Brain, Behavior, and Immunity 113 (2023) 203–211

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Role of inflammation in the socioeconomic inequalities of neurocognitive disorders

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ARTICLE INFO

Keywords:
Socioeconomic inequalities
Inflammation
Neurocognitive disorders
C-reactive protein
White blood cells
Fibrinogen

ABSTRACT

Background: Socioeconomic position has been shown to be associated with inflammation. However, little is known about the role of inflammation in socioeconomic inequalities in relation to neurocognitive disorders in later life and the potential underlying inflammatory mechanisms. This study has used longitudinal data to investigate the mediation effects of inflammation in the relationship between socioeconomic position and neurocognitive disorders in older adults.

Methods: Using data from the English Longitudinal Study of Ageing (ELSA, n = 4,815), we ascertained neurocognitive disorders using a recognised consensus criterion and included the following categories: (1) No Cognitive Impairment (NOCI) (2) Cognitive Impairment No Dementia (CIND) and (3) Dementia. We examined whether socioeconomic position (education, occupation, and wealth) measured in 2008/09 was associated with neurocognitive disorders measured in 2018/19. Mediation analyses were carried out to investigate the role of inflammatory markers [C-Reactive Protein (CRP), plasma fibrinogen and white blood cells (WBC)] in the association between socioeconomic inequalities and subsequent neurocognitive disorders. Sensitivity analyses were conducted to assess the mediating role of lifestyle behaviours and body mass index (BMI).

Results: Higher education, occupation and wealth were longitudinally associated with a lower likelihood of cognitive impairment and dementia. WBC mediated the association between latent socioeconomic position and CIND [β = -0.037 (CI: −0.06 to −0.01)], but not the association with dementia. Indirect effects were attenuated but remained significant when other mediators, such as lifestyle behaviours and BMI were considered. In a separate analysis accounting for main confounders, CRP and fibrinogen mediated the association between education and CIND, all three inflammatory biomarkers mediated the association of occupation and CIND, while WBC mediated the association between wealth and CIND.

Conclusion: These findings emphasise that socioeconomic inequalities in mid and later life could contribute to the prevalence of neurocognitive disorders in later life. Our results provide some evidence for the biological embedding of WBC in the association between socioeconomic inequalities and cognitive impairment via elevated inflammation. Future studies should explore other plausible biological mechanisms.

1. Introduction

The role of neuroinflammation in relation to neurocognitive disorders is an area of increasing research interest (Cai et al., 2022). Elevated levels of acute phase proteins such as fibrinogen and C-reactive protein (CRP) might signal both a state of neuroinflammation as well as a cause of other inflammatory responses (Gruys et al., 2005). Prospective studies have found an association between higher CRP levels in midlife and Mild Cognitive Impairment (MCI) in participants without dementia (Fernandes et al., 2020; Roberts et al., 2009). Another ELSA study has observed an association between consistently elevated CRP levels and poor episodic memory in older adults aged 75 and above. In contrast, the

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https://doi.org/10.1016/j.bbi.2023.07.013
Received 11 January 2023; Received in revised form 20 July 2023; Accepted 22 July 2023
Available online 24 July 2023

association with fibrinogen was only noticeable in middle-aged adults (Tampubolon, 2016). Besides CRP and fibrinogen, neurodegeneration is sometimes accompanied by leucocytosis or elevated peripheral white blood cells (WBCs) (Unda et al., 2021). In other words, systemic inflammation can evoke an immune response by repeatedly activating WBCs and chronic elevation of WBCs has been linked to cognitive impairment (Libby, 2007). This has been partially supported by Huang et al. (2022) *meta*-analysis of thirty-six case-control studies, including 2, 947 participants with neurocognitive disorders. Their analyses showed significantly elevated WBCs in patients with MCI compared with age-matched healthy controls (Huang et al., 2022). Taken together, studies in this line of research were mainly clinical and underpowered, with noticeable heterogeneity, precluding the study's ability to draw definite conclusions.

C-reactive protein (CRP) is one of the cytokines which has attracted increased attention as an indicator of inflammatory status linked with socioeconomic stress (Juster et al., 2010; Sproston and Ashworth, 2018). Low-grade systemic inflammation in response to various socio-environmental challenges, could contribute to negative health outcomes through homeostatic dysregulation, metabolic dysfunction, tissue damage, and stimulation of hypothalamus-pituitary axis (Bennett et al., 2018; Straub, 2017). Numerous longitudinal studies exploring the link between various socioeconomic markers such as education, living conditions, occupation, or income and C-reactive protein (CRP) have been consistent in showing that being less socioeconomically advantaged is linked with elevated levels of CRP in mid and later life (Hintikka et al., 2009; Hughes et al., 2015; Janicki-Deverts et al., 2008). This has also been supported by a *meta*-analysis carried out using twelve British surveys comprising 30,037 participants aged 22–64, exploring the link between occupation and biomarkers (Hughes et al., 2017), which showed elevated CRP levels for unemployed participants in mid-life compared to their employed counterparts. However, except for two, all surveys included in the *meta*-analysis were cross-sectional and had a single biomarker data collection, thus failing to establish temporal sequencing between SEP and subsequent levels of inflammation (Hughes et al., 2017). The latest study, which used data from the English Longitudinal Study of Ageing (ELSA), explored the associations between distinct SEP markers and a wide range of inflammatory markers, showing that socioeconomic indicators, i.e. higher levels of wealth and education, are prospectively associated with lower levels of WBC and CRP levels and education/occupation with fibrinogen (Hamilton and Steptoe, 2022).

