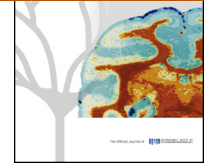




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# Social isolation in childhood and adult inflammation: Evidence from the National Child Development Study



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## KEYWORDS

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NCDS;  
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## Summary

**Background:** Social isolation is known to be associated with poorer health amongst adults, including coronary heart disease. It is hypothesized that this association may be mediated by inflammation. There has been little prospective research on the long-term impact of social isolation in childhood on adult health or the pathways which might be involved. The aim of this study was to investigate whether social isolation in childhood is associated with increased adult inflammation and the mechanisms involved across the life course.

**Methods:** This study used multiply-imputed data on 7462 participants of the National Child Development Study in Great Britain. The association between child social isolation (7–11 yrs) and levels of C-reactive protein (CRP) in middle age (44 yrs) was examined. We additionally investigated the role of adult social isolation, psychological distress, health behaviors and socioeconomic factors as potential mediators using path analysis and concurrent measurements made across the life course.

**Results:** Socially isolated children had higher levels of C-reactive protein in mid-life (standardized coefficient = 0.05,  $p \leq 0.001$ ). In addition, children who were socially isolated tended to have lower subsequent educational attainment, be in a less advantaged social class in adulthood, were more likely to be psychologically distressed across adulthood and were more likely to be obese and to smoke. All of these factors partially explained the association between childhood social isolation and CRP. However, this association remained statistically significant after considering all mediators simultaneously.

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*Conclusions:* Social isolation in childhood is associated with higher levels of C-reactive protein in mid-life. This is explained in part through complex mechanisms acting across the life course. Identification and interventions targeted toward socially isolated children may help reduce long-term adult health risk.

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## 1. Introduction

Chronic low-grade inflammation is known to be associated with adverse health outcomes, such as type II diabetes (Bassuk et al., 2004), depression (Danner et al., 2003), and coronary heart disease (Danesh et al., 2004). Many studies have shown associations between childhood adversities and raised C-reactive protein (CRP) levels – a reliable marker of low-grade inflammation (Pepys and Hirschfield, 2003). Childhood adversities known to be associated with increased adult inflammation include socioeconomic disadvantage (Phillips et al., 2009; Carroll et al., 2011; Miller and Cole, 2012), abuse and neglect (Danese et al., 2007), parental divorce (Lacey et al., 2013), as well as combined adverse childhood events scores (Slopen et al., 2010, 2013).

One childhood adversity which is not frequently investigated in relation to adult health is social isolation. Humans have a fundamental need to be socially connected to and supported by others (Baumeister and Leary, 1995). Social isolation in adulthood is known to be detrimental to health being associated with, for example, coronary heart disease (Kawachi et al., 1996). Chronic inflammation is thought to be one pathway linking psychosocial diversity to heart disease (Uchino, 2006). Few studies have addressed longer-term processes between childhood social isolation and adult health. Chronic isolation has been linked to school dropout, problem drinking, and depression (Asher and Paquette, 2003) – risk factors for poorer adult health. However, little research has explored whether childhood social isolation is associated with objective markers of poorer adult health, such as inflammation.

Two studies using the Dunedin birth cohort have begun to investigate this association. Caspi and colleagues (2006) found that childhood social isolation, as indicated by items of the Rutter behavior scale, was associated with cardiovascular risk factors at age 26 (overweight, hypertension, raised glycated hemoglobin concentration, low maximum oxygen consumption and elevated total cholesterol). Danese et al. (2009) found that children with high levels of social isolation had a 60% increased risk of a CRP value >3 mg/L at age 32, compared to children who experienced a very low level of isolation.

A number of pathways are hypothesized to be important between child isolation and adult health. Firstly, poor social relations in childhood may result in lower educational attainment and this has many consequences including adverse trajectories of occupational and social position (Brown and Taylor, 2008). Secondly, child social isolation may increase psychological distress in adult life (Katz et al., 2011; Takizawa et al., 2014). Danese et al. (2009) also found that severe child social isolation was associated with increased depressive symptoms in adulthood. Thirdly, childhood social isolation may increase the risk of adult social

