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Understanding associations of early-life adversities with mid-life inflammatory profiles: Evidence from the UK and USA

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ABSTRACT

Objectives: In two cohorts, we aimed to establish associations between early-life adversities and adult inflammation, and whether adult (a) adiposity or (b) socioeconomic disadvantage are key intermediaries.
Methods: In both cohorts (N = 7661, 1958 British birth cohort; N = 1255, MIDUS), information was used on adult inflammatory markers (C-reactive protein (CRP), fibrinogen and (MIDUS only) interleukin-6 (IL-6)), adiposity and socioeconomic disadvantage, and early-life adversities (neglect, emotional neglect, physical, psychological, sexual abuse and childhood disadvantage).
Results: Early-life adversities varied from 1.6% (sexual abuse, 1958 cohort) to 14.3% (socioeconomic disadvantage, MIDUS). Across the two cohorts, associations were consistent for physical abuse, e.g. 16.3%(3.01,29.7) and 17.0%(−16.4,50.3) higher CRP in the 1958 cohort and MIDUS respectively. Associations attenuated after accounting for adult adiposity, e.g. physical abuse (1958 cohort) and sexual abuse (MIDUS, non-white participants) associations were abolished. Some associations attenuated after adjustment for adult socioeconomic disadvantage; e.g. 1958 cohort neglect–CRP associations reduced from 23.2%(13.7,32.6) to 17.7%(8.18,27.2). Across the cohorts, no associations were found for psychological abuse or emotional neglect; associations for childhood socioeconomic disadvantage were inconsistent.
Conclusions: Specific early-life adversities are associated with adult inflammation; adiposity is a likely intermediary factor. Weight reduction and obesity prevention may offset pro-inflammatory related adult disease among those who experienced early-life adversities.

1. Introduction

Early-life adversities such as child maltreatment and socioeconomic disadvantage are associated with several unfavourable health outcomes. Child maltreatment (abuse and neglect) is associated with mental ill-health, obesity and poor cardiovascular disease (CVD) risk profiles with effects perpetuating into adulthood (Clark et al., 2010; Norman et al., 2012; Gilbert et al., 2009; Power et al., 2015); early-life socioeconomic disadvantage is also associated with poor adult outcomes including several chronic diseases and mortality (Power et al., 2013; Galobardes et al., 2004). One focus of current research is to delineate the full extent of long-terms outcomes, whilst another line of enquiry is directed at potential mechanisms by which early-life adversities become embedded biologically to exert long-term effects (Hertzman and Boyce, 2010). Regarding the latter, one possible mechanism identified in the literature involves the inflammatory response: some evidence exists to suggest that early-life adversities are associated with later inflammation (Coelho et al., 2014; Matthews et al., 2014; Danese et al., 2007; Tabassum et al., 2008; Baumeister et al., 2016; Liu et al., 2017) and inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) predict subsequent health outcomes including depression, CVD and mortality (Swerdlow et al., 2012; Kaptoge et al., 2010; Sarwar et al., 2012; Miller and Raison, 2016).

There are several shortcomings and gaps in the evidence to date on early-life adversities and inflammation, as highlighted elsewhere (Coelho et al., 2014). First, associations may have been missed because many previous studies are based on small samples with low prevalence of child maltreatment. Second, while the literature is more extensive on links between early adversities and adiposity (Senese et al., 2009; Danese and Tan, 2014) and between adiposity (including adiposity gain) and inflammatory markers (Timpson et al., 2011; Welsh et al., 2010; Fransson et al., 2010), few studies (Matthews et al., 2014; Matthews et al., 2016; Raposa et al., 2014) examine whether early adversities are related to adult inflammation via their link with

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Table 1
Definition of early-life adversities and representative variables from the 1958 British birth cohort and MIDUS.

	Definition[1]	1958 British birth cohort			MIDUS		
Childhood measures		1958 cohort variables	Reference age (y)	Age of ascertainment (method[2])	MIDUS variables	Reference age (y)	Mean age of ascertainment (method[2])
Neglect[3]	Failure to meet a child's basic physical, emotional, medical/dental, or education need; failure to provide adequate nutrition, hygiene, or shelter; or failure to ensure a child's safety	- Child looks undernourished, scruffy or dirty - Mother never, or hardly ever takes child out - Father never, or hardly ever takes child out - Mother shows little or no interest in child's educational progress - Father shows little or no interest in child's educational progress - Mother and father never, or hardly ever read to, or reads with the child	7y & 11y	7 & 11y (T) 7 & 11y (P) 7 & 11y (P) 7 & 11y (T) 7 & 11y (T) 7y (P)	N/A	N/A	N/A
Emotional neglect[4]		- How affectionate was your mother toward you? - - How affectionate was your father toward you?	0-16y	45y (S)[5] 45y (S)[5]	- I felt loved: rarely/never	0-18y[6]	57.3y (S)
Physical abuse	Intentional use of physical force or implements against a child that results in, or has the potential to result in, physical injury.	- I was physically abused by a parent – punched, kicked or hit or beaten with an object, or needed medical treatment	0-16y	45y (S)[5]	- I got hit so hard by someone in my family that I had to see a doctor or go to the hospital: often/very often; - OR - people in my family hit me so hard that it left me with bruises or marks: often/very often; - OR - - I got hit or beaten so badly that it was noticed by someone like a teacher, neighbour or doctor: sometimes/often/very often	0-18y[6]	57.3y (S)
Psychological abuse	Intentional behaviour that conveys to a child that s/he is worthless, flawed, unloved, unwanted, endangered, or valued only in meeting another's needs[7].	- I was verbally abused by a parent (or parent-figure) - I suffered humiliation, ridicule, bullying or mental cruelty from a parent (or parent-figure)	0-16y	45y (S)[5] 45y (S)[5]	- - people in my family said hurtful or insulting things to me: often/very often	0-18y[6]	57.3y (S)
Sexual abuse	Any completed or attempted sexual act, sexual contact, or non-contact sexual interaction with a child by a caregiver.	- I was sexually abused by a parent (or parent-figure)	0-16y	45y (S)[5]	- I believe that I was sexually abused: often/very often	0-18y[6]	57.3y (S)
			Birth & 7y	7y (P)		NA[8]	46.2y[9] (S)

