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Original Contribution

Effects of Socioeconomic Position on Inflammatory and Hemostatic Markers: A Life-Course Analysis in the 1958 British Birth Cohort

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The cumulative effects of socioeconomic position (SEP) on cardiovascular disease have been described, but the pathways are unclear. In this study, the authors examined the effects of life-course SEP on inflammatory and hemostatic markers: fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen. Data from the 1958 British birth cohort, including data on persons who underwent a biomedical follow-up in 2002–2004, were used. Social class was determined at three stages of respondents' lives: childhood (birth), early adulthood (age 23 years), and midlife (age 42 years). A cumulative indicator score of SEP was calculated that ranged from 0 (always in the highest social class) to 9 (always in the lowest social class). In men and women, associations were observed between cumulative indicator score and fibrinogen ($p < 0.001$), C-reactive protein ($p < 0.001$), von Willebrand factor antigen ($p \leq 0.05$), and tissue plasminogen activator antigen ($p < 0.001$ only in women). The trends in fibrinogen and C-reactive protein remained after adjustment for body mass index, smoking, and physical activity. However, the trends became nonsignificant for von Willebrand factor antigen and tissue plasminogen activator antigen in women. Risk exposure related to SEP accumulates across the life course and contributes to raised levels of fibrinogen and C-reactive protein, while childhood SEP influences hemostatic markers more than does adult SEP.

cohort studies; C-reactive protein; fibrinogen; hemostasis; inflammation; social class; tissue plasminogen activator; von Willebrand factor

Abbreviations: CIS, cumulative indicator score; SEP, socioeconomic position.

Meta-analyses of results from prospective studies suggest that inflammatory markers such as fibrinogen and C-reactive protein and hemostatic markers such as von Willebrand factor antigen and tissue plasminogen activator antigen are part of the evolving understanding of cardiovascular disease risk, including atherosclerosis, stroke, and myocardial infarction (1–6). The question of whether or not associations between these biomarkers and cardiovascular disease risk are independent of other vascular disease risk factors is controversial (7, 8).

Previous studies have demonstrated the importance of socioeconomic position (SEP) as a potential confounder of the associations between inflammatory and hemostatic markers and coronary heart disease (9–16). Reported associations between SEP and biomarkers suggest that persons with lower SEP have elevated levels of fibrinogen (10, 13,

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16, 17), C-reactive protein (9, 13, 15), and von Willebrand factor antigen (14). There is some evidence that the association between SEP and these biomarkers is independent of established risk factors such as lifestyle and demographic indicators (13, 16). However, other studies have shown attenuation in the strength of the associations of fibrinogen (11), C-reactive protein (9, 18), and von Willebrand factor antigen (14) with SEP after adjustment for risk factors for coronary heart disease. There is no consensus in the literature as to whether childhood SEP or recent SEP is more strongly related to these biomarkers. The importance of the early childhood socioeconomic environment with regard to fibrinogen levels (19, 20) and coronary heart disease (21) later in life has been described. Some studies have found that current SEP is an important predictor of fibrinogen (11, 13, 19), C-reactive protein (12, 13, 15), and von Willebrand factor antigen (14) levels. The impact of cumulative exposure to disadvantage over the life course (10, 16, 22–28), in addition to time sequencing, has been hypothesized to be important to health (28). However, little is known about the cumulative effects of SEP on inflammatory and hemostatic markers over the life course among middle-aged persons.

In a cohort of Britons born during 1 week in 1958, we investigated the effects of SEP measured concurrently by occupational class at three time points in the life course (birth, age 23 years, and age 42 years) on circulating levels of fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen measured in adulthood. We examined whether the association of biomarkers with SEP was cumulative—that is, whether the increased exposure to adverse SEP was associated with raised levels of inflammatory and hemostatic markers—and whether the associations between cumulative SEP and the biomarkers were attributable to major risk factors for coronary heart disease.

MATERIALS AND METHODS

The 1958 British birth cohort is a continuing longitudinal representative survey of predominantly White persons (97 percent) living in the United Kingdom who were born during 1 week in 1958. The subsequent surveys were completed when participants were aged 7, 11, 16, 23, 33, and 42 years. A detailed description of the cohort members at age 42 years is provided elsewhere (20, 29–31). In 2002–2004, all cohort members who were still in contact with the cohort study team and who, at age 41–42 years, had not required a proxy interview were invited to participate in a clinical examination in their homes at age 44–45 years. The size of the eligible sample in 1958 was 17,638; by age 45 years, 86 percent of the total cohort remained eligible. However, participation did not increase, because contact was not attempted for 19 percent of the eligible sample (30). The target sample at age 45 years was 12,069 persons (68 percent of the original sample), of whom 9,377 participated in the medical survey. Despite attrition, participants remained representative of the original sample, including with respect to blood samples (30). Ethical approval for the medical examination was obtained from the South East Multi-Centre Research Ethics Committee.

