Full-length Article

Adverse childhood experiences and adult inflammation: Findings from the 1958 British birth cohort

Mingyi Chen, Rebecca E. Lacey *

Research Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK

ABSTRACT

Background: The relationship between adverse childhood experiences (ACE) and poorer health across the life course is well established. Increased chronic inflammation might be one mechanism through which these associations operate. The aim of this study was to explore the relationship between ACE and adult inflammation using a prospective longitudinal study. We also investigated whether associations were explained by life course socioeconomic, psychological and health behavioural factors, and whether associations differed by gender.
Methods: Multiply imputed data on 7464 participants of the National Child Development Study (1958 British birth cohort) were used. Prospectively collected data on ACE included care placement, physical neglect, parental separation, family history of offences, mental illness, domestic conflict and alcohol misuse across childhood (0–16 years). Adult inflammation was indicated by C-reactive protein (CRP), fibrinogen and Von Willebrand factor (vWF) at age 44/45. Multivariable linear regression models were used to estimate associations between ACE and adult inflammation.
Results: Graded associations for ACE with CRP and fibrinogen were observed (e.g. CRP: 1 ACE: 4.61% higher, 95% CI: −3.13, 12.97; 2+ ACE: 16.35% higher, 95% CI: 6.87, 26.66). Socioeconomic and health behavioral factors were found to particularly explain these associations. After inclusion of all covariates associations between ACE and mid-life inflammation were no longer significant. Associations did not differ for men and women.
Conclusions: ACE were associated in a graded manner with adult inflammation in a British birth cohort. The association was explained by life course socioeconomic and health behavioral factors, in particular. This study highlights the importance of protecting children from ACE and its negative health effects, and in supporting children through education and into skilled, secure work.

1. Introduction

Childhood adversities, including household dysfunction and physical neglect, are an important public health concern in many countries. For example, the number of children who were abused was estimated to approach 520,000 in the UK in 2011 and this has increased over time (Radford et al., 2011). Similarly, Gilbert and colleagues (2009) showed that self-reported physical and psychological abuse may be reported by up to between 29% and 33% of children, respectively, in Eastern European countries. Also the annual prevalence of childhood sexual abuse might be as high as 15–30% for girls and 5–15% for boys in Australia, Canada, New Zealand and the United States (Gilbert et al., 2009). Whilst self-reported survey data are likely to be preferential to administrative data sources, they are still likely to be underestimations of the true population prevalence.

Numerous studies have shown that childhood adversities have the potential to increase the risk of many diseases and even increase the likelihood of premature mortality (Brown et al., 2009; Danese et al., 2009; Felitti et al., 1998; Kelly-Irving et al., 2013a). Inflammation might be one mechanism through which adverse childhood experiences (ACE) affect later health. Chronic inflammation is associated with the increased risk of many non-communicable diseases, such as cancer, autoimmune diseases and diabetes (Baecklund et al., 2006; Festa et al., 2000; Shacter and Weitzman, 2002). Biological theories underpin a feasible direct link between ACE and adult inflammation; being repeatedly exposed to ACE can affect the human stress regulatory system, which is accompanied by an increase in chronic inflammation (Lupien et al., 2009; McEwen, 2012; Shonkoff et al., 2012). The detrimental effects of early life stress on the human stress response

---

* Corresponding author.
  E-mail address: rebecca.lacey@ucl.ac.uk (R.E. Lacey).

system, once made, are long-term, thus resulting in chronic inflammation over the life course (Hertzman and Boyce, 2010).

Accompanying the direct association between ACE and inflammation, previous studies imply that socioeconomic factors, psychological distress and health behaviors might also mediate the association between ACE and adult inflammation. For instance, in the Dunedin cohort study socioeconomic factors partially explained the association between childhood abuse and adult inflammation (Danese et al., 2007). Considering that individual achievement could be substantially influenced by parental social class and education, educational attainment and social class were hypothesized as one of the pathways linking ACE and inflammation in the present study (Erola et al., 2016). Furthermore, childhood trauma has been associated with increased risk of psychopathology across the life course (Danese and Baldwin, 2017) and consistent findings have been published on the role of psychological distress between childhood adversities, including household financial burden, physical and sexual abuse, and elevated inflammatory biomarkers (Danese et al., 2007; Taylor et al., 2006). Hence, psychological distress was also included as another potential mediator here.

In a recent review by Nusslock and Miller (2016), bidirectional pathways between inflammation and neural circuitry were proposed. ACE might exaggerate this bidirectional mechanism whereby chronic systemic inflammation acts on the brain to facilitate self-medication through smoking and the consumption of high calorie foods (Nusslock and Miller, 2016). Indeed health behaviors such as smoking, alcohol misuse, and lack of physical activity, were found to also link with ACE and adult inflammation (Danese et al., 2007). For example, parental separation was found to increase the risk of smoking and binge drinking and in turn unhealthy drinking behaviors were related to increased chronic inflammation (Alho et al., 2004; Martindale and Lacey, 2017; Ohsawa et al., 2005). Thus, health behaviors were included as another potential pathway between ACE and inflammation.

There is some suggestion that gender differences exist in the relationship between ACE and adult inflammation. Previous work found that women who experienced child maltreatment had higher risk of premature mortality (Brown et al., 2009; Cheng et al., 2015). Also women who experienced ACE had higher risk of heart disease in the National Survey of Midlife Development in the United States (Friedman et al., 2015) and higher risk of cardiovascular disease in the Canadian National Population Health Survey (Garad et al., 2017). Gender differences in associations between ACE and later health have been little investigated, particularly in relation to inflammation.

One of the main limitations of many papers published exploring the association between ACE and adult inflammation is that they've relied on retrospectively-collected data on ACE. It is known that the reporting of early life adversities is limited by recall bias, and recent studies have shown that there is a high level of discordance between prospective and retrospective reporting of ACE (Newbury et al., 2018), which is affected by adult stressors, such as mental illness and work stress (Colman et al., 2014). Another limitation, linked to the above, is that many papers have adopted a cross-sectional study design (Coelho et al., 2014). Furthermore, less research has been conducted utilizing British longitudinal data, such as the British birth cohort studies. These series of studies have prospectively-collected data on ACE across childhood, reported by the cohort member's parents, teachers and health visitors, making them ideal datasets for investigating associations between ACE and life course health.

