Socioeconomic determinants of inflammation and neuroendocrine activity: A longitudinal analysis of compositional and contextual effects

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ABSTRACT

Socioeconomic determinants are well-established modulators of inflammation and neuroendocrine activity. Less clear is whether neighbourhood-contextual or individual-compositional factors are more closely associated with gradients in these biomarkers. Here, we examine how immune and neuroendocrine activity are cross-sectionally and longitudinally nested in meso-level socioeconomic characteristics. Participants, male and female, aged ≥50, were recruited from the English Longitudinal Study of Ageing (ELSA). Neighbourhood (Index of Multiple Deprivation [IMD]) and individual (Wealth/Education/Occupational Social Class [Occupation]) factors were drawn from wave 4 (baseline; 2008). Immune and neuroendocrine biomarkers (indexed by C-reactive protein [CRP; $n = 3,968$]; fibrinogen [$n = 3,932$]; white blood cell counts [WBCC; $n = 4,022$]; insulin-like growth factor-1 [IGF-1; $n = 4,056$]) were measured at baseline and 4-years later (wave 6; 2012). Covariates at baseline included demographic, clinical, and lifestyle variables. Lower socioeconomic status was associated with heighted inflammation and lower neuroendocrine activity unadjusted both cross-sectionally and longitudinally. With few exceptions, cross-sectional associations remained significant after full adjustment. Prospectively, low IMD remained associated with higher CRP and WBCC; wealth with WBCC; and education and occupation with fibrinogen and WBCC. IMD-biomarker associations were reduced when wealth was simultaneously taken into account. Lifestyle accounted for the greatest variance in associations between socioeconomic indicators and inflammation (≤42.11%), but demographics were more salient to neuroendocrine activity (≤88.46%). Neighbourhood-contextual factors were stronger indicators of aberrant biomarker activity than individual-compositional factors in cross-sectional analyses but were largely explained by wealth differences prospectively. Therefore, immune and neuroendocrine changes depended on the composition of the population living in an area, rather than the area itself.

1. Introduction

Immune and neuroendocrine processes are of vital importance in health and disease. Pro-inflammatory markers include C-reactive protein (CRP), fibrinogen, and leukocyte numbers (white blood cell counts [WBCC]). By contrast, insulin-like growth factor-1 (IGF-1) is a key marker of the neuroendocrine function involved in anabolic processes. Inflammation has downregulation effects on IGF-1 secretion (Kiecolt-Glaser et al., 2002), while the IGF-1-axis has anti-inflammatory effects on inflammation (Rajpathak, 2008). Advances in molecular medicine and epidemiology have implicated inflammation as a principal biological pathway that underlies an array of health conditions and age-related physiological decline (Furman, 2019; Scrivo et al., 2011; Dantzer et al., 2008). While IGF-1 promotes normal nerve and developmental growth,

muscle mass and function, tissue survival, synaptic plasticity, and antiapoptotic-mediated signalling cascades, it also has a discrete role in human frailty, cognitive decline, and neuronal disorders (Arroba et al., 2018). The economic burden (Schmidt, 2017) and the gravity of these accumulative costs to health (ERFC, 2010) have prompted a more in depth study of the factors contributing to inflammatory and neuroendocrine processes. One important determinant from a biobehavioural perspective is an inequality in socioeconomic resources, specifically material deprivation.

Material deprivation can cause psychological stress, and is known to actuate a systemic level response through psychoneuroimmunological (PNI) and neuroendocrine pathways (Steptoe et al., 2019; Barrington, 2014; Steptoe, 2012). Among developed countries, the UK has one of the largest gradients in deprivation (Marmot, 2020), with 7.8 million people

in persistent poverty (ONS, 2019). This is a concern for policy makers, not least, because of growing health disparities (Sinha et al., 2021). There is greater exposure to stress (Owen et al., 2003) and communicable disease in deprived areas, while individuals within those areas are, on average, more likely to engage in harmful health behaviours (Muscatell et al., 2020). Still, they tend to have fewer educational, social, and psychological resources with which to cope (Owen et al., 2003), with less availability of medical services and a reduced inclination to access care (Alley, 2006). Elucidating the complex nature of poverty and the level of deprivation burden that is most impactful to biological processes is key to narrowing health disparities (Ralston et al., 2014).

An important distinction can be drawn between contextual and compositional socioeconomic indicators that are aggregated at the neighbourhood and individual level respectively (Berger, 2019). Contextual factors refer to characteristics of the place in which people live, and combine information from multiple domains, across education, employment, income, skills, training, housing, crime; health and disability (Ministry of Housing, 2004), in order to capture the multidimensional nature of deprivation and the poverty it signifies. In contrast, compositional factors relate to the idiosyncratic characteristics of the individuals within a neighbourhood. Extant literature supports that deprived populations are disproportionately exposed to environments characterised as pro-inflammatory (Ribeiro et al., 2018). Although compositional factors have been shown to predict facility in inflammatory and neuroendocrine states (Muscatell et al., 2020), it is conceivable that contextual determinants are more proximal risk factors (Kirkbride et al., 2010). Such that health and disease are predominately shaped by social and spatial context.

Though socioeconomic indicators are well-established upstream determinants of systemic low-grade inflammation and neuroendocrine activity (Steptoe, 2012; Muscatell et al., 2020; Berger, 2019), our interest is in the relative strength of contextual and compositional factors and prospective nature of these associations, as well as the extent to which different sets of covariates account for the gradient in outcomes. Differentiating between contextual and compositional effects is key to understanding how the environment confers risk on health after accounting for individual-level risk factors (Arcaya et al., 2015). Ignoring this distinction increases the likelihood of an invalid transfer of results obtained at the ecological level to the individual level (the ecological fallacy), as is the case when failing to account for ecology or context (the individualistic fallacy). Overlooking their dependent nature, along with the source of the dependency, can lead to significant findings where none exist (Kawachi and Berkman, 2003). Equally, understanding how inflammation and neuroendocrine processes are nested in compositional and contextual socioeconomic factors could bring some clarity to the structure of disadvantage (Sinha et al., 2021). and help to inform the focus, level, and magnitude of policies and interventions targeted at narrowing the health divide.

Furthermore, older cohorts are increasingly relevant to the understanding of socioeconomic determinants of immune and neuroendocrine activity for two principal reasons. First, material deprivation is related to the acceleration of core phenotypic, functional, molecular, and cellular aging processes (Steptoe and Zaninotto, 2020; Crimmins, 2020). Second, inflammaging (Franceschi et al., 2018) and somatopause (Junnila et al., 2013) are aspects of ageing that lead to the gradual elevations of low-grade circulating inflammatory markers and decrements in the expression of IGF-1 circulating levels over time.

We assessed cross-sectional and longitudinal associations of neighbourhood-contextual and individual-compositional indicators on biomarker activity in a population-based sample of UK older adults, additionally examining the role of demographic, lifestyle, and clinical covariates in these associations. Given that cytokines are pleiotropic, misspecification of effects is possible when making isolated selections within a study (O'Connor et al., 2014), so associations were tested using plasma concentrations of CRP, fibrinogen, and WBCC, in addition to serum IGF-1, a growth-related hormone that declines with age

(Colangelo et al., 2009). Though neighbourhood-contextual indicators have been found to have more moderate effects on health than individual-compositional indicators (Colangelo et al., 2009; Grundy, 2001), neighbourhood-contextual indicators were expected to be stronger drivers of biomarker activity cross-sectionally and longitudinally up to four-years later. First, because individual-compositional indicators have different meaning and are less salient at older ages (Grundy, 2001). Second, because neighbourhood-contextual indicators have been the strongest and most consistent predictors of poor health in this population (Yen et al., 2009). As has been observed elsewhere (Hamilton et al., 2021), factors associated with lifestyle were expected to account for greater variance in associations than demographic or clinical factors.