Health inequalities research, particularly in relation to cognitive impairment, has shown that being socioeconomically disadvantaged is linked with an increased risk of cognitive impairment. However, less is known about the specific role of each dimension of socioeconomic position (SEP) and the potential biological pathways from SEP that contribute to neurocognitive disorders in older adults (Braveman and Gottlieb, 2014; Morgan et al., 2022).

Evidence from previous studies suggest that SEP is a multidimensional concept and different socioeconomic markers might represent different aspects of an individual's life (Geyer et al., 2006). For instance, wealth might be an appropriate objective measure of SEP in later life compared to other distal markers such as education or occupation or income (Cubbin et al., 2011). It is important to note that poor measurement of SEP can result in measurement error, and this will likely offset any associations between the SEP measure and the health outcome (Galobardes et al., 2007; Singh-Manoux et al., 2002).

In short, adverse socioeconomic environments and persistent stress might upregulate chronic inflammatory processes, release pro-inflammatory cytokines and disrupt the neurobiological processes underlying processing speed, memory, and learning (Liu et al., 2017). However, generally, a lack of understanding persists in relation to the neuroinflammatory pathways through which the "*social becomes embodied*", thereby increasing the risk of neurocognitive disorders and leading to health inequalities among older adults (McEwen, 2012).

The overall aim of this study was to examine the inflammatory mechanism underlying socioeconomic inequalities in neurocognitive disorders over ten years of follow-up in a large, nationally representative sample of English community-dwelling older adults. We hypothesised that socioeconomic inequalities in neurocognitive disorders in older English adults would likely be embedded through inflammatory biomarkers in mid and later life.

2. Methods

2.1. Data and participants

The English Longitudinal Study of Ageing (ELSA) is an ongoing nationally representative longitudinal survey of the population aged 50 + in England (Steptoe et al., 2013). The first wave of data collection was carried out in 2002/03, with follow-ups every two years after that. The study was replenished with new samples called refreshment samples at waves 3 (2006/07), 4 (2008/09), 6 (2012/13), 7 (2014/15) and 9 (2018/19). Wave 4 was chosen as the baseline for this study because it had the most significant refreshment boost sample ensuring adequate statistical power for this analysis. The biological data (e.g., blood samples, body mass index, etc.) were collected during nurse visits. Neurocognitive disorders were assessed at wave 9 (2018/19), the latest wave of data collection available during the time of analysis. The mediating factors were measured four years after baseline at wave 6 (2012/13). A total of 9,886 people took part in the core assessment at wave 4, and from these, 4,815 participants had complete outcome data and were included in the final analysis. Attrition rates are presented in Supplementary Table S1. Data are freely available and can be accessed via the UK Data Service: https://discover.ukdataservice.ac.uk. Ethical approval was obtained for all waves from the National Research and Ethics Service. All participants provided informed consent at every wave.

2.2. Study variables

2.2.1. Neurocognitive disorders

Neurocognitive disorders were operationalised in ELSA (Cadar et al., 2020), using the consensus criteria according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and following the diagnostic algorithm implemented in the Cognitive Function and Ageing Studies (CFAS) (Richardson et al., 2019). This algorithm is shown to have good predictive accuracy for dementia in population-based settings (Matthews et al., 2008; Stephan et al., 2011). Based on the presence or absence of self-reports of a physician's dementia diagnosis, objective tests for cognitive impairment, subjective reports of memory complaints, and functional impairment, separate cognitive status groups were derived. These were (i) No Cognitive Impairment (NOCI), (ii) Mild Cognitive Impairment (MCI), (iii) Other Cognitive Impairment No Dementia (OCIND) and (iv) Dementia. Since MCI was only a small group in this study, OCIND was regrouped with MCI to create a Cognitive Impairment No Dementia (CIND) group. Therefore, for the main analysis, we used the following categories: (1) NOCI, (2) CIND and (3) Dementia. Additional details regarding the definition of each neurocognitive disorders can be found in the first section of the Supplementary Material.

2.2.2. Socioeconomic indicators

Socioeconomic position was measured using three indicators: educational qualifications, occupational social class, and household wealth. These were based on self-reports collected during the computer-assisted personal interview at wave 4 (2008/09). Levels of educational qualifications were grouped as low (primary education or less), middle (secondary education), and high (tertiary education). Occupational class was measured using the three-class version of the National Statistics-Socioeconomic Classification Scheme based on current or most recent occupation. It included the following categories: "managerial/

professional occupations," "intermediate occupations," and "routine/manual occupations" (Rose and Pevalin, 2003). Participants who had never worked or were long-term unemployed formed a small group. Therefore, this was combined with the routine/manual occupational group. Wealth status refers to non-pension household wealth, including financial, physical, and housing wealth. This was calculated net of debts and included the value of any properties, financial assets covering all types of savings, the value of any business assets and physical wealth, such as artwork and jewellery (Steptoe et al., 2013). Household non-pension wealth was then transformed into quintiles, with quintile 1 being the most deprived and quintile 5 being the most affluent. Wealth was selected as it is a better indicator of economic circumstances than income in this age group (Allin et al., 2009).