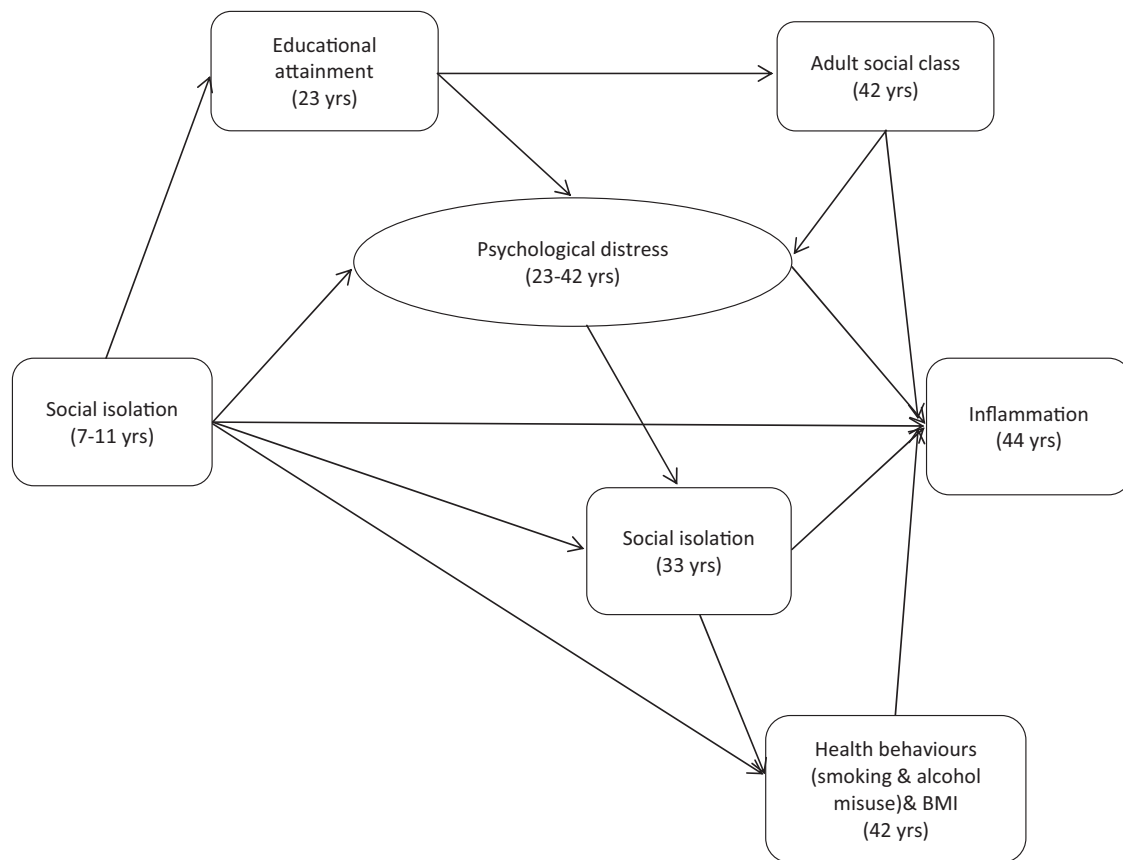
isolation through the development of social and emotional mal-adaptation (Coplan et al., 2012). Caspi and colleagues (2006) found that child social isolation was strongly associated with adolescent and adult isolation, and that adult social isolation was in turn strongly associated with cardiovascular risk factors at the age of 26. Finally, social isolation in childhood may lower self-esteem and increase the risk of uptake and maintenance of adverse health behaviors, such as smoking (Niemela et al., 2011), problem alcohol consumption (Zimmerman et al., 1997) and overeating (Ackard et al., 2003). All of these factors in turn have been associated with poor health in adulthood. For instance, an association between adult socioeconomic position and inflammation has been shown numerous times, e.g. Ramsay et al. (2008), as have associations between adult social isolation (Shankar et al., 2011), psychological distress (Taylor et al., 2006), smoking (Koenig et al., 1999), alcohol misuse (Albert et al., 2003), and BMI (Festa et al., 2001), with inflammation.

Unlike previous studies we propose that mechanisms acting between child social isolation and inflammation are linked in complex ways. We therefore consider pathways in combination with each other. We extend previous work by utilizing a British birth cohort with follow-up into middle-age (more than a decade greater than previously examined), by accounting for missing data and by explicitly modeling the mechanisms involved. We conceptualize social isolation in this study as social withdrawal or social rejection, and this is reflected in our measure of child social isolation. Our hypothesis is that children who are socially isolated have higher CRP levels in midlife, and that this is accounted for by complex pathways across the life course acting through adult social isolation, health behaviors, material disadvantage and psychological distress. Fig. 1 shows the conceptual model tested in this study.