Inflammatory and hemostatic markers were assessed from venous blood samples that were obtained without prior fasting and mailed to collaborating laboratories. Fibrinogen was measured by the Clauss method (Biomerieux, Basingstoke, United Kingdom). C-reactive protein was assayed by immunonephelometry (Dade Behring, Milton Keynes, United Kingdom). Von Willebrand factor antigen and tissue plasminogen activator antigen were measured by enzyme-linked immunosorbent assay (DAKO plc (High Wycombe, United Kingdom) and Biopool AB (Umea, Sweden), respectively). The intra- and interassay coefficients of variation for fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen were 2.6 percent and 3.7 percent, 4.7 percent and 8.3 percent, 3.3 percent and 4.2 percent, and 6.5 percent and 6.6 percent, respectively.

Height and weight were measured during the medical survey. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Data on smoking and physical activity were collected by questionnaire at age 42 years. The respondents were classified as never smokers, ex-smokers, or current smokers. At age 42 years, participants responded to a single question about the frequency of leisure-time physical activity. Three levels of reported physical activity were created: high ($\geq$4 days/week), intermediate (1–3 days/week), and none/low (no activity or less frequent activity).

Socioeconomic position

In the present study, we used occupational class to represent SEP. Registrar General's social class, a United Kingdom measure of social class based on occupation, was determined from information obtained directly from the participants when they were adults and obtained from their parents during their childhoods. The Registrar General's social classes are described as: I—professional occupations; II—managerial and technical occupations; IIIN—skilled occupations (nonmanual); IIIM—skilled occupations (manual); IV—partly skilled occupations; and V—unskilled occupations. For purposes of analysis, we merged social classes I and II as social class 1 and social classes IV and V as social class 4, while social class IIIN (nonmanual) was labeled social class 2 and social class IIIM (manual) was labeled social class 3. Social class categories were merged in this way because of small numbers in some categories. At age 42 years, out of 9,377 participants who were visited, 582 were considered missing because of incomplete information on occupational class at the three time points selected for this study. This resulted in 8,795 participants. An additional 2,844 participants had missing information on biomarkers. Consequently, the sample size for analysis was 5,951 participants. Social class trajectories over the life course were calculated from 1) social class at birth or, if data were missing (n = 515 out of 8,795; 6 percent), at age 7 years; 2) social class at age 23 years or, if data were missing (n = 1,132 out of 8,795; 13 percent), at age 33 years; and 3) recent social class, defined as social class at age 42 years.

A cumulative indicator score (CIS) of SEP at three different life stages (childhood (birth), early adulthood (age 23 years), and midlife (age 42 years)) was constructed by means of a total social-class life-course score ranging from 0 to 9. Social classes 1–4 were assigned scores of 0, 1, 2, and

3, respectively. These scores were added to create the CIS. Hence, CIS values ranged from 0 (0 + 0 + 0, i.e., social class 1 on all three occasions) to 9 (3 + 3 + 3, i.e., social class 4 on all three occasions). Likewise, a CIS of 1 corresponds to 0 + 1 + 0, 0 + 0 + 1, and 1 + 0 + 0, while a CIS of 8 corresponds to 2 + 3 + 3, 3 + 2 + 3, and 3 + 3 + 2.

Statistical analysis

All analyses were conducted separately for men and women, because likelihood ratio tests showed significant interaction between sex and SEP ($p < 0.05$) for all of the biomarkers. The normality of biomarkers was assessed, and fibrinogen and C-reactive protein were log-transformed prior to analyses. Geometric mean values are presented, and the natural logs of the concentrations were used in the regression models. The relation between each of the biomarkers and social class was explored using analysis of variance. Regression analysis was used to explicitly test for a trend in the mean values of the outcome variable across social class by entering social class as a continuous variable in the model. All p values presented are two-sided, and the statistical significance level for hypothesis testing was set at 0.05. Mutually adjusted mean values were determined in models with terms present for 1) social class at birth and recent social class, 2) social class at birth and at age 23 years, and 3) simultaneous adjustment of social class on three occasions. Unadjusted and adjusted associations of CIS with each of the biomarkers were estimated using simple and multiple regression analysis. Body mass index, smoking status, and physical activity were entered into the model as traditional risk factors for coronary heart disease. Finally, the percentage reduction in the CIS difference was calculated by including CIS as a linear term in the regression model and comparing the regression coefficients for CIS without and with adjustment for the risk factors. The multivariate analyses included respondents with complete data on all variables ($n = 5{,}860$). Additional analyses of the potential impact of fieldwork (hour of blood sample collection, month of examination, and delay in processing of blood sample), modeled as a random effect, showed a negligible influence on associations with social class (data not shown). Analyses were carried out using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

We restricted our analyses to persons with complete information on occupational class at the three specified time points. This gave us 8,795 respondents, of whom 52 percent were males. In the results reported here, no statistical differences were found in adult social class distribution between persons with complete data and the original sample ($p = 0.08$). However, fewer participants were of an unskilled manual class (social class 4) in childhood in the complete data as compared with the original sample (20 percent vs. 22 percent; $p \leq 0.01$).