2.2.3. Mediators: Inflammatory markers

Three inflammatory markers were measured at wave 6 (2012/3): CRP, plasma fibrinogen and WBC. Study members were asked to abstain from eating, smoking, drinking alcohol or doing vigorous exercise for 30 min before the nurse visit. CRP was measured using the N Latex CRP mono immunoassay on the Behring Nephelometer analyser II. To differentiate individuals with chronic inflammation, participants with CRP values > 10 mg/L were excluded from this analysis as this could be indicative of acute inflammation or infections. Further details of the blood sample analyses, the internal quality control, and the external quality assessment of the laboratory can be obtained from the Health Survey for England (HSE) 2004 technical report (HSE, 2004) since both the HSE and ELSA employed the same guidelines and protocols for the blood analyses (de Oliveira et al., 2017; Sproston and Mindell, 2006). Because of the skewed distribution, the CRP and fibrinogen measures have been log-transformed.

2.2.4. Covariates

Age, sex, marital status, baseline health, depressive symptoms, and medication use were the main covariates. Lifestyle behaviours (smoking status, physical activity, diet, and alcohol drinking) and body mass index were intermediate variables on the causal pathways linking socioeconomic position and cognitive impairment (Deckers et al., 2019). Hence, they were included in the models as additional mediators rather than confounders in order to avoid the issue of overadjustment bias in mediation analysis (Schisterman et al., 2009). In this competitive mediation model accounting for confounders and additional mediators, we were able to analyse the extent to which WBC explained the association between SEP and cognitive impairment. A more detailed description of the variables can be found in the Supplementary file.

2.3. Statistical analyses

Socio-demographic differences in the prevalence of neurocognitive disorders were analysed with t-tests and Chi^2 tests for continuous and categorical variables. Logistic regression analyses examined the associations between education, occupation, wealth, and subsequent neurocognitive disorders. The logistic regression results were presented as odds ratios (ORs) with 95% confidence intervals (CI).

A structural equation framework was used for the mediation analysis (Kelloway, 2014). First, we constructed a latent SEP variable by estimating a SEP measurement model. All SEP indicators are measured at baseline assessment. We specified our structural model (Fig. 1), which included directional associations based on empirical evidence reviewed in the introduction. Finally, a comprehensive mediation model was tested in the presence of inflammatory as well as the competing lifestyle mediators.

We estimated the direct, indirect, and total effect of the association between socioeconomic position and CIND/dementia via each inflammatory marker. The direct effect represented the pathway from SEP to outcome while controlling for inflammatory biomarkers and confounders. The indirect effect quantified the amount of mediation through inflammatory markers in the association between SEP and neurocognitive disorders. The total effect refers to the sum of SEP's direct and indirect effects on CIND or dementia. The proportion of the mediated effect was calculated by dividing the indirect effect by the total effect. For the mediation analysis, the multi-category outcome variable was converted into a set of dummy variables (Hayes and Preacher, 2014). These were (1) CIND [denoted by the combined category: MCI (n = 123) + OCIND (n = 1639)] versus NOCI (n = 2851) and (2) Dementia (n = 202) versus NOCI (n = 2851). Similarly, each socioeconomic indicator was converted into a set of dummy variables. Although the term 'effects' is used here in the context of mediation analyses, we are not implying a definite causal relationship since this is an observational study.

Missing values in the explanatory variables, covariates, and mediators for the final sample with complete outcome data were imputed using Multiple Imputation by Chained Equations (MICE) (Azur et al., 2011; van Ginkel et al., 2020). Bias-corrected bootstrapping analyses with 1000 bootstrap samples were conducted by pooling estimates from 30 imputed datasets (Asparouhov and Muthen, 2022; Hayes, 2009). Our primary model tested the mediation path between SEP markers and cognitive impairment accounting for age, sex, marital status, baseline cognitive status, health comorbidities, depressive symptoms, and medication use. All analyses accounted for sampling weights.