2. Method

2.1. Participants and procedures

Fully anonymised data were drawn from the English Longitudinal Study of Aging (ELSA), a multi-disciplinary prospective cohort study that began in 2002. The sample includes nationally representative men and women aged 50 years and older (Steptoe et al., 2013). Data collection is performed in participants' homes, through computer-assisted personal interviews (CAPI) and self-completion questionnaires biennially, then nurse visits every 4 years for biological samples. Cross-sectional data and longitudinal exposures were taken from wave 4 (baseline; 2008) and longitudinal outcomes from wave 6 (follow-up; 2012). 7,568 participants had measures on all exposures and covariates at baseline. However, not all participants provided blood samples for assay, due to problems in scheduling visits from study nurses and ineligibility (e.g., anticoagulant medication; haematological disorders; a history of convulsions). Though 6,466 participants had complete data on any of the biomarkers at baseline, 5,841 participants had complete data on all biomarkers at baseline, which was reduced to 3,562 at follow-up four years later. Each biomarker was analysed independently. After exclusions on CRP values >20 mg/L ($n = 116$), the analytic sample for CRP was 3,968 (36.92%), 3,932 (36.58%) for fibrinogen, 4,022 (37.42%) for WBCC, and 4,056 (37.73%) for IGF-1. There were no substantial differences in the characteristics and biomarker levels between participants included and excluded from analyses. Participants provided written consent and ethical approval was granted by the National Research Ethics Service (London Multicentre Research Ethics Committee).

3. Exposures | Wave 4

3.1. Contextual (neighbourhood-level) socioeconomic indicators

The 2004 Index of Multiple Deprivation for England (IMD; i.e., neighbourhood deprivation) is a relative measure of deprivation that combines multiple area-level socioeconomic indicators into a single deprivation score. It is predicated on 38 indicators, across seven domains: education; employment; income; skills and training deprivation; barriers to housing and services; living environment deprivation and crime; health and disability (Supplementary [S] Table 1). The seven domains were measured at the 'lower level super output area' (LSOA), a statistical unit introduced in the 2001 Census that contains 1,500 households on average. Details of both theoretical and practical implementation of this measure, including its reliability and validity, have been published elsewhere (Noble et al., 2006). Neighbourhood deprivation was demarcated into tertiles; the first representing the most deprived on a gradient to the third that represents the least deprived (reference category).

3.2. Compositional (individual-level) socioeconomic indicators

Wealth. Calculated by summating total household wealth, as determined by net wealth from property, possessions, housing, liquid assets; cash, savings, investments, artwork, and jewellery, net of debt, exclusive of pension wealth. Wealth was divided into tertiles; the first representing the least wealth and the third representing the greatest wealth (reference category).

Education. Categorised into higher education (i.e., degree or equivalent; reference category); primary and secondary school qualifications (i.e., A-level, higher education below degree, GCSE [General Certificate of Secondary Education] or equivalent); and no qualifications.

Occupational Social Class (Occupation). A three-category version of the National Statistics Socio-Economic Classification (ONS, 2010): managerial and professional (reference category); intermediate; routine and manual.

4. Outcomes | Wave 6

4.1. Immune and neuroendocrine biomarkers

High-sensitivity plasma C-reactive protein (CRP; mg/L), plasma fibrinogen (g/L), leukocytes (white blood cell counts [WBCC]; 10^9/L), and serum insulin-like growth factor-1 (IGF-1; mmol/L) were dispatched to the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK) for processing and analysis. Blood samples deemed insufficient or unsuitable (e.g., haemolysed; received >5 days post-collection) were discarded. Exclusion criteria included coagulation, haematological disorders, being on anticoagulant medication or having a history of convulsions.

C-reactive Protein. High-sensitivity plasma CRP (mg/L) was assayed using the N Latex CRP mono Immunoassay on the Behring Nephelometer II analyser (Dade Behring, Milton Keynes, UK). Intra and inter-assay coefficients of variation were <2%. The lower detection limit of the assay was 0.2 mg/L. CRP values >20 mg/L were excluded from analyses ($n = 116$), as these were taken to reflect acute inflammatory processes rather than chronic inflammation (Hamilton et al., 2021; Ridker, 2005). CRP was treated as continuous, with higher values indicating greater levels of inflammation.

Fibrinogen. Plasma fibrinogen (g/L) was analysed using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 coagulation analyser (Organon Teknika, Durham, USA). Intra and inter-assay coefficients of variation were <7%. The lower detection limit of the assay was 0.5 g/L. Fibrinogen was treated as continuous, with higher values indicating greater levels of inflammation.

Leukocytes (White Blood Cell Counts [WBCC]). WBCC was analysed as continuous counts per 10^9/L; measured on a haematology-automated analyser (Abbott Diagnostics Cell-Dyn 4000 and Sysmex XE), with higher values indicating greater levels of inflammation.

Insulin-like Growth Factor-1 (IGF-1). Serum IGF-1 (nmol/L) was measured using the DPC Immulite 2000 method, by an electrochemiluminescent immunoassay on IDS ISYS Analyser. Inter and intra-assay coefficients of variation were <14%. IGF-1 was treated as continuous, with lower values indicating greater neuroendocrine activity.

4.2. Covariates

Factors likely to confound analyses were selected *a priori*, including *demographic variables*: age (≥50 years); sex (male; female); *clinical variables*: body mass index (BMI; calculated as weight in kilograms divided by height in meters squared [underweight:≤18.5; normal:18.6–24.9; overweight:25–29.9; obese:≥30 kg/m2]); limiting longstanding illness (binary:- any chronic illness, disability, or infirmity that limits activity); and mobility difficulties (binary:- one or more difficulties mobilising [walking 100 yards; sitting 2-hours; rising from chairs after sitting long

periods; climbing stairs; stooping, kneeling, crouching; reaching or extending arms above shoulders; pulling or pushing large objects; lifting or carrying objects over 10lb; picking-up a 5p coin]); *lifestyle variables*: smoking status (binary:- non-smokers/ex-smokers or smokers); alcohol consumption (binary:- low <3 or high 3 day weekly); physical activity (binary:- sedentary or moderate/vigorous weekly activity). Reference categories were being male, of normal weight, not having a limiting longstanding illness, being fully mobile, a non-smoker/ex-smoker, having low alcohol consumption, and being physically active.

Imputation. Missingness ranged from 0.00-52.33% (Table S2). Given the possibility of bias in complete case analyses (Sterne, 2009; White et al., 2011), missing values on exposures and covariates were imputed using missForest based on Random Forests, an iterative imputation method, in RStudio v.1.4.1717. In the presence of nonlinearity and interactions missForest outperformed prominent imputation methods, such as multivariate imputation by chained equations and *k*-nearest neighbours (Stekhoven and Bühlmann, 2012). Missing at random (MAR) implies that estimates can be reliably computed for all participants with missing data if all the variables that are associated with the missing data generating mechanism are used in the imputation models (Ploubidis et al., 2014). Therefore, since socioeconomic variables are the main correlates of attrition in ELSA (Steptoe et al., 2013) and were used as predictors in the imputation models, this assumption was likely to be met. The imputation of the missing values yielded a minimal error for continuous variables (Normalized Root Mean Squared Error = 0.02%) and categorical variables (proportion of falsely classified = 0.20%). Imputed and observed data were homogenous (Table S2).