(*continued on next page*)

Table 1 (*continued*)

Childhood measures	Definition[1]	1958 British birth cohort			MIDUS		
		1958 cohort variables	Reference age (y)	Age of ascertainment (method[2])	MIDUS variables	Reference age (y)	Mean age of ascertainment (method[2])
Childhood socioeconomic disadvantage		- sum of social class at birth and a household disadvantage measure (range: 0–4; from information on amenities (bathroom, indoor lavatory, hot water) and household crowding at 7y). Disadvantage defined as manual class and a household score of 2+.			- sum of 3 components (range 0–6): on welfare during childhood (0: no, 2: yes); childhood financial level vs others (0: better, 1: same, 2: worse); highest parental education (0: some college or more, 1: high school/ general educational development certificate, 2: < high school). Disadvantage defined as score of 4+.		

[1] From Gilbert et al. (2009).

[2] (S): self-report; (T): teacher-report; (P): parent-report.

[3] 1958 cohort: 11 indicators were summed to create a score (range 0–11); scores > 3 were classified as experiencing child neglect.

[4] 1958 cohort: defined as either parent "not at all affectionate toward me".

[5] 1958 cohort: for retrospective (45y) reports, information was obtained via direct computer data entry from questions from the Personality and Total Health Through Life Project (Rosenman et al., 2004), details of which are provided elsewhere (Pinto Pereira et al., 2017). Participants were instructed: "The following are statements about your childhood. For each, please say whether the statement applies to you." Response options were: "Yes" "No" or "Can't say".

[6] MIDUS: questions refer to participant's experiences in childhood and teenage years.

[7] UK definition includes harmful (unintentional) parent-child interactions: 'the persistent emotional maltreatment of a child such as to cause severe and persistent adverse effects on the child's emotional development' (From: Working together to safeguard children. A guide to interagency working to safeguard and promote the welfare of children, 2015).

[8] Questions refer to childhood.

[9] Refers to white participants only; mean age of ascertainment for non-white participants: 50.7y.

adiposity (or adiposity gain) over periods of the life-course. Such knowledge gaps are important because Mendelian randomisation studies suggest that adiposity causally influences inflammation (Timpson et al., 2011; Welsh et al., 2010). Alternatively, because socioeconomic disadvantage in adulthood is associated with elevated inflammation (Gruenewald et al., 2009; Loucks et al., 2010), associations for early-life adversities could reflect life-course continuities in disadvantage (Tabassum et al., 2008; Liu et al., 2017). Finally, evidence is limited on the relationship between specific types of early-life adversities and inflammatory markers, in particular for maltreatments, which are typically examined together without an understanding of possible differential effects. Relationships could vary by type of early-life adversity (Baumeister et al., 2016) and potentially, this may shed light on the mechanisms involved.

1.1. Aims of the study

Using data from two cohorts, from the UK and USA, we addressed several of these outstanding questions. Specifically, we investigated associations between early-life adversities, adult inflammatory markers, adiposity and adult socio-economic disadvantage. Inclusion of two populations provides an opportunity, to the extent that study design allows, to standardise research aims and analytic approach and to assess replicability of findings across populations. Specific aims, were to establish (i) whether early-life adversities are associated with markers of inflammation (CRP, fibrinogen, IL-6) in adulthood and whether associations vary by type of early-life adversity; and (ii) whether associations are consistent with the hypotheses that (a) adiposity (or adiposity trajectory) or (b) adult socioeconomic disadvantage are key intermediaries between early-life adversities and pro-inflammation states.

2. Methods

2.1. Study samples

1958 British birth cohort is an on-going longitudinal study of all born in one week in March 1958 across England, Scotland and Wales (n = 17,638) with a further 920 immigrants with the same birth week recruited up to age 16y (Power and Elliott, 2006). Information was collected at several ages throughout child and adulthood. At 45y, 9377 (78% of 11,971 invited) individuals participated in a biomedical survey; respondents were broadly representative of the total surviving cohort (Atherton et al., 2008). Ethical approval was given for various follow-up surveys, including the biomedical survey by the South East Multi-centre Research Ethics Committee; informed consent was obtained from participants at different ages.

Midlife in the United States (MIDUS), initiated in 1994-5, included a national sample of English-speaking, non-institutionalized adults (age: 25y-75y; n = 7108) in households with at least one telephone (Brim et al., 2004). A second wave of data collection 9–10y later (MIDUS-II) provided information on 4963 of the original cohort. An additional 592 African American, Wisconsin residents were enrolled at this stage. Of 3191 MIDUS-II participants medically able to travel, 1255 consented to participate in a biomarker project which entailed travel to a clinical research centre for an overnight stay (Dienberg Love et al., 2010). Biomarker project participants were broadly similar to those of MIDUS-II (Dienberg Love et al., 2010) and MIDUS-II participants were similar to those of MIDUS-I (Radler and Ryff, 2010). Each MIDUS centre obtained institutional review board approval and participants provided informed consent.

Information on age and year of data collection of early-life adversities, inflammatory markers, potential intermediary factors and covariates (described below) in the 1958 cohort and MIDUS are detailed in Supplementary Figure 1.

2.2. Early-life adversities

In the 1958 cohort neglect was identified from information collected prospectively in childhood (7y and 11y) from parental (usually mother) interviews and the child's teacher using structured questionnaires. Emotional neglect and abuse by a parent (physical, psychological or sexual) during childhood (to 16y) was reported at 45y (yes/no) using a confidential direct computer data entry questionnaire. Childhood socioeconomic disadvantage was identified from prospectively recorded information on social class at birth, household amenities (bathroom, indoor lavatory, hot water) and household crowding at 7y (details in Table 1).