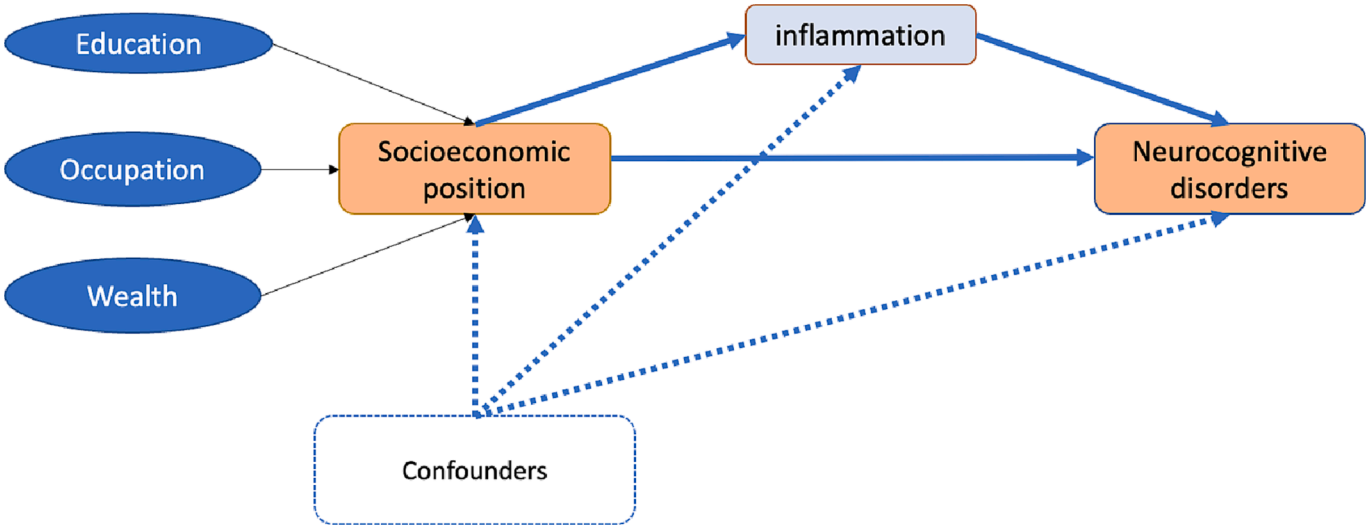

Fig. 1. Theoretical diagram showing the pathway between SEP and neurocognitive disorders.

Descriptive statistics were analysed using the statistical software package STATA version 17 (StataCorp, 2021). Mediation analyses were performed using MPlus version 8 software (Muthen et al., 2017).

2.3.1. Sensitivity analyses

We carried out several sensitivity analyses to explore different explanations for our results. Mediation analyses were carried out separately for the OCIND (versus NOCI) and MCI (versus NOCI) to check whether these associations are different for different cognitive groups. In another sensitivity analysis, we repeated analysis with additional mediators' (lifestyle behaviours and BMI) to determine whether associations persist after taking away the effects of competing mediators. Given the possibility that contemporaneous factors (e.g., acute infection) might influence the levels of WBC count, the main analysis was also replicated by averaging the repeated measures of WBC across multiple waves 4, 6 and 8/9.

3. Results

3.1. Baseline sample characteristics

Table 1 describes the characteristics of the baseline sample. The proportion of women was slightly higher (56%) than men. Participants were predominantly married/cohabiting. The majority had an intermediate level of education (57%). There was no evidence of an interaction between sex or age and SEP in the regression analysis; therefore, we did not carry out separate investigations for different age or sex groups.

Overall, 59.2% of respondents had NOCI, 36.59% reported CIND, and 4.2% had dementia at wave 9. As presented in Table 1, the mean age of those with MCI, CIND and dementia was higher than those with NOCI ($p < 0.001$). CIND and dementia appear to be the lowest among the participants in the highest education group ($p < 0.001$). Similarly, a lower proportion (30.76%) of participants were categorised as having CIND in the managerial/professional category. NOCI cases were high in the highest wealth quintile compared to the lowest quintile ($p < 0.001$). Nearly a quarter (22%) of the participants in the lowest quintile of total wealth had dementia, compared with only 15% in the highest wealth quintile ($p < 0.001$). A comparison of the observed and imputed data demonstrated that these values were broadly similar (Supplementary Table S2).

3.2. Association between SEP and neurocognitive disorders

Table 2 presents results from the logistic regression models of socioeconomic indicators on neurocognitive disorders adjusted for age, sex, marital status, baseline cognitive status, health comorbidities, depressive symptoms, and medication use. Being in the highest education group was associated with lower odds of CIND [OR = 0.72, CI: (0.61 to 0.85), $p < 0.001$], but not with dementia. This analysis revealed that participants from managerial/professional occupational classes had 38% and 42% lower odds of CIND and dementia, respectively, than those from routine/ manual occupational classes. Similarly, in comparison to the lowest wealth quintile, all higher wealth quintiles had lower odds of CIND [highest wealth quintile: OR = 0.61, CI: (0.50 to 0.75), $p < 0.001$] and dementia [highest wealth quintile: OR = 0.53, CI: (0.34 to 0.878), $p < 0.001$].

3.3. Mediation analysis

The adjusted mediation models for the role of inflammatory CRP, fibrinogen, and WBC in the association between SEP and CIND/dementia are shown in Table 3. An additional analysis was conducted for each SEP indicator and its indirect effect on CIND via different biomarkers (Table 4).

3.3.1. Mediation in relation to latent SEP and CIND

The association of SEP with CIND was mediated by WBC. The

Table 1
Baseline characteristics of the sample according to categories of cognitive impairment (N = 4,815).