Inflammatory and hemostatic markers and social class

Table 1 shows mean concentrations of the biomarkers in the four categories of social class at the three time points. Social class gradients were observed at all three time points for fibrinogen and C-reactive protein in both men and women ($p \leq 0.005$). Thus, respondents in more disadvantaged social classes (social classes 3 and 4) had elevated levels of these inflammatory markers in comparison with respondents in a less disadvantaged social class (social class 1). However, the associations of von Willebrand factor antigen and tissue plasminogen activator antigen with social class did not show a consistent linear trend. In men, trends in the relation of von Willebrand factor antigen with social class were found at all three time points ($p < 0.005$), but tissue plasminogen activator antigen did not show significant trends in social class at age 23 years or age 42 years. In women, von Willebrand factor antigen did not show trends for recent social class ($p = 0.67$), although a trend was apparent for von Willebrand factor antigen by social class at birth and social class at age 23 years. In women, a trend for the relation between tissue plasminogen activator antigen and social class was observed at all three time points. These analyses were also repeated using respondents' social class at age 16 years rather than social class at age 23 years, and results were found to be unaffected. When analyses were performed using social class at birth and at age 23 years without taking into account the values for social class at ages 7 and 33 years, the results were the same as when imputed values were used.

Mutual adjustment for social class at birth and adult social class

Table 2 shows that among men, raised levels of fibrinogen, C-reactive protein, and von Willebrand factor antigen were associated with disadvantaged social class in childhood and adulthood, while tissue plasminogen activator antigen was associated with social class only at birth. Among women, raised levels of fibrinogen, C-reactive protein, and tissue plasminogen activator antigen were associated with adverse social class on both occasions. However, mean levels of von Willebrand factor antigen and tissue plasminogen activator antigen were more strongly associated with social class at birth than with recent social class. For von Willebrand factor antigen in women and tissue plasminogen activator antigen in men, the regression coefficients for social class at birth were larger than the coefficients for recent social class following mutual adjustment (social class at birth and recent social class, respectively: for von Willebrand factor antigen in women, $\beta = 1.66$ vs. $\beta = 0.03$; for tissue plasminogen activator antigen in men, $\beta = 0.16$ vs. $\beta = -0.04$). The results from mutual adjustment of social class at birth for social class at age 23 years and vice versa are reported in supplemental table 1, which is posted on the *Journal*'s website (http://aje.oxfordjournals.org/). In these analyses, when social class at age 23 years (supplemental table 1) or, for women, head of household's social class (results not shown) was used rather than most recent social class, similar results were obtained.

Table 3 shows results from the regression analyses with social class at the three time points fitted individually and simultaneously. In general, associations remained significant; however, in men, social class at birth was not associated with

TABLE 1. Mean levels of fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen by social class at three life points in the 1958 British birth cohort, United Kingdom, 2002–2004