## 2. Methods

### 2.1. Sample

This study used data from the National Child Development Study (NCDS) which aimed to recruit all babies born in Great Britain during one week of 1958, achieving a sample of 17,414 (98.2%) (Power and Elliott, 2005). Participants were surveyed at the following ages: 7, 11, 16, 23, 33, 42, 44, 46, and 50 yrs. Information was collected from multiple sources on educational, social, medical, economic and aspects of participants' lives. Informed consent was sought from respondents for each survey and ethical approval was obtained from the South East and London multicenter research ethics committees (Shepherd, 2012). The age 44 survey took the form of a biomedical assessment, during which blood samples were taken on a sub-sample



**Figure 1** Proposed conceptual model of pathways between child social isolation and adult inflammation.

of participants. We used information on participants from childhood through to age 44 from whom blood samples were taken ( $n = 8233$ , 87.8% of target).

## 2.2. Measures

### 2.2.1. Adult inflammation

CRP was measured in citrated plasma by high-sensitivity nephelometric analysis of latex particles coated with CRP-monoclonal antibodies (Elliott et al., 2008). Inter and intra-assay coefficients of variation were <10%. This is the only inflammatory marker measured in this cohort. Participants with values of  $\geq 10$  mg/L ( $n = 230$ ), indicative of recent infection and pathology (Pepys and Hirschfield, 2003), were removed from the analyses. CRP values were positively skewed and were therefore log-transformed.

### 2.2.2. Childhood social isolation

As previously mentioned we conceptualized social isolation as social rejection or withdrawal. Taking Caspi et al.'s (2006) approach two items from the Rutter behavior scale A (parent-reported) were taken from the survey at age 7 and the same two items also taken from age 11. The two items were – 'prefers to do things on his/her own rather than with others' (social withdrawal) and 'is bullied by other children' (social rejection). Responses to both items at both surveys were 'does not apply' (coded 0), 'applies somewhat' (coded 1) and 'certainly applies' (coded 2). An isolation score was

created which summed the responses across all four variables (two items across both surveys), creating a variable with a range of 0 (equivalent to no problems at age 7 or 11) to 8 (equivalent to severe problems at age 7 and 11). Scores of 7 and 8 were combined into a single category as there were few participants with a score of 8 ( $n = 10$ ). Unfortunately items directly comparable to those used in Caspi et al. (2006) were not available until age 16 in this cohort, as they used a later form of the Rutter behavior scale which was not available in our study in 1965 and 1969.

### 2.2.3. Pathway variables

**2.2.3.1. Socioeconomic factors.** Educational attainment was taken as the highest qualification achieved by age 23 (no qualifications, Certificate of Secondary Education (CSE) or Ordinary-level (O-level), Advanced-level (A-level), or degree/higher qualification). For reference, CSE/O-level qualifications are broadly comparable to US high school (or general equivalency) degree, A-level is equivalent to 'some college' and degree plus is equivalent to a completed bachelor's degree or higher (Crosby and Hawkes, 2007). Adult social class (highest in the household) was measured using the Registrar General's Social Class (RGSC) schema, based upon occupation (I – professional, II – managerial/technical, IIINM – skilled non-manual, IIIM – skilled manual, IV – semi-skilled manual and V – unskilled).

**2.2.3.2. Psychological distress.** Psychological distress was measured using Rutter's Malaise Inventory at ages 23, 33 and 42, comprising 24 yes/no items regarding emotional and

somatic symptoms (Rutter, 1970). A hierarchical factor analysis was conducted, firstly deriving two factors for each age (one emotional and one somatic) which have previously been identified (Rodgers et al., 1999). Secondly, an overall factor was derived using just the three emotional factors derived in the previous step. This ensures that an association seen with CRP is not driven by physical symptoms captured by the Malaise Inventory and also measures psychological distress across adulthood.

**2.2.3.3. Adult social isolation.** Social isolation was measured at age 33. Participants were asked to list up to four people who could provide help in six situations indicative of different forms of support – personal advice, confiding support, distress support, domestic help, financial support and household DIY. Following the approach by Matthews et al. (1999) responses were summed for the emotional (personal advice, confiding support and distress support) and practical support items (household DIY, financial support and domestic help). Participants with <3 sources of emotional or practical support were classified as socially isolated.