During the MIDUS biomarker project, participants completed the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). Participants were asked about their child and teenage experiences of emotional neglect and physical, psychological and sexual abuse, rating each item on a five-point scale (never to very often). We selected items that were comparable to those available in the 1958 cohort (Table 1). Childhood socioeconomic disadvantage was identified from information on family welfare status, family financial level relative to others, and parental education (details in Table 1).

2.3. Inflammatory markers

In the 1958 cohort, non-fasting venous blood samples were obtained by nurses using standardized protocols during home visits, when participants were 45y, and posted to central laboratories. CRP was assayed by nephelometry (Dade Behring) and fibrinogen levels measured using the Clauss method (Clauss, 1957) on citrated plasma samples after one thaw cycle.

During the MIDUS biomarker project (age range: 35-86y), fasting venous blood samples were obtained using standardized protocols. High sensitivity CRP was assayed by nephelometry (Dade Behring); fibrinogen was measured using the BNII nephelometer (Dade Behring); and IL-6 levels via a high-sensitivity enzyme-linked immunosorbent assay (ELISA, Quantikine).

Further details, including blood collection protocols and laboratory standard operating procedures for the inflammatory markers are described elsewhere for both the 1958 cohort (Tabassum et al., 2008; Technical report on the National Child Development Study Biomedical Survey 2002-2004; Haemostasis Laboratory, University of Glasgow, Glasgow Royal Infirmary: Standard Operating Procedure for Determination of clottable (Clauss) fibrinogen, 2005; Haemostasis Laboratory, University of Glasgow, Glasgow Royal Infirmary: Standard Operating Procedure for High sensitivity CRP assay, 2005) and MIDUS (Dienberg Love et al., 2010; Midlife in the United States).

2.4. Potential intermediary factors

Adiposity: Height, weight, waist and hip circumferences were measured at the time of blood draw (45y in 1958 cohort; biomarker project in MIDUS). Body mass index (BMI; kg/m^2) and waist-to-hip ratio (WHR) were calculated. In the 1958 cohort, 16y height and weight were measured by trained medical staff (Lake et al., 1997); BMI was calculated.

Adult socioeconomic disadvantage: Five components were summed to create a score (range: 0–10; from least to most disadvantaged). In the 1958 cohort, score components included education level (by 46y) and adult (42–45y) social class, housing tenure and two items on financial difficulties (difficulty paying bills; ability to afford food/clothing). In MIDUS, score components, reported at the time of the MIDUS phone interview and self-administered survey prior to biomarker data collection, were education level, income (family-adjusted poverty to income ratio), financial situation, enough money to meet needs and difficulty paying bills. For some analyses, a binary adult measure was used that identified the most disadvantaged 15% (approximately) of the population.

Table 2
Characteristics of participants in 1958 British birth cohort and MIDUS (N(%) or Mean (SD)).

	1958 British birth cohort			MIDUS		
	N	Men	Women	N	Men	Women
Sex	7661	3833 (50.0)	3828 (50.0)	1255	542 (43.2)	713 (56.8)
Age at blood draw[1]	7661	45.2 (44.3–46.0)	45.2 (44.3–46.0)	1255	57.9 (36–86)	56.9 (35–86)
Race White	7419	3634 (98.2)	3649 (98.2)	1253	443 (81.7)	524 (73.7)
Early-life adversities						
Neglect	6966	381 (11.0)	330 (9.44)	N/A	N/A	N/A
Emotional neglect	7661	429 (11.2)	439 (11.5)	1249	25 (4.64)	58 (8.17)
Abuse						
Physical	7661	219 (5.71)	239 (6.24)	1251	21 (3.88)	44 (6.20)
Psychological	7661	297 (7.75)	437 (11.4)	1251	26 (4.80)	78 (11.0)
Sexual	7661	18 (0.47)	105 (2.74)	1242	9 (1.67)	73 (10.4)
Childhood socioeconomic disadvantage	6918	362 (10.5)	402 (11.6)	1249	60 (11.1)	118 (16.7)
Inflammatory markers						
CRP (mg/litre)[2]	7659	0.96 (0.50,2.06)	1.01 (0.44,2.61)	1235	1.15 (0.59,2.59)	1.83 (0.79,4.27)
Fibrinogen (g/l)	7650	2.88 (0.58)	3.03 (0.65)	1235	3.32 (0.81)	3.62 (0.91)
IL6 (pg/ml)	N/A	N/A	N/A	1243	2.83 (2.80)	3.20 (3.21)
Potential intermediaries						
Adiposity (at blood draw)						
BMI (kg/m^2)	7636	27.7 (4.18)	26.9 (5.48)	1254	29.7 (5.38)	29.9 (7.44)
WHR	7633	0.93 (0.06)	0.81 (0.06)	1253	0.97 (0.08)	0.84 (0.08)
Adult socioeconomic disadvantage[3]	7069	461 (13.2)	460 (12.9)	1251	41 (7.61)	114 (16.0)

[1] Mean (range).
[2] Median (inter-quartile range).
[3] Binary measure identifying the most disadvantaged 15% (approximately) of the population, see '*Potential intermediary factors*' for more details.

Covariates: were selected a-priori and available in both cohorts, including gender (Rudnicka et al., 2007; Friedman et al., 2015), age (Friedman et al., 2015), race (non-white, white) (Friedman et al., 2015; Kelley-Hedgepeth et al., 2008) and season (Rudnicka et al., 2007) (spring, summer, fall, winter).