Social class*	Men ($n = 3,134$)			Women ($n = 2,817$)		
	Social class in childhood (birth)	Social class in early adulthood (age 23 years)	Social class in midlife (age 42 years)	Social class in childhood (birth)	Social class in early adulthood (age 23 years)	Social class in midlife (age 42 years)
Fibrinogen (g/liter)†						
Social class 1	2.75 (1.19)‡	2.74 (1.20)	2.76 (1.21)	2.81 (1.22)	2.89 (1.23)	2.89 (1.23)
Social class 2	2.76 (1.20)	2.76 (1.22)	2.77 (1.22)	2.91 (1.23)	2.92 (1.22)	2.94 (1.23)
Social class 3	2.82 (1.22)	2.85 (1.21)	2.85 (1.20)	2.97 (1.23)	3.07 (1.21)	3.00 (1.20)
Social class 4	2.84 (1.22)	2.84 (1.22)	2.89 (1.21)	3.02 (1.21)	2.72 (1.23)	3.02 (1.23)
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
C-reactive protein (mg/liter)†						
Social class 1	0.89 (2.77)	0.91 (2.68)	0.99 (2.68)	0.95 (2.85)	1.06 (3.18)	1.11 (3.15)
Social class 2	0.96 (2.53)	1.00 (2.69)	1.11 (2.72)	1.09 (3.09)	1.14 (2.97)	1.15 (2.91)
Social class 3	1.12 (2.65)	1.15 (2.64)	1.14 (2.60)	1.26 (3.12)	1.52 (3.06)	1.36 (2.97)
Social class 4	1.16 (2.65)	1.23 (2.61)	1.17 (2.94)	1.26 (2.94)	1.35 (3.00)	1.33 (3.06)
p for trend	<0.001	<0.001	<0.001	<0.001	<0.001	0.005
von Willebrand factor antigen (IU/dl)						
Social class 1	120.8 (40.2)	119.5 (40.4)	120.2 (39.9)	117.9 (40.3)	117.8 (40.3)	119.5 (41.9)
Social class 2	119.4 (38.1)	121.3 (39.8)	125.8 (39.5)	118.0 (39.5)	120.8 (41.1)	121.9 (40.5)
Social class 3	122.2 (40.1)	124.4 (40.0)	125.2 (40.8)	121.4 (40.2)	125.7 (39.5)	120.8 (41.0)
Social class 4	127.7 (40.4)	125.6 (39.4)	124.2 (38.4)	122.5 (42.6)	121.4 (40.1)	120.4 (38.1)
p for trend	0.004	<0.001	0.004	0.031	0.053	0.667
Tissue plasminogen activator antigen (ng/ml)						
Social class 1	5.63 (2.63)	5.74 (2.63)	5.80 (2.78)	4.08 (2.37)	4.27 (2.58)	4.27 (2.48)
Social class 2	5.68 (3.05)	5.95 (2.89)	6.15 (2.88)	4.05 (2.64)	4.34 (2.61)	4.34 (2.59)
Social class 3	5.86 (2.93)	5.85 (3.03)	5.85 (2.74)	4.56 (2.63)	4.74 (2.61)	4.85 (2.85)
Social class 4	6.07 (2.83)	5.84 (2.84)	5.71 (3.57)	4.43 (2.51)	4.54 (2.39)	4.55 (2.58)
p for trend	0.004	0.58	0.94	0.001	0.02	0.008

* Social class 1, professional and managerial; social class 2, nonmanual; social class 3, manual; social class 4, unskilled.
† Geometric mean values are presented.
‡ Numbers in parentheses, standard deviation.

fibrinogen levels, while recent social class was not associated with C-reactive protein levels in mutually adjusted analysis. In women, social class at age 23 years was not associated with fibrinogen and recent social class was not associated with C-reactive protein in the simultaneously adjusted analyses. In the case of von Willebrand factor antigen and tissue plasminogen activator antigen, only social class at birth remained associated when results were mutually adjusted for social class at ages 23 and 42 years.

Inflammatory and hemostatic markers and potential coronary heart disease risk factors

The association of fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen with potential risk factors for coronary heart disease was examined (see supplemental table 2 (http://aje.oxfordjournals.org/)). Mean levels of fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen were positively associated with raised body mass index. Current smokers had raised levels of biomarkers in comparison with never smokers. In women, smoking was not associated with C-reactive protein levels. In men, a high frequency of physical activity was associated with lower levels of biomarkers. In women, physical activity levels were not associated with levels of von Willebrand factor antigen or tissue plasminogen activator antigen.

Analyses examining the relation of each risk factor with CIS (table 4) indicated that persons with CIS values of 0 had a lower mean body mass index, a low prevalence of current smoking, and low rates of physical inactivity in comparison with persons with higher CIS values ($p < 0.001$).

Inflammatory and hemostatic markers and CIS

Unadjusted (model 1) and risk-factor-adjusted (model 2) associations of biomarkers with CIS are shown in table 5. In men, CIS was associated with logarithmic concentrations of

TABLE 2. Mutually adjusted mean levels of fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen by social class in childhood and midlife in the 1958 British birth cohort, United Kingdom, 2002–2004

Social class*	Men (n = 3,134)				Women (n = 2,817)			
	Fibrinogen (g/liter)†	C-reactive protein (mg/liter)†	von Willebrand factor antigen (IU/dl)	Tissue plasminogen activator antigen (ng/ml)	Fibrinogen (g/liter)†	C-reactive protein (mg/liter)†	von Willebrand factor antigen (IU/dl)	Tissue plasminogen activator antigen (ng/ml)
Social class in childhood (birth)								
Social class 1	2.76	0.91	121.5	5.65	2.82	0.97	117.9	4.11
Social class 2	2.77	0.97	119.7	5.69	2.91	1.09	118.0	4.04
Social class 3	2.81	1.11	122.0	5.85	2.96	1.24	121.4	4.54
Social class 4	2.82	1.14	127.0	6.08	3.00	1.23	122.5	4.40
Difference per increase in social class grade‡	0.01	0.08	1.59	0.16	0.02	0.09	1.66	0.15
95% confidence interval	0.00, 0.01	0.05, 0.12	0.16, 3.03	0.05, 0.26	0.01, 0.03	0.04, 0.13	0.12, 3.19	0.05, 0.24
p for trend	0.034	<0.001	0.029	0.003	<0.001	<0.001	0.034	0.003
Social class in midlife (age 42 years)								
Social class 1	2.76	1.00	120.7	5.83	2.91	1.11	119.9	4.29
Social class 2	2.77	1.11	125.8	6.16	2.93	1.15	121.7	4.32
Social class 3	2.85	1.11	124.7	5.80	2.99	1.31	120.6	4.84
Social class 4	2.88	1.12	123.6	5.67	3.00	1.28	120.0	4.50
Difference per increase in social class grade‡	0.01	0.05	1.47	−0.04	0.01	0.05	0.03	0.09
95% confidence interval	0.01, 0.02	0.01, 0.08	0.15, 2.79	−0.14, 0.05	0.00, 0.01	0.01, 0.09	−1.33, 1.40	0.01, 0.18
p for trend	<0.001	0.008	0.029	0.36	0.002	0.013	0.96	0.04

