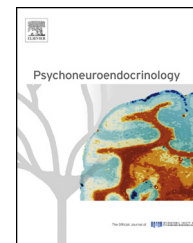


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# Parental separation in childhood and adult inflammation: The importance of material and psychosocial pathways<sup>☆</sup>

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## KEYWORDS

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Material disadvantage;  
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Relationships

## Summary

**Background:** Childhood adversities are known to be associated with poorer health outcomes. A potential mechanism may be through changes in inflammatory processes. One such childhood adversity is separation of parents, however relatively little is known about the association between parental separation and inflammation in adulthood. The aims of this study were to (1) investigate whether parental separation is associated with inflammation in mid-life, (2) focus upon the mechanisms that may be involved in translating childhood adversities, such as parental separation, into poorer health outcomes in adulthood.

**Methods:** We examine the association of parental separation in childhood, defined as the breakdown of the parent's partnership, and levels of C-reactive protein (CRP) in middle age. The role played by material (through material disadvantage and educational attainment), psychosocial (through parent–child relationship quality and psychological distress) and adiposity (through BMI) mechanisms is investigated using path analysis in a multiply-imputed dataset from a British birth cohort with concurrent measurements made throughout the life course ( $n = 7462$ ).

**Results:** Participants that report parental separation have higher CRP levels at age 44 than those who grew up with both parents ( $\beta = 0.16$ , 95% CI: 0.06, 0.27). This association is largely explained by BMI, material and psychosocial factors. Material disadvantage after separation and educational attainment seem to be particularly important in this association.

**Conclusions:** Parental separation increases CRP in adulthood via chains of disadvantage across the life course. This study points towards potential points for intervention and highlights a need to support separating families in order to minimise the long-term impact on adult health.

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## 1. Introduction

Many studies have reported an association between childhood adversity and CRP levels, a reliable marker of low-grade inflammation (Pepys and Hirschfield, 2003), across the life course. Chronic inflammation is correlated with poorer health outcomes, such as depression (Danner et al., 2003; Howren et al., 2009), type II diabetes (Bassuk et al., 2004) and coronary heart disease (Danesh et al., 2004). Therefore investigating risk factors for inflammation in adulthood, and the mechanisms through which they act, is likely to be fruitful in mitigating the effects of low grade inflammation and subsequent disease. Childhood adversities previously investigated include low socioeconomic position (e.g. Phillips et al., 2009; Chen et al., 2011; Miller and Cole, 2012), maltreatment and abuse (Danese et al., 2007, 2009), as well as broader adverse childhood event (Slopen et al., 2010, 2012) and family environment scores (Taylor et al., 2006). These studies suggest that childhood adversity is associated with higher CRP levels in adolescence and adulthood. However, this association may vary by the type of childhood adversity investigated. The disadvantages of these studies are three fold; firstly many are cross-sectional in design and therefore use retrospective measures of childhood adversities, which may be prone to recall bias. Secondly many studies have used small convenience samples and finally existing studies have generally ignored missing data and conducted complete case analyses. It is known that those who have complete information on all variables of interest differ from those who have missing data (Klebanoff and Cole, 2008), being more advantaged with regards to health and social circumstances. We focus on one specific type of childhood adversity (parental separation) in this study as it is likely that the mechanisms involved vary for different adversities. Parental separation in childhood has been linked previously to poorer physical and mental health in adulthood and to stress biomarkers, such as cortisol (Kraft and Luecken, 2009).

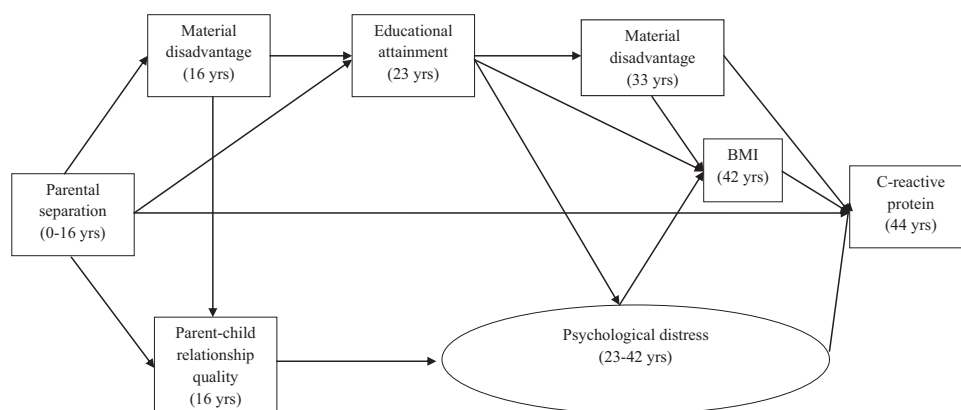
Relatively little is known about the mechanisms through which the experience of childhood adversity might influence chronic inflammation in adulthood. Two main pathways involving material and psychosocial factors are suggested. Regarding material pathways parental separation is associated with increased material disadvantage and a reduction in living standards at different stages of the life course (Elliott et al.,