The aim of this study was to investigate the association between ACE and adult inflammation in a longitudinal study in Great Britain and to explore the life course mechanisms through which this association might operate. Three biomarkers were selected to indicate adult inflammation. Therefore, the possible social-biological pathways linking ACE with later disease outcomes were to be clarified and examined. Firstly, our hypothesis was that there is a graded relationship between ACE and adult inflammation; the more ACE a child experiences, the higher the level of inflammation in mid-life (Dube et al., 2003, 2002; Felitti et al., 1998). Secondly, we hypothesized that the strength of the association differed for men and women, with a stronger association likely for women (Dube et al., 2003; Mersky et al., 2013). Thirdly, by utilizing a multidisciplinary longitudinal study we were able to examine the potential life course socioeconomic, behavioral and psychological mechanisms linking ACE with inflammation in mid-life.

2. Methods

2.1. Data

This study used the National Child Development Study (NCDS, also known as the 1958 British birth cohort), which comprised all live births (n = 17,415, 98.2% of all births) during one week in 1958 in Great Britain (England, Wales and Scotland). At present, data have been collected from a total of ten main surveys when the cohort members were aged 0, 7, 11, 16, 23, 33, 42, 46, 50, and 55 years. In 2004, when participants were aged 44/45, a subsample of 9377 cohort members participated in a biomedical survey. Further details about the NCDS are recorded elsewhere (Power and Elliott, 2005). Information collected from ages 0, 7, 11, 16, 23, 42 and 44/45 was used in this study to explore the relationship between ACE and adult inflammation.

2.2. Ethical considerations

Informed consent was obtained from both the cohort members and their legal guardians for adult and childhood sweeps, respectively. Ethical approval was obtained from the National Research Ethics Advisory Panel. This study conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.3. Measures

2.3.1. Adverse childhood experiences

Childhood adversities have been defined in different manners in previously published papers, including household dysfunction, physical abuse, and substance misuse problems of family members (Felitti et al., 1998; Fergusson and Horwood, 2003; Rosenman and Rodgers, 2004). After reviewing the relevant definitions in other epidemiological studies and international committees, ACE were defined in this study as stressful intrafamilial events and traumatic conditions which are beyond the control of the participants when they were young (Barboza Solís et al., 2015; Rosenman and Rodgers, 2004). These conditions may co-occur and have synergistic effects, impairing normal stress regulation system over time and thus leaving lasting health effects (Dong et al., 2004).

The NCDS has a wealth of prospectively collected ACE data; information on ACE was collected from the child's parent, health visitor or teacher when the cohort members were aged 7, 11 and 16 years (Kelly-Irving et al., 2013a,b). The ACE included in this study were:

1. Care placement: Was the cohort member ever in local authority or voluntary care when they were aged 7, 11 or 16?
2. Physical neglect: Did the child appear dirty or undernourished when they were aged 7 or 11?

3. Record of offending: Did the child live in a household where a family member was in prison or on probation (age 11 years) or in contact with the probation service at 7 or 11 years? Has the child ever been in prison or on probation at 16 years?
4. Parental separation: Has the child ever been separated from either parent because of death, divorce, or separation when they were aged 7, 11 or 16?
5. The occurrence of mental illness: Has anyone in the child's household had contact with mental health services at 7 or 11 years? Did a family member have a mental illness when they were aged 7, 11 or 16?
6. Domestic conflict: Was domestic tension apparent to the health visitor conducting the interview with the cohort member's mother at age 7?
7. Alcohol misuse: Did a family member have alcohol misuse problems when the cohort member was aged 7?

Participants were considered to not have experienced any of the above adversities if they answered "no" to all. ACE score was calculated by tallying the number of positive responses to all seven adversities across all three surveys (age 7, 11 and 16). The total ACE score therefore ranged from 0 to 16. As the number of participants with ACE scores higher than 3 was small, a three-category variable was created (no adversities, one adversity, or two or more adversities) consistent with the approach employed by many other studies (Felitti et al., 1998; Kelly-Irving et al., 2013a,b).

2.3.2. Adult inflammation

C-reactive protein (CRP), fibrinogen and von Willebrand factor (vWF) were used to indicate inflammation, all of which were measured from blood samples taken by a research nurse in the biomedical survey at age 44/45. Whilst all play a role in inflammatory processes, fibrinogen and vWF also have clotting and endothelial functions. Whilst less commonly used in epidemiological analysis as an inflammatory marker, the role of vWF in inflammation is becoming increasingly recognized (Kawecki et al., 2017). CRP was measured on citrated plasma by high-sensitivity nephelometric analysis (Dade Behring, Milton Keynes, UK) of latex particles covered in CRP-monoclonal antibodies (Elliott et al., 2008). CRP ranged from 0.2 mg/L (lower limit of sensitivity) to 10 mg/L in the analytical sample, as CRP concentrations above 10 mg/L indicative of acute pathology and infection were removed from the analyses (n = 228) (Pepys and Hirschfield, 2003). Fibrinogen was measured using the Clauss method and vWF antigen was measured by Decollates enzyme-linked immunosorbent assay (DAKO plc, High Wycombe, UK) (Elliott et al., 2008). The inter- and intra-assay variation coefficients, respectively, for each inflammatory marker were as follows: 8.3% and 4.7% for CRP; 3.7% and 2.6% for fibrinogen; 4.2% and 3.3% for vWF (Tabassum et al., 2008). The distributions of all three inflammatory markers were positively skewed, and thus were log-transformed for subsequent analyses.

2.3.3. Potential life course mediators

Three groups of potential mediating variables were considered in this study: socioeconomic factors; psychological distress; and health behaviors.

2.3.3.1. Socioeconomic factors.
Socioeconomic factors included in this study were educational attainment at age 23 and adult occupational social class at age 42 in this study. The former referred to the highest education qualification achieved by age 23 (categorized as: no qualifications, Ordinary-levels/Certificate of Secondary Education, Advanced-levels (A-levels) or higher qualification). Adult social class was indicated by the Registrar General's Social Class (RGSC) schema. RGSC social class takes the categories: professional (highest), managerial/technical, skilled non-manual,

skilled manual, semi-skilled manual, and unskilled manual (lowest). Social class was taken at age 42 rather than from an earlier survey (e.g. age 33) as social class is likely to be more stable and hence accurately measured at this later age, particularly for women in this cohort.

2.3.3.2. Psychological distress.
The Malaise Inventory, comprised of 24 yes/no items, captured self-reported emotional and somatic symptoms at age 42 (Rutter, 1970). The total Malaise Inventory score ranged from 0 to 23 in our sample. Further information on the Malaise Inventory can be found in supplement 1.

