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"LIFE COURSE SOCIOECONOMIC POSITION IS ASSOCIATED WITH INFLAMMATORY MARKERS: THE FRAMINGHAM OFFSPRING STUDY"

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Abstract

Associations between life course socioeconomic position (SEP) and novel biological risk markers for coronary heart disease such as inflammatory markers are not well understood. Most studies demonstrate inverse associations of life course SEP with C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen, however little is known about associations between life course SEP and other inflammatory markers including intercellular adhesion molecule-1 (ICAM-1), tumor necrosis factor II (TNFR2), lipoprotein phospholipase A_2 (Lp-PLA_2) activity, monocytechemoattractant protein-1 (MCP-1) or P-selectin. The objectives of this analysis were to determine whether three life course SEP frameworks ("accumulation of risk", "social mobility" and "sensitive periods") are associated with the aforementioned inflammatory markers. We examined 1413 Framingham Offspring Study participants (mean age 61.2±8.6 years, 54% women), using multivariable regression analyses. In age- and sex-adjusted regression analyses, cumulative SEP ("accumulation of risk" SEP framework), for low vs. high SEP, was inversely associated with CRP, IL-6, ICAM-1, TNFR2, Lp-PLA_2 activity, MCP-1 and fibrinogen. We found that there were few consistent trends between social mobility trajectories and most inflammatory markers. Own educational attainment was inversely associated with 7 of 8 studied inflammatory markers, while father's education, father's occupation and own occupation were inversely associated with 4, 5 and 4 inflammatory markers, respectively, in age- and sex-adjusted analyses. The strengths of association between SEP and inflammatory markers were typically substantially accounted for by CHD risk markers (smoking, body mass index, systolic blood

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pressure, total:HDL cholesterol ratio, fasting glucose, medications, depressive symptomatology) suggesting these may be important mechanisms that explain associations between SEP and the studied inflammatory markers.

Keywords

USA; socioeconomic position; inflammatory markers; life course; social mobility; heart disease

INTRODUCTION

Socioeconomic disparities in coronary heart disease (CHD) exist in many developed countries, where people of lower childhood or adulthood socioeconomic position (SEP) typically have higher risk for incident CHD (Galobardes et al., 2006b; Gonzalez et al., 1998). There is interest in investigating whether biological risk markers for CHD are related to life course SEP, as a way to evaluate if there is mechanistic evidence consistent with the inverse associations found between SEP and CHD in observational studies. Extensive progress has been made in recent decades on the involvement of inflammatory processes in atherosclerosis and subsequent risk for CHD, however little is known about associations between life course SEP and many inflammatory markers. Below we introduce major frameworks by which life course SEP is conceptualized, as well as evidence on roles of several inflammatory markers in specific atherosclerotic processes, leading to gaps in knowledge between life course SEP and inflammatory markers.

Galobardes et al. defined several phases for life course SEP including childhood SEP (e.g. parent's education or parent's occupation), young adulthood SEP (e.g. educational attainment), active professional life SEP (e.g. occupation or income), and retirement SEP (e.g. wealth or household conditions) (Galobardes et al., 2006a). A number of frameworks to conceptualize life course SEP have been hypothesized (Figure 1), including the "accumulation of risk" framework (which focuses on the total cumulative amount of exposure to SEP across the life course), the "social mobility" framework, which recognizes that people have evolving (e.g. increasing, decreasing or stable) SEP across their life span, and the "sensitive periods" framework which suggests that there are certain time periods in the life course when an exposure may have a stronger effect on disease risk than it would during other phases in life (D Kuh & Ben-Shlomo, 2004; D. Kuh et al., 2003).

Novel risk markers for CHD include inflammatory markers. Substantial evidence suggests there is an important inflammatory component in the pathogenesis of atherosclerosis and the pathophysiology is becoming better understood (Libby, 2006). Several inflammatory markers are inversely associated with CHD, including interleukin-6 (IL-6) (Cesari et al., 2003), monocytechemoattractant protein-1 (MCP-1) (de Lemos et al., 2003), tumor necrosis factor-α (TNF-α) (often measured as soluble tumor necrosis factor receptor II (TNFR2)) (Pai et al., 2004), C-reactive protein (CRP)(Danesh et al., 2004; Ridker et al., 2005), fibrinogen (Keavney et al., 2006), ICAM-1 (Malik et al., 2001), P-selectin (Armstrong et al., 2006) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) (Garza et al., 2007). Whether these inflammatory markers are causally related to CHD, rather than simply predictive of CHD, is still under investigation (Elliott et al., 2009; Keavney et al., 2006).