**2.2.3.4. Health behaviors.** Smoking status was collected at age 42 as 'never smoked', 'ex-smoker' or 'current smoker'. The CAGE questionnaire was used to identify problem drinking at age 42. Participants with a CAGE score of 1 or more were identified as alcohol misusers. Body mass index (BMI) was self-reported at age 42. A sensitivity analysis suggested that this correlated highly with measured BMI at ages 33 and 44 ( $r=0.739$  BMI33–BMI42,  $r=0.821$  BMI42–BMI44,  $r=0.783$  BMI33–BMI42). We used BMI from age 42 as this fitted well in our conceptual model, being prior to CRP measurement at age 44 but after, or concurrent to, many other pathway variables.

#### 2.2.4. Covariates

Gender, childhood BMI and parental divorce were included as covariates. Information on parental divorce by age 7 (prior to the childhood social isolation measures) was collected from the parental interview. Parental divorce in childhood is known to be associated with raised CRP in adulthood (Lacey et al., 2013) and also greater peer isolation (Teja and Stolberg, 1994). We additionally controlled for child BMI measured at age 7. Child BMI is also known to be associated with both increased adult health risk (Biro and Wien, 2010) and increased risk of social isolation (Strauss and Pollack, 2003).

### 2.3. Statistical analysis

Missing data were accounted for by multiple imputation by chained equations, imputing missing information on all variables for those participants who had CRP values. Imputation models included all analysis variables, variables predictive of missingness (e.g. indicators of social disadvantage) and the same measures from preceding and subsequent waves, where available. 20 imputed datasets were created and the estimates from regression models for each dataset were combined using Rubin's rules (1987). Table 1 shows a comparison of observed and imputed data. The imputed and observed data look similar, therefore suggesting that the imputation has been conducted appropriately. The final sample for analysis was 7462.

Multivariate linear regression models were run, firstly testing the association between childhood isolation and CRP, controlling for gender, child BMI and parental divorce. As a preliminary step to the analysis of pathways successive linear models were run including each group of pathway variables one at a time, followed by a final model controlling for all pathway variables simultaneously. To formally test the proposed mechanisms path analysis was conducted. The model was refined according to modification indices and statistically non-significant associations were removed starting with that closest to 1. The 'total effect' of childhood social isolation was then decomposed into its 'direct' and 'indirect' components. To clarify, the path modeling term of 'indirect effect' refers to the proportion of the association between social isolation and CRP which is attributable to the mechanisms considered in the model (e.g. adult social isolation, health behaviors, socioeconomic factors and psychological distress). The 'direct effect' does not necessarily mean a causal effect, but could also represent residual confounding or other mechanisms which were not considered in the present analyses. The 95% confidence intervals for the indirect and direct effects were calculated using a bias-corrected bootstrapping method with 1000 replications. This method is recommended to reduce bias associated with the assumption of multivariate normality when testing mediation and the standard errors of indirect effects (Preacher and Hayes, 2008).

## 3. Results

### 3.1. Childhood isolation and inflammation

Table 1 shows the distribution of social isolation, CRP, pathway and control variables in the sample. Results of preliminary regression analyses (standardized coefficients) testing the association between childhood isolation and adult CRP are shown in Supplementary Table. Model 1 shows that a one standard deviation increase in child isolation increased adult CRP by 0.06 standard deviations (equivalent to 1.07 mg/L increase in CRP) after accounting for gender, parental divorce and child BMI. Approximately 1.3% of the variability in CRP was accounted for by these factors ( $R\text{-squared}=1.25\%$ ). The second model is additionally adjusted for socioeconomic variables (educational attainment and social class). The association between social isolation and CRP changed very little and remained statistically significant ( $\beta=0.05$ ,  $p=\leq 0.001$ ,  $R\text{-squared}=4.2\%$ ). This was also the case in model 3 which controlled for adult psychological distress ( $\beta=0.06$ ,  $p=\leq 0.001$ ,  $R\text{-squared}=1.7\%$ ). Adult social isolation appeared to be less important; adding this variable in model 4 did not change the estimate for the main association, nor was adult social isolation associated with adult CRP ( $p=0.922$ ). Model 5 controlled for health behaviors. The association between childhood social isolation and CRP remained statistically significant ( $\beta=0.05$ ,  $p=\leq 0.001$ ,  $R\text{-squared}=1.3\%$ ). The proportion of CRP variance explained rose to 15.1% in this model, suggesting that health behaviors and adult BMI explain more than other factors in previous models. After controlling for all pathway variables simultaneously (model 6) childhood social isolation was still associated with an increase