2.5. Analysis

We used linear regression to assess associations of each type of early-life adversity with inflammatory markers separately. For ease of interpretation and to maintain consistency across outcomes, all inflammatory markers were log-transformed and multiplied by 100, whereby the regression coefficients can be interpreted as the symmetric percentage difference in means (Cole and Altman, 2017). We tested interactions between each type of adversity and gender and, in MIDUS, between each adversity and race. For the former, there was little evidence of effect modification; results are presented for genders combined. For race, where interactions were found, results are presented separately, otherwise results are presented for races combined. We first adjusted models for gender, race (where appropriate) and age (Model 1); second, we additionally adjusted for covariates (season and childhood socioeconomic disadvantage; Model 2). Next, we assessed two-way tetrachoric correlations between examined early-life adversities, because previous studies had suggested that different adversities co-occur (Dong et al., 2004). Most early-life adversities were weakly or only modestly correlated (< 0.65) except for physical and psychological abuse (approximately 0.8 in both cohorts). We therefore adjusted associations for all types of early-life adversity simultaneously in models 1 and 2. Finally, we considered intermediaries of early-life adversity–adult inflammation associations, in models that simultaneously adjusted for all early-life adversities, by additionally adjusting for concurrent adiposity (BMI and WHR; Model 3) and adult socioeconomic disadvantage (Model 4).

We examined relationships for potential intermediary factors, of: (i) early-life adversities with adult adiposity (BMI and WHR) and socioeconomic disadvantage, and (ii) adult adiposity and socioeconomic disadvantage with inflammatory markers. To investigate whether the BMI trajectory was relevant to adult inflammatory status we examined 16y and 45y BMI, stratifying by tertiles of BMI at each age, in the 1958 cohort (data not available for MIDUS).

In some instances, confidence intervals for effect estimates were influenced by low prevalence of adversities (e.g. sexual abuse in 1958 cohort) and the smaller sample in MIDUS. Hence, we considered consistency of associations and effect sizes in our interpretation, as well as statistical significance. We conducted two sensitivity analyses. First, because differences in acute infection could affect associations between early-life adversities and inflammatory markers, we repeated analyses excluding participants with CRP ≥ 10 mg/l (n = 230 (3.0%) 1958 cohort, n = 54 (4.4%) MIDUS); results were broadly unchanged (Supplementary Table 1). Second, in the 1958 cohort, to examine whether associations were robust to choice of cut-off for neglect, we repeated analyses using a more stringent cut-point (> 4). Results confirm associations presented (Supplementary Table 2).

Missing data: In the 1958 cohort, 9315 (of 9377) participants at 45y completed the childhood maltreatment questionnaire; of these, 7661 with a measure of CRP or fibrinogen were included in analyses. Missing data ranged from 0.01% (45y height) to 26.8% (16y weight). The MIDUS sample consisted of biomarker project participants (n = 1255); missing data ranged from 0.2% (race) to 2.0% (CRP and fibrinogen). In both cohorts, to minimise data loss, missing data were imputed using multiple imputation chained equations. Following guidelines (Sterne et al., 2009), imputation models included all model variables, plus main predictors of missingness (1958 cohort: 7-year internalising and externalising behaviours and cognitive ability (Atherton et al., 2008); MIDUS: key indicators of adult social status (education, income, current financial situation, enough money to meet needs, difficulty paying bills and employment status)). Regression analyses were run across 20 imputed data-sets and overall estimates were obtained. Imputed results were broadly similar to those obtained using observed values; the former are presented. Analyses were carried out in STATA version 14 (1958 cohort) and SAS version 9.4 (MIDUS).

3. Results

Prevalence of early-life adversities varied from ~2% (sexual abuse) to ~11% (socioeconomic disadvantage/emotional neglect) in the 1958

Table 3
Mean percentage difference (95% CI) in inflammatory markers, by early-life adversities.

		1958 British birth cohort		MIDUS		
		CRP	Fibrinogen	CRP	Fibrinogen	IL6
Neglect	Model 1[1]	31.3 (22.2,40.5)	4.72 (3.19,6.25)			
	Model 2[2]	23.8 (14.4,33.1)	3.67 (2.10,5.24)			
Emotional neglect	Model 1[1]	4.75 (−3.70,13.2)	1.35 (−0.08,2.78)	20.5 (−7.56, 48.6)	5.23 (−0.75, 11.2)	9.76 (−6.83, 26.4)
	Model 2[2]	2.28 (−6.13,10.7)	1.00 (−0.42,2.43)	17.6 (−10.9, 46.1)	4.88 (−1.14, 10.9)	6.75 (−10.3, 23.8)
Physical abuse	Model 1[1]	23.0 (11.7,34.3)	3.92 (2.00,5.84)	26.8 (−3.59, 57.3)	6.66 (−0.29, 13.6)	16.8 (−5.21, 38.8)
	Model 2[2]	20.0 (8.75,31.2)	3.46 (1.55,5.37)	23.2 (−7.59, 54.0)	6.18 (−0.75, 13.1)	13.0 (−9.20, 35.1)
Psychological abuse	Model 1[1]	13.9 (4.75,23.0)	2.77 (1.23,4.31)	9.89 (−15.0, 34.8)	5.99 (1.16, 10.8)	7.22 (−7.99, 22.4)
	Model 2[2]	11.6 (2.51,20.6)	2.44 (0.90,3.98)	7.26 (−17.6, 32.1)	5.37 (0.53, 10.2)	5.59 (−9.83, 21.0)
Sexual abuse[3]						
White participants	Model 1[1]	14.8 (−6.64,36.1)	1.97 (−1.66,5.59)	31.6 (6.17, 57.0)	5.91 (0.35, 11.5)	19.5 (3.62, 35.5)
	Model 2[2]	8.56 (−12.7,29.8)	1.20 (−2.42,4.81)	16.7 (−11.4, 44.8)	1.62 (−4.59, 7.83)	9.89 (−7.44, 27.2)
Non-white participants	Model 1[1]			59.2 (7.90, 110)	13.2 (2.47, 23.9)	38.0 (6.41, 69.5)
	Model 2[2]			57.9 (6.61, 109)	14.1 (3.39, 24.9)	36.3 (4.64, 68.0)
Childhood socioeconomic disadvantage	Model 1[1]	20.8 (12.2,29.5)	2.13 (0.66,3.60)	2.64 (−16.7, 22.0)	0.30 (−3.67, 4.26)	6.23 (−6.15, 18.6)
	Model2[4]	20.7 (12.0,29.3)	2.18 (0.71,3.65)	2.93 (−16.3, 22.2)	0.34 (−3.65, 4.33)	6.13 (−6.18, 18.4)

[1] Adjusted for age, race and gender.
[2] Additionally adjusted for season and childhood socioeconomic disadvantage (as a continuous variable).
[3] MIDUS: p-value for race interaction for CRP, fibrinogen and IL-6: 0.09, 0.06 and 0.04 respectively.
[4] Additionally adjusted for season.