1993). This disproportionately affects lone-mother headed households (Aassve et al., 2007), the most common outcome of parental separation. Parental separation has also been associated in many studies with reduced educational attainment (Amato and Keith, 1991; Ely et al., 1999; Ross and Mirowsky, 1999). Although education is not a material factor per se it is thought to be the main way in which material disadvantage is transmitted across the life course. In turn both material disadvantage and educational attainment have been linked to increased CRP levels (Hemingway et al., 2003; Owen et al., 2003; Alley et al., 2006). It is also possible that the level of material disadvantage in childhood affects risk of parental divorce, as suggested by the Family Stress Model (Conger et al., 1992).

Regarding psychosocial pathways, parent–child relationships may deteriorate as a consequence of parental relationship breakdown and there is much evidence to suggest that parental separation is associated with poorer quality parent–child relations (Zill et al., 1993; Amato and Booth, 1996). Also there is a well-established link between parental separation and adult psychological distress (Amato and Keith, 1991; Rodgers et al., 1997; Lacey et al., 2012). Poor parent–child relationship quality has also been associated with increased reporting of psychological distress in adulthood (Morgan et al., 2012). Finally adult psychological distress has been linked to CRP in previous work (Surtees et al., 2008; Copeland et al., 2012; Miller and Cole, 2012). Therefore it is possible that these factors are involved, and interlinked, in a psychosocial pathway linking parental separation in childhood to CRP in adulthood.

Material and psychosocial mechanisms are also linked across the life course and this is something we additionally investigate. Obesity is often considered a condition of low-grade inflammation (Das, 2001) and the association of BMI with CRP is well established (Visser et al., 1999). Evidence suggests that both material (Wang and Beydoun, 2007) and psychosocial disadvantage (Luppino et al., 2010) are associated with increased BMI. It is therefore possible that material and psychosocial factors are linked to increased CRP via BMI as shown by others (Taylor et al., 2006).

The aim of this study was to (1) investigate whether parental separation in childhood was associated with CRP in adulthood, and (2) whether this association could be explained by material factors and psychosocial factors acting



**Figure 1** Conceptual model showing the role of material factors, psychosocial factors and BMI between parental separation (0–16 yrs) and CRP (45 yrs).

across the life course. Our study represents an enhancement of previous research as we use prospective data from a large British birth cohort in which concurrent measures were made; we focus on a single measure of childhood adversity and we account for a number of factors that may confound our association such as material factors before parental separation. The specific pathways investigated are presented in Fig. 1.

## 2. Methods

### 2.1. Sample

This study uses data from the National Child Development Study (NCDS). This study was initiated as the Perinatal Mortality Study aiming to recruit all the babies born during a single week of 1958 (achieved sample = 17,414, 98.2% of target) in Great Britain (Power and Elliott, 2005). Participants have been followed-up at the following ages so far: 7, 11, 16, 23, 33, 42, 44, 46 and 50 years. The study is multi-disciplinary collecting information on educational, economic, medical, developmental and social aspects of participants' lives from multiple sources. This study uses information from birth through 44 years as this latter wave is a biomedical survey and the only wave in which blood samples were collected. This wave collected data on a sub-sample of NCDS participants (achieved sample = 9377, 78% of target) (Elliott et al., 2008). In this study we use those participants from whom blood samples were taken from this survey ( $n = 8233$ , 87.8% of target).

### 2.2. Measures

#### 2.2.1. C-reactive protein (CRP)

Blood samples were collected at age 44 years during the biomedical survey. CRP was measured in citrated plasma by high-sensitivity nephelometric analysis of latex particles coated with CRP-monoclonal antibodies (Elliott et al., 2008). CRP was the only inflammatory marker collected in this dataset. Participants with levels  $\geq 10$  mg/L, indicative of infection, pathology or trauma, were excluded from this analysis. CRP values were missing for 136 people who were taking warfarin or were pregnant, 9 participants whose results were not recorded, 413 participants who provided consent but blood was not taken, and 586 participants who refused to provide a blood sample. Those with missing CRP levels were more likely to be male but did not differ on other analysis variables. Values were positively skewed and were therefore log-transformed.