* Social class 1, professional and managerial; social class 2, nonmanual; social class 3, manual; social class 4, unskilled.

† Geometric mean values are presented with log-transformed regression coefficients. Multiplied by 100, these represent the percentage change per increase in social class—for example, for C-reactive protein among men, an 8% increase in social class at birth when mutually adjusted for recent social class.

‡ Mutually adjusted (social class in childhood and midlife) regression coefficient per increase in social class grade.

fibrinogen ($\beta = 0.009$, $p < 0.001$), logarithmic concentrations of C-reactive protein ($\beta = 0.051$, $p < 0.001$), and concentrations of von Willebrand factor antigen ($\beta = 1.123$, $p < 0.001$) and was less strongly associated with tissue plasminogen activator antigen levels ($\beta = 0.026$, $p = 0.22$). In women, a linear trend was observed between CIS and all biomarkers—fibrinogen ($\beta = 0.012$, $p < 0.001$), C-reactive protein ($\beta = 0.055$, $p < 0.001$), von Willebrand factor antigen ($\beta = 0.671$, $p = 0.05$), and tissue plasminogen activator antigen ($\beta = 0.083$, $p < 0.001$). These relations were also apparent in never smokers (results not shown).

In model 2, further adjustment for traditional coronary heart disease risk factors (body mass index, smoking, and physical activity) showed that the effects of CIS remained in men for concentrations of fibrinogen, C-reactive protein, and von Willebrand factor antigen ($p < 0.01$). In women, after adjustment for the adult risk factors (model 2), CIS was no longer associated with von Willebrand factor antigen and tissue plasminogen activator antigen ($p > 0.05$) but associations remained essentially unchanged for concentrations of fibrinogen and C-reactive protein ($p < 0.001$). For fibrinogen, the risk factors explained 55 percent of the gradient in CIS in men and 42 percent in women. For C-reactive protein, the risk factors explained 57 percent of the gradient in men and 40 percent in women. For von Willebrand factor antigen, the risk factors explained 26 percent of the gradient in men and 45 percent in women (nonsignificant trend).

Respondents with a high CIS had higher mean levels of biomarkers than respondents with a CIS of 0. When adjusted for additional risk factors, most of the results remained unchanged. These data are shown in supplemental table 3 (men) and supplemental table 4 (women) (http://aje.oxfordjournals.org/).

DISCUSSION

Our results indicated that increased exposure to adverse SEP across the life course was associated with elevated levels of inflammatory markers (fibrinogen and C-reactive protein) in midlife, supporting a cumulative life-course model for these factors (22–27). These associations were largely, but not fully, explained by health-related behaviors.

TABLE 3. Unadjusted and simultaneously adjusted beta coefficients (β) from regression analyses of the relation of fibrinogen, C-reactive protein, von Willebrand factor antigen, and tissue plasminogen activator antigen with social class at three life stages in the 1958 British birth cohort, United Kingdom, 2002–2004