With regard to associations between life course SEP and inflammatory markers, most studies demonstrate inverse associations of life course SEP with CRP, IL-6, fibrinogen and white blood cell count (Brunner et al., 1996; Gimeno et al., 2007; Gimeno et al., 2008; Koster et al., 2006; Lawlor et al., 2005b; Loucks et al., 2006; Nazmi & Victora, 2007; Pollitt et al., 2007, 2008; Tabassum et al., 2008), however little is known about associations between life course

SEP and other inflammatory markers including TNFR2, MCP-1, ICAM-1, P-selectin and Lp-PLA_2.

The objectives of this study were to determine whether three life course SEP frameworks (i.e. "accumulation of risk", "social mobility", and "sensitive periods" SEP frameworks) are associated with several markers representing diverse inflammatory pathwaysand processes, including CRP, IL-6, ICAM-1, P-selectin, TNFR2, Lp-PLA_2 activity, MCP-1 and fibrinogen. Further objectives were to evaluate whether CHD risk markers (including smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, cholesterol-lowering medication use, anti-hypertensive medication use and depressive symptomatology) may be explanatory mechanisms for any observed associations between life course SEP and inflammatory markers. It should be emphasized, as discussed by Hallqvist et al., that it is likely not possible to critically test individual contributions of accumulation of risk *vs*. social mobility *vs*. sensitive periods due to mutual confounding between the three SEP frameworks (Hallqvist et al., 2004). Consequently, we do not propose to statistically compare the contributions of each of these SEP frameworks to each other. As triangulation of methodological approaches enables a more thorough understanding of health determinants, we utilized the three life course SEP framework to offer three approaches to evaluatethe potential association of life course SEP with inflammatory markers. Utilizing information from all three SEP frameworks will provide a more complete picture of life course SEP determinants of inflammatory markers than if findings were presented on only one of the life course SEP frameworks.

MATERIALS AND METHODS

Study sample

The Framingham Heart Study is a community-based observational cohort that was initiated in 1948. The Framingham Offspring Study began in 1971 with recruitment of 5124 men and women who were offspring (or offspring's spouses) of the Original Framingham Heart Study participants. The design and selection criteria of the Framingham Offspring Study have been described elsewhere (Kannel et al., 1979). All study participants received routine medical history and physical examinations, laboratory assessments of cardiovascular risk factors, and anthropometric measurements approximately every 3 to 4 years. Framingham participants signed informed consent and the Framingham Study is reviewed annually by the Boston University Medical Center Institutional Review Board.

Father's education was measured directly from fathers in the Original Cohort of the Framingham Heart Study. All other variables were measured in the Offspring Cohort. Own occupation was measured in Offspring Examination 2 (1979-1982) and Examination 7 (1998-2001). Own education was measured in Examination 2 and Examination 3 (1984-1987). Inflammatory markers and covariates were measured during Examination 7. There were 3475 Framingham Offspring Study participants in the National Heart, Lung and Blood Institute (NHLBI) data repository dataset who completed Examination 7. Of these, 1451 participants did not have fathers in the Original Framingham Study (362 participants had only a mother in the Original Cohort, and 1089 participants were spouses of participants in the Offspring Cohort and had no father in the Original Cohort) from which measures of father's education were directly obtained. In order to be eligible for the Framingham Offspring study, participants needed to be offspring of a male or female Original Framingham Study participant, or a spouse of the offspring. An additional 78 participants had fathers who were missing the education variable. A further 180 participants were missing own education or occupation variables. We further restricted the participants to those ≥28 years when education and occupation were measured, resulting in 97 participants being excluded. Restricting participants to ≥28 years was done in order to allow at least 10 years from expected graduation of high school to obtain further education and become established in an occupational category. An additional 94

subjects with prevalent CVD were excluded, resulting in 1575 participants. Of these, the number of participants missing inflammatory marker variables were as follows: CRP: 62; P-selectin: 63; ICAM-1: 66; MCP-1: 99; interleukin-6: 65; TNFR2: 103; and Lp-PLA_2 activity: 64. As CRP is the most widely recognized inflammatory marker to date with regard to being a potential risk marker for CHD, analyses report sample sizes for CRP analyses (n=1513).