2.3.3.3. Health behavior pathway.
Health behaviors included problem alcohol consumption, smoking, physical exercise and BMI. Information on health behaviors was taken from age 42 as the information available was more detailed than that available at an earlier survey (e.g. age 33). Alcohol misuse was extracted from a set of four questions comprising the CAGE (Ewing, 1984) questionnaire: "Have you ever felt you needed to Cut down on your drinking? Have people Annoyed you by criticizing your drinking? Have you ever felt Guilty about drinking? Have you ever felt you needed a drink first thing in the morning (Eye-opener) to steady your nerves or to get rid of a hangover?" The respondent was considered to have alcohol misuse problems if they answered "yes" to two or more items. Smoking status was categorized as: never smoker, ex-smoker and current smoker. Physical activity was reflected by a binary variable (regular exercise: yes, no) and body mass index (BMI) was a continuous variable constructed from self-reported height and weight (kg/m^2). The derived self-reported BMI at age 42 correlated highly with measured BMI at ages 33 and 44 (e.g. r = 0.739 BMI33-BMI42).

2.3.4. Confounding variables

To more accurately estimate the association between ACE and adult inflammation, confounding factors were also included. Potential confounders included the socioeconomic background of cohort members, and the health status of the cohort member in early life and their parents. Socioeconomic deprivation is a risk factor for childhood adversity (Gillham et al., 1998) and is also associated with increased adult inflammation (Danese et al., 2009). Overcrowding (<1.5 people per room, more than 1.5 people per room), mother's education (left school at or before minimum age, or stayed at school beyond minimum age) and paternal social class (RGSC, coded the same as own social class at age 42) were used to reflect socioeconomic deprivation at birth. Additionally, maternal factors, including maternal age at birth of the cohort child (years), and maternal smoking during pregnancy (categorized as: never, sometimes, moderately, heavily), were also included as both of these factors are associated with child adversities and adult inflammation (Gilman et al., 2008; Hedin and Janson, 2000). Other confounders included parity (primiparous, one, two or more), breast feeding (categories as: no, up to one month, or more than one month), and birth weight (ounces). Again these factors are associated with adult inflammation (McDade et al., 2014) and also ACE (Laucht et al., 2000). These confounders were based on previously published research using this dataset (Kelly-Irving et al., 2013b) and in this dataset were associated with both exposure (ACE score) and at least one inflammation outcome.

2.4. Missing data

The response rates for each wave have been good; at age 16, 84.1% remained, 72.0% remained at age 23 and 65.6% remained at age 42. Sample loss was mainly due to attrition through residential moves and refusal (Power and Elliott, 2005). However, missing data introduces bias to the sample and limits the ability

to generalize findings to a wider population. Missing data were therefore accounted for using multiple imputation by chained equations. This method is particularly good for accounting for uncertainty in the imputations, and is generally superior to other imputation methods, such as single imputation (Sterne et al., 2009). Twenty imputed datasets were created imputing information on all analysis variables under the 'missing at random' assumption. The imputation models included all analysis variables plus variables predictive of missingness, such as indicators of social disadvantage and poor health (see supplement 2). Participants with observed information on each inflammatory marker were used in subsequent analyses, following Von Hippel's 'multiple imputation and deletion' approach (Von Hippel, 2007). This is a more conservative approach to multiple imputation but an approach in which bias is further minimized by the inclusion of outcome variables in the imputation models. Subsequent analyses therefore included 7692 participants for CRP, 7683 for fibrinogen and 7693 for vWF. The observed and imputed data are compared for each analytic variable in Tables 1 And 2. The observed and imputed data presented in these tables are similar, suggesting that the multiple imputation has been conducted appropriately. Descriptive analyses are presented for cohort members who had at least one observed inflammatory marker (n = 7464).

2.5. Statistical analyses

Linear regression models were used to estimate associations between ACE and each inflammatory marker. Six regression

Table 1
Prevalence of ACE in the National Child Development Study (7–16 years) by gender.

	Missingness[a]	Observed	Imputed		
	%	Total %	Men %	Women %	Total %
Age 7					
Care placement	8.4	1.7	1.6 $chi^2 = 0.22$, p = 0.64	1.8	1.7
Physical neglect	8.3	3.4	4.1 $chi^2 = 7.16$, p = 0.001	2.8	3.5
Offending	17.6	1.4	1.5 $chi^2 = 1.92$, p = 0.17	1.7	1.6
Parental separation	12.2	3.4	3.2 $chi^2 = 2.18$, p = 0.33	3.8	3.5
Mental illness	20.0	3.2	3.1 $chi^2 = 1.25$, p = 0.26	3.6	3.4
Domestic conflict	26.4	1.6	1.5 $chi^2 = 2.08$, p = 0.15	2.0	1.7
Alcohol misuse	19.8	0.8	1.0 $chi^2 = 0.001$, p = 0.97	1.0	1.0
Total ACE score					
0	31.9	90.3	87.9	88.0	88.0
1		7.5	9.2	8.9	9.1
2+		2.2	2.9 $chi^2 = 0.08$, p = 0.96	3.1	3.0
Age 11					
Care placement	6.9	2.3	2.4 $chi^2 = 0.02$, p = 0.90	2.5	2.4
Physical neglect	6.6	3.5	3.9 $chi^2 = 2.20$, p = 0.14	3.2	3.6
Offending	6.6	1.4	1.4 $chi^2 = 0.94$, p = 0.33	1.5	1.4
Parental separation	6.6	7.4	6.6 $chi^2 = 10.37$, p = 0.001	8.5	7.5
Mental illness	6.6	1.7	1.7 $chi^2 = 0.18$, p = 0.68	1.6	1.7
Total ACE score					
0	6.9	86.3	86.5	85.6	86.0
1		11.6	11.6	12.0	11.8
2+		2.1	1.9 $chi^2 = 3.09$, p = 0.21	2.4	2.2
Age 16					
Care placement	9.0	2.3	2.4 $chi^2 = 0.10$, p = 0.75	2.4	2.4
Offending	8.6	5.1	7.3 $chi^2 = 76.72$, p < 0.001	2.9	5.1
Parental separation	8.6	8.9	8.5 $chi^2 = 2.18$, p = 0.14	9.4	8.9
Mental illness	10.0	1.7	1.8 $chi^2 = 0.78$, p = 0.38	1.5	1.7
Total ACE score					
0	10.4	84.9	83.0	86.0	84.5
1		13.0	14.5	12.1	13.3
2+		2.2	2.6 $chi^2 = 13.88$, p = 0.001	1.9	2.2

NB percentages are reported as the actual numbers vary across the 20 imputed datasets; Chi^2 tests test for gender differences in individual ACE items and scores.
[a] Missingness expressed as a proportion of those with at least one inflammatory marker (n = 7464).