Table 4
Mean percentage difference (95% CI) in inflammatory markers by mutually adjusted early-life adversities.

		1958 British birth cohort		MIDUS		
		CRP	Fibrinogen	CRP	Fibrinogen	IL6
Neglect	Model 1[1]	23.2 (13.8,32.6)	3.51 (1.93,5.09)			
	Model 2[2]	23.2 (13.7,32.6)	3.53 (1.95,5.12)			
	Model 3[3]	16.3 (8.14,24.4)	2.78 (1.27,4.29)			
	Model 4[4]	17.7 (8.18,27.2)	2.66 (1.06,4.26)			
Emotional neglect	Model 1[1]	−3.82 (−12.7,5.07)	−0.07 (−1.58,1.44)	11.7 (−18.3, 41.7)	2.43 (−3.73, 8.59)	2.41 (−15.9, 20.7)
	Model 2[2]	−3.74 (−12.6,5.15)	−0.05 (−1.56,1.46)	12.1 (−17.9, 42.2)	2.64 (−3.43, 8.72)	2.53 (−15.8, 20.8)
	Model 3[3]	0.41 (−7.44,8.27)	0.42 (−1.01,1.86)	8.90 (−17.9, 35.7)	2.33 (−3.47, 8.14)	0.04 (−16.7, 16.7)
	Model 4[4]	−4.65 (−13.5,4.21)	−0.20 (−1.70,1.31)	10.5 (−19.5, 40.4)	2.33 (−3.71, 8.38)	1.01 (−16.6, 18.7)
Physical abuse	Model 1[1]	16.1 (2.81,29.5)	2.42 (0.15,4.68)	16.3 (−17.2, 49.7)	2.62 (−5.38, 10.6)	9.22 (−15.5, 33.9)
	Model 2[2]	16.3 (3.01,29.7)	2.40 (0.13,4.66)	17.0 (−16.4, 50.3)	2.88 (−5.04, 10.8)	9.07 (−15.7, 33.9)
	Model 3[3]	8.41 (−3.37,20.2)	1.55 (−0.61,3.71)	15.1 (−14.4, 44.7)	2.61 (−5.05, 10.3)	8.51 (−14.7, 31.7)
	Model 4[4]	16.0 (2.74,29.3)	2.35 (0.09,4.60)	13.0 (−20.2, 46.3)	2.21 (−5.68, 10.1)	5.64 (−18.7, 30.0)
Psychological abuse	Model 1[1]	5.17 (−5.80,16.1)	1.38 (−0.49,3.24)	−6.01 (−33.6, 21.6)	3.37 (−2.04, 8.78)	−1.67 (−19.0, 15.7)
	Model 2[2]	5.09 (−5.88,16.1)	1.37 (−0.50,3.23)	−6.83 (−34.4, 20.7)	2.89 (−2.50, 8.29)	−1.23 (−18.8, 16.3)
	Model 3[3]	5.91 (−3.78,15.6)	1.47 (−0.31,3.24)	−7.25 (−31.2, 16.7)	2.77 (−2.49, 8.02)	−1.03 (−17.2, 15.1)
	Model 4[4]	5.00 (−5.93,15.9)	1.35 (−0.50,3.21)	−6.35 (−34.1, 21.4)	2.99 (−2.40, 8.37)	−0.79 (−18.2, 16.7)
Sexual abuse[5]						
(white participants)	Model 1[1]	−2.10 (-24.0,19.8)	−0.94 (−4.67,2.78)	10.4 (−17.7, 38.6)	0.38 (−5.76, 6.52)	7.90 (−9.34, 25.1)
	Model 2[2]	−2.61 (−24.5,19.3)	−0.89 (−4.61,2.84)	11.1 (−17.0, 39.1)	0.33 (−5.79, 6.45)	8.14 (−9.04, 25.3)
	Model 3[3]	−0.45 (−19.9,19.0)	−0.63 (−4.18,2.91)	−12.7 (−37.3, 12.0)	−2.46 (−8.29, 3.37)	−4.29 (−18.8, 10.2)
	Model 4[4]	−6.16 (−28.0,15.7)	−1.45 (−5.16,2.26)	9.15 (−18.8, 37.1)	−0.06 (−6.17, 6.05)	6.66 (−10.2, 23.6)
(non-white participants)	Model 1[1]			75.5 (20.5, 130)	13.6 (2.02, 25.1)	33.9 (0.12, 67.7)
	Model 2[2]			72.4 (17.7, 127)	13.5 (1.97, 25.1)	32.3 (−1.44, 66.1)
	Model 3[3]			24.8 (−24.5, 74.1)	6.22 (−4.82, 17.3)	10.3 (−22.4, 42.9)
	Model 4[4]			71.2 (16.6, 125)	13.4 (1.82, 24.9)	31.0 (−2.41, 64.4)
Childhood socioeconomic disadvantage	Model 1[1]	16.4 (7.64,25.1)	1.40 (−0.09,2.89)	−3.44 (−23.2, 16.4)	−1.12 (−5.19, 2.96)	2.79 (−9.98, 15.6)
	Model 2[2]	16.2 (7.50,24.9)	1.44 (−0.05,2.94)	−3.19 (−22.9, 16.6)	−1.08 (−5.18, 3.02)	2.67 (−10.0, 15.4)
	Model 3[3]	5.05 (−2.70,12.8)	0.24 (−1.18,1.66)	−4.49 (−22.1, 13.1)	−1.26 (−5.12, 2.59)	2.16 (−9.80, 14.1)
	Model 4[4]	13.2 (4.47,22.0)	0.97 (−0.52,2.47)	−5.52 (−25.4, 14.3)	−1.51 (−5.61, 2.59)	0.53 (−12.0, 13.1)