		NOCI	CIND	Dementia	P value
		2,851(59.21%)	1,762 (36.59%)	202 (4.2%)	
Age	Mean (SD)	61.84 (6.47)	65.46 (7.87)	70.71 (8.50)	<0.001[b]
Sex	Male	1250 (43.84)	767 (43.53)	90 (44.55)	0.982[c]
	Female	1,601 (56.16)	995 (56.47)	112 (55.45)	
Currently married	No	743 (26.06)	621 (35.24)	63 (31.19)	<0.001[c]
	Yes	2,108 (73.94)	1,141 (64.76)	139 (68.81)	
Health comorbidities	None	1,895 (66.47)	966 (54.82)	93 (46.04)	<0.001[c]
	One	794 (27.85)	621 (35.24)	84 (41.58)	
	Two or more	162 (5.68)	175 (9.9)	25 (12.38)	
Depressive symptoms	Mean (SD)	2.67 (1.09)	2.99 (1.33)	3.19 (1.42)	<0.001[b]
Medication use	No	1,211 (44.48)	670 (38.02)	85 (42.08)	0.01[c]
	Yes	1,640 (57.52)	1,092 (61.98)	117 (57.92)	
Education	Low	405 (14.21)	473 (26.84)	70 (34.65)	<0.001[c]
	Middle	1,661 (58.26)	1,006 (57.09)	105 (51.98)	
	High	785 (27.53)	283 (16.06)	27 (13.37)	
Occupation	Managerial/professional occupations	610 (21.4)	579 (32.86)	76 (37.62)	<0.001[c]
	Intermediate occupations (non-manual)	979 (34.34)	641 (36.38)	76 (37.62)	
	Routine/manual occupations	1,262 (44.27)	542 (30.76)	50 (24.75)	
Wealth	First quintile (lowest)	262 (9.19)	316 (17.93)	45 (22.28)	<0.001[c]
	Second quintile	436 (15.29)	346 (19.64)	42 (20.79)	
	Third quintile	563 (19.75)	373 (21.17)	42 (20.79)	
	Fourth quintile	683 (23.96)	341 (19.35)	42 (20.79)	
	Fifth quintile (highest)	907 (31.81)	386 (21.91)	31 (15.35)	
ln (CRP) (mg/L)	Median (IQR)	0.33 (-0.35, 0.99)	0.47 (-0.2, 1.16)	0.53 (-0.22, 1.30)	<0.001 [a]
ln (Fibrinogen)(g/L)	Median (IQR)	1.06 (0.95, 1.16)	1.06 (0.95, 1.19)	1.09 (0.99, 1.19)	<0.001 [a]
WBC (counts per 10^9/L)	Mean (SD)	6.23 (1.87)	6.56 (1.93)	6.47 (2.04)	<0.001[b]

SD = Standard Deviation, IQR = Inter Quartile Range, NOCI = No Cognitive Impairment, CIND = Cognitive Impairment No Dementia, ln = Log transformed, CRP= C-Reactive protein, WBC= White blood Cell.
CIND is a combined category of Mild Cognitive Impairment (MCI) and Other Cognitive Impairment No Dementia (OCIND).
[a] $p < 0.001$, obtained by Wilcoxon rank sum test of medians
[b] $p < 0.001$, obtained by *t*-test
[c] $p < 0.001$, obtained from χ^2 test

Table 2
Adjusted associations of SEP with neurocognitive disorders in ELSA (N = 4,815).

	CIND			Dementia		
	OR	95% CI	P value	OR	95% CI	P value
Education						
Low	Ref:					
Middle	0.99	0.89, 1.13	0.68	0.90	0.64, 1.25	0.15
High	0.72	0.61, 0.85	<0.001	0.80	0.50, 1.30	0.13
Occupation						
Routine/manual occupations	Ref:					
Intermediate occupations (non-manual)	1.05	0.91, 1.20	0.37	0.99	0.70, 1.40	0.43
Managerial/ professional occupations	0.72	0.63, 0.83	<0.001	0.58	0.40, 0.85	<0.001
Wealth						
First quintile (lowest)	Ref:					
Second quintile	0.63	0.50, 0.82	<0.001	0.52	0.34, 0.88	<0.001
Third quintile	0.66	0.54, 0.80	<0.001	0.53	0.33, 0.87	<0.001
Fourth quintile	0.65	0.50, 0.82	<0.001	0.55	0.33, 0.90	<0.001
Fifth quintile (highest)	0.61	0.50, 0.75	<0.001	0.53	0.34, 0.87	<0.001

SEP = Socioeconomic position, NOCI = No Cognitive Impairment, CIND = Cognitive Impairment No Dementia, OR = Odds Ratio, CI = Confidence Interval. All models were adjusted for age, sex, marital status, baseline cognitive status, health comorbidities, depressive symptoms, and medication use.
CIND is a combined category of Mild Cognitive Impairment (MCI) and Other Cognitive Impairment No Dementia (OCIND).

indirect effect of WBC on CIND was β = -0.037 [CI: (-0.06 to −0.01), p = 0.02]. The proportion of the association between SEP and CIND mediated by WBC was 3.70%. There was also compelling evidence of a direct pathway from SEP to CIND once the indirect effect via WBC was accounted for. Therefore, the mediation effect of WBC on SEP and CIND was suggestive of partial mediation. No evidence for the mediating roles of CRP and fibrinogen was found. Overall, the total effect of SEP on CIND was significant [β = -0.81, CI: (-1.02 to −0.61), p < 0.001].

3.3.2. Mediation in relation to separate SEP markers and CIND

CRP and fibrinogen remained mediators of the association between highest educational attainment (versus no qualifications) and subsequent CIND, explaining a total of 5.4% [CRP indirect effect: β = -0.02, CI: (-0.03 to −0.002), p = 0.03] and 5.4% [Fibrinogen indirect effect: β = -0.02, CI: (-0.02 to −0.004), p = 0.01] of these associations.

Similarly, mediated effect of managerial and professional occupations (versus routine/manual occupations) on CIND through CRP [indirect effect: β = -0.02, CI: (-0.03 to −0.005), p = 0.006], fibrinogen [indirect effect: β = -0.015, CI: (-0.03 to −0.002), p = 0.03], and WBC [indirect effect: β = -0.019, CI: (-0.03 to-0.002), p = 0.006], were significant.