Table 2
Characteristics of the study sample for all analysis variables.

	Missingness[a] %	Observed %	Imputed %
Exposure			
Total ACE score (7–16 yrs)			
0	40.7	75.7	72.1
1		15.0	16.2
2+		9.3	11.8
Outcomes			
CRP (mg/L, 44/45 yrs)			
Median [IQR]	0.03	0.9 [0.5, 2.1]	0.9 [0.5, 2.1]
Fibrinogen (g/L, 44/45 yrs)			
Median [IQR]	0.2	2.9 [2.5, 3.3]	2.9 [2.5, 3.3]
vWF (IU/dL, 44/45 yrs)			
Median [IQR]	0.03	117 [92, 145]	117 [92, 145]
Mediators			
Educational attainment (23 yrs)			
No qualifications	16.8	10.9	11.7
O-levels/CSE		49.6	49.6
A-level or higher		39.6	38.6
Social class (42 yrs)			
Professional	8.7	9.1	8.8
Managerial/technical		47.6	46.8
Skilled non-manual		20.5	20.5
Skilled manual		15.8	16.3
Semi-skilled manual		5.6	6.0
Unskilled manual		1.5	1.6
Psychological distress (42 yrs)			
Median [IQR]	3.7	3 [1, 5]	3 [1, 5]
Alcohol misuse (42 yrs)			
Yes	4.4	87.3	87.3
No		12.7	12.7
Smoking status (42 yrs)			
Never smoker	3.2	45.7	45.6
Ex-smoker		26.1	26.1
Current smoker		28.2	28.3
Physical activity (42 yrs)			
Yes	3.2	24.2	24.4
No		75.8	75.7
BMI (42 yrs)			
	9.5	25.6 (4.5)	25.6 (4.5)
Confounders			
Maternal age (birth)			
Mean (SD)	5.2	27.5 (5.6)	27.5 (5.6)
Overcrowding (birth)			
<1.5 persons per room	15.5	87.1	86.8
≥1.5 persons per room		12.9	13.2
Father's social class (birth)			
Professional	6.0	4.8	4.9
Managerial/technical		14.2	14.3
Skilled non-manual		10.1	10.1
Skilled manual		50.5	50.4
Semi-skilled manual		12.1	12.1
Unskilled manual		8.2	8.3
Maternal education (birth)			
Stayed beyond minimum age	25.2	52.5	52.3
Left at or before minimum age		47.5	47.7
Maternal smoking in pregnancy (birth)			
No	6.3	67.6	67.6
Occasionally smoked		6.0	6.0
Smoked moderately		15.0	15.1
Smoked heavily		11.4	11.4
Parity (birth)			
Primiparous	5.1	37.2	37.2
One		31.6	31.6
Two or more		31.3	31.3
Breastfeeding (7 yrs)			
No	12.8	29.8	29.9
Up to 1 month		23.9	24.0
Longer than 1 month		46.3	46.1
Birthweight (ounces, birth)			
Mean (SD)	8.0	117.9 (18.1)	117.9 (18.2)

A-level = Advanced level; CRP = C-reactive protein; CSE = Certificate of Secondary Education; IQR = interquartile range; O-levels = Ordinary levels; SD = standard deviation; vWF = von Willebrand Factor. [a]Missingness expressed as a proportion of those with at least one inflammatory marker (n = 7464).

Table 3
Results from multivariable linear regression models testing the association between ACE and adult inflammation.

	% difference (95% CIs)					
	Model 1[a] Crude association	Model 2[b] Adj. confounders	Model 3[c] Model 2+ socioeconomic factors	Model 4[d] Model 2+ psychological distress	Model 5[e] Model 2+ health behavioral factors	Model 6[f] Fully adjusted
CRP (n = 7462)						
ACE						
None	Ref	Ref	Ref	Ref	Ref	Ref
1	**9.51 (1.40, 18.27)**	4.61 (−3.13, 12.97)	0.77 (−6.00, 8.95)	3.87 (−3.82, 12.18)	0.88 (−5.95, 8.21)	−0.81 (−7.60, 6.49)
2+	**25.69 (15.59, 36.67)**	**16.35 (6.87, 26.66)**	**9.02 (0.05, 18.79)**	**15.07 (5.70, 25.28)**	**9.15 (0.57, 18.46)**	6.08 (−2.32, 15.20)
vWF (n = 7693)						
ACE						
None	Ref	Ref	Ref	Ref	Ref	Ref
1	1.89 (−0.39, 4.23)	0.70 (−1.56, 3.01)	0.12 (−2.12, 2.42)	0.64 (−1.62, 2.95)	0.36 (−1.88, 2.66)	0.02 (−2.21, 2.30)
2+	**3.30 (0.79, 5.87)**	1.33 (−1.20, 3.93)	0.37 (−2.17, 2.98)	1.22 (−1.31, 3.82)	0.72 (−1.84, 3.33)	0.16 (−2.40, 2.79)
Fibrinogen (n = 7683)						
ACE						
None	Ref	Ref	Ref	Ref	Ref	Ref
1	**2.15 (0.73, 3.59)**	**1.62 (0.20, 3.05)**	0.85 (−0.57, 2.29)	**1.49 (0.08, 2.92)**	0.82 (−0.51, 2.16)	0.46 (−0.87, 1.81)
2+	**4.62 (3.06, 6.20)**	**3.21 (1.67, 4.79)**	**1.87 (0.32, 3.45)**	**2.98 (1.43, 4.56)**	**1.79 (0.29, 3.33)**	1.17 (−0.34, 2.71)

[a] Model 1: crude association.
[b] Model 2: adjusted for confounders.
[c] Model 3: model 2 + adjusted for socioeconomic factors.
[d] Model 4: model 2 + adjusted for psychological distress.
[e] Model 5: model 2 + adjusted for health behaviors.
[f] Model 6: adjusted for all confounders and mediators.

models were run for each outcome. First, the crude association between ACE and each outcome was estimated (model 1). Second, we controlled for confounders (model 2). We then explored the potential mediating role of life course socioeconomic (model 3), behavioral (model 4) and psychological factors (model 5), separately. A final model (model 6) included all confounders and potential mediators simultaneously. Interactions between gender and ACE were tested throughout using likelihood ratio tests. All results from regression models are expressed as percentage difference to aid interpretation from the log-transformed inflammatory markers. All analyses were conducted in Stata version 14 (StataCorp, 2015).