4.3. Statistical analyses

Baseline characteristics were expressed as means and proportions. Logarithmic transformation was performed on CRP, WBCC, and IGF-1 values because of their originally skewed distribution. Fibrinogen was normally distributed. Cross-sectional analyses used a series of linear regressions to assess associations between exposures and outcomes at wave 4 (2008). Longitudinal analyses extended this to outcomes at wave 6 (2012). Analyses were weighted using inverse probability weights to ensure national representation and to take account of differential nonresponse at follow-up (ELSA Study, 2019). The most deprived category was reported against the least deprived reference. Results were presented as unstandardised (B) regression coefficients with standard errors (SE). Analyses were two-tailed. The basic model for the analysis can be expressed as: $\hat{Y}_i = B_0 + B_1 X_{1i} + B_2 X_{2i} + \ldots + B_p X_{pi} + u_i$ where $\hat{Y}$ is the predicted value of the outcome; B_0 is the value of $\hat{Y}$ when all exposures equal zero; B_1 through B_p are the estimated regression coefficients, X_1-X_p are distinct covariates, and u is the error term). Each regression coefficient represents the change in $\hat{Y}$ relative to a one-unit change in the respective exposure. Independent multivariate models were fitted to understand the role of different sets of covariates on associations. Biomarkers were modelled independently as CRP was linearly correlated with fibrinogen ($r = 0.310$), WBCC ($r = 0.262$), and IGF-1 ($r = 0.158$) at $p<0.001$. No further issues existed with collinearity and all models met regression assumptions. The unadjusted model (1), that conditioned on the baseline biomarker being measured, was included in all models. Model 2 adjusted for age and sex (*demographic variables*). Model 3 adjusted for BMI, limiting longstanding illness, and mobility difficulties (*clinical variables*); Model 4 adjusted for smoking status, alcohol consumption, and physical activity (*lifestyle variables*); Model 5 adjusted for all covariates. To test the extent to which different models explained associations, the B for outcomes were calculated using the percentage of the protective association explained (PPAE); a well-established epidemiological method (Steptoe and Jackson, 2020) using the formula: (where X is the model tested) PPAE = (B [crude model 1 and model X] – B [crude model 1]/(1-B [crude model 1]). Data analyses were conducted in Stata 17.1 (StataCorp, TX, USA).

4.4. Sensitivity analyses

Six sensitivity analyses were carried out on longitudinal associations. First, sets of covariates were added sequentially rather than independently. Second, due to the potentially confounding effects of inflammaging and somatopause, the moderating effect of age was tested (dichotomised by mean age [$\geq$64.25 years]). Third, immune and neuroendocrine levels have been shown to be higher in men than women (Freeman et al., 2016; Iyer, 2022), so the role of sex as an effect modifier was tested. Fourth the exclusion of CRP values thought to represent acute inflammatory processes ($\geq$20 mg/L) was reassessed on the basis of arguments put forward by Giollabhui and colleagues, 2020, so regressions were repeated including those values. Fifth, analyses used complete cases to compare the efficiency and coverage of confidence intervals for the estimated coefficients and to ensure results were not an artefact of the imputed data. Association analyses replicated that in imputed data. The analytical sample formation is illustrated in Figure S1. Finally, changes in residence over time may have influenced the longitudinal role of neighbourhood-contextual and individual-compositional factors in immune and neuroendocrine responses, so analyses were redistricted to non-movers.

5. Results

Descriptive statistics for the exposures and outcomes are shown in Table 1. The sample comprised 3,562 individuals for whom total baseline data was available. Of these, 44.67% were male, 55.33% female, aged on average 64.26 years ($\pm$8.35; $_{range}$50-99). Participants were, on average, overweight (72.38%), moderately to vigorously active (75.77%), with no limiting longstanding illness (72.18%), and were non-smokers (87.73%), who consumed alcohol less than three days in a given week (63.42%). But there was an equal balance of those with and without mobility difficulties. Biomarkers were stable on average from baseline to follow-up, although individual trajectories varied widely.

5.1. Cross-sectional associations between compositional and contextual socioeconomic indicators and biomarkers

All associations between compositional and contextual socioeconomic indicators and biomarker activity were significant in the unadjusted model (Table 2). The association between IMD (a neighbourhood-contextual factor) and IGF-1 remained significant in the fully adjusted model (β = -0.055, CI = -0.084–-0.026, p<0.001), but the relationships with CRP (β = 0.026, CI = -0.023–0.075, p = 0.303), fibrinogen (β = 0.001, CI = -0.044–0.045, p = 0.972), and WBCC (β = -0.011, CI = -0.034–0.012, p = 0.358) were no longer significant when covariates were taken into account. When fully adjusted, lower wealth (an individual-compositional factor) was associated with higher concentrations of CRP (β = 0.104 CI = 0.054–0.155, p<0.001), fibrinogen (β = 0.086, CI = 0.040–0.132, p<0.001), and WBCC (β = 0.032 CI = 0.008–0.056, p = 0.010), and with lower IGF-1 (β = -0.065, CI = -0.095–-0.035, p<0.001). After full adjustment, with two exceptions; education and IGF-1 (β = -0.012, CI = -0.040–0.015, p = 0.375); occupation and WBCC (β = 0.010, CI = -0.010–0.028, p = 0.341), associations between individual-compositional socioeconomic indicators and biomarkers were significant (Education: CRP β = 0.050, CI = 0.006–0.094, p = 0.025; fibrinogen β = 0.069, CI = -0.030–0.109, p<0.001; WBCC β = 0.030, CI = 0.010–0.051, p = 0.004; Occupation: CRP β = 0.061, CI = 0.018–0.103, p = 0.006; fibrinogen β = 0.041, CI = 0.002–0.080, p = 0.037; IGF-1 β = -0.031, CI = -0.056–-0.005, p = 0.018).

5.2. Longitudinal associations between compositional and contextual socioeconomic indicators and biomarkers

Across the 4-year follow-up period, all compositional and contextual

Table 1
Sample characteristics.