There was an indirect path from wealth to CIND via WBC [highest versus lowest wealth quintile: β = -0.02, CI: (-0.05 to −0.006), p < 0.001. In other words, differences in WBC levels explained 5.3% of the difference between the highest and lowest wealth quintiles on subsequent CIND.

3.3.3. Mediation in relation to SEP and dementia

The total effect of SEP on dementia was significant [β = -0.97, CI (-1.50 to −0.44), p < 0.001]. In addition, the direct effect of SEP on dementia was significant (Table 3). The mediation analysis showed that the indirect effects were absent, indicating that inflammatory markers do not mediate the link between latent SEP or SEP markers and dementia. Neither a significant total nor a direct/indirect effect was found in any models exploring the association between SEP indicators and dementia.

3.4. Sensitivity analysis

Mediation analyses were carried out separately for the OCIND and MCI categories, and the indirect effects were prominent for OCIND outcomes in relation to the WBC mediator (Supplementary Table S3). Indirect associations between SEP and the MCI subtype via inflammatory biomarkers were not significant, probably attributable to the small sample size. In the sensitivity analysis, adjusting for age, sex, marital status, baseline cognitive status, health comorbidities, depressive symptoms, medication use and additional mediators (lifestyle behaviours and BMI), WBC remained a significant mediator of the association between latent SEP and CIND [β = -0.02, CI: (-0.04 to −0.004), p = 0.02], but the effect size was reduced (Supplementary Table S4). This was also reflected in the analysis using separate SEP markers where WBC explained the association between occupation/wealth and CIND, while

Table 3
Mediating effect of inflammation in the association between SEP and neurocognitive disorders (N = 4,815).

Independent variable	Mediator	Outcome variable	Indirect effect		Direct effect		Total effect		Proportion via mediation
Wave 4	Wave 6	Wave 9	Coefficient b, 95 % CI	P value	Coefficient b, 95 % CI	P value	Coefficient b, 95 % CI	P value	%
SEP	ln (CRP)	CIND	−0.02 (-0.05, 0.06)	0.12	−0.79 (-1.01, −0.58)	<0.001	−0.81 (-1.02, −0.61)	<0.001	–
SEP	ln (Fibrinogen)	CIND	−0.02 (-0.06, 0.004)	0.08	−0.79 (-1.01, −0.58)	<0.001	−0.81 (-1.02, −0.61)	<0.001	–
SEP	WBC	CIND	−0.03 (-0.06, −0.01)	0.02	−0.78 (-1.00, −0.57)	<0.001	−0.81 (-1.02, −0.61)	<0.001	3.7%
SEP	ln (CRP)	Dementia	−0.04 (-0.11, 0.03)	0.27	−0.93(-1.47, −0.40)	<0.001	−0.97 (-1.50, −0.44)	<0.001	–
SEP	ln (Fibrinogen)	Dementia	0.01 (−0.05, 0.06)	0.88	−0.96(-1.47, −0.40)	<0.001	−0.97 (-1.50, −0.44)	<0.001	–
SEP	WBC	Dementia	−0.01 (−0.06, 0.03)	0.52	−0.93(-1.47, −0.40)	<0.001	−0.97 (-1.50, −0.44)	<0.001	–

SEP = Socioeconomic position, NOCI = No Cognitive Impairment, CIND = Cognitive Impairment No Dementia, CI = Confidence interval, CRP = C-reactive protein, WBC = White blood cells, ln = Log transformed.
All models were adjusted for age, sex, marital status, baseline cognitive status, health comorbidities, depressive symptoms, and medication use.
Bias-corrected confidence interval reported. CIND is a combined category of Mild Cognitive Impairment (MCI) and Other Cognitive Impairment No Dementia (OCIND).

Table 4
Mediating effect of inflammation in the association between individual SEP markers and neurocognitive disorders (N = 4,815).

Independent variable	Mediator	Outcome variable	Indirect effect		Direct effect		Total effect		Proportion via mediation
Wave 4	Wave 6	Wave 9	Coefficient b, 95 % CI	P value	Coefficient b, 95 % CI	P value	Coefficient b, 95 % CI	P value	%
Education									
Highest education level	ln (CRP)	CIND	−0.02(-0.03, −0.002)	0.03	−0.35 (-0.51, −0.81)	<0.001	−0.37(-0.53, −0.20)	<0.001	5.4%
Highest education level	ln (Fibrinogen)	CIND	−0.02(-0.03, −0.004)	0.01	−0.35 (-0.51, −0.81)	<0.001	−0.37(-0.53, −0.20)	<0.001	5.4%
Highest education level	WBC	CIND	−0.01(-0.02, 0.00)	0.05	−0.36 (-0.51, −0.81)	<0.001	−0.37(-0.53, −0.20)	<0.001	–
Occupation									
Managerial/Professional occupation	ln (CRP)	CIND	−0.02 (-0.03, −0.005)	0.006	−0.35 (-0.47, −0.20)	<0.001	−0.37(-0.50, −0.22)	<0.001	5.4%
Managerial/Professional occupation	ln (Fibrinogen)	CIND	−0.015(-0.03, −0.002)	0.03	−0.36 (-0.49, −0.21)	<0.001	−0.37(-0.50, −0.22)	<0.001	4%
Managerial/Professional occupation	WBC	CIND	−0.019 (-0.03, −0.002)	0.006	−0.36 (-0.49, −0.21)	<0.001	−0.37(-0.50, −0.22)	<0.001	5.1%
Wealth									
Highest wealth quintile	ln (CRP)	CIND	−0.01 (-0.02,0.004)		−0.48(-0.67, −0.28)		−0.52(−0.74, −0.31)		–
Highest wealth quintile	ln (Fibrinogen)	CIND	−0.01(-0.02, 0.002)		−0.51(-0.71, −0.30)		−0.52(−0.74, −0.31)		–
Highest wealth quintile	WBC	CIND	−0.02(-0.05, −0.006)		−0.50(-0.71, −0.28)		−0.52(−0.74, −0.31)		5.3%