Childhood socioeconomic disadvantage entered as binary variable, when it is the exposure of interest; otherwise entered as a continuous variable.
[1] Adjusted for age, race, gender and simultaneously for other types of early-life adversities.
[2] Additionally adjusted for season.
[3] Model 2 + adjustment for BMI and WHR (in 1958 cohort modelled with a gender interaction).
[4] Model 2 + adjustment for adult socioeconomic disadvantage (range: 0–10).
[5] MIDUS: p-value for race interaction for CRP, fibrinogen and IL-6: 0.10, 0.09 and 0.05 respectively.

Table 5
Mean percentage difference (95% CI) in inflammatory markers, by adult adiposity and socioeconomic disadvantage.

	1958 British birth cohort[1]		
	CRP	Fibrinogen	IL-6
Adiposity (at blood draw)			
BMI	10.8 (10.3,11.3)	1.17 (1.08,1.26)	
+ additional adjustments[2]	10.6 (10.1,11.1)	1.14 (1.05,1.23)	
WHR*100	7.08 (6.67,7.49)	0.76 (0.69,0.83)	
+ additional adjustments[2]	6.90 (6.48,7.31)	0.73 (0.66,0.81)	
Adult socioeconomic disadvantage	25.3 (16.9,33.8)	4.26 (2.85,5.68)	
+ additional adjustments[2]	20.4 (11.8,29.0)	3.56 (2.14,4.99)	
	MIDUS[3]		
BMI	7.74 (6.75, 8.73)	1.04 (0.83, 1.26)	3.73 (3.14, 4.33)
+ additional adjustments[2]	7.70 (6.71, 8.70)	1.04 (0.82, 1.25)	3.72 (3.12, 4.31)
WHR*100	3.75 (2.71, 4.79)	0.47 (0.28, 0.66)	2.14 (1.49, 2.80)
+ additional adjustments[2]	3.74 (2.69, 4.79)	0.49 (0.30, 0.68)	2.13 (1.46, 2.79)
Adult socioeconomic disadvantage	21.9 (0.09, 43.8)	4.00 (−0.75, 8.74)	22.5 (8.19, 36.9)
+ additional adjustments[2]	18.6 (−3.88, 41.0)	3.28 (−1.48, 8.05)	21.3 (6.93, 35.7)

All models adjusted for age, race and gender.
[1] In the 1958 birth cohort, there was an interaction between gender and adiposity whereby stronger associations were observed in women e.g. for unadjusted associations between BMI and CRP p-interaction < 0.01: 8.95% (8.16,9.74) in men; 11.9% (11.3,12.6) in women. Gender adjusted results shown in table.
[2] Additionally adjusted for season and childhood socioeconomic disadvantage (as a continuous variable).
[3] There was no interaction between race and adult adiposity/disadvantage on inflammatory markers.

cohort and ~5% (physical abuse) to ~14% (socioeconomic disadvantage) in MIDUS; in particular, physical abuse prevalence was similar across cohorts (Table 2).

3.1. Early-life adversities and adult inflammation

Several associations were observed between early-life adversities and inflammatory markers. In the 1958 cohort, in covariate adjusted models, neglect, physical abuse, psychological abuse and childhood socioeconomic disadvantage were associated with CRP and fibrinogen; e.g. physical abuse was associated with 20.0% (8.75,31.2) higher CRP and 3.46% (1.55,5.37) higher fibrinogen (Table 3, model 2). In MIDUS, psychological abuse was associated with 5.37% (0.53,10.2) higher fibrinogen. Sexual abuse was associated with all inflammatory markers in non-whites but not whites ($p_{race\text{-}interaction}$ = 0.04 for IL-6 and borderline for CRP and fibrinogen) e.g. IL-6 was higher by 36.3% (4.64,68.0) in non-whites versus 9.89% (−7.44,27.2) in whites (Table 3). In some instances, effect estimates in MIDUS were similar in magnitude and direction to those for the 1958 cohort (e.g. for physical abuse and CRP) but confidence intervals for MIDUS included 1. We next examined models that simultaneously adjusted for all types of early-life adversity. In the 1958 cohort, associations remained for neglect and physical abuse and, for childhood socioeconomic disadvantage with CRP (Table 4, Model 2); e.g. physical abuse was associated with 16.3% (3.01,29.7) higher CRP. In MIDUS, associations remained for sexual abuse in non-whites (e.g. 72.4% (17.7, 127) higher CRP) and the magnitude of association for physical abuse was similar to the 1958 cohort, but with wide confidence intervals (17.0% (−16.4,50.3)).

3.2. Adiposity and adult socioeconomic disadvantage

There were several associations between early-life adversities and adult adiposity or socioeconomic disadvantage (Supplementary Table 3). In the 1958 cohort, neglect, physical abuse and childhood socioeconomic disadvantage were associated with higher BMI and WHR; e.g. by 0.71 kg/m^2 (0.33,1.08) for neglect. In MIDUS, emotional neglect and sexual abuse were associated with greater adiposity; e.g. by 3.97 kg/m^2 (2.02,5.92) for sexual abuse. Again, there were instances where effect estimates were similar in both cohorts, but not always statistically significant, e.g. for physical abuse and WHR the estimate was 0.62 (0.04,1.20) in the 1958 cohort and 0.70 (−1.33,2.73) in MIDUS. In both cohorts, adult adiposity was associated with all inflammatory markers (Table 5); e.g. 1-unit higher BMI was associated with 10.6% (10.1,11.1) and 7.70% (6.71,8.70) higher CRP in the 1958 cohort and MIDUS respectively. In the 1958 cohort, associations with inflammatory markers were stronger for concurrent than for 16y BMI or for the 16y-to-45y trajectory, e.g. CRP was higher by 97.3% (86.8,108) to 109% (100,117) for the highest concurrent BMI tertile, for different levels of 16y BMI (Supplementary Table 4).