#### 2.2.2. Parental separation in childhood

Parental separation in this study covers both divorce and the breakdown of cohabiting relationships. This measure was prospectively derived from birth to 16 years. At age 7 this information was provided by the health visitor interviewing the family. At ages 11 and 16 this was derived from information on the identity of parental figures and reasons for any change reported by the mother. If there was a change in parental figures and the reason given for this change was 'divorce' or 'separation' these children were recorded as having experienced parental separation.

#### 2.2.3. Material pathway factors

Material disadvantage at age 16 years was measured using several variables all reported by the participant's mother: housing tenure, free school meal receipt, overcrowding ( $\geq 1.5$  person per room), perceived financial hardship in the past year, access to household amenities (inside lavatory, cooking facilities and hot water), whether a child shared a bed with others, and benefit receipt. A single scale was created from these items using multiple correspondence analysis. This is a method of data reduction similar to principal components analysis but is more appropriate when nominal variables are involved. High scores are indicative of material advantage.

Educational attainment was measured as the highest qualification achieved by age 23 years (no qualifications, CSE/O-level (NVQ1-2), A-level (NVQ3), higher/degree (NVQ4+)). Adult material disadvantage was indicated by participant's occupational social class. This was classified using the Registrar General's Social Class (RGSC) schema, based upon occupation, and has the following categories: I (professional), II (managerial and technical), IIINM (skilled non-manual), IIIM (skilled manual), IV (semi-skilled manual) and V (unskilled). Individuals who were not working were included in group V as this is likely to be associated with disadvantage.

#### 2.2.4. Psychosocial pathway factors

Parent-child relationship quality was measured using two items at age 16 years 'I get on well with my mother' and 'I get on well with my father'. Responses were on a Likert scale ranging from (1) 'very true' to (5) 'very untrue'. The mean of these two items was taken. If participants only had one parent only the score for that parent was used.

Rutter's Malaise Inventory was used to measure psychological distress at ages 23, 33 and 42. This comprises 24 yes/no items on both emotional and somatic symptoms (Rutter, 1970). A hierarchical factor analysis was conducted, firstly deriving two factors for each wave (one emotional and one somatic, as have been identified by previous work (Rodgers et al., 1999)) and then deriving an overall factor from just the three emotional factors obtained from the first step. This approach is preferable to measuring psychological distress at a single wave and reduces the chances of finding a strong association with CRP which is driven by physical symptoms captured by the Malaise Inventory.

#### 2.2.5. Body Mass Index (BMI)

BMI was taken from age 42 using self-reported height and weight. While objective measures of BMI were available at other ages in NCDS, BMI at age 42 years fitted best in our conceptual model as it follows adult psychological distress and material disadvantage and is prior to CRP measured at age 44. Sensitivity analyses showed that BMI at 42 years correlated highly with measured BMI at the preceding and following waves ( $r = 0.739$  BMI33–BMI42,  $r = 0.821$  BMI42–BMI45,  $r = 0.783$  BMI33–BMI45). Also associations involving BMI in our conceptual model (e.g. BMI to CRP) were almost identical regardless of the BMI measure used.

#### 2.2.6. Covariates

Father's social class (RGSC) from the birth survey was used as an indicator of material disadvantage prior to separation in