**Table 1** Sample characteristics and a comparison of observed and imputed data.

	% missing	Observed, <i>N</i> (%)	Imputed (%) <sup>a</sup>
<i>Main exposure</i>			
Childhood social isolation, median [IQR]	26.4	2 [1, 4]	2 [1, 4]
<i>Main outcome</i>			
CRP, median [IQR], mg/L (44 yrs)	0 <sup>b</sup>	0.94 [0.46, 2.08]	0.94 [0.46, 2.08]
<i>Socioeconomic pathway</i>			
Educational attainment (23 yrs)			
No qualifications	16.7	674 (10.9)	11.7
CSE 2-5/O-level		3080 (49.6)	49.7
A-level		1157 (18.6)	18.3
Higher qualification/degree		1302 (21.0)	20.4
Household social class (42 yrs)			
I	8.7	618 (9.1)	8.7
II		3240 (47.6)	46.4
IIINM		2147 (31.5)	31.8
IIIM		635 (9.3)	10.2
IV		152 (2.2)	2.5
V		18 (0.3)	0.3
<i>Psychological distress</i>			
Adult malaise score (23–42 yrs)			
Mean of hierarchical factor score [SD]	26.0	−0.04 [0.8]	−0.01 [0.8]
<i>Adult social isolation</i>			
Socially isolated (33 yrs)			
No	11.1	5352 (80.7)	80.1
Yes		1280 (19.3)	19.9
<i>Health behaviors</i>			
Smoking status (42 yrs)			
Never smoker	3.2	3302 (45.7)	45.7
Ex-smoker		1887 (26.1)	26.1
Current smoker		2034 (28.2)	28.3
Problem drinking (42 yrs)			
CAGE score = 0	4.3	4943 (69.2)	69.2
CAGE score ≥ 1		2196 (30.8)	30.8
BMI, mean [SD], kg/m <sup>2</sup> (42 yrs)	9.5	25.6 [4.5]	25.7 [4.5]
<i>Control variables</i>			
Gender (0 yrs)			
Male	0	3768 (50.5)	50.5
Female		3694 (49.5)	49.5
Parental divorce (7 yrs)			
No	16.3	6026 (96.5)	96.4
Yes		221 (3.5)	3.6
Child BMI, mean [SD], kg/m <sup>2</sup> (7 yrs)	23.8	15.8 [1.7]	15.8 [1.7]

*Abbreviations:* IQR, interquartile range; CRP, C-reactive protein; CSE, Certificate of Secondary Education; O-level, Ordinary-level; A-level, Advanced-level; NM, non-manual; M, manual; SD, standard deviation; CAGE, cut down annoyed guilty eye-opener – items used to screen for problem alcohol consumption.

<sup>a</sup> Only %s are given for imputed data as *N*s vary across the 20 imputed datasets.

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

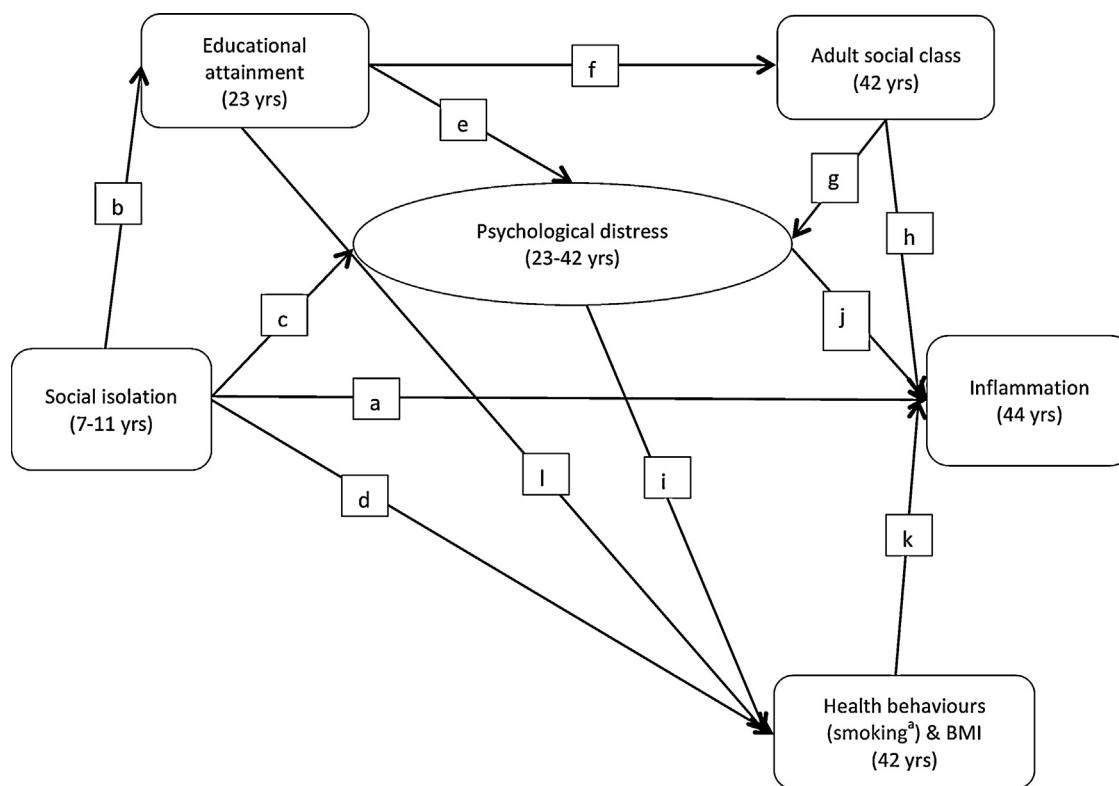
in adult CRP ( $\beta=0.04$ ,  $p=0.002$ , R-squared = 16.1%). In all models pathway variables, with the exception of adult social isolation, remained independent predictors of adult CRP.