3. Results

3.1. Sample characteristics

Table 1 shows the prevalence of each childhood adversity used to construct the ACE score at ages 7, 11 and 16, along with a comparison of observed and imputed data on each item. The most commonly reported adversities at all ages were parental separation due to death or partnership dissolution, and mental illness. Focusing on the imputed data as these were taken forward in the analyses, few gender differences were observed; boys were more likely to be physically neglected by age 7 (4.1% boys vs. 2.8% girls) and to be in a household where offending was reported at age 16 (7.3% boys vs. 2.9% girls). However girls were more likely to experience parental separation by age 11 (8.5% girls vs 6.6% boys). There were no gender differences in the total ACE scores at ages 7 and 11, however boys of age 16 had higher ACE scores than girls.

As associations between ACE and inflammation did not differ by gender (described further in Section 3.2) the description of the study sample is presented for men and women combined (Table 2). The total ACE score across all three childhood sweeps (ages 7–16) is shown in Table 2. Focusing on the imputed values, almost one third of the sample reported at least one adverse childhood experience, with 16.2% reporting one and 11.8% reporting two or more

adversities. Median inflammation levels were 0.9 mg/L for CRP, 2.9 g/L for fibrinogen and 117 IU/dL for vWF. Almost half of the sample (49.6%) had O-level or CSE level qualifications (secondary school leaving examinations) as their highest educational qualification. Also almost half of the sample were in managerial or technical occupations at age 42. Psychological distress had a median level of 3 out of 24 on the Malaise Inventory. 12.7% of the sample reported alcohol misuse and 28.3% were current smokers at age 42. Only a quarter of participants reported regular physical activity and the mean BMI of the sample was 25.6 kg/m^2.

3.2. Regression results

As mentioned above, no gender-ACE interactions were found, therefore the associations between ACE and inflammation are presented for men and women combined (Table 3). Dose response relationships were observed between ACE scores and all three inflammatory outcomes in crude models (model 1). However upon adjustment for confounding variables, the association between ACE score and vWF was no longer statistically significant in model 2 or any subsequent model. Upon adjustment for confounders, ACE score still exhibited a graded relationship with CRP (1 ACE: 4.61% higher, 95% CI: −3.13, 12.97; 2+ ACE: 16.35% higher, 95% CI: 6.87, 26.66). In models 3–5, the three groups of potential mediating variables were included. After inclusion of socioeconomic factors (model 3), having an ACE score of 2 or more was still significantly associated with raised CRP (9.02% higher, 95% CI: 0.05, 18.79) however it was attenuated compared to model 2. A similar interpretation can be applied to model 5 where health behaviors were included. Less attenuation was seen when adult psychological distress was included in the model (model 4). No difference was seen when somatic versus emotional symptoms from the Malaise Inventory were adjusted for in model 4 (data not shown). After accounting for all three groups of mediating variables simultaneously, ACE score was no longer associated with CRP in mid-life, suggestive of mediation. A similar of pattern of results was observed for fibrinogen.

4. Discussion

Using a large, prospective British birth cohort design we found that ACE scores were related in a dose dependent manner with inflammation in mid-life, as indicated by CRP and fibrinogen. This finding is in line with the results of other population studies (Coelho et al., 2014; Danese et al., 2008, 2007; Slopen et al., 2010; Taylor et al., 2006), *meta*-analyses (Baumeister et al., 2015) and preclinical research (Diz-Chaves et al., 2013; Viviani et al., 2014). Associations between ACE and vWF were not observed after accounting for a prior confounders. This is consistent with previous work which found no association between other social experiences, such as work-family life courses and partnership histories, using this cohort (Keenan et al., 2016; Lacey et al., 2013). This might suggest that vWF is less affected by stressful social circumstances. In this study we found no gender differences in associations between ACE and adult inflammation. Few other studies have examined gender differences in associations between ACE and adult health thus far.

As early life adversities are likely to co-occur we employed the cumulative risk approach and created an ACE score in line with many previous studies e.g.(Felitti et al., 1998). Further investigation of the component adversities making up the ACE score (shown in supplement 3) showed that the experience of offending, physical neglect and parental separation were particularly associated with CRP in mid-life. With regards to fibrinogen, all component adversities with the exception of alcohol misuse were associated with higher fibrinogen in mid-life and the associations observed for each adversity were of a similar magnitude. Associations between component adversities and vWF were less consistent and should be interpreted with caution given that there was less variation in values of vWF across the sample and hence limited statistical power (range 7–59%) in this analytic sample.

Three mechanisms, socioeconomic pathways, psychological pathways and health behaviors pathways, were hypothesized and tested in this study. Our findings suggest that the occurrence of ACE appears to set children down a path of life course disadvantage, particularly with regards to educational attainment, socioeconomic position and the uptake of risky health behaviors. Such findings are consistent with conceptual models proposed by previous papers, elaborating how health-threatening behaviors exacerbate inflammatory tendencies via impaired interpersonal relationship and poor self-management capacities (Miller et al., 2011). Concurrently published papers also corroborate with this study that adversities from the familial environment are responsible for school performance, psychological distress, and health-risk behaviors (Murray et al., 2012; Schilling et al., 2007). For instance, Font and Maguire-Jack (2015) found that between 15 and 20% of the association between child abuse and adult health risks in the Behavioral Risk Factor Surveillance System 2012 survey was explained by socioeconomic factors including educational attainment and income. This mediation was particularly the case for parental separation and domestic conflict. The potential mediating factors included in our study have also been found by previous published work to link with adult risk of inflammation (Pollitt et al., 2007; Taylor et al., 2006).

By adopting adult inflammatory biomarkers as outcomes, we were able to investigate the social-biological interface through which ACE might affect later health. Researchers hypothesized that ACE occurring at developmentally sensitive periods have the potential to interrupt normal development of physiological systems (Miller et al., 2011), particularly when the adversities experienced are severe or repeated (Shonkoff et al., 2012). Under repeated stimulation from ACE, stress-related hormones could be released excessively. This could result in dysregulation of the HPA axis and the sympathetic-adrenocortical axis, which are accompanied increased chronic inflammation (Danese et al., 2011; McEwen, 2012). Epigenetic processes may also play a small role. For instance, ACE may affect pro-inflammatory gene expression, which might induce the over-production of CRP (Miller et al., 2009).