Analyses on excluded versus included participants found that excluded and included participants were similar with regard to smoking, body mass index, fasting glucose, IL-6, TNFR, Lp-PLA_2 activity, P-selectin, fibrinogen, cholesterol-lowering medication use, and depressive symptomatology. Excluded participants were more likely to be older ($p<0.001$), have higher systolic blood pressure ($p=0.001$), CRP ($p=0.008$), ICAM-1 ($p=0.001$), MCP-1 ($p=0.005$), and lower total:HDL cholesterol ratio ($p=0.04$), compared with included participants. Furthermore, excluded participants were more likely than included participants to be taking anti-hypertensive medication ($p=0.006$), have ≤high school education ($p<0.0001$), have a manual occupation ($p=0.001$), and have fathers with ≥high school education ($p=0.009$).

Independent Variables

Childhood SEP (Father's Education and Father's Occupation)—Childhood SEP was measured in primary analyses by father's educational attainment, obtained directly from Offspring cohort participants' fathers who were enrolled in the Original Framingham Heart Study. Father's educational level was measured at enrollment between 1948 and 1950 when their mean age was 44 years (range: 28–62), categorized into 3 groups: <high school (n=799), high school (n=418) and >high school (n=452). Sensitivity analyses used father's occupation measured during Original Framingham Heart Study Examination 6 where all participants were greater than age 28 years. Father's occupation was categorized identically to Offspring occupation described below.

Young Adulthood SEP (Own Educational Attainment)—Own education was measured directly from Framingham Offspring Study participants at Examination 3 (1984-1987); if Examination 3 education was missing, then Examination 2 assessment (1979-1982) was used (n=197). Education was categorized into 3 groups: ≤12 (n=612), 13-16 (n=719) and ≥17 (n=338) years education. Pearson's correlation coefficient for associations between educational attainment at Examination 2 and Examination 3 was 0.89.

Active Professional Life SEP (Own Occupation)—Own occupation was measured from Offspring participants at Examination 7 (age range: 41-81 years). If participants were coded as missing, retired, unemployed, or housewife in Examination 7, then occupation from Examination 2 (1979-1982) was used (n=685; age range: 28-67 years; mean age: 47.7 years).Those who were missing occupation at Examinations 2 and 7 were excluded from analyses. No participants were coded as retired or unemployed at both exams 2 and 7. Thus, 984 had occupation data from Examination 7, and the remaining 685 participants utilized occupation data from Examination 2.Included participants were age ≥28 years at the time of occupation assessment in order to allow at least 10 years between typical age of high school graduation to complete education and obtain an occupation. Occupation was categorized as laborer (n=306), clerical/sales (n=203), housewife (n=375), technical/supervisor (n=195), and executive/professional (n=590).These occupation categorizations were broadened to only two or three categories for analyses, as detailed in the SEP Frameworks section below.Some misclassification of occupation is expected due to the wide age range for when it was measured, as described in more detail in the Discussion section.

SEP Frameworks—Analyses that used an **accumulation of risk** framework used a cumulative SEP score (range: 0-6) including father's education (<high school=0, high