	Social class in childhood (birth)		Social class in early adulthood (age 23 years)		Social class in midlife (age 42 years)	
	β	95% CI*	β	95% CI	β	95% CI
Men ($n = 3,134$)						
Fibrinogen (g/liter)†						
Unadjusted association	0.01	0.00, 0.02	0.01	0.01, 0.02	0.02	0.01, 0.02
p for trend		<0.001		<0.001		<0.001
Adjusted association‡	0.01	−0.00, 0.01	0.01	0.00, 0.01	0.01	0.00, 0.02
p for trend		0.085		0.031		0.003
C-reactive protein (mg/liter)†						
Unadjusted association	0.10	0.06, 0.13	0.10	0.07, 0.14	0.07	0.03, 0.09
p for trend		<0.001		<0.001		<0.001
Adjusted association‡	0.07	0.03, 0.11	0.08	0.04, 0.12	0.01	−0.03, 0.05
p for trend		<0.001		<0.001		0.629
von Willebrand factor antigen (IU/dl)						
Unadjusted association	2.13	0.76, 3.50	2.25	0.94, 3.56	1.89	0.63, 3.15
p for trend		0.004		<0.001		0.004
Adjusted association‡	1.45	0.01, 2.90	1.41	−0.14, 2.96	0.81	−0.67, 2.30
p for trend		0.050		0.074		0.283
Tissue plasminogen activator antigen (ng/ml)						
Unadjusted association	0.14	0.04, 0.24	0.03	0.07, 0.12	−0.00	−0.09, 0.09
p for trend		0.004		0.58		0.94
Adjusted association‡	0.15	0.05, 0.26	0.01	−0.10, 0.12	−0.05	−0.15, 0.06
p for trend		0.004		0.864		0.379
Women ($n = 2,817$)						
Fibrinogen (g/liter)†						
Unadjusted association	0.02	0.02, 0.03	0.01	0.01, 0.02	0.01	0.01, 0.02
p for trend		<0.001		<0.001		<0.001
Adjusted association‡	0.02	0.01, 0.03	0.01	−0.00, 0.01	0.01	0.00, 0.01
p for trend		<0.001		0.089		0.029
C-reactive protein (mg/liter)†						
Unadjusted association	0.10	0.05, 0.14	0.09	0.05, 0.14	0.06	0.02, 0.10
p for trend		<0.001		<0.001		0.005
Adjusted association‡	0.08	0.03, 0.12	0.07	0.02, 0.11	0.03	−0.01, 0.07
p for trend		0.001		0.006		0.203
von Willebrand factor antigen (IU/dl)						
Unadjusted association	1.83	0.36, 3.30	1.63	0.16, 3.09	0.52	−0.78, 1.83
p for trend		0.031		0.053		0.667
Adjusted association‡	1.60	0.09, 3.10	1.41	−0.20, 3.03	−0.23	−1.66, 1.20
p for trend		0.038		0.086		0.757
Tissue plasminogen activator antigen (ng/ml)						
Unadjusted association	0.17	0.07, 0.26	0.11	0.02, 0.21	0.11	0.03, 0.20
p for trend		0.001		0.02		0.008
Adjusted association‡	0.141	0.04, 0.24	0.05	−0.05, 0.16	0.07	−0.02, 0.17
p for trend		0.005		0.328		0.114

* CI, confidence interval.
† Regression coefficients (β) were log-transformed.
‡ Simultaneously adjusted for social class at three life stages.

TABLE 4. Association (mean value or prevalence) between risk factors for coronary heart disease and cumulative indicator score of socioeconomic position in the 1958 British birth cohort, United Kingdom, 2002–2004

Risk factor	Cumulative indicator score of socioeconomic position									*p* for trend	Total sample
	0	1	2	3	4	5	6	7	8	9		
Men	*n* = 282	*n* = 195	*n* = 428	*n* = 353	*n* = 444	*n* = 282	*n* = 511	*n* = 377	*n* = 173	*n* = 46		*n* = 3,091
Mean body mass index*	26.7	26.6	27.3	27.9	28.1	28.4	27.9	28.2	28.5	27.3	<0.001	27.8
95% CI†	26.3, 27.1	26.2, 27.1	26.9, 27.7	27.5, 28.4	27.8, 28.5	27.8, 28.9	27.6, 28.3	27.7, 28.6	27.9, 29.2	26.0, 28.6		27.6, 27.9
Current smoker (%)	9.2	11.8	13.1	12.7	15.8	24.5	28.9	32.9	38.1	41.3	<0.001	20.9
95% CI	5.8, 12.6	7.2, 16.3	9.9, 16.3	9.3, 16.2	12.4, 19.2	19.4, 29.5	25.0, 32.9	28.1, 37.6	30.9, 45.4	26.9, 55.7		9.5, 22.3
Physical inactivity (%)	25.9	23.6	28.0	27.2	28.6	37.6	37.4	38.7	38.1	34.8	<0.001	31.9
95% CI	20.8, 31.0	17.6, 29.6	23.8, 32.3	22.5, 31.8	24.4, 32.8	31.9, 43.2	33.2, 41.6	33.8, 43.6	30.9, 45.4	20.9, 48.7		30.3, 33.6
Women	*n* = 192	*n* = 164	*n* = 429	*n* = 394	*n* = 569	*n* = 332	*n* = 310	*n* = 184	*n* = 137	*n* = 58		*n* = 2,769
Mean body mass index	25.5	25.9	26.5	26.9	26.5	26.8	27.5	28.0	27.5	27.7	<0.001	26.8
95% CI	24.8, 26.1	25.1, 26.7	26.0, 27.0	26.4, 27.5	26.1, 26.9	26.2, 27.3	26.9, 28.2	27.2, 28.9	26.6, 28.4	25.9, 29.5		26.6, 27.0
Current smoker (%)	8.8	13.4	15.6	19.0	18.1	28.0	27.7	43.5	39.4	53.4	<0.001	22.7
95% CI	4.8, 12.9	8.2, 18.6	12.2, 19.0	15.1, 22.9	14.9, 21.3	23.2, 32.8	22.7, 32.7	36.3, 50.7	31.2, 47.6	40.5, 66.4		21.1, 24.2
Physical inactivity (%)	31.2	25.0	30.3	29.7	33.6	33.1	39.0	47.8	44.5	43.1	<0.001	34.1
95% CI	24.7, 37.8	18.3, 31.6	25.9, 34.6	25.2, 34.2	29.7, 37.4	28.0, 38.2	33.6, 44.5	40.6, 55.1	36.2, 52.9	30.2, 55.9		32.3, 35.8