SEP = Socioeconomic position, NOCI = No Cognitive Impairment, CIND = Cognitive Impairment No Dementia, CI = Confidence Interval, CRP = C-reactive protein, WBC = White blood cells, ln = Log transformed.
All models were adjusted for age, sex, marital status, baseline cognitive status, health comorbidities, depressive symptoms, and medication use.
CIND is a combined category of Mild Cognitive Impairment (MCI) and Other Cognitive Impairment No Dementia (OCIND).

the effects of other markers became insignificant when competing mediators were considered (Supplementary Table S5). Results remained significant in the analysis using aggregated WBC scores (Supplementary Table S6).

4. Discussion

Our study investigated the relationship between SEP and neurocognitive disorders and tested whether inflammatory biomarkers such as CRP, fibrinogen, and WBC mediated these associations in a large-scale longitudinal study.

Consistent with previous research and our hypotheses, the findings of this study suggest significant socioeconomic inequalities in neurocognitive disorders. Household wealth, a largely under-researched indicator of SEP, emerged as the most potent independent contributor to cognitive impairment (conceptualised as an "intermediate state between normal cognitive state and dementia") in later life. These results add to the literature on socioeconomic inequalities in ageing and suggest that disparities in neurocognitive disorders emerge from an early stage of the disease.

Our findings also corroborate the existing evidence on the link between education and cognitive impairment. The educational disadvantage in early life is a well-known risk factor for cognitive impairment and dementia. However, the association differs depending on the follow-up time and cognitive measure used (Hughes and Ganguli, 2009; Lee et al., 2010; Sharp and Gatz, 2011). Earlier studies have found that participants who had spent fewer years in school showed increasing odds and risk of MCI in mid-life (Iraniparast et al., 2022; Matyas et al., 2019; Vadikolias et al., 2012). An eight-year follow-up study using ELSA also yielded a consistent finding that education contributes to the initial levels of cognitive function but does not influence age-related cognitive decline (Zaninotto et al., 2018). In this study, an association between the highest educational level and dementia was not found. This is in line with a previous ELSA study exploring the association between education and dementia (Cadar et al., 2018). It is possible that the risk for dementia may be contingent on the socio-cultural environment, i.e., rising trends in education levels might be associated with improved cognition or reduced trends in dementia incidence (Matthews et al., 2016; Nichols et al., 2022). Another hypothesis postulated in the literature is that formal schooling was disrupted during the war and immediate post-war years for many older English adults, making education level less critical for the cohort born and raised around World War II (Cipriani and Borin, 2015; Kosmidis et al., 2011).

To our knowledge, this is the first study exploring the mediating role of inflammatory markers in the association between wealth and neurocognitive disorders. Our results show a persistent negative association between higher wealth and dementia. Compared to other SEP measures, wealth reflects more accurately the economic situation of older people for whom there might be little income from employment (Cadar et al., 2018). Occupational social class was also added as an alternate measure of SEP in the analysis, and the results suggest that occupation is also a determinant of CIND and dementia.

A few studies have explored the individual contributions of different inflammatory biomarkers to cognition. Still, to the best of our knowledge, no studies have estimated the indirect effects of SEP on neurocognitive disorders via inflammation. A small but significant mediating effect of WBC was found in the association between latent SEP marker and CIND, highlighting that SEP-related differentials might occur partly via the neuroinflammatory mechanism. Results also suggest that the meditating role of inflammation in the relationship between SEP and neurocognitive disorders is not similar across all indicators of SEP. Contributions of CRP and fibrinogen partly explained some of the educational and occupational inequalities in cognitive impairment; however, only WBC mediated the association between wealth and cognitive impairment. It is known that all the SEP indicators studied here tap into a common construct of SEP. However, each SEP indicator might also be a unique representation of a socioeconomic resource and might have different effects on CIND through different inflammatory pathways (Krieger, 2001). Further attenuation of results after including lifestyle behaviours and BMI suggests that other factors might be in the pathway linking SEP and cognitive impairment. It is possible that adverse health behaviours such as smoking, lower physical activity, excessive drinking, poor nutrition and adiposity, more prevalent among those belonging to disadvantaged backgrounds, may elevate the pro-

inflammatory cytokines such as CRP, WBC and fibrinogen (Petrovic et al., 2018). Such systemic markers of inflammation can infiltrate and break down the blood–brain barrier, which further exacerbates inflammation by allowing further infiltration of immune cells, thus inducing neuropathological changes in the brain (Farrall and Wardlaw, 2009; Haroon et al., 2012). This corroborates with the earlier mediation study examining the biological embedding of early adverse socioeconomic environment on executive function among middle-aged females (D'Amico et al., 2022). In their research, an allostatic load score, as well as its immune sub-score comprising Insulin-like growth factor-1, CRP, fibrinogen, tumour necrosis factor-alpha, interleukin-6, E-selectin, and intracellular adhesion molecule-1 were found to mediate the associations; however, no distinction between stages of neurocognitive disorders or different markers were made (D'Amico et al., 2022). No mediating effect was seen for SEP and dementia in our study, which could be attributed to fewer respondents with dementia.