**Table 1** Descriptive information and comparison of observed and imputed data ( $n = 7462$ ).

	Missingness (%)	Observed (%)	Imputed (%)	Imputed data	
				Parental separation (%)	No parental separation (%)
CRP (45 yrs)					
Median (mg/l)	0 <sup>e</sup>	0.94	0.94	1.11	0.93 <sup>a</sup>
Parental separation (0–16 yrs)					
Yes	27.8	91.7	90.9		
No		8.3	9.1		
Material disadvantage score (16 yrs)					
Mean	23.6	−0.01	−0.02	−0.79	0.05 <sup>b</sup>
Educational qualifications (23 yrs)					
No qualifications	16.7	10.9	11.4	21.4	10.4 <sup>c</sup>
CSE 2–5/O-level		49.6	49.9	56.3	49.2
A-level		18.6	18.3	12.2	18.9
Higher qualification/degree		21.0	20.4	10.1	21.5
Social class (42 yrs)					
I (highest)	15.4	5.7	5.5	3.5	5.7 <sup>c</sup>
II		39.0	38.0	33.2	38.5
IIINM		20.5	20.3	18.8	20.5
IIIM		20.1	20.4	23.2	20.1
IV		11.6	12.3	16.4	11.9
V (lowest)		3.1	3.5	4.9	3.3
Parent–child relationship quality (16 yrs)					
Very good quality	23.8	28.6	28.4	20.5	29.2 <sup>c</sup>
1.5		12.4	12.3	11.4	12.4
2		37.1	37.1	34.3	37.4
2.5		10.1	10.2	13.5	9.9
Uncertain		7.6	7.8	12.8	7.3
3.5		2.3	2.3	3.9	2.1
4		1.6	1.6	2.5	1.5
4.5		0.1	0.1	0.5	0.1
Very poor quality		0.3	0.3	1.2	0.2
Adult malaise (23–42 yrs)					
Mean of hierarchical factor score	26.0	−0.03	0.001	0.24	−0.02 <sup>b</sup>
Body Mass Index (42 yrs)					
Mean (kg/m <sup>2</sup> )	9.5	25.6	25.7	25.9	25.7 <sup>d</sup>
Smoking status (42 yrs)					
Never smoker	3.2	45.7	45.6	33.8	46.8 <sup>c</sup>
Ex-smoker		26.1	26.1	26.3	26.1
Current smoker		28.2	28.3	40.0	27.1
Problem drinking (CAGE) (42 yrs)					
No	4.3	69.2	69.2	65.4	69.6 <sup>c</sup>
Yes (CAGE score > 1)		30.8	30.8	34.6	30.4
Gender (0 yrs)					
Men	0	50.5	50.5	46.1	50.9 <sup>c</sup>
Women		49.5	49.5	53.9	49.1
Father's social class (0 yrs)					
I (highest)	9.5	4.9	4.9	3.0	5.0 <sup>c</sup>
II		14.3	14.2	9.7	14.6
IIINM		10.2	10.1	11.3	9.9
IIIM		50.7	50.5	53.6	50.2
IV		12.0	12.1	13.2	12.1
V (lowest)		7.9	8.2	9.2	8.1

**Abbreviations:** CRP: C-Reactive Protein; CAGE: Cut down, Annoyed, Guilty and Eye opener – items used to screen for problem alcohol consumption; CSE: Certificate of Secondary Education. NB only %s given as Ns vary across the 20 imputed datasets.

<sup>a</sup>  $p < 0.001$ , obtained by Wilcoxon rank sum test of medians.

<sup>b</sup>  $p < 0.001$ , obtained by  $t$ -test.

<sup>c</sup>  $p < 0.001$ , obtained from  $\chi^2$  test.

<sup>d</sup>  $p > 0.05$ , obtained by  $t$ -test.

<sup>e</sup> No missing values as analysis is on those with CRP values.

order to control for selection effects (coding is the same as for participant's own social class above). This is the only available indicator of socioeconomic position available in this wave. We also controlled for smoking status at age 42 (never smoked, ex-smoker, current smoker), problem drinking at age 42 (CAGE score > 1) and sex.

### 2.2.7. Statistical analysis

Missing data is a problem for longitudinal studies, potentially resulting in reduced statistical power, bias and unrepresentativeness. Indeed complete cases in this dataset were found to differ on most variables used in this analysis, being much more socially advantaged than those who had missing information. Therefore a complete case analysis would be inappropriate. We therefore used multiple imputation by chained equations (MICE) to account for missing data and account for differential attrition. This approach is useful where there is missing data on many variables, such as in this study. The imputation model contained all analysis variables, variables predictive of missingness (e.g. indicators of disadvantage), and variables thought to provide useful information to fill in gaps (e.g. same measures from preceding or subsequent waves). We imputed 20 datasets for those with a CRP value (MICE was implemented prior to removing those with CRP values  $\geq 10$  mg/L) and subsequent analyses were run across all 20 datasets. Table 1 shows the proportion of missing information for each variable and also compares the

observed and imputed data, suggesting that the imputation has been appropriately conducted. Our final sample size was 7462.