school=1, >high school=2), own education (≤12 years=0, 13-16 years=1, ≥17 years=2) and own occupation (laborer=0, clerical/sales/housewife=1, executive/professional/supervisory/ technical=2). Higher cutpoints were used for own educational categories, compared with father's (i.e.owneducation categorized as: ≤12, 13-16 and ≥17 years education; father's education categorized as: <high school, high school and >high school) to account for secular trends of increased normative levels of education across generations. Analyses that used a **social mobility** framework utilized dichotomous categories of father's education (lower: <high school, higher: ≥high school) and own occupation (lower: laborer, higher: housewife/ clerical/ sales/ supervisory/ technical/ professional/ executive). Analyses tested the association of four possible types of social mobility across the life course: stable high SEP (high childhood and adulthood SEP), decreasing SEP (high childhood SEP and low adulthood SEP), increasing SEP (low childhood SEP and high adulthood SEP), and stable low SEP (low childhood and adulthood SEP). Using the occupation categorizations described above, we expect there will be SEP misclassification, however given the large variety of occupations in society, and the contributing factors to occupation-based SEP (such as income and social prestige), this appeared to be an acceptable approximation of occupation-based SEP that took into account factors such as income, social prestige and educational requirements. Analyses assessing the **sensitive periods** framework assessed associations between each individual SEP measure (i.e. father's education, own education, own occupation) and inflammatory marker concentrations, further adjusting for all SEP measures other than the independent SEP variable.

Dependent Variables

Inflammatory markers were measured during Examination 7 (1998-2001). Fasting morning serum samples were collected then stored at −80°C. Serum CRP was measured once using a high-sensitivity assay (Dade Behring BN100 nephelometer, Deerfield, IL; inter-assay CV 3.2%). IL-6, ICAM-1, TNFR2, MCP-1, and P-selectin concentrations were measured in duplicate and averaged using commercially-available Enzyme-Linked Immunoassay kits (R&D Systems, Minneapolis, MN) following previously described quality control procedures (Keaney et al., 2003; Keaney et al., 2004). Lp-PLA_2 activity was measured by DiaDexus, Inc., San Francisco, CA.Biomarker measurement reproducibility was good (intra-assay coefficients of variation for IL-6, 3.1%; ICAM-1, 3.7%; TNFR2, 2.2%; MCP-1, 3.8%; P-selectin, 3.0%, Lp-PLA_2 activity, 4.3%).

Covariates

CHD risk markers were measured at Examination 7 (1998-2001). Current cigarette smoking was determined by self-report if it occurred regularly in the past year. Systolic blood pressure was calculated as the average of the clinic physician's two seated systolic blood pressure measurements. Body mass index was calculated as theweight in kilograms divided by the square of the height in meters(kg/m^2). Fasting glucose was measured with a hexokinase reagentkit (A-gent glucose test, Abbott, South Pasadena, California); intra-assay coefficientsof variation ranged from 2% to 3%. High density lipoprotein and total cholesterol concentrations were measuredby automated enzymatic techniques (McNamara & Schaefer, 1987).Depressive symptomatology was measured using the Center for Epidemiologic Studies Depression (CES-D) scale, and was analyzed as a continuous variable. Medication use was classified by self-report.

Statistical analysis

Sex- and age-standardized descriptive statistics (means and proportions) were generated for CHD risk factors (systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, body mass index, smoking and anti-hypertensive medication use) and prevalent CVD, according to cumulative SEP score.

Due to non-normality in the distributions, the inflammatory markers were natural log-transformed. Age- and sex-adjusted mean inflammatory marker concentrations were obtained using linear regression on natural log-transformed variables, then back-transformed to obtain estimates of the mean concentrations.

Multivariable regression analyses evaluated associations of life course SEP with log-transformed inflammatory marker concentrations. Analyses adjusted for potential confounders including age and sex, as well as CHD risk markers including smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, cholesterol-lowering medication use, anti-hypertensive medication use and depressive symptomatology. The three SEP variables (father's education, own education and own occupation) were not correlated highly enough to be of concern to simultaneously adjust for all three in a single multivariable model (correlation coefficients ranged from 0.27 to 0.51).Consequently, all three measures of SEP were simultaneously adjusted for in analyses testing the sensitive periods framework. Generalized Estimating Equations (GEE) were used to account for clustering of outcomes by family. There were 1051 clusters, with the minimum cluster size of 1 (indicating these participants are not part of a cluster)and maximum cluster size of 6.There was no evidence of effect modification by sex, consequently sexes were pooled. Analyses were conducted using the statistical program SAS version 9.1(SAS Institute, Cary, NC).