* Weight (kg)/height (m)^2.
† CI, confidence interval.

Moreover, we found that socioeconomic circumstances across the life course at various stages also contributed independently to raised levels of fibrinogen and C-reactive protein. By contrast, we found that hemostatic markers (von Willebrand factor antigen and tissue plasminogen activator antigen) were influenced by early life conditions after adjustment for current and early adulthood conditions.

The associations between inflammation, hemostasis, and atherosclerosis have been well reported (1–5, 32). Evidence suggests a relation between SEP and progressive atherosclerosis (33). The finding that atherosclerosis begins in childhood and progresses with age (27) suggests that using a life-course perspective is appropriate in this context. Our data accord with previous findings from the Whitehall II Study and other studies that levels of fibrinogen, C-reactive protein, and von Willebrand factor antigen were elevated among men in lower concurrently assessed social positions (9, 13, 14, 17). Moreover, in the unadjusted analysis, the size of the difference between persons with the highest and lowest cumulative SEPs was 1.01 g/liter for fibrinogen, which is larger than that previously described (16), and 1.05 mg/liter for C-reactive protein, which is the same as that previously described (15), suggesting that the differences observed are substantial.

Mutual adjustment for social class on three occasions across the life course demonstrates that the three selected time points are important in the understanding of the establishment of raised inflammatory and hemostatic markers in midlife. Childhood social class was more strongly related to raised levels of von Willebrand factor antigen and tissue plasminogen activator antigen in comparison with social class at ages 23 and 42 years. One possible explanation might be that poorer childhood circumstances promote endothelial dysfunction (of which von Willebrand factor antigen and tissue plasminogen activator antigen are markers) (34), which is a key feature of early atherosclerosis (35). Low birth weight and infection in childhood are related to endothelial dysfunction (36, 37), and these may be additional mechanisms by which childhood socioeconomic circumstances relate to these adult biomarkers. In contrast, poorer circumstances in middle age may be more strongly associated with fibrinogen and C-reactive protein—partly markers of later atherosclerosis, which has a greater inflammatory component (35). The effects of cumulative SEP across the life course on fibrinogen and C-reactive protein are consistent with a report from the British Women's Heart and Health Study on an older age group (38).

The findings of the present study are relevant to the ongoing discussion on the effects of socioeconomic inequalities across the life course in cardiovascular health. This approach explicitly places more emphasis on a greater range of biologic and social experiences in childhood, adolescence, and early adulthood than either the lifestyle model or the programming model (39–41). However, there may be several interrelated pathways within these models that have different associations with later health. For example, the accumulation hypothesis states that adverse influences/events occur at different stages in life and accumulate over time, and the critical period model argues that early life influences biologic development independently; this is also

TABLE 5. Change in the regression coefficient (β) of the cumulative indicator score of socioeconomic position without and with adjustment for risk factors for coronary heart disease in the 1958 British birth cohort, United Kingdom, 2002–2004

	Model 1*			Model 2†			% change in β‡
	β§	95% CI¶	*p* for trend	β§	95% CI¶	*p* for trend	
Men ($n = 3,091$)							
Fibrinogen (g/liter)	0.009	0.006, 0.011	<0.001	0.004	0.001, 0.006	0.009	−55
C-reactive protein (mg/liter)	0.051	0.036, 0.066	<0.001	0.022	0.008, 0.037	0.002	−57
von Willebrand factor antigen (IU/dl)	1.123	0.539, 1.708	<0.001	0.828	0.229, 1.428	0.007	−26
Tissue plasminogen activator antigen (ng/ml)	0.026	−0.016, 0.068	0.22	−0.035	−0.076, 0.006	0.10	−235
Women ($n = 2,769$)							
Fibrinogen (g/liter)	0.012	0.008, 0.015	<0.001	0.007	0.003, 0.010	<0.001	−42
C-reactive protein (mg/liter)	0.055	0.035, 0.074	<0.001	0.033	0.015, 0.051	<0.001	−40
von Willebrand factor antigen (IU/dl)	0.671	−0.013, 1.355	0.05	0.366	−0.334, 1.067	0.30	−45
Tissue plasminogen activator antigen (ng/ml)	0.083	0.040, 0.127	<0.001	0.025	−0.017, 0.067	0.25	−70