Chi-squared tests, *t*-tests and Wilcoxon rank sum tests were used to assess bivariate associations between parental separation and all analysis variables. Linear regression was used to test the unadjusted and adjusted association between parental separation and CRP. Path analysis was then used to simultaneously estimate all associations in our conceptual model, adjusted for all control variables. The model was then refined according to the modification indices and non-statistically significant associations were removed, starting with the association with a *p* value closest to 1. The final model therefore represents all associations which are statistically significant at the 5% level. A Wald test was used to test the relative weight of purely material and psychosocial pathways in order to assess which group was more important.

## 3. Results

### 3.1. Sample characteristics

8.4% of the sample had experienced parental separation during childhood (Table 1). For those who experienced parental separation, median CRP was significantly higher at

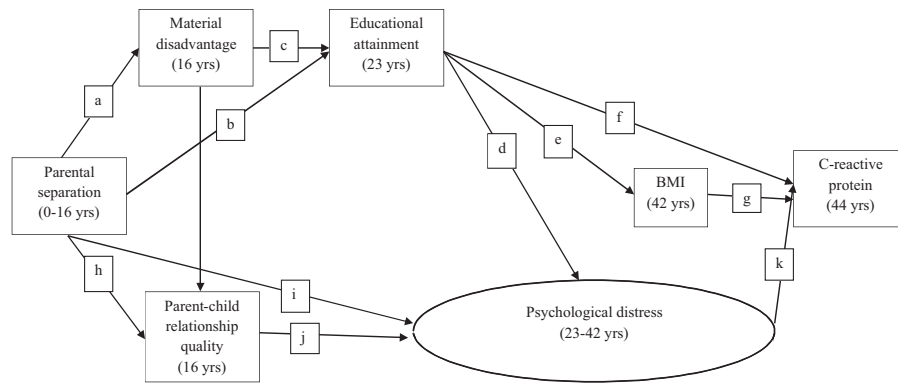
**Table 2** Association between parental separation (0–16 yrs) and adult CRP (45 yrs).

	Standardised regression coeff. ( $\beta$ )	95% CI	<i>p</i>
<b>Unadjusted association</b>			
Parental separation (0–16 yrs)			
No separation	Ref		
Separation	0.16	0.06, 0.27	0.002
<b>Adjusted association<sup>a</sup></b>			
Parental separation (0–16 yrs)			
No separation	Ref		
Separation	0.10	0.01, 0.21	0.042
Smoking status (42 yrs)			
Never smoker	Ref		
Ex-smoker	0.07	0.01, 0.14	0.018
Current smoker	0.31	0.25, 0.37	<0.001
Problem drinking (CAGE) (42 yrs)			
No	Ref		
Yes (CAGE score >1)	–0.01	–0.06, 0.05	0.886
Gender (0 yrs)			
Men	Ref		
Women	0.01	–0.04, 0.06	0.592
Father's social class (0 yrs)			
I (highest)	–0.30	–0.42, –0.18	<0.001 <sup>b</sup>
II	–0.31	–0.38, –0.23	
IIINM	–0.20	–0.29, –0.11	
IIIM	Ref		
IV	0.05	–0.04, 0.13	
V (lowest)	0.03	–0.06, 0.13	

*Abbreviations:* CAGE: Cut down; Annoyed/Guilty and Eye opener – items used to screen for problem alcohol consumption; CI: confidence interval

<sup>a</sup> Association between parental separation and CRP controlling for sex, father's social class, smoking status and problem drinking.

<sup>b</sup> *p* value for trend.



**Figure 2** Final model of material and psychosocial mechanisms linking parental separation and adult inflammation in the NCDS.

1.11 mg/L, compared to 0.93 mg/L for those who did not. Those who experienced separation were less materially advantaged, had lower educational attainment and were more likely to be in a manual social class. Also those in the separation group were more likely to report poorer quality parent–child relations and psychological distress. Those who grew up with two parents were less likely to be a smoker or a problem drinker at age 42, and were less likely to have fathers from social classes I and II. However BMI did not vary by parental separation status.

### 3.2. Association between parental separation and CRP

Table 2 shows the results from linear regression analyses. Those who experienced parental separation in childhood had

higher CRP levels at age 44 than those who did not. This association only slightly attenuated on adjustment for control variables (father’s social class, smoking, problem drinking and gender). In addition father’ social class and smoking status were associated with CRP.