Supplementary table related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.psychneuen.2014.08.007>.

### 3.2. Pathways between childhood isolation and inflammation

In order to test the mechanisms between childhood social isolation and adult CRP path analysis was conducted. The final model and estimates are shown in Fig. 2 and Table 2. Fig. 2 differs from Fig. 1 as associations were





<sup>a</sup>Alcohol misuse was removed as was not significantly associated with CRP

**Figure 2** Final model of pathways linking child social isolation and adult inflammation (effect estimates and path descriptions given in Table 2).

**Table 2** Standardized path coefficients for pathways between child social isolation and adult CRP.

Path label	Description	$\beta^a$	P
a	Child social isolation → CRP	0.03	0.002
b	Child social isolation → educational attainment	-0.11	≤0.001
c	Child social isolation → psychological distress	0.07	≤0.001
d	Child social isolation → never smoker	Ref	
	Child social isolation → ex-smoker	-0.08	0.001
	Child social isolation → current smoker	0.03	0.280
	Child social isolation → BMI	0.02	0.036
e	Educational attainment → psychological distress	-0.19	≤0.001
f	Educational attainment → social class	-0.53	≤0.001
g	Social class → psychological distress	0.09	≤0.001
h	Social class → CRP	0.12	≤0.001
i	Psychological distress → BMI	-0.04	0.001
j	Psychological distress → CRP	0.06	≤0.001
k	Never smoker → CRP	Ref	
	Ex-smoker → CRP	-0.02	0.182
	Current smoker → CRP	0.13	≤0.001
	BMI → CRP	0.34	≤0.001
l	Educational attainment → BMI	-0.14	≤0.001

Abbreviations: CRP, C-reactive protein; BMI, body mass index; Ref, reference category.

Model fit: TLI=0.965; CFI=0.976; RMSEA=0.018.

<sup>a</sup> Confidence intervals are not available with STDYX estimates with imputed data in MPlus. Path model is adjusted for gender, parental divorce and child BMI.

added in response to modification indices and some of the hypothesized associations were removed as they were not statistically significant. In particular, paths operating through adult social isolation and problem alcohol consumption were removed as neither variable was associated with adult CRP ( $p=0.969$  and  $p=0.636$ , respectively). Two additional paths were added between educational attainment and adult BMI, and between psychological distress and adult BMI in response to modification indices.

Looking firstly at the socioeconomic pathway we found that children who were socially isolated tended to have lower educational attainment by age 23. Educational attainment was strongly associated with occupational social class at age 42. Social class was in turn associated with CRP levels at age 44 (CRP levels decrease with increasing disadvantage as indicated by social class). Adult psychological distress was also found to be an important mediator; as child isolation increases psychological distress scores also increase. Psychological distress was in turn associated with increased CRP levels at age 44. Health behaviors were also found to be important mediators of the association between child isolation and adult CRP. In particular, socially isolated children were more likely to be ex-smokers compared to never smokers, though no differences were observed for current smoking status. Smoking status was associated with CRP, with current smokers having higher CRP levels on average. Child social isolation was not found to be associated with alcohol misuse, as mentioned above. In addition, child social isolation was associated with having a higher BMI at age 42, a risk factor for increased CRP.