* Model for the association between the biomarkers and cumulative indicator score.
† Model with results adjusted for body mass index, smoking, and physical activity.
‡ Change in the regression coefficient of the cumulative indicator score in model 2 as compared with model 1 ($[\beta_{\text{model 1}} - \beta_{\text{model 2}}]/\beta_{\text{model 1}}$).
§ The regression coefficient (β) represents the amount of change in the concentration of the biomarker (logarithmic in the case of fibrinogen and C-reactive protein) for a 1-point increase in cumulative indicator score.
¶ CI, confidence interval.

known as ''biological programming'' (39, 42). Our report shows the lack of a stepwise gradient in CIS (supplemental tables 3 and 4), in addition to the fact that most of the biomarkers did not survive full mutual adjustment for SEP at three time points (table 3). These results indicate that the effects of accumulation and critical periods are interrelated in our report, which is in line with the findings of Hallqvist et al. (28). Nevertheless, the effects of social class on different occasions across the life course appear in this report to be central to the understanding of socioeconomic inequalities in cardiovascular health at midlife in the British population. Therefore, these markers of inflammation (if they are shown to play a causal role) can be added to the list of potential biologic explanations for the increased risk of coronary heart disease observed in persons with lower life-course SEP.

We showed that differences in the concentrations of these biomarkers by cumulative SEP were partly mediated by health-related behaviors. These findings are in accord with those of other studies showing similar-sized attenuation in the associations of SEP with fibrinogen (11), C-reactive protein (9), and von Willebrand factor antigen (14). Additionally, our results describing the reduction in the gradient of CIS with C-reactive protein after risk factor adjustments partially confirm the findings of a study in a younger cohort that the effects of SEP on C-reactive protein are mediated by measures of adiposity (43). We observed no association between tissue plasminogen activator antigen and cumulative SEP. To our knowledge, no other studies have examined this association.

Health inequalities can partly be explained by factors, such as differences in health-related behaviors, metabolic covariates, and lifestyle and behavioral factors, that are associated with lower SEP (44). A number of these mediating factors have life-course influences themselves; for example, the trajectory of obesity can be set or influenced by early-life factors. Additionally, inflammatory and hemostatic markers are associated with smoking, physical inactivity, and obesity (45–47). Our results following adjustment for these measures show a reduction in the strength of biomarkers with the accumulation of social class, which argues for health-related behaviors as partial mediators of social differences in coronary heart disease.

This study had several strengths. First, the findings were based on multiple measures of social class over a period of 42 years and showed significant associations between frequency of living in a less privileged social class and markers of inflammation and hemostasis. Second, unlike other studies, our study used four categories of social class over the life course, allowing a more fine-grained analysis of social position. The linear relation between indicators of SEP and health warrants an examination of the accumulation hypothesis that goes beyond simple dichotomies of SEP. Third, our study had the advantage of having measured occupational class directly from the participants and thus did not rely on recall, which may have created some degree of recall error. Finally, we believe our findings are more robust than those of other studies because of the limited age range of the respondents and the large size of the cohort.

There were also a number of limitations to this study. First, not all respondents who were part of the perinatal survey in 1958 were seen at follow-up. However, investigators have recently reported that biases between respondents and nonrespondents are negligible in this cohort (20, 30, 31). Second, we did not address the issue of reverse causation—that is, the possibility that poor subclinical health caused lower social class. Thirdly, some of the associations between the biomarkers and CIS remained after adjustment for health

behaviors, which suggests that the relations under investigation may be accounted for by other, unmeasured variables. Additionally, it is possible that the impact of these health behaviors may be even larger than assessed here because of the errors associated with measuring these variables. Finally, we were unable to conduct an analysis stratified by race/ethnicity, since the sample was 97 percent White.

We conclude that generally, along with critical periods, there is a cumulative impact of socioeconomic factors across the life course on markers of inflammation (fibrinogen, C-reactive protein) which is partly explained by conventional cardiovascular disease risk factors. Moreover, early-life factors are associated with hemostatic markers (von Willebrand factor antigen, tissue plasminogen activator antigen), in addition to accumulation of von Willebrand factor antigen in men and tissue plasminogen activator antigen in women. Our data do not support an accumulation model for tissue plasminogen activator antigen in men or for von Willebrand factor antigen in women. Our findings suggest that the development of poor cardiovascular health occurs at a number of time points across the life course and that targeting a single time point in the life course may be insufficient to tackle the development of cardiovascular disease.

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