RESULTS

Fifty-four percent of participants were women, and the mean age was 61.2 (8.6 SD) years. Higher cumulative SEP levels were associated with more favorable cardiovascular risk factors including smoking, body mass index, systolic blood pressure, fasting glucose, cholesterol-lowering medications, antihypertensive medications, and depressive symptomatology in age- and sex-adjusted analyses (Table 1). There were no associations between cumulative SEP score and total:HDL cholesterol ratio. Those with a low cumulative SEP score (0 or 1) were more likely to be older and more likely to be female (women tended to have lower educational attainment than men, and fewer females were in very high level occupations; data not shown) than participants with a high SEP score (4-6) (Table 1). Age- and sex-adjusted analyses describing the logarithmically back-transformed mean inflammatory marker concentrations showed inverse associations of cumulative SEP with CRP, IL-6, ICAM-1, TNFR2, Lp-PLA_2 activity, MCP-1 and fibrinogen (Table 1). There was an inverse U association between cumulative SEP and P-selectin. Effect sizes varied depending on inflammatory marker, shown in detail in Table 1. For example, participants with high cumulative SEP scores (SEP score=4-6) had lower mean CRP concentrations (1.99, 95% CI: 1.81, 2.19 mg/L) than participants with low cumulative SEP scores (SEP score = 0 or 1; mean CRP concentration = 2.47, 95% CI: 2.22, 2.75 mg/L).

In regression analyses testing the **accumulation of risk SEP framework**, cumulative SEP was inversely associated with CRP, IL-6, ICAM-1, TNFR2, Lp-PLA_2activity, MCP-1 and fibrinogen after adjusting for age and sex (Table 2). There was an inverse U association between cumulative SEP and P-selectin. Further adjustment for CHD risk markers substantially reduced effect sizes.

In analyses testing the **social mobility SEP framework**, participants with declining SEP across their life course (as measured by father's education and own occupation) had elevated concentrations of IL-6, ICAM-1, and TNFR2, compared with participants who had high SEP in childhood and adulthood after adjusting for age and sex (Table 3). Furthermore, participants who had low SEP in both childhood and adulthood were more likely to have elevated CRP and TNFR2 compared with those who had high SEP in childhood and adulthood in age- and sex-adjusted analyses. Participants who experienced low childhood SEP and high adulthood SEP

were more likely to have elevated ICAM-1, TNFR2, and Lp-PLA_2 activity compared with participants who had high SEP in childhood and adulthood, after adjusting for age and sex (Table 3). Further adjustment for CHD risk markers typically accounted for a substantial amount of the strength of the associations of SEP with inflammatory markers.

For multivariable regression analyses evaluating the **sensitive periods SEP framework**, there were inverse associations of own education with 7 of the 8 investigated inflammatory markers (CRP, IL-6, ICAM-1, TNFR2, P-selectin, MCP-1 and fibrinogen) after adjusting for age and sex (Table 4). Father's education andown occupation were inversely associated with 4 of the 8 explored inflammatory markers (father's education inversely associated with CRP, ICAM-1, TNFR2 and Lp-PLA_2 activity; ownoccupation inversely associated with CRP, IL-6, ICAM-1 and TNFR2). Adjustment for all SEP measures demonstrated that educational attainment had evidence of inverse associations with several inflammatory markers (CRP, ICAM-1, P-selectin, MCP-1 and fibrinogen) independently of other SEP measures (Table 4). There was little evidence of associations of father's education or own occupation with most inflammatory markers independent of other SEP measures. Further adjustment for CHD risk markers typically accounted for a substantial amount of the strength of association between SEP measures and inflammatory markers (Table 4).

Sensitivity analyses evaluated associations of the life course SEP frameworks with inflammatory markers, where father's occupation was used as a measure of childhood SEP instead of father's education. Findings were generally similar, with point estimates typically somewhat stronger when using father's occupation (Tables S1-S3). Father's occupation was inversely associated with CRP, IL-6, ICAM-1, TNFR2 and MCP-1 in analyses adjusted for age and sex. Associations remained for father's occupation with CRP, IL-6 and TNFR2 after further adjustment for own education and occupation (Table S3). Additional adjustment for CHD risk markers typically accounted for a substantial amount of the association strength between father's occupation and inflammatory markers (Table S3).