The path model suggests that the mechanisms operating across the life course are particularly complex as each group of pathway variables are also interlinked. For instance, educational attainment is not only associated with social class, but also independently with adult psychological distress and adult BMI. Similarly adult psychological distress is negatively related to adult BMI (as psychological distress increases, BMI decreases).

Even after considering all pathways simultaneously childhood social isolation was still associated with increased CRP many years later ( $\beta=0.03$ ,  $p=0.002$ , equivalent to 1.03 mg/L increase per standard deviation of child social isolation), consistent with the preliminary regression results. The 'direct' and 'indirect effects' were decomposed and the results suggest that the indirect mechanisms investigated accounted for more than half of the 'total effect' of child social isolation on adult CRP (total effect = 0.058 95% CI: 0.036, 0.080, indirect effect = 0.031 95% CI: 0.022, 0.040 therefore the % of total effect explained by indirect mechanisms =  $0.031/0.058 = 0.535$  or 53.5%). The overall 'indirect effect' was statistically significant ( $p \leq 0.001$ ). More specifically the indirect mechanisms operating via adult BMI (child isolation  $\rightarrow$  adult BMI  $\rightarrow$  CRP) and that operating via socioeconomic factors (child isolation  $\rightarrow$  educational attainment  $\rightarrow$  social class  $\rightarrow$  CRP) appear to be the most important (data not shown).

#### 4. Discussion

These findings provide further evidence of the life-long impact of childhood circumstances, and adversities, on adult

health. In particular, observations suggest that childhood isolation is related to an inflammatory marker in mid-life, only part of this relationship being accounted for by mediating psycho-social and behavioral factors. C-reactive protein has repeatedly been described as a predictor of adverse health outcomes (Danesh et al., 2004). Our results therefore provide evidence of potential mechanisms by which childhood social isolation might be related to poorer health in adulthood. Our findings extend those from the Dunedin study in which CRP was measured at age 32 (Danese et al., 2009) and indicate that effects persist later into life. Our findings also complement Caspi et al. (2006) who find that socially isolated children have heightened risk of cardiovascular diseases as indicated by hypertension, obesity, hypercholesterolemia, raised glycated hemoglobin concentration and low maximum oxygen consumption.

In addition, we extend these previous observations to enhance the understanding of mediating pathways between child isolation and adult inflammation. Our mediation model was developed using previous literature linking childhood social isolation with adult health outcomes, particularly drawing on Caspi et al. (2006). Their hypothesis was that isolated children had a higher risk of cardiovascular disease because they were more likely to be socially isolated across the life course, were more likely to engage in risky health behaviors such as smoking, heavy drinking and physical inactivity, and were more likely to be depressed as adults. These factors in turn were thought to be associated with indicators of increased cardiovascular risk. We therefore included these same mediators in our model, but additionally included a path involving adult socioeconomic factors. There is evidence from the same cohort study that socially isolated children tended to have lower educational attainment, which has consequences for adult socioeconomic attainment (Brown and Taylor, 2008).

Our findings suggest that this association is indeed explained in part by a complex web of life course mechanisms. Two pathways involved socioeconomic factors and adult psychological distress. In particular social isolation in childhood predicted lower educational attainment and increased psychological distress, as has been previously described for this cohort (Katz et al., 2011; Ammermueller, 2012; Takizawa et al., 2014). In addition child social isolation was associated with the uptake of risky health behaviors, with increased adult BMI and smoking, as shown by other studies of pathways from childhood adversities to adult inflammation. For instance, Raposa et al. (2014) found that the association between early adversity and adult inflammation was largely explained by smoking and BMI. Similar to our study they found that alcohol consumption was not involved as a mediator, although they looked at frequency of drinking rather than alcohol misuse. The association of ever smoking but not current smoking at age 42 suggests that child social isolation is associated with smoking initiation rather than cessation.

The finding that child isolation is not associated with adult isolation disagrees with the notion that childhood social isolation represents a developmental mal-adaption (Hymel et al., 1990). However, this finding may relate to the measure of adult isolation used in this study. Recent data suggest that bullying in childhood is associated with isolation in adult life, when participants in this cohort were

aged 50 (Takizawa et al., 2014). Unfortunately we were not able to use the same measure of adult isolation as this was only available after measurement of CRP.