4.1. Strengths and limitations

This study has some limitations. Inflammation was only measured at one time-point. We were therefore unable to assess when changes in inflammation may have occurred. We were also not able to investigate change in inflammation over time for this same reason. The increased inflammatory marker levels seen at age 44/45 might be a consequence of accumulative effects from a set of stressful events throughout the life span, or the effects of more proximal disadvantages, such as material deprivation, low education qualification, psychological distress, and risky health behaviors (Lacey et al., 2013). This aspect should be further explored in a dataset where repeated measures of inflammation and life course socioeconomic, psychological and health behavioral factors are present simultaneously. Also, whilst we have assumed in this study that BMI might partially explain the association between ACE and inflammation as adipose tissue is pro-inflammatory (Das, 2001), it is also possible that inflammation might affect physical health (for example, through cytokine-induced sickness behavior (Dantzer and Kelley, 2007)) and thus increase BMI.

This study also has many strengths. The key strength of this study was that a prospective cohort study design was exploited and all measures used in analysis were prospectively collected. There are relatively few studies thus far that have used prospectively collected ACE information in addition to health indicators in mid-life. This aids the minimization of recall bias and temporality which are present in most previous studies in this field. Secondly, our findings are generalizable to the British population of a similar age. This was further supported by the use of multiple imputation to account for missing data, and in particular to reduce bias attributable to missing values. Data were imputed under the 'missing at random' assumption which means that participants with missing and complete data did not differ once observed information was taken into account. Given that the NCDS is a multi-disciplinary study with information on multiple aspects of participants' lives, this assumption is likely to hold. Analyses were first run for the 3689 participants with observed information on all analytic variables ('complete cases', data not shown) and then on participants following multiple imputation. The findings of both analyses were similar, but as multiple imputation results in less bias and a larger sample size, the results from the analyses on imputed data are presented in this study. Thirdly, by using a multi-disciplinary study, we were able to investigate life course mechanisms which spanned several life domains and to investigate this in relation to biological markers. Many previous studies have focused on one explanatory mechanism (Coelho et al., 2014; Slopen et al., 2010). Finally, more than one outcome variable was used to indicate adult inflammation to avoid the contingency of the positive statistical results, and come up with more internally consistent conclusions than using only one inflammatory marker. By utilizing more than one inflammatory marker we were also able to better indicate the physiological processes that might be involved.

5. Conclusions

In conclusion, experiencing ACE is associated with higher adult inflammation, which might have consequences for chronic diseases, such as ischemic heart diseases and cancer. Therefore, more

effort is required to support children who experience care placements, physical neglect, parental separation, domestic conflict and family member with alcohol misuse problem, psychiatric problem and offending history (Bentley et al., 2016). Furthermore, findings from this study also suggest that socioeconomic and health behavioral factors might explain associations between ACE and adult inflammation. Therefore, interventions which aim to modify better support children through the education system and in finding high quality, secure jobs, as well as targeting the uptake of risky health behaviors might help to ameliorate associations with later poor health.

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbi.2018.02.007.

References

Alho, H., Sillanaukee, P., Kalela, A., Jaakkola, O., Laine, S., Nikkari, S., 2004. Alcohol misuse increases serum antibodies to oxidized LDL and C-reactive protein. Alcohol Alcohol. 39, 312–315. https://doi.org/10.1093/alcalc/agh059.

Baecklund, E., Iliadou, A., Askling, J., Ekbom, A., Backlin, C., Granath, F., Catrina, A.I., Rosenquist, R., Feltelius, N., Sundström, C., Klareskog, L., 2006. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 54, 692–701. https://doi.org/10.1002/art.21675.

Barboza Solís, C., Kelly-Irving, M., Fantin, R., Darnaudéry, M., Torrisani, J., Lang, T., Delpierre, C., 2015. Adverse childhood experiences and physiological wear-and-tear in midlife: findings from the 1958 British birth cohort. Proc. Natl. Acad. Sci. https://doi.org/10.1073/pnas.1417325112. 201417325.

Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C.M., Mondelli, V., 2015. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Psychiatry Mol. https://doi.org/10.1038/mp.2015.67.

Bentley, H., O'hagan, O., Raff, A., Bhatti, I., Reid, C., Barrett, J., Laing, V., Witcombe-Hayes, S., Stanley, K., Sconce, S., Mccrindle, L., Jütte, S., Lynch, C., Miller, P., Byrne, A., Pearson, L., Holdsworth, E., Brown, A., Fisher, J., 2016. How safe are our children? The most comprehensive overview of child protection in the UK 2016. London.

Brown, D.W., Anda, R.F., Tiemeier, H., Felitti, V.J., Edwards, V.J., Croft, J.B., Giles, W.H., 2009. Adverse childhood experiences and the risk of premature mortality. Am. J. Prev. Med. 37, 389–396. https://doi.org/10.1016/j.amepre.2009.06.021.

Cheng, E.R., Park, H., Wisk, L.E., Mandell, K.C., Wakeel, F., Litzelman, K., Chatterjee, D., Witt, W.P., 2015. Examining the link between women's exposure to stressful life events prior to conception and infant and toddler health: the role of birth weight. J. Epidemiol. Community Health jech-2015-205848. doi:10.1136/jech-2015-205848

Coelho, R., Viola, T.W., Walss-Bass, C., Brietzke, E., Grassi-Oliveira, R., 2014. Childhood maltreatment and inflammatory markers: a systematic review. Acta Psychiatr. Scand. 129, 180–192. https://doi.org/10.1111/acps.12217.

Colman, I., Jones, P., Kuh, D., Weeks, M., Naicker, K., Richards, M., Croudace, T., 2014. Early development, stress and depression across the life course: pathways to depression in a national British birth cohort Fulltext – Early development, stress and depression across the life course: pathways to depression in a national British birth cohor. Psychol. Med. 44, 2845–2854.

Danese, A., Baldwin, J.R., 2017. Hidden Wounds? Inflammatory links between childhood trauma and psychopathology. Annu. Rev. Psychol. 68, 517–544. https://doi.org/10.1146/annurev-psych-010416-044208.

Danese, A., Caspi, A., Williams, B., Ambler, A., Sugden, K., Mika, J., Werts, H., Freeman, J., Pariante, C., Moffitt, T., Arseneault, L., 2011. Biological embedding of stress through inflammation processes in childhood. Mol. Psychiatry 16, 244–246.

Danese, A., Moffitt, T., Harrington, H., Milne, B., Polanczyk, G., Pariante, C., Poulton, R., Caspi, A., 2009. Adverse childhood experiences and adult risk factors for age-related disease. Arch. Pediatr. Adolesc. Med. 163, 1135–1143.