Variable		Baseline (N = 3,562)	
		N / Mean (SD)	% / Range
Age		64.26 (8.35)	50–99
Sex	Male	1,591	44.67
	Female	1,971	55.33
BMI (kg/m2)	Underweight ($\leq$18.5)	21	0.59
	Normal (18.6–24.9)	963	27.04
	Overweight (25–29)	1,580	44.36
	Obese ($\geq$30)	998	28.02
Limiting Longstanding Illness	No	2,571	72.18
	Yes	991	27.82
Mobility Difficulties	No	1,753	49.27
	Yes	1,807	50.73
Smoking Status	Non-smokers/Ex-smokers	3,125	87.73
	Smokers	437	12.27
Alcohol Consumption	<3 days a week	2,259	63.42
	$\geq$3 days a week	1,303	36.58
Physically Activity	Moderately/Vigorously Active	2,699	75.77
	Sedentary	863	24.23
Change of Residence (2008-2013)	No	3,400	95.45
	Yes	162	4.55
IMD	Lowest Tertile	998	28.02
	Middle Tertile	1,598	44.86
	Highest Tertile	966	27.12
Wealth	Lowest Tertile	1,079	30.21
	Middle Tertile	1,537	43.15
	Highest Tertile	949	26.64
Education	Higher	1,263	35.46
	Primary/Secondary/Tertiary	1,174	32.96
	Alternative or None	1,125	31.58
OSC	Managerial/Professional	1,353	37.98
	Intermediate Occupations	919	25.80
	Routine/Manual	1,290	36.22
CRP* (mg/L; Baseline)		1.11 (0.63)	0.18–3.04
CRP* (mg/L; Follow-up)		1.03 (0.59)	0.10–3.05
Fb (g/L; Baseline)		3.31 (0.52)	1.30–5.40
Fb (g/L; Follow-up)		2.94 (0.50)	1.30–5.30
WBCC* (10^9/L; Baseline)		1.80 (0.29)	-0.22–3.92
WBCC* (10^9/L; Follow-up)		1.82 (0.28)	0.72–3.48
IGF-1* (nmol/L; Baseline)		2.72 (0.35)	1.39–4.17
IGF-1* (nmol/L; Follow-up)		2.74 (0.32)	1.39–4.04

Notes: ELSA, waves 4–6 (2008/09–2012/13); N = observations; % = percentage frequencies; SD = standard deviations; BMI = Body Mass Index; IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; CRP = C-reactive protein; Fb = Fibrinogen; WBC = White Blood Cell Counts (leukocytes); IGF-1 = Insulin-Growth Factor-1; * Log-transformed variable.

socioeconomic indicators were longitudinally associated with biomarker activity in basic models adjusted only for baseline biomarker levels (Table 3). Overall, lower socioeconomic status was associated with greater future inflammation and lower IGF-1 concentration. Some attenuation was seen after full adjustment, but IMD (a neighbourhood-contextual factor) remained associated with CRP (β = 0.042, CI = 0.002–0.082, p = 0.039) and WBCC (β = 0.023, CI = 0.005–0.042, p = 0.014). As were individual-contextual factors, specifically wealth with WBCC (β = 0.035, CI = 0.016–0.055, p <0.001), education with fibrinogen (β = 0.034, CI = 0.001–0.070, p = 0.050) and WBCC (β = 0.020, CI = 0.002–0.037, p = 0.029), and occupation with fibrinogen (β = 0.034, CI = 0.001–0.067, p = 0.045) and WBCC (β = 0.024, CI = 0.008–0.041, p = 0.003). Other associations were lost after taking covariates into account ([IMD: fibrinogen β = 0.029, CI = -0.009–0.067, p = 0.135; IGF-1 β = -0.015, CI = -0.032–0.003, p = 0.095]; [Wealth:

Table 2
Cross-sectional relationships of compositional and contextual socioeconomic indicators with immune and neuroendocrine biomarkers.

Adjustments		CRP* (N = 3,968)			Fb (N = 3,932)			WBCC* (N = 4,022)			IGF-1* (N = 4,056)		
		β (SE)	95 % CI	p	β (SE)	95 % CI	p	β (SE)	95 % CI	p	β (SE)	95 % CI	p
Contextual Indicators	IMD												
	Model 1: Crude model	0.131 (0.027)	0.078–0.183	<0.001	0.084 (0.023)	0.038–0.130	<0.001	0.038 (0.012)	-0.013–0.062	0.002	-0.060 (0.015)	-0.089–-0.031	<0.001
	Model 5: Fully Adjusted d	0.026 (0.025)	-0.023–0.075	0.303	0.001 (0.023)	-0.044–0.045	0.972	-0.011 (0.012)	-0.034–0.012	0.358	-0.055 (0.015)	-0.084–0.026	<0.001
Compositional Indicators	Wealth												
	Model 1: Crude model	0.285 (0.026)	0.233–0.336	<0.001	0.230 (0.023)	0.185–0.275	<0.001	0.101 (0.012)	0.078–0.125	<0.001	-0.091 (0.015)	-0.120–0.062	<0.001
	Model 5: Fully Adjusted d	0.104 (0.026)	0.054–0.155	<0.001	0.086 (0.023)	0.040–0.132	<0.001	0.032 (0.012)	0.008–0.056	0.010	-0.065 (0.015)	-0.095–0.035	<0.001
	Education												
	Model 1: Crude model	0.114 (0.024)	0.067–0.161	<0.001	0.117 (0.021)	0.076–0.158	<0.001	0.049 (0.011)	0.027–0.071	<0.001	-0.067 (0.014)	-0.094–0.041	<0.001
	Model 5: Fully Adjusted d	0.050 (0.022)	0.006–0.094	0.025	0.069 (0.020)	-0.030–0.109	<0.001	0.030 (0.011)	0.010–0.051	0.004	-0.012 (0.014)	-0.040–0.015	0.375
	OSC												
	Model 1: Crude model	0.171 (0.023)	0.126–0.216	<0.001	0.139 (0.020)	0.099–0.178	<0.001	0.047 (0.011)	0.026–0.068	<0.001	-0.057 (0.014)	-0.085–0.030	<0.001
	Model 5: Fully Adjusted d	0.061 (0.022)	0.018–0.103	0.006	0.041 (0.020)	0.002–0.080	0.037	0.010 (0.010)	−0.010–0.028	0.341	-0.031 (0.013)	-0.056–0.005	0.018

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; p = significance value.

*Log transformed variable.

[a] Demographic variables: age and sex.

[b] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties.

[c] Lifestyle variables: smoking status, alcohol consumption, and physical activity.

[d] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity.

Table 3
Longitudinal relationships of compositional and contextual socioeconomic indicators with immune and neuroendocrine biomarkers.

Adjustments	CRP* (N = 3,968)			Fb (N = 3,932)			WBCC* (N = 4,022)			IGF-1* (N = 4,056)		
	β (SE)	95 % CI	p	β (SE)	95 % CI	p	β (SE)	95 % CI	p	β (SE)	95 % CI	p
Contextual Indicators												
IMD												
Model 1: Crude model [a]	0.068 (0.020)	0.028–0.108	<0.001	0.053 (0.019)	0.016–0.091	0.005	0.034 (0.009)	0.015–0.052	<0.001	-0.017 (0.009)	-0.034–-0.001	0.050
Model 5: Fully Adjusted [b]	0.042 (0.021)	0.002–0.082	0.039	0.029 (0.019)	-0.009–0.067	0.135	0.023 (0.010)	0.005–0.042	0.014	-0.015 (0.009)	-0.032–-0.003	0.095
Compositional Indicators												
Wealth												
Model 1: Crude model [a]	0.076 (0.020)	0.037–0.116	<0.001	0.076 (0.019)	0.038–0.113	<0.001	0.050 (0.009)	0.032–0.069	<0.001	-0.029 (0.009)	-0.046–-0.011	0.001
Model 5: Fully Adjusted [b]	0.028 (0.021)	-0.014–0.070	0.194	0.031 (0.020)	-0.017–0.052	0.119	0.035 (0.010)	0.016–0.055	<0.001	-0.015 (0.009)	-0.034–-0.003	0.099
Education												
Model 1: Crude model [a]	0.058 (0.018)	0.022–0.094	0.002	0.078 (0.017)	0.044–0.112	<0.001	0.030 (0.009)	0.013–0.047	<0.001	-0.026 (0.008)	-0.042–-0.011	0.001
Model 5: Fully Adjusted [b]	0.020 (0.019)	-0.018–0.058	0.298	0.034 (0.018)	0.001–0.070	0.050	0.020 (0.009)	0.002–0.037	0.029	0.002 (0.008)	-0.014–0.019	0.777
OSC												
Model 1: Crude model [a]	0.056 (0.018)	0.022–0.091	0.001	0.064 (0.016)	0.032–0.097	<0.001	0.033 (0.008)	0.017–0.049	<0.001	-0.021 (0.008)	-0.037–-0.006	0.006
Model 5: Fully Adjusted [b]	0.028 (0.018)	-0.007–0.063	0.118	0.034 (0.017)	0.001–0.067	0.045	0.024 (0.008)	0.008–0.041	0.003	-0.006 (0.008)	-0.021–0.009	0.449

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; p = significance value.