### 3.3. Pathways

Results of testing the path model are shown in both Fig. 2 and Table 3. The final model in Fig. 2 differs from the initial path model as associations have been added in response to the modification indices and also some associations have been removed as they were not statistically significant. The most notable association that was removed was the direct path between parental separation and CRP. Upon modelling the indirect paths through material and psychosocial factors, this

**Table 3** Path analysis results for final model.

Path label	Association tested	Standardised regression coeff. ( $\beta$ )	p Value
a	Parental separation → material disadvantage	−0.24	<0.001
b	Parental separation → education	−0.06	<0.001
c	Material disadvantage → education	0.33	<0.001
d	Education (no qual) → psychological distress	Ref	<0.001 <sup>a</sup>
	Education (CSE) → psychological distress	−0.26	
	Education (A-level) → psychological distress	−0.30	
	Education (Higher) → psychological distress	−0.33	
e	Education (no qual) → BMI	Ref	<0.001 <sup>a</sup>
	Education (CSE) → BMI	−0.14	
	Education (A-level) → BMI	−0.15	
	Education (Higher) → BMI	−0.21	
f	Education (no qual) → CRP	Ref	<0.001 <sup>a</sup>
	Education (CSE) → CRP	−0.27	
	Education (A-level) → CRP	−0.48	
	Education (Higher) → CRP	−0.61	
g	BMI → CRP	0.33	<0.001
h	Parental separation → parent–child relationship qual.	0.08	<0.001
i	Parental separation → psychological distress	0.04	0.001
j	Parent–child relationship qual. → psychological distress	0.14	<0.001
k	Psychological distress → CRP	0.04	0.002

Abbreviations: BMI: Body Mass Index; CRP-C-Reactive Protein; CSE: Certificate of Secondary Education. Model fit: RMSEA = 0.062; CFI = 0.469; TLI = 0.400; Rsq for CRP = 0.149; NB confidence intervals are not available for STDYX estimates with imputed data in MPlus. Model adjusted for sex, smoking status (42 yrs), problem alcohol consumption (42 yrs), father’s social class (0 yrs).

<sup>a</sup> p Value for trend.

direct pathway was no longer statistically significant, suggesting that these factors largely mediate the association between parental separation and CRP. As we added each group of pathway variables the model fit indices suggested an improved model fit (i.e. RMSEA reduced towards 0, CFI and TLI increased towards 1).

Adolescent material disadvantage and educational attainment appeared to be important in mediating the association between parental separation and adult CRP. In particular the results suggest that children who experienced separation tended to be more materially disadvantaged and tended to do less well in education. Social class at age 42 was removed as the associations passing through this variable were not statistically significant. The associations which involve educational attainment appear to be particularly strong (comparing standardised estimates). Psychosocial factors are also important in mediating the overall association; those who experienced parental separation reported poorer quality parent–child relationships and were more likely to be psychologically distressed in adulthood. A link was found between material and psychosocial mechanisms; those who had a lower level of educational attainment were more likely to be psychologically distressed.

There is also evidence that BMI is involved in the relationship between educational attainment and inflammation in mid-life, but only in partially mediating the effect of educational attainment on CRP. BMI was not involved in translating psychosocial disadvantage into adult inflammation.

All the associations in the model exist after controlling for father's social class at birth as an indicator of disadvantage prior to parental separation, taking account that families who separate tend to be more disadvantaged prior to the separation process. We additionally tested the relative importance of material and psychosocial mechanisms using a Wald test, and find that material factors are more important ( $p < 0.001$ ) in the association between parental separation and adult CRP.

#### 4. Discussion

In this study we find that parental separation occurring during childhood is associated with increased inflammation in adulthood in a large British birth cohort study. This finding is supported by previous work which finds a relationship between childhood adversities and adult inflammation (e.g. Taylor et al., 2006; Danese et al., 2007, 2008, 2009; Slopen et al., 2010; Appleton et al., 2012; Tietjen et al., 2012).

The mechanisms through which parental separation leads to a pro-inflammatory profile in adult life include material factors, psychosocial factors and, more proximally, BMI. The findings suggest that parental separation appears to set individuals down a path of disadvantage characterised by increased material disadvantage, reduced educational attainment which is associated directly with increased inflammation but also operates through increased adult psychological distress and increased BMI. These findings concur with others who find that parental separation is associated with long-term disadvantage in both material (Amato et al., 1991; Ely et al., 1999) and psychosocial (Cooney, 1994; Rodgers et al., 1997; Chapman et al., 2004) domains of life,

and link to Sweeting and West's concept of the 'unhealthy life career' hypothesis connecting disadvantage in the family of origin to adult health (Sweeting and West, 1995). Links between reduced educational attainment, increased psychological distress, and increased CRP in mid-life corroborate previous work (Hemingway et al., 2003; Copeland et al., 2012). While the effect of educational attainment on CRP was partially explained by increased BMI amongst those with lower qualifications, BMI was not linked to psychosocial mechanisms as previously found by others (Taylor et al., 2006).