The overall results partially support the theoretical hypothesis that inflammation particularly, leucocytosis or elevation of WBCs play some role in neurodegenerative disorders (Heneka et al., 2010; Lecca et al., 2022). The attenuation of results after considering lifestyle behaviours and BMI might suggest the complexity of these mechanisms. Inflammatory effects were seen for the prodromal stages of dementia (CIND), suggesting the likely influence of inflammation in the early stages of the cognitive decline continuum (Cisbani and Rivest, 2021; Parachikova et al., 2007). Nevertheless, epidemiological evidence on the neuroinflammatory embedding of adverse socioeconomic conditions is still emerging, so comparisons with other studies are not possible at this stage.

4.1. Strengths and limitations

This study has several strengths and limitations. First, as with any secondary analysis, this observational study is constrained by the existing data, and we are aware of the potential of uncontrolled confounding. This means the associations observed might not merit a conclusion of causation (Hammerton and Munafò, 2021). Second, the diagnosis of cognitive impairment with no dementia was determined using brief cognitive tests which might have limited diagnostic accuracy. The best approach to classify neurocognitive disorders remains a comprehensive clinical assessment, which is difficult to obtain in extensive population-based studies. Third, we could not rule out the possibility of genetic confounding by factors such as APOE genotype, as this information was only collected from a sub-sample of ELSA. Fourth, the observational nature of the study makes it difficult to differentiate between the various types of dementia, therefore, the results might not be clinically relevant. Additionally, any individual subset analyses to further classify dementia might impact the power of the study. Lastly, attrition is imminent in any longitudinal study of ageing and bias due to selective mortality or dementia-related loss to follow-up could be another concern in this study, as cognitive impairment strongly predicts both.

The main strength of this study is the use of a longitudinal and nationally representative sample of older adults in England to investigate socioeconomic position, inflammation, and neurocognitive disorders. Second, this study has adopted the recent DSM classification criteria of cognitive impairment, which cover a broader range of cognitive impairment, allowing us to identify a larger group of cognitively impaired subjects without dementia, including both MCI and OCIND cases (Caracciolo et al., 2008). Most UK studies have used global cognitive scales, which capture limited neurocognitive domains (Davis et al., 2017; Landy et al., 2017; Richards et al., 2019; Tsui et al., 2020). However, past research has implied that fluid abilities (e.g., memory, processing speed) may be more susceptible to cerebrovascular diseases than crystallised abilities, especially at early stages of cognitive decline (Murman, 2015). Above all, many studies fail to exclude cases of dementia when measuring mild neurocognitive disorders. Both these drawbacks are addressed in this study. Furthermore, we used wealth which has been recognised as a more appropriate measure for inequalities in health among older adults than income. Lastly, several measures of inflammation were included in the analyses, together with many counfounders including baseline cognitive status.

5. Conclusion

This study underscores the socioeconomic inequalities of neurocognitive disorders in concordance with the results of other studies. It reinforces the need for better education, occupation, and economic resources as preventative measures across the lifecourse against cognitive impairment and other health inequalities. More importantly, it contributes to the evidential framework exploring the biological mechanisms of inequalities in neurocognitive conditions in later life. Since the role of inflammation is small, there can be many other plausible behavioural, psychosocial (social support, isolation, and loneliness) and other biological mechanisms which underlie the observed associations. These processes are not necessarily mutually exclusive and could be closely intertwined.

6. Contributors

Aswathikutty Gireesh and Dr Dorina Cadar generated the idea of this study and proposed the analytic plan. Analysis, interpretation of the data and article write-up were carried out by Aswathikutty Gireesh, with the support from Dr Dorina Cadar, Prof Amanda Sacker and Prof Anne McMunn. All authors contributed significantly to the conception, design, and revision of the article. Aswathikutty Gireesh conducted the data analysis and takes responsibility for the integrity of the data and accuracy of the data analysis.

7. Availability of data and materials

The ELSA was developed by a team of researchers based at University College London, the Institute for Fiscal Studies, and the National Centre for Social Research.

The data are linked to the UK Data Archive and freely available through the UK data services and can be accessed here: https://discover.ukdataservice.ac.uk.

Ethical approval

Ethical approval for each of the ELSA waves was granted from the National Research Ethics Service (London Multicentre Research Ethics Committee) (MREC/01/2/91) (http://www.nres.npsa.nhs.uk). All participants provided informed consent.

Funding

ELSA is funded by the National Institute on Aging (R01AG017644), and by UK Government Departments coordinated by the National Institute for Health and Care Research (NIHR).

Dr. Dorina Cadar is supported by the National Institute on Ageing (grant R01AG17644) and the ESRC (ES/T012091/1 & ES/S013830/1).

Prof. Anne McMunn is supported by the ESRC ES/W013185/1 and ES/W001454/1.

Aswathikutty Gireesh is supported by the ESRC and the Biotechnology and Sciences Research Council (BBSRC) (ES/P000347/1).

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

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.07.013.

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