Danese, A., Moffitt, T., Pariante, C., Ambler, A., Poulton, R., Caspi, A., 2008. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. Arch. Gen. Psychiatry 65, 409–415.

Danese, A., Pariante, C., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc. Natl. Acad. Sci. U.S.A. 104, 1319–1324.

Dantzer, R., Kelley, K.W., 2007. Twenty years of research on cytokine-induced sickness behavior. Brain. Behav. Immun. 21, 153–160. https://doi.org/10.1016/j.bbi.2006.09.006.

Das, U., 2001. Is obesity an inflammatory condition? Nutrition 17, 953–966.

Diz-Chaves, Y., Astiz, M., Bellini, M.J., Garcia-Segura, L.M., 2013. Prenatal stress increases the expression of proinflammatory cytokines and exacerbates the inflammatory response to LPS in the hippocampal formation of adult male mice. Brain. Behav. Immun. 28, 196–206. https://doi.org/10.1016/J.BBI.2012.11.013.

Dong, M., Giles, W.H., Felitti, V.J., Dube, S.R., Williams, J.E., Chapman, D.P., Anda, R.F., 2004. Insights into causal pathways for ischemic heart disease: adverse childhood experiences study. Circulation 110, 1761–1766. https://doi.org/10.1161/01.CIR.0000143074.54995.7F.

Dube, S.R., Anda, R.F., Felitti, V.J., Edwards, V.J., Croft, J.B., 2002. Adverse childhood experiences and personal alcohol abuse as an adult. Addict. Behav. 27, 713–725. https://doi.org/10.1016/S0306-4603(01)00204-0.

Dube, S.R., Felitti, V.J., Dong, M., Chapman, D.P., Giles, W.H., Anda, R.F., 2003. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. Pediatrics 111, 564–572. https://doi.org/10.1542/peds.111.3.564.

Elliott, J., Johnson, J., Shepherd, P., 2008. User guide to the biomedical survey 2002–2004 dataset. Centre for Longitudinal Studies Institute of Education, London.

Erola, J., Jalonen, S., Lehti, H., 2016. Parental education, class and income over early life course and children's achievement. Res. Soc. Stratif. Mobil. 44, 33–43. https://doi.org/10.1016/J.RSSM.2016.01.003.

Ewing, J.A., 1984. Detecting alcoholism. The CAGE questionnaire. JAMA 252, 1905–1907.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. Am. J. Prev. Med. 14, 245–258. https://doi.org/10.1016/S0749-3797(98)00017-8.

Fergusson, D., Horwood, L., 2003. Resilience to childhood adversity: results of a 21-year study. In: Luthar, S. (Ed.), Resilience and Vulnerability Adaptation in the Context of Childhood Adversities. Cambridge University Press, Cambridge, pp. 130–155.

Festa, A., Howard, G., Mykkänen, L., Tracy, R.P., Haffner, S.M., 2000. Chronic subclinical inflammation as part of the insulin resistance syndrome the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 102, 42–47.

Font, S.A., Maguire-Jack, K., 2015. Pathways from childhood abuse and other adversities to adult health risks: The role of adult socioeconomic conditions. Child Abuse Negl. 51, 390–399. https://doi.org/10.1016/j.chiabu.2015.05.013.

Friedman, E.M., Montez, J.K., Sheehan, C.M., Guenewald, T.L., Seeman, T.E., 2015. Childhood adversities and adult cardiometabolic health: does the quantity, timing, and type of adversity matter? J. Aging Health 27, 1311–1338.

Garad, Y., Maximova, K., MacKinnon, N., McGrath, J.J., Kozyrskyj, A.L., Colman, I., 2017. Sex-specific differences in the association between childhood adversity and cardiovascular disease in adulthood: evidence from a national cohort study. J. Cardiol. Can. https://doi.org/10.1016/j.cjca.2017.05.008.

Gilbert, R., Widom, C.S., Browne, K., Fergusson, D., Webb, E., Janson, S., 2009. Burden and consequences of child maltreatment in high-income countries. Lancet 373, 68–81. https://doi.org/10.1016/S0140-6736(08)61706-7.

Gillham, B., Tanner, G., Cheyne, B., Freeman, I., Rooney, M., Lambie, A., 1998. Unemployment rates, single parent density, and indices of child poverty: their relationship to different categories of child abuse and neglect. Child Abus. Neglectl. 22, 79–90.

Gilman, S.E., Gardener, H., Buka, S.L., 2008. Maternal smoking during pregnancy and children's cognitive and physical development: a causal risk factor? Am. J. Epidemiol. 168, 522–531. https://doi.org/10.1093/aje/kwn175.

Hedin, L.W., Janson, P.O., 2000. Domestic violence during pregnancy: the prevalence of physical injuries, substance use, abortions and miscarriages. Acta Obstet. Gynecol. Scand. 79, 625–630. https://doi.org/10.1080/j.1600-0412.2000.079008625.x.

Hertzman, C., Boyce, T., 2010. How experience gets under the skin to create gradients in developmental health. Annu. Rev. Public Health 31, 329–347. https://doi.org/10.1146/annurev.publhealth.012809.103538.

Kawecki, C., Lenting, P.J., Denis, C.V., 2017. von Willebrand factor and inflammation. J. Thromb. Haemost. 15, 1285–1294. https://doi.org/10.1111/jth.13696.

Keenan, K., Ploubidis, G.B., Silverwood, R.J., Grundy, E., 2016. Life-course partnership history and midlife health behaviours in a population-based birth cohort. J. Epidemiol. Community Health jech-2015-207051. doi:10.1136/jech-2015-207051

Kelly-Irving, M., Lepage, B., Dedieu, D., Bartley, M., Blane, D., Grosclaude, P., Lang, T., Delpierre, C., 2013a. Adverse childhood experiences and premature all-cause mortality. Eur. J. Epidemiol. 28, 721–734. https://doi.org/10.1007/s10654-013-9832-9.

Kelly-Irving, M., Lepage, B., Dedieu, D., Lacey, R., Cable, N., Bartley, M., Blane, D., Grosclaude, P., Lang, T., Delpierre, C., 2013b. Childhood adversity as a risk for cancer: findings from the 1958 British birth cohort study. BMC Public Health 13, 767. https://doi.org/10.1186/1471-2458-13-767.