* Log transformed variable.

[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1.

[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity.

CRP β = 0.028, CI = -0.014–0.070, p = 0.194; fibrinogen β = 0.031, CI = -0.017–0.052, p = 0.119; IGF-1 β = -0.015, CI = -0.034–-0.003, p = 0.099]; [Education: CRP β = 0.020, CI = -0.018–0.058, p = 0.298; IGF-1 β = 0.002, CI = -0.014–0.019, p = 0.777]; [Occupation: CRP β = 0.028, CI = -0.007–0.063, p = 0.118; IGF-1 β = -0.006, CI = -0.021–0.009, p = 0.449]).

5.3. Associations between neighbourhood-contextual indicators and biomarkers after accounting for individual-compositional indicators

Table 4 details analyses testing the extent to which associations between IMD (a neighbourhood-contextual factor) and biomarkers survived adjustment for individual-level indicators. In the unadjusted models, IMD was significantly associated with all immune and neuroendocrine biomarkers (Table 4; CRP β = 0.068, CI = 0.028–0.108, p <0.001; fibrinogen β = 0.053, CI = 0.016–0.091, p = 0.005; WBCC β = 0.034, CI = 0.015–0.052, p <0.001; IGF-1 β = -0.017, CI = -0.034–-0.001, p = 0.050). After full adjustment, IMD was longitudinally associated with higher CRP (β = 0.042, CI = 0.002–0.082, p = 0.039) and WBCC (β = 0.023, CI = 0.005–0.042, p = 0.014) over the four-year period. These associations remained robust to the inclusion of education (CRP β = 0.041, CI = 0.000–0.081, p = 0.049; WBCC β = 0.021, CI = 0.002–0.040, p = 0.030) and occupation (CRP β = 0.040, CI = 0.000–0.081, p = 0.050; WBCC β = 0.020, CI = 0.001–0.039, p = 0.043), but they were not longer significant after wealth and other covariates together were taken into account (CRP β = 0.039, CI = -0.004–0.082, p = 0.073; WBCC β = 0.015, CI = -0.005–0.035, p = 0.146).

5.4. Percentage of protective association explained (PPAE) for models assessing compositional and contextual socioeconomic indicators in biomarker activity

Covariates accounted for a varying degree of the association between socioeconomic indicators and biomarkers (Table 5). The three sets of covariates in combination, accounted for 11.76–92.31% of the PPAE. *Clinical variables* (BMI; limiting longstanding illness; mobility difficulties) explained between 9.09-35.29% of the variance. *Lifestyle variables* (smoking status; alcohol consumption; physical activity) accounted for the greatest PPAE in CRP, fibrinogen, and WBCC (≤42.11%). But *demographic variables* (age; sex) were most salient to IGF-1 (≤88.46%).

5.5. Sensitivity analyses

First, there was a consistent pattern of results when covariates were added sequentially rather than independently to the longitudinal analyses, suggesting that findings were not biased by model strategy (Table S3). Second, there were no significant interactions between compositional and contextual socioeconomic indicators and age, suggesting that inflammaging and somatopause were not biasing results (Table S4). Third, sex did not relate to the pattern of results, as there were no significant interactions between compositional and contextual socioeconomic indicators and sex (Table S5). Fourth, results were materially unchanged when CRP values ≥20 mg/L were included in analyses, suggesting that associations were robust to the inclusion of these very high values (Table S6). Fifth, there was a substantial overlap in confidence intervals between the analyses performed in complete cases versus imputed data in the main analyses, suggesting that the use of imputed data did not bias results (Table S7). Finally, when analyses were restricted to people who did not move their residence over the study period, results were again materially unchanged (Table S8).

6. Discussion

In this large longitudinal population study of UK older adults, neighbourhood contextual and individual compositional indicators of socioeconomic status were associated with heightened inflammation

Table 4

Differences in the relationship between neighbourhood factors and biomarkers explained by individual socioeconomic indicators.

Adjustments	CRP* (N = 3,968)			Fb (N = 3,932)			WBCC* (N = 4,022)			IGF-1* (N = 4,056)		
	β (SE)	95 % CI	p	β (SE)	95 % CI	p	β (SE)	95 % CI	p	β (SE)	95 % CI	p
IMD												
Model 1: Crude model [a]	0.068 (0.020)	0.028–0.108	0.001	0.053 (0.019)	0.016–0.091	0.005	0.034 (0.009)	0.015–0.052	<0.001	-0.017 (0.009)	-0.034–0.001	0.050
Model 5: Fully Adjusted [b]	0.042 (0.021)	0.002–0.082	0.039	0.029 (0.019)	-0.009–0.067	0.135	0.023 (0.010)	0.005–0.042	0.014	-0.015 (0.009)	-0.032–0.003	0.095
**IMD	Wealth**												
Model 1: Crude model + Wealth [a]	0.047 (0.022)	0.004–0.090	0.031	0.028 (0.021)	-0.012–0.068	0.174	0.019 (0.010)	-0.001–0.039	0.067	-0.005 (0.010)	-0.024–0.014	0.612
Model 5: Fully Adjusted + Wealth [b]	0.039 (0.022)	-0.004–0.082	0.073	0.022 (0.020)	-0.019–0.062	0.294	0.015 (0.010)	-0.005–0.035	0.146	-0.010 (0.009)	-0.028–0.009	0.314
**IMD	Education**												
Model 1: Crude model + Education [a]	0.059 (0.021)	0.019–0.100	0.004	0.040 (0.019)	0.002–0.077	0.040	0.029 (0.010)	0.010–0.048	0.003	-0.012 (0.009)	-0.030–0.006	0.182
Model 5: Fully Adjusted + Education [b]	0.041 (0.021)	0.000–0.081	0.049	0.024 (0.019)	-0.014–0.062	0.216	0.021 (0.010)	0.002–0.040	0.030	-0.016 (0.009)	-0.033–0.002	0.085
**IMD	OSC**												
Model 1: Crude model + OSC [a]	0.060 (0.021)	0.019–0.100	0.004	0.039 (0.019)	0.000–0.077	0.047	0.027 (0.010)	0.008–0.046	0.005	-0.014 (0.009)	-0.032–0.004	0.128
Model 5: Fully Adjusted + OSC [b]	0.040 (0.021)	0.000–0.081	0.050	0.022 (0.020)	-0.017–0.060	0.270	0.020 (0.010)	0.001–0.039	0.043	-0.015 (0.009)	-0.033–0.003	0.102

Notes: IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class; β = unstandardised regression coefficient; SE = standard error; CI = confidence interval; p = significance value.

* Log transformed variable.