For adult socioeconomic disadvantage, there were associations for all early-life adversities in the 1958 cohort and for all, except psychological and sexual abuse, in MIDUS; e.g. child disadvantage was associated with adult disadvantage (ORs: 1.52 (1.23,1.89) in 1958 cohort; 2.01 (1.31,3.08) in MIDUS, Supplementary Table 3). In both cohorts, adult disadvantage was associated with inflammatory markers: CRP and fibrinogen in the 1958 cohort (e.g. 20.4% (11.8,29.0) higher CRP); IL-6 in MIDUS (21.3% (6.93,35.7) higher, Table 5).

3.3. Intermediary role of adult adiposity and socioeconomic disadvantage

With regard to a potential intermediary role for adiposity, Model 3 (Table 4) shows that, in both cohorts, many associations between early-life adversities and inflammatory markers attenuated after accounting for BMI and WHR; e.g. associations were completely attenuated for physical abuse in the 1958 cohort and for sexual abuse in MIDUS. After accounting for adult socioeconomic disadvantage, some associations attenuated (e.g. neglect, in 1958 cohort), but others were little affected (e.g. physical abuse and, in MIDUS, sexual abuse) (Table 4, Model 4). Neglect (1958 cohort) remained associated with inflammatory markers after adjustment for adult adiposity and socioeconomic disadvantage.

4. Discussion

Using two general population cohorts in the UK and USA our study has four important findings. First, we showed that several early-life adversities are associated with elevated markers of inflammation many years later in adulthood. Specifically, consistently across the cohorts, similar patterns of associations for physical abuse were seen with approximately 16% higher CRP and 2% higher fibrinogen. Associations were also observed for neglect and sexual abuse among non-whites (data available respectively in 1958 cohort and MIDUS only). Second, in both cohorts, we found associations between several early-life adversities and elevated adult adiposity and socioeconomic disadvantage; and between adult adiposity or socioeconomic disadvantage and inflammation. Third, consistently across the cohorts, adjustment for adult adiposity attenuated early adversities–adult inflammation associations, providing support for a likely intermediary role of adiposity. Fourth, consistently across cohorts, no associations were observed for emotional neglect or psychological abuse, while childhood socioeconomic disadvantage associations with inflammatory markers were inconsistent.

A key strength of our study is inclusion of two populations with some potentially differing confounding structures (e.g. UK's universal welfare provision vs USA's private care) and, to the extent that study design allowed, we standardised definitions and approaches. The latter

is important because, as highlighted elsewhere, previous studies use heterogeneous definitions of adversities and differing statistical approaches (Baumeister et al., 2016). Although our analysis could be considered as exploratory and residual confounding cannot be excluded, subsequent studies are required to confirm our findings. However, inclusion of two cohorts is based on the premise that, if an association is causal it would be evident in both cohorts, adding weight to our findings with regard to causality (Brion et al., 2011). It was possible to examine several early-life adversities and to account for co-occurrence by simultaneous adjustment; the range of covariates was limited by availability across the two cohorts. Availability of two adiposity (central and general) measures and rich data on adult socioeconomic circumstances was valuable for the purpose of investigating their respective intermediary roles, and although these data were not temporally distinct from the inflammatory markers, the direction of the hypothesized mediation pathway is based on study designs that address causal direction, namely Mendelian randomisation (Timpson et al., 2011; Welsh et al., 2010). Limitations are acknowledged, mainly relating to comparability of cohort data and composition. As mentioned above, confidence intervals for effect estimates were influenced, in some instances, by low prevalence of adversities (e.g. sexual abuse in 1958 cohort) and smaller MIDUS sample. Reflecting the populations from which the samples were drawn, the 1958 cohort comprises similarly aged, predominantly Caucasian individuals, whilst MIDUS has a more diverse ethnic make-up and age range. Assessment of exposures differed in the two studies and some were available in only one study. Such differences could explain inconsistencies in results, e.g. childhood disadvantage was ascertained differently (prospectively in the 1958 cohort; retrospectively in MIDUS) and the measures varied between the two populations. In the 1958 cohort, neglect was prospectively measured using multiple sources (parent and teacher) to reduce misclassification (Kendall-Tackett and Becker-Blease, 2004), but only captures some (failure to meet a child's basic physical, emotional, or educational needs) and not all aspects of neglect (Gilbert et al., 2009) and we lacked a comparable measure in MIDUS. For abuse, we selected items from the validated CTQ scale used in MIDUS (Bernstein et al., 2003) to be comparable with the 1958 cohort, but differences remain. Notably, the perpetrator of abuse was the parent in the 1958 cohort, but undefined in MIDUS, possibly explaining the higher prevalence of sexual abuse in MIDUS. As with all long-term studies, attrition occurred over time in these cohorts and (except for prospectively ascertained childhood disadvantage and neglect in the 1958 cohort) it is not possible to determine whether particular early-life adversities predict attrition. Although participants were broadly representative of the original cohorts (Atherton et al., 2008; Dienberg Love et al., 2010; Radler and Ryff, 2010), we show elsewhere that 1958 cohort individuals with childhood adversities (e.g. socioeconomic disadvantage and neglect) were more likely than others to be lost to follow-up at 45y (Atherton et al., 2008; Denholm et al., 2013) and thus, are under-represented in the present study. Similarly, in MIDUS, childhood socioeconomic disadvantage (reported in MIDUS-I) was associated with lower probability of participation in MIDUS-II. Whilst the possibility of attrition bias cannot be ruled out, our previous work, in the 1958 cohort, on child neglect associations with other adult outcomes suggests that its effect is likely to be negligible (Geoffroy et al., 2016). Despite attrition and differences in study design, prevalence of early-life adversities in both cohorts were generally within ranges reported elsewhere (Gilbert et al., 2009; May-Chahal and Cawson, 2005). Moreover, in both cohorts, further sample reductions due to missing data were addressed using multiple imputation. We included commonly measured inflammatory markers at one time-point, but did not measure IL-6 in the 1958 cohort. CRP was assayed with different sensitivity in the two studies, potentially creating type II errors in the context of small effects (Baumeister et al., 2016). Analyses excluding participants with CRP $\geq$ 10 mg/l suggest that findings were robust to a possible influence of acute infection.