After considering all mediators child social isolation was still associated with increased CRP in mid-life. After considering all mediators, child social isolation was still associated with increased CRP in mid-life in accordance with Danese et al. (2009). The effect size seen is clinically significant as a one standard deviation increase in child social isolation (equivalent to a score of 1.5 on this variable) produced an increase in CRP of 1.07 mg/L. For comparison, Danesh et al. (1998) reported a 70% increased risk of coronary heart disease amongst those in the highest tertile of the CRP distribution (mean CRP of this group = 2.4 mg/L). This mean CRP level is approximately equivalent to that produced by a two standard deviation increase in child social isolation in our study, assuming the same associations of CRP and event rate.

It is possible that child isolation exerts a direct effect upon physiological functioning and that our findings provide further evidence of the 'biological embedding' of early life stress to enact permanent changes in health (Hertzman, 1999). The mechanisms by which this occurs may include changes in direct beta cell mediated inflammation (Nance and Sanders, 2007; Irwin and Cole, 2011). Recent data from animals and humans suggest that the adverse social environment (social disadvantage in man and 'social defeat' in mice) results in changes in blood cell composition and pro-inflammatory gene expression (Powell et al., 2013) potentially leading to mechanisms that may predispose to changes such as cytokine induced 'sickness behavior' (Dantzer and Kelley, 2007) or adverse health (Hingorani and Casas, 2012). However, long-term changes in gene expression in this context have yet to be described. Raised levels of inflammatory markers may also be due to unmeasured sub-clinical health such as atheroma (Drakopoulou et al., 2009). However, we were unable to account for this in our analyses. It is also possible that this remaining 'direct effect' was explained by residual confounding or other mechanisms not considered in this study.

This study is not without its limitations. CRP was only measured at age 44 therefore we do not know from which point this may be raised; for example, it is possible that CRP might be chronically raised from early adulthood, or some other age, but we are unable to distinguish the point of change in this study. There was no formal measure of childhood social isolation available, however our measure comprises a question relating to peer withdrawal (isolation) and a question relating to peer rejection (bullying) which likely represent different aspects of social isolation. When we looked separately at each of these questions, the associations we saw were largely driven by the bullying item although the other item about preferring to be alone was still associated with raised CRP without considering the bullying item (results not shown). These observations may support the findings of Rubin et al. (1991) who suggest that the type of isolation in childhood may determine consequent outcomes. Thus peer rejection may have more adverse sequelae than peer withdrawal because this may be more outside of the child's control. Therefore our findings implicate a role of low control on inflammatory marker levels. We do not have a multi-dimensional measure of child isolation, for example covering the family, school, and

religious ties. It might be that some children are well integrated within one domain, such as the family, but not in others, such as with peers. We additionally do not have measures of the subjective experience of social isolation, such as loneliness, in this dataset in childhood or adulthood. Previous research by Cacioppo and other authors has shown that the subjective experience, particularly loneliness, is more likely to result in adverse health outcomes than objective measures of isolation (Uchino et al., 1996; McDade et al., 2006; Cornwell and Waite, 2009). However, we hypothesized that the socially withdrawn or socially rejected child would have a higher probability of remaining in an environment that fails to provide sufficient social support. This is likely to be perceived as stressful, which in turn activates stress mechanisms in the body resulting in increased CRP levels by mid-life. We also do not take account of comorbidities contemporaneous to our measure of CRP. However, data from the Health Survey for England (Craig and Mindell, 2012) have shown that the prevalence of disease is low for this age group. For example, the prevalence of diabetes is <3%, ischemic heart disease or stroke is <2% and around 6% have any cardiovascular disease. It is possible that the association is confounded by sub-clinical illness leading to fatigue and reduced engagement with others. However, we were not able to capture this in our study.

This study also has a number of strengths, such as the use of a large sample representative of the British population of a similar age. Missing data were accounted for, thereby reducing bias associated with differential non-response. The data were collected prospectively thereby minimizing recall bias and offered a long follow-up period of 44 yrs. In addition, path analysis is more appropriate than standard regression techniques for examining explanatory pathways, therefore adding strength to the literature base on the mechanisms linking childhood adversities to later health.

In conclusion, child social isolation is associated with increased adult inflammation as measured by CRP. This is explained in part through complex mechanisms acting across the life course. Identification and interventions targeted toward isolated children may help reduce long-term adult health risk. In particular, interventions toward preventing smoking uptake, maintaining healthy BMIs and encouraging educational attainment may be useful. Further research is also required to investigate pathways into child isolation, as interventions targeted toward these may also help alleviate health risk in later life.

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## Conflicts of interest

None of the authors report any conflict of interest.

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