[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1.

[b] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity.

Table 5

The percentage of protective association between socioeconomic indicators and biomarkers by different sets of covariates.

Adjustments		CRP* (N = 3,968)	Fb (N = 3,932)	WBCC* (N = 4,022)	IGF-1* (N = 4,056)
Contextual Indicators	**IMD**				
	Model 1: Crude model [a]				
	Model 2: Model 1 + demographic [b]	-2.94	-5.66	-2.94	-17.65
	Model 3: Model 1 + clinical [c]	20.59	18.87	11.76	35.29
	Model 4: Model 1 + lifestyle [d]	26.47	39.62	23.53	29.41
	Model 5: Fully Adjusted [e]	38.24	45.28	32.35	11.76
Compositional Indicators	**Wealth**				
	Model 1: Crude model [a]	–	–	–	–
	Model 2: Model 1 + demographic [b]	3.95	2.63	2.00	24.14
	Model 3: Model 1 + clinical [c]	31.58	19.74	10.00	34.48
	Model 4: Model 1 + lifestyle [d]	38.16	42.11	18.00	31.03
	Model 5: Fully Adjusted [e]	63.16	59.21	30.00	48.28
	Education				
	Model 1: Crude model [a]	–	–	–	–
	Model 2: Model 1 + demographic [b]	17.24	19.23	0.00	88.46
	Model 3: Model 1 + clinical [c]	29.31	16.67	13.33	23.08
	Model 4: Model 1 + lifestyle [d]	32.76	29.49	20.00	26.92
	Model 5: Fully Adjusted [e]	65.52	56.41	33.33	92.31
	OSC				
	Model 1: Crude model [a]	–	–	–	–
	Model 2: Model 1 + demographic [b]	7.14	10.94	−3.03	47.62
	Model 3: Model 1 + clinical [c]	23.21	14.06	9.09	23.81
	Model 4: Model 1 + lifestyle [d]	30.36	31.25	18.18	28.57
	Model 5: Fully Adjusted [e]	50.00	46.88	27.27	71.43

Notes: PPAE = percentage of protective association explained; IMD = Index of Multiple Deprivation (i.e., Neighbourhood Deprivation); OSC = Occupational Social Class.

* Log transformed variable.

[a] Baseline neuroimmune biomarkers respectively controlled for: CRP = C-reactive protein; Fb = fibrinogen; WBC = white blood cell counts; IGF-I = insulin-like growth factor-1.

[b] Demographic variables: age and sex.

[c] Clinical variables: BMI, limiting longstanding illness, and mobility difficulties.

[d] Lifestyle variables: smoking status, alcohol consumption, and physical activity.

[e] All variables: age, sex, BMI, limiting longstanding illness, mobility difficulties, smoking status, alcohol consumption, and physical activity.

and low IGF-1 concentrations in models adjusted for baseline bio-markers, implying a higher risk to the overall systemic status of individuals with fewer socioeconomic resources. It is striking that these socioeconomic effects were observed over a 4-year period, and that many remained independent of a comprehensive selection of covariates. In particular, associations between all four socioeconomic indicators and greater WBCC remained significant after taking demographic, clinical, and lifestyle factors into account. Contrary to our hypothesis, neighbourhood contextual indicators were weaker drivers of inflammation and neuroendocrine activity than were individual compositional indicators. Certainly, in the case of WBCC, neighbourhood effects survived individual differences in education and occupation, but significance was lost when wealth was taken into account. As expected, lifestyle factors accounted for a greater proportion of the variance in socioeconomic associations with inflammation than the other sets of covariates, but this was not so for concentrations of IGF-1 where demographics were more salient.

Interestingly, the variations in immune and neuroendocrine activity observed between our cross-sectional and longitudinal associations allude to possible socioeconomic differences in immune and neuroendocrine expression over time. While contexts and health can change over time (Kawachi and Berkman, 2003), consistent UK geographical patterns of deprivation have been reported over a century (Ralston et al., 2014; Dorling et al., 2000), with more stability in the deprivation profile seen in geographically larger areas. (Ralston et al., 2014).

There are reciprocal relationships between the complex physiological processes aimed at homeostatic balance, that could explain differences in effect sizes, and the temporal changes seen in the biological pattern of results within our data cross-sectionally and longitudinally (O'Connor, 2008). Fibrinogen is involved in processes other than inflammation, such as haemostasis and angiogenesis. CRP, by contrast, has high sensitivity to insult, as the major human acute-phase protein, so the rapidity and magnitude of effects may be more substantial (Hamilton et al., 2021). IGF-1 in circulation is downregulated by inflammatory cytokines, (Rajpathak, 2008) so cytokine expression may have attenuated the independent predictive value of socioeconomic determinants in IGF-1 at the cellular level. Interactions as crosstalk and antagonism are possible, since low IGF-1 also antagonises the CRP mechanism through the activation of a number of intracellular signalling pathways, which may have reduced CRP expression prospectively (O'Connor, 2008).

The magnitude of associations between socioeconomic determinants and inflammation varies widely across individual studies (Muscatell et al., 2020; Nazmi and Victora, 2007); attributable in part to variations in sample characteristics and study design, including principals used to limit confounding bias. (VanderWeele, 2019) But *meta*-analytic findings by Muscatell and colleagues (2020) from 43 papers ($n = 111,156$) revealed that populations of lower socioeconomic status, defined by income, education, or occupation, experience higher levels of systemic inflammation, indexed by CRP and interlukin-6. Although less consistent for fibrinogen and WBCC, this is echoed by our cross-sectional findings for CRP and IGF-1, with additional evidence provided on the upregulation of WBCC longitudinally in a sample of community dwelling older adults. In other words, deprivation can set individuals on an adverse immune-neuroendocrine trajectory that can even be observed among non-clinical populations. Extant literature has shown that CRP is higher among those with less wealth (Nazmi and Victora, 2007; Koster, 2006; Jousilahti, 2003), lower education (Fraga, 2015; Loucks, 2006), and lower occupation (Fraga, 2015; Hemingway, 2003). While wealth (Jousilahti, 2003; Wilson, 1993), education (Owen et al., 2003; Jousilahti, 2003; Wilson, 1993; Steptoe, 2003), and occupation (Owen et al., 2003; Fraga, 2015; Wilson, 1993) have been shown to be correlates of change in circulating fibrinogen, and lower education and occupation are known to be associated with elevated WBCC (Owen et al., 2003; Fraga, 2015). However, most studies are cross-sectional, so no inferences can be made on the causal direction of these results. Still, although unadjusted longitudinal neighbourhood-contextual effects

have been observed with CRP and fibrinogen, only associations with fibrinogen remained statistically significant after full adjustment (Pollitt, 2007). This has been echoed at the individual-compositional level (Pollitt, 2008; Nazmi et al., 2010), with larger effects also seen in WBCC over CRP (Pollitt, 2008).

A substantial literature support that where you live, over and above individual characteristics, shape individual health and health inequalities among populations (Steptoe, 2012; Berger, 2019; Kirkbride et al., 2010; Iyer, 2022; Pollitt, 2007; Sullivan, 2019). However, our results cast doubt on research that has implicated neighbourhood determinants in inflammation and neuroendocrine processes without consideration being given to individual effects in the study design. One study of patients with coronary artery disease found that neighbourhood deprivation was associated with lower cardiovascular stress reactivity with no differences in immune or neuroendocrine response (Sullivan, 2019). These results were independent of individual-level factors, and after accounting for variation in the probability of residing in a deprived or affluent neighbourhood by using a propensity weighting scheme. Further research is needed to elucidate the exact contextual mechanisms for environmental factors that appear to modulate inflammation and neuroendocrine activity.