Our findings add to the sparse literature on associations between child maltreatment and inflammation; in particular, we add to a review (Baumeister et al., 2016) of predominantly small samples (only 3 of 18 included CRP studies and none of 15 IL-6 studies had a sample > 1000). Despite limitations of available studies, the review noted that relationships with inflammatory markers vary by type of early-life adversity. Our consistent findings for physical abuse associations and lack of associations for emotional neglect and psychological abuse, highlight the need to consider specific early-life adversities in relation to inflammation. Consistent with the review, we found a positive, non-significant association for physical and sexual abuse with IL-6; in contrast to null findings in the review, we found associations for several early-life adversities (neglect, physical abuse, childhood socioeconomic disadvantage and (MIDUS only) sexual abuse in non-whites) and CRP. Discrepancies could be due to differences in early-life adversity measures, e.g. the review included general indicators of family environment such as parental divorce, rather than specific adversities. Our 1958 cohort finding of a child socioeconomic disadvantage association with elevated adult CRP agrees with a larger review (for 14 of 21 included studies N > 1000) (Liu et al., 2017). Regarding magnitude of associations, our findings concur with previous work suggesting small effects for abuse (Baumeister et al., 2016) and moderate associations for childhood socioeconomic disadvantage (Liu et al., 2017).

Specific associations for early-life adversities might be expected if associations for potential intermediaries show parallel specificity. In the 1958 cohort, associations for neglect, physical abuse and childhood socioeconomic disadvantage with adult inflammation, were evident also with adult adiposity, likewise in MIDUS, for sexual abuse. Thus, like others (Liu et al., 2017; Matthews et al., 2016), our results suggest that adult adiposity may be intermediate between childhood socioeconomic disadvantage and CRP. Importantly, we extend the literature (Matthews et al., 2014) by showing that adiposity is a likely intermediary for child physical abuse and neglect links with adult inflammation. Also, we showed that associations of concurrent BMI with inflammatory markers were stronger than for childhood BMI or the child-to-adult BMI trajectory, thereby addressing an identified gap, on the dearth of studies examining lifetime BMI and adult inflammation (Liu et al., 2017). We found similar attenuation patterns by adiposity of early-life adversity–inflammation associations across the two cohorts. Feasibility of an intermediary role for adiposity fits with literature linking child maltreatment with adult adiposity (Danese and Tan, 2014), and with the detrimental causal influence of obesity on inflammation (Timpson et al., 2011; Welsh et al., 2010). Examining adult socioeconomic disadvantage as a potential intermediary we found, in both cohorts, that early-life adversities were associated with adult socioeconomic disadvantage and in turn, adult disadvantage was associated with elevated inflammation levels. Our findings are consistent with previous studies (Danese et al., 2007; Gruenewald et al., 2009; Loucks et al., 2010); and provide weak support for an intermediary role of adult socioeconomic disadvantage in associations between early-life adversities and adult inflammation, as suggested elsewhere (Danese et al., 2007; Liu et al., 2017). For neglect (the only adversity associated with inflammatory markers after accounting for adult adiposity), other intermediaries may be involved.

Compared to CRP, fewer studies examine the relationship and potential pathways between early-life adversities and IL-6. While limited to one cohort, we had a larger sample than most previous work (Baumeister et al., 2016) and found positive but non-significant associations with early-life adversities, in particular, sexual and physical abuse. Sexual abuse associations with IL-6 and other inflammatory markers, were stronger for non-whites than whites, an observation that is consistent with previous work in MIDUS using a composite index of early-life adversities (Slopen et al., 2010). Findings such as these are noteworthy because IL-6 has a causal role in the development of coronary heart disease (Swerdlow et al., 2012); it is therefore important to investigate this association in other populations and races. Future

studies may also consider measurement issues: blood was taken from MIDUS participants after a clinical centre overnight stay which may increase sleep disturbance; with possibly greater effects on IL-6 than on CRP (Irwin et al., 2016). Such disturbances could potentially weaken findings for IL-6 compared to CRP.

In conclusion, our study highlights the importance of considering specific early-life adversities. We showed that childhood neglect and physical abuse have deleterious associations with inflammatory profiles in adulthood; parallel associations were seen with adult adiposity that were consistent with the observed attenuating effect of adiposity in early-life adversity–adult inflammation relationships. Early-life adversities are associated with several chronic diseases such as CVD, that may have an inflammatory pathophysiology (Swerdlow et al., 2012; Kaptoge et al., 2010; Sarwar et al., 2012; Miller and Raison, 2016), thus inflammation may be an important link between specific early-life adversities and such health outcomes. Our findings suggest that weight reduction and obesity prevention may be beneficial to offset pro-inflammatory related adult disease among those who experienced specific early-life adversities.

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Disclosure

Drs. Pinto Pereira and Stein Merkin and Profs Seeman and Power report no biomedical financial interests or potential conflict of interests.

Appendix A. Supplementary data

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