working memory has been shown to have the highest predictive weight for academic performance (Cortés Pascual et al., 2019) as well as reasoning abilities and problem-solving (Best et al., 2009), all of which are strongly linked to educational attainment (Handley et al., 2004). In addition, the finding that inflammation was related to EF independently of covariates emphasizes the need to identify increased inflammation at an earlier age to prevent not only short-term cognitive impairment but also potential long-term cognitive decline at an older age (Esteban-Cornejo et al., 2016). More longitudinal studies assessing the above relationships starting in early childhood are needed.

Although the current project did not provide evidence that immune function plays a role in the relationship between SES and intelligence, it is equally important to consider how higher SES brings about better cognitive performance and how the opposite effects, i.e., lower IQ due to lower SES and elevated inflammation, would have on children from lower SES families. Therefore, a policy tackling socioeconomic disadvantage targeted at the family and the child level would be

beneficial for child cognitive development. Families and children should be supported to escape poverty and create better prospects.

Such relevant policies have been developed by the government with the aim to tackle the causes of disadvantage and transform families' lives. The Department for Work and Pensions and the Department for Education published in 2011 a report with regard to a new approach to child poverty which was presented to the Parliament (Work et al., 2011). In this report, they discussed supporting families to achieve financial independence as well as supporting family life and children's life chances and how the place someone lives in can determine the quality of life. Under the obligation of the Child Poverty Act 2010 (Kennedy, 2010), this strategy set out plans to end child poverty by 2020. One of the keynotes in that report was that delivering social justice and social mobility would be essential for transforming families' and children lives. In addition, they would emphasize greatly on early interventions at the family level by targeting at-risk groups who face particular barriers and would also support children who were at risk of poor education outcomes from the early years to higher education. It is also noted that using data from large-scale longitudinal studies will enable us to explore the well-being and the development of the children at the national level. Hence, providing further evidence for the effects of low SES on children's cognitive performance and attainment, as this research thesis did, will allow relevant policies to continue supporting those at risk. Furthermore, another Key Issues report that was published for the UK Parliament in 2015 also discussed the vision for 2020 regarding the child poverty issue (Taylor-Robinson & Bennett, 2020) and suggested that as the previous and current targets were not going to be met, the Government could amend the Child Poverty Act and

introduce a new one which would prioritise children in fiscal policy and close gaps in educational achievement.

Similarly, a more recent report by the Social Mobility Commission (Mobility & Commission, 2016) on how socio-economic circumstances influence children's life chances indicated that, worryingly, in areas vital to child development and attainment at school gaps were widening between high and low SES families. These areas were related to parental involvement and investment, children's well-being and behaviour as well as their participation in sport and physical and cultural activity and engagement with the school overall. In previous reports, the commission has called on the government to, among others, establish and develop an innovation fund to help and improve parents' skills, halve the child development gap at age 5 by 2025 and ensure that all children develop the skills and expertise that will help them to thrive at school.

Notably, the American Psychological Association (APA) has been advocating for government policies and programs that reduce poverty and inequality and has addressed the needs of low-income populations and how SES affects people's mental and physical health. Some of the public policies supported by the APA were concerning data and increased intentional research to identify those at risk and develop effective interventions that meet the needs of low SES people, increase in the minimum wage to help those living below the poverty line and other programmes that support the nutrition, childcare and family and medical insurance leave of families living below the poverty line. Although APA's advocacy is targeted to the people in the United States, those policies could be applicable in the UK as well given that the impact of socioeconomic disadvantage is global. It is apparent that relevant programmes that aim to tackle the effects of low SES on families and

children have already been developed and thus, it is suggested that longitudinal research should continue to provide evidence to help policymakers work towards helping children at families at risk.

8.4 Concluding remarks

This thesis explored the direct paths from objective and subjective socioeconomic factors to cognitive ability and executive functioning in middle childhood and adolescence and the indirect paths of those relationships through the biological mechanism of inflammation. First, it provided evidence for an association between objectively measured family SES with childhood inflammation through upsetting childhood experiences. Following that, findings showed that inflammation explains a small part of the relationship between parental perceptions of financial difficulties and EF (specifically working memory) in childhood, but it was not able to provide evidence for the mediating role of inflammation in the relationship between SES and cognitive ability. Although the indirect associations were weak, this study outlines the importance of understanding how objective and subjective socioeconomic factors influence health outcomes which in turn have effects on cognitive performance in children. Future research should explore other potential mechanisms such as children's psychopathology, genetics as well as family and area environment that may link different socioeconomic factors with cognitive ability and EF in childhood. Furthermore, studies should examine whether these associations may be bidirectional. Finally, relevant policies that have been developed to tackle the impact of socioeconomic disadvantage on families and children's development should continue to work towards the prevention of the harmful effects that poverty has on child health.

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