As is documented elsewhere (Steptoe, 2012) socioeconomic differences in inflammation and neuroendocrine activity were mostly explained by variations in lifestyle; smoking status, alcohol consumption and physical activity specifically. This confirms our hypotheses. The PPAE for each model has not been described in this context before. Lifestyle explained up to a half of the variance in associations between socioeconomic factors and inflammation. Remarkably, the PPAE for the demographics model accounted for over four fifths of the association between socioeconomic indicators and neuroendocrine activity. This was an unexpected result but may be explained by the sensitivity of IGF-1 to the somatopause. Lifestyle factors have previously been identified as mediators between neighbourhood-contextual factors and inflammatory markers such as CRP (Pollitt, 2007).

There are a number of strengths of the present study. We used a large, well-characterised general population longitudinal cohort linked to census indicators of objectively measured contextual characteristics (Steptoe et al., 2013). We provide information on pre-disease mechanisms that allow for a richer understanding of the deprivation-health gradient before disease become evident (Sinha et al., 2021). We also benefited from a comprehensive calculation of wealth that is unavailable in most studies; computed on the basis of precise information on multiple individual components rather than a broad categorisation of assets (Steptoe et al., 2013) Although the multiple imputation strategy did not manage missing data on outcomes, results were consistent with complete case analyses.

However, results should be interpreted in light of some limitations. Models based on nested counterfactuals rest on strong assumptions about confounding (Bours, 2020). But, as with all observational studies, we cannot exclude the risk of unobserved confounding and residual confounding due to time varying intervals between the assessment of exposures and outcomes. Second, we did not take the length of residence into account, although we did assess whether participants had moved during the study period. Additionally, covariates were measured at baseline, and we did not analyse time-varying covariates. While ELSA is a demographically representative cohort, the majority of the sample are of White European origin and are older age, so findings may not be generalisable to other ethnic or younger groups (Steptoe et al., 2013). Residential areas within the UK are not monolithic, so although the index of multiple deprivation is calculated at a detailed level of areas, typically with 1,000–3,000 residents, most areas are heterogenous (Noble et al., 2006). Contextual indicators may therefore be underestimated for some and overestimated for others in the same area, leading to the ecological fallacy (Loney and Nagelkerke, 2014).

7. Conclusion

We produced several interesting findings in this prospective population-based study that examined associations of socioeconomic determinants at the contextual and compositional level with immune and neuroendocrine activity, while taking into account the role of covariates. We found that neighbourhood associations were primarily dependent on the characteristics of people living in the area, rather than the area itself. Examining disparities in immune and neuroendocrine status through the lens of compositional factors can improve the surveillance of important equity issues (Arcaya et al., 2015) and steer interventions toward individual-level prescriptions, over a broader society approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2022.10.010.

References

Alley, D.E., et al., 2006. Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. Brain Behav. Immun. 20, 498–504.

Arcaya, M.C., Arcaya, A.L., Subramanian, S.V., 2015. Inequalities in health: definitions, concepts, and theories. Global Health Action 8, 27106.

Arroba, A.I., Campos-Caro, A., Aguilar-Diosdado, M., Valverde, Á.M., 2018. IGF-1, Inflammation and Retinal Degeneration: A Close Network. Front. Aging Neurosci. 10, 203.

Barrington, W.E., et al., 2014. Neighborhood socioeconomic deprivation, perceived neighborhood factors, and cortisol responses to induced stress among healthy adults. Health & Place 27, 120–126.

Berger, E., et al., 2019. Multi-cohort study identifies social determinants of systemic inflammation over the life course. Nat Commun 10, 773.

Bours, M.J.L., 2020. A nontechnical explanation of the counterfactual definition of confounding. J. Clin. Epidemiol. 121, 91–100.

Colangelo, L.A., Chiu, B., Kopp, P., Liu, K., Gapstur, S.M., 2009. Serum IGF-I and C-reactive protein in healthy black and white young men: The CARDIA Male Hormone Study. Growth Horm IGF Res 19, 420–425.

ELSA, 2019. Study Documentation. https://www.elsa-project.ac.uk/study-documentation.

Crimmins, E.M., 2020. Social hallmarks of aging: Suggestions for geroscience research. Ageing Research Reviews 63, 101136.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 9, 46–56.

Dorling, D., Mitchell, R., Shaw, M., Orford, S., Smith, G.D., 2000. The Ghost of Christmas Past: health effects of poverty in London in 1896 and 1991. BMJ 321, 1547–1551.

Fraga, S., et al., 2015. Association of socioeconomic status with inflammatory markers: A two cohort comparison. Prev. Med. 71, 12–19.

Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. Nature Reviews Endocrinology 14, 576–590.

Freeman, J.A., Bauldry, S., Volpe, V.V., Shanahan, M.J., Shanahan, L., 2016. Sex Differences in Associations Between Subjective Social Status and C-Reactive Protein in Young Adults. Psychosom Med 78, 542–551.

Furman, D., et al., 2019. Chronic inflammation in the etiology of disease across the life span. Nat Med 25, 1822–1832.

Giollabhui, N.M., et al., 2020. To exclude or not to exclude: considerations and recommendations for C-Reactive Protein values higher than 10 mg/L. Brain Behav Immun 87, 898–900.

Grundy, E., 2001. The socioeconomic status of older adults: How should we measure it in studies of health inequalities? J. Epidemiol. Community Health 55, 895–904.

Hamilton, O.S., Cadar, D., Steptoe, A., 2021. Systemic inflammation and emotional responses during the COVID-19 pandemic. Transl Psychiatry 11, 1–7.

Hemingway, H., et al., 2003. Social and psychosocial influences on inflammatory markers and vascular function in civil servants (the Whitehall II study). The American Journal of Cardiology 92, 984–987.

Iyer, H.S., et al., 2022. Impact of neighborhood socioeconomic status, income segregation, and greenness on blood biomarkers of inflammation. Environ. Int. 162, 107164.

Jousilahti, P., 2003. Association of markers of systemic inflammation, C reactive protein, serum amyloid A, and fibrinogen, with socioeconomic status. J. Epidemiol. Community Health 57, 730–733.

Junnila, R.K., List, E.O., Berryman, D.E., Murrey, J.W., Kopchick, J.J., 2013. The GH/IGF-1 axis in ageing and longevity. Nat Rev Endocrinol 9, 366–376.

Kawachi, I., Berkman, L.F., 2003. Neighborhoods and Health. Oxford University Press.

Kiecolt-Glaser, J.K., McGuire, L., Robles, T.F., Glaser, R., 2002. Psychoneuroimmunology: Psychological influences on immune function and health. J. Consult. Clin. Psychol. 70, 537–547.

Kirkbride, J.B., 2010. Impact of Contextual Environmental Mechanisms on the Incidence of Schizophrenia and Other Psychoses. In: Gattaz, W.F., Busatto, G.),, . (Eds.), Advances in Schizophrenia Research 2009. (Springer, pp. 67–96. https://doi.org/10.1007/978-1-4419-0913-8_4.

Koster, A., et al., 2006. Association of Inflammatory Markers With Socioeconomic Status. J. Gerontol. Series A 61, 284–290.