Some additional pathways were suggested by the model modification indices which were added to the final model, representing additional linkages between material and psychosocial mechanisms. In particular a link between educational attainment and adult psychological distress was added, and it is well established that socioeconomic factors, of which education can be considered, are associated with psychological health.

Upon testing the relative weight of material and psychosocial mechanisms, material factors were found to be particularly important and this may represent the more objective nature of the measurements used, compared to those used to capture the quality of parent–child relationships and psychological distress. Associations involving educational attainment appear to be the strongest and this may suggest that supporting children through education may help to limit the long-term consequences for individual health. After taking into account all mechanisms, there was no longer a statistically significant association between parental separation and adult CRP, suggesting that these mechanisms largely explain this association.

The results of this study suggest that social disadvantages investigated in our model may lead to biological change through alterations in low grade inflammation, a risk factor for later pathology. The potential biological mechanisms involved are complex. Material and psychosocial stress have been linked to changes in the hypothalamic-pituitary-adrenal (HPA) axis, and chronically raised cortisol levels may potentially decrease glucocorticoid sensitivity leading to raised inflammation (Fagundes et al., 2013). Stress-induced autonomic function may also be enhanced in those who experience chronic stress and this may be an additional source of chronic inflammation through raised noradrenaline (Fagundes et al., 2013). With regards to timing across the life course it is possible that inflammatory marker levels are chronically disrupted from childhood and additionally impacted on by further stressors across the life course. It is also possible that it is the last links in the chain of disadvantage – disadvantaged material circumstances, reduced educational attainment, psychological distress, and high BMI – which are associated with increased low-grade inflammation. Unfortunately the design of this dataset does not allow us to disentangle the timing of change.

Additional disadvantages and advantages of this study need to be addressed. We have no measures of family conflict or maltreatment in childhood in this cohort and it may be that parental separation is, in part, a proxy for these additional childhood adversities. Previous work has shown that parental conflict and not divorce is associated with poorer health outcomes (Amato et al., 1995; Morrison and Coiro, 1999; Cummings and Davies, 2002; McIntosh, 2003). Our approach

to missing data assumes that data are missing at random, meaning that missingness depends upon observed characteristics of participants. This is a reasonable assumption because this is a multidisciplinary study and we included many variables in the imputation model. The approach represents an advantage over complete case analysis which assumes data to be completely missing at random. Another limitation is that we were not able to adequately investigate whether the timing of parental separation is important for the associations investigated as this information is not available beyond the broad inter-sweep periods in which it occurred (i.e. between 0 and 7 years, 8 and 11 years and 12 and 16 years). Using these broad age bands we found that the relationship between parental separation and later CRP did not vary significantly by the age ranges at which it occurred. However, this sub-analysis is clearly limited by available information.

This study also has a number of strengths. Firstly all measures that we used were prospectively collected, thereby limiting recall bias. A large British birth cohort is used which is representative of, and therefore generalisable to, people who grew up in Great Britain of a similar age. This study had a large sample size and this was maximised by accounting for missing data. A limitation of many previous studies is that they use simple multivariate regression, controlling for mediators of interest. In this study we employ a more appropriate analytical strategy which allows for the temporal ordering of variables and explicit modelling of direct and indirect pathways of interest. This allowed for the investigation of how material and psychosocial factors interacted across the life course.

In conclusion our study highlights the importance of supporting families undergoing separation in order to minimise the long-term impact upon children's health and disease vulnerability as we show that experiencing parental separation sets children on a life course trajectory of increased disadvantage compared to their peers who grow up in 'intact' families. This study also provides evidence for the targeting of interventions in order to reduce the long-term impact of separation; for example, pathways through education appear to be particularly important and supporting children through education may be beneficial.

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The funding bodies were not involved in the analysis, interpretation of data, writing of the report, or decision to submit this paper for publication.

## Conflict of interest

All authors report no conflict of interest in relation to this work.

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