Lacey, R.E., Kumari, M., McMunn, A., 2013. Parental separation in childhood and adult inflammation: The importance of material and psychosocial pathways. Psychoneuroendocrinology 38, 2476–2484.

Laucht, M., Esser, G., Baving, L., Gerhold, M., Hoesch, I., Ihle, W., Steigleider, P., Stock, B., Stoehr, R., Weindrich, D., Schmidt, M., 2000. Behavioral sequelae of perinatal insults and early family adversity at 8 years of age. J. Am. Acad. Child Adolesc. Psychiatry 2 (39), 1229–1237.

Lupien, S.J., McEwen, B.S., Gunnar, M.R., Heim, C., 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci. 10, 434–445. https://doi.org/10.1038/nrn2639.

Martindale, S.E., Lacey, R.E., 2017. Parental separation in childhood and adult smoking in the 1958 British birth cohort. Eur. J. Public Health 27, 723–728. https://doi.org/10.1093/eurpub/ckw265.

McDade, T.W., Metzger, M.W., Chyu, L., Duncan, G.J., Garfield, C., Adam, E.K., 2014. Long-term effects of birth weight and breastfeeding duration on inflammation in early adulthood. Proceedings. Biol. Sci. 281, 20133116. https://doi.org/10.1098/rspb.2013.3116.

McEwen, B., 2012. Brain on stress: how the social environment gets under the skin. Proc. Natl. Acad. Sci. U.S.A. 109, 17180–17185.

Mersky, J.P., Topitzes, J., Reynolds, A.J., 2013. Impacts of adverse childhood experiences on health, mental health, and substance use in early adulthood: a cohort study of an urban, minority sample in the U.S. NIH Public Access. Child Abus. Negl. 37, 917–925. https://doi.org/10.1016/j.chiabu.2013.07.011.

Miller, G., Chen, E., Cole, S.W., 2009. Health psychology: developing biologically plausible models linking the social world and physical health. Annu. Rev. Psychol. 60, 501–524. https://doi.org/10.1146/annurev.psych.60.110707.163551.

Miller, G., Chen, E., Parker, K., 2011. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol. Bull. 137, 959–997.

Murray, J., Farrington, D.P., Sekol, I., 2012. Children's antisocial behavior, mental health, drug use, and educational performance after parental incarceration: a systematic review and meta-analysis. Psychol. Bull. 138, 175–210. https://doi.org/10.1037/a0026407.

Newbury, J., Arseneault, L., Moffitt, T., Caspi, A., Danese, A., Baldwin, J., Fisher, H., 2018. Measuring childhood maltreatment to predict early-adult psychopathology: comparison of prospective informant-reports and retrospective self-reports. J. Psychiatr. Res. 96, 57–64. https://doi.org/10.1016/J.JPSYCHIRES.2017.09.020.

Nusslock, R., Miller, G.E., 2016. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol. Psychiatry 80, 23–32. https://doi.org/10.1016/j.biopsych.2015.05.017.

Ohsawa, M., Okayama, A., Nakamura, M., Onoda, T., Kato, K., Itai, K., Yoshida, Y., Ogawa, A., Kawamura, K., Hiramori, K., 2005. CRP levels are elevated in smokers but unrelated to the number of cigarettes and are decreased by long-term smoking cessation in male smokers. Prev. Med. (Baltim) 41, 651–656. https://doi.org/10.1016/j.ypmed.2005.02.002.

Pepys, M., Hirschfield, G., 2003. C-reactive protein: a critical update. J. Clin. Invest. 111, 1805–1812.

Pollitt, R., Kaufman, J., Rose, K., Diez-Roux, A., Zeng, D., Heiss, G., 2007. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur. J. Epidemiol. 22, 55–66.

Power, C., Elliott, J., 2005. Cohort profile: 1958 British birth cohort. Int. J. Epidemiol. 35, 34–41.

Radford, L., Corral, S., Bradley, C., Fisher, H., Bassett, C., Howat, N., Collishaw, S., 2011. Child abuse and neglect in the UK today. London.

Rosenman, S., Rodgers, B., 2004. Childhood adversity in an Australian population. Soc. Psychiatry Psychiatr. Epidemiol. 39, 695–702. https://doi.org/10.1007/s00127-004-0802-0.

Rutter, M., 1970. Education, Health and Behaviour. Longman, Harlow.

Schilling, E.A., Aseltine, R.H., Gore, S., Gore, S., 2007. Adverse childhood experiences and mental health in young adults: a longitudinal survey. BMC Public Health 7, 30. https://doi.org/10.1186/1471-2458-7-30.

Shacter, E., Weitzman, S.A., 2002. Chronic inflammation and cancer. Oncology (Williston Park). 16 (217–26), 229–232.

Shonkoff, J.P., Garner, A.S., Siegel, B.S., Dobbins, M.I., Earls, M.F., Garner, A.S., McGuinn, L., Pascoe, J., Wood, D.L., 2012. The lifelong effects of early childhood adversity and toxic stress. Pediatrics. https://doi.org/10.1542/peds.2011-2663.

Slopen, N., Lewis, T., Gruenewald, T., Mujahid, M., Ryff, C., Albert, M., Williams, D., 2010. Early life adversity and inflammation in African Americans and whites in the midlife in the United States survey. Psychosom. Med. 72, 694–701.

StataCorp, 2015. Stata version 14.2.

Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A.M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338.

Tabassum, F., Kumari, M., Rumley, A., Lowe, G., Power, C., Strachan, D.P., 2008. Effects of socioeconomic position on inflammatory and hemostatic markers: a life-course analysis in the 1958 British birth cohort. Am. J. Epidemiol. 167, 1332–1341. https://doi.org/10.1093/aje/kwn055.

Taylor, S., Lehman, B., Kiefe, C., Seeman, T., 2006. Relationship of early life stress and psychological functioning to adult c-reactive protein in the coronary artery risk development in young adults study. Biol. Psychiatry 60, 819–824.

Viviani, B., Boraso, M., Valero, M., Gardoni, F., Marco, E.M., Llorente, R., Corsini, E., Galli, C.L., Di Luca, M., Marinovich, M., López-Gallardo, M., Viveros, M.-P., 2014. Early maternal deprivation immunologically primes hippocampal synapses by redistributing interleukin-1 receptor type I in a sex dependent manner. Brain. Behav. Immun. 35, 135–143. https://doi.org/10.1016/J.BBI.2013.09.008.

Von Hippel, P., 2007. Regression with missing Ys: An improved strategy for analyzing multiply imputed data. Sociol. Methodol. 37, 83–117.