Loney, T., Nagelkerke, N.J., 2014. The individualistic fallacy, ecological studies and instrumental variables: a causal interpretation. Emerg. Themes Epidemiol. 11, 18.

Loucks, E.B., et al., 2006. Association of Educational Level with Inflammatory Markers in the Framingham Offspring Study. Am. J. Epidemiol. 163, 622–628.

Marmot, M., 2020. Health equity in England: the Marmot review 10 years on. BMJ 368, m693.

ERFC, 2010. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis | Elsevier Enhanced Reader. https://reader.elsevier.com/reader/sd/pii/S0140673609617177?token=B3F0D30F1E0FF924EC8864EF3430943D2335442398F280BA8039A15F872F34BBA0A456168756CB9800F05F68559164E4&originRegion=eu-west-1&originCreation=20220303174720 (2010) doi:10.1016/S0140-6736(09)61717-7.

Ministry of Housing, C. and L. G. Index of Deprivation 2004 - Health Domain. https://data.gov.uk/dataset/b0b2a3e2-cd44-468b-90a8-8c6c63fabbb2/index-of-deprivation-2004-health-domain (2014).

Muscatell, K.A., Brosso, S.N., Humphreys, K.L., 2020. Socioeconomic status and inflammation: a meta-analysis. Mol. Psychiatry 25, 2189–2199.

Nazmi, A., Diez Roux, A., Ranjit, N., Seeman, T. E. & Jenny, N. S. Cross-sectional and longitudinal associations of neighborhood characteristics with inflammatory markers: Findings from the multi-ethnic study of atherosclerosis. *Health & Place* 16, 1104–1112 (2010).

Nazmi, A., Victora, C.G., 2007. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. BMC Public Health 7, 212.

Noble, M., Wright, G., Smith, G., Dibben, C., 2006. Measuring multiple deprivation at the small-area level. Environ Plan A 38, 169–185.

O'Connor, J.C., et al., 2008. Regulation of IGF-I function by proinflammatory cytokines: At the interface of immunology and endocrinology. Cell. Immunol. 252, 91–110.

O'Connor, T.G., Moynihan, J.A., Caserta, M.T., 2014. Annual Research Review: The neuroinflammation hypothesis for stress and psychopathology in children – developmental psychoneuroimmunology. J. Child Psychol. Psychiatry 55, 615–631.

ONS. The National Statistics Socio-economic classification (NS-SEC) - Office for National Statistics. https://www.ons.gov.uk/methodology/classificationsandstandards/oth erclassifications/thenationalstatisticssocioeconomicclassificationnssecrebasedonsoc 2010.

ONS, Persistent poverty in the UK and EU - Office for National Statistics. https://www. ons.gov.uk/peoplepopulationandcommunity/personalandhouseholdfinances/incom eandwealth/datasets/persistentpovertyintheukandeu (2019).

Owen, N., Poulton, T., Hay, F.C., Mohamed-Ali, V., Steptoe, A., 2003. Socioeconomic status, C-reactive protein, immune factors, and responses to acute mental stress. Brain Behav. Immun. 17, 286–295.

Ploubidis, G.B., Benova, L., Grundy, E., Laydon, D., DeStavola, B., 2014. Lifelong Socio Economic Position and biomarkers of later life health: Testing the contribution of competing hypotheses. Soc. Sci. Med. 119, 258–265.

Pollitt, R.A., et al., 2007. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur. J. Epidemiol. 22, 55–66.

Pollitt, R.A., et al., 2008. Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood. J. Epidemiol. Community Health 62, 484–491.

Rajpathak, S.N., et al., 2008. Insulin-like growth factor-(IGF)-axis, inflammation, and glucose intolerance among older adults. Growth Horm. IGF Res. 18, 166–173.

Ralston, K., Dundas, R., Leyland, A.H., 2014. A comparison of the Scottish Index of Multiple Deprivation (SIMD) 2004 with the 2009 + 1 SIMD: does choice of measure affect the interpretation of inequality in mortality? Int. J. Health Geographics 13, 27.

Ribeiro, A.I., Amaro, J., Lisi, C., Fraga, S., 2018. Neighborhood Socioeconomic Deprivation and Allostatic Load: A Scoping Review. Int. J. Environ. Res. Public Health 15, 1092.

Ridker, P.M., 2005. C-Reactive Protein, Inflammation, and Cardiovascular Disease. Tex Heart Inst J 32, 384–386.

Schmidt, J.C., et al., 2017. Burden of Disease in England compared with 22 peer countries. A report for NHS. England 33. https://assets.publishing.service.gov.uk/ government/uploads/system/uploads/attachment_data/file/856938/GBD_NHS_En gland_report.pdf.

Scrivo, R., Vasile, M., Bartosiewicz, I., Valesini, G., 2011. Inflammation as "common soil" of the multifactorial diseases. Autoimmun. Rev. 10, 369–374.

Sinha, K., Davillas, A., Jones, A.M., Sharma, A., 2021. Do socioeconomic health gradients persist over time and beyond income? A distributional analysis using UK biomarker data. Economics & Human Biology 43, 101036.

Stekhoven, D.J., Bühlmann, P., 2012. MissForest—non-parametric missing value imputation for mixed-type data. Bioinformatics 28, 112–118.

Steptoe, A., et al., 2003. Influence of Socioeconomic Status and Job Control on Plasma Fibrinogen Responses to Acute Mental Stress. Psychosom. Med. 65, 137–144.

Steptoe, A., Jackson, S.E., 2020. Association of Noncognitive Life Skills With Mortality at Middle and Older Ages in England. JAMA Netw Open 3, e204808.

Steptoe, A., Zaninotto, P., 2020. Lower socioeconomic status and the acceleration of aging: An outcome-wide analysis. PNAS 117, 14911–14917.

Steptoe, A., Hiltl, T.-J., Dowd, J.B., Hamer, M., 2019. Socioeconomic status and central adiposity as determinants of stress-related biological responses relevant to cardiovascular disease risk. Brain Behav. Immun. 77, 16–24.

Steptoe, A., Breeze, E., Banks, J., Nazroo, J., 2013. Cohort Profile: The English Longitudinal Study of Ageing. Int J Epidemiol 42, 1640–1648.

Steptoe, A. Socioeconomic Status, Inflammation, and Immune Function. *The Oxford Handbook of Psychoneuroimmunology* https://www.oxfordhandbooks.com/view/ 10.1093/oxfordhb/9780195394399.001.0001/oxfordhb-9780195394399-e-13 (2012) doi:10.1093/oxfordhb/9780195394399.013.0013.

Sterne, J.A.C., et al., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.

Sullivan, S., et al., 2019. Neighborhood poverty and hemodynamic, neuroendocrine, and immune response to acute stress among patients with coronary artery disease. Psychoneuroendocrinology 100, 145–155.

VanderWeele, T.J., 2019. Principles of confounder selection. Eur J Epidemiol 34, 211–219.

White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: Issues and guidance for practice. Stat. Med. 30, 377–399.

Wilson, T.W., et al., 1993. Association between plasma fibrinogen concentration and five socioeconomic indices in the Kuopio ischemic heart disease risk factor study. Am. J. Epidemiol. 137, 292–300.

Yen, I.H., Michael, Y.L., Perdue, L., 2009. Neighborhood Environment in Studies of Health of Older Adults: A Systematic Review. Am. J. Prev. Med. 37, 455–463.