DISCUSSION

This study provided evidence that cumulative life course SEP is inversely associated with many inflammatory markers including CRP, IL-6, ICAM-1, TNFR2, LP-PLA_2 activity, MCP-1 and fibrinogen in age- and sex-adjusted analyses. Own education was associated with almost all studied inflammatory markers (CRP, IL-6, ICAM-1, TNFR2, P-selectin, MCP-1 and fibrinogen), while father's education, father's occupation and own occupation were associated with several but not all inflammatory markers in age- and sex-adjusted analyses (father's education: CRP, ICAM-1, TNFR2, Lp-PLA_2 activity; father's occupation: CRP, IL-6, ICAM-1, TNFR2 and MCP-1; offspring occupation: CRP, IL-6, ICAM-1 and TNFR2). There were minimal consistent trends between social mobility trajectories and the most inflammatory markers, with evidence that low SEP at any time in the life course conferred risk for elevated inflammatory markers. The associations between the SEP measures and inflammatory markers were typically substantially accounted for by adjusting for CHD risk markers, suggesting these may be important mechanisms that explain some of the association between SEP and the studied inflammatory markers.

Prior Literature

The association of adulthood SEP with inflammatory markers has been well studied for CRP and fibrinogen, and less so for other inflammatory markers addressed in this report. A systematic review showed that 20 of 21 studies demonstrated inverse associations between adulthood SEP and CRP in minimally adjusted analyses. Further adjustment for demographic, anthropometric and other covariates typically reduced strengths of association, and only 9 of 16 multivariate-adjusted studies showed significant inverse associations (Nazmi & Victora,

2007). Inverse associations of adulthood SEP with IL-6 and fibrinogen have been found in most studies using large sample sizes (n>1000), with effect sizes typically substantially reduced after adjusting for variables that may be partly on the causal pathway, such as smoking and obesity (Brunner et al., 1996; Gimeno et al., 2007; Koster et al., 2006; Loucks et al., 2006; Ramsay et al., 2008). These findings are in general agreement with those reported in the present study. Little is known about the association between adulthood SEP and other inflammatory markers addressed in this article including TNFR2, MCP-1, ICAM-1, P-selectin and Lp-PLA_2. For associations of SEP with tumor necrosis factor, in two large studies (n>1000), adulthood SEP was shown to be inversely associated with TNF-α concentrations in multivariable-adjusted analyses (Koster et al., 2006; Panagiotakos et al., 2005). We showed previously in the Framingham Offspring study that educational attainment was inversely associated with ICAM-1 and MCP-1 in multivariable-adjusted analyses (Loucks et al., 2006). Analyses reported in our current paper were in general support of other studies, which showed inverse associations of education and occupation with CRP, IL-6, ICAM-1, and TNFR2 concentrations after adjusting for age and sex, and general reductions in effect size after further adjusting for CHD risk markers.

With regard to associations between childhood SEP and inflammatory marker concentrations, less is known on this topic compared with adulthood SEP and inflammatory markers. However, a reasonable number of studies showed inverse associations of childhood SEP (typically measured as father's occupation or father's education) with CRP concentrations (e.g. (Lawlor et al., 2005b; Tabassum et al., 2008)) and at least 2 studies demonstrated no association (Gimeno et al., 2008; Pollitt et al., 2007). Our findings supported others' demonstrated inverse associations between childhood SEP and CRP as well as fibrinogen in age- and sex-adjusted analyses (Brunner et al., 1996; Pollitt et al., 2007; Tabassum et al., 2008). Our findings demonstrated father's education and father's occupation were inversely associated with a trend in fibrinogen concentrations, but the 95% confidence intervals for the effect point estimates just encompassed the referent point estimate, suggesting a null or weak association. With regard to other inflammatory markers addressed in this report (i.e. IL-6, ICAM-1, TNFR2, Lp-PLA_2, P-selectin and MCP-1), very little is known about their associations with childhood SEP. Mendall and colleagues showed that father's occupational prestige was inversely associated with mean IL-6 concentrations in 198 British men aged 50 to 69 years after adjustment for several CHD risk factors; no association was found with TNF-α (Mendall et al., 1997). To our knowledge, very little is known about association of childhood SEP with ICAM-1, TNFR2, P-selectin, MCP-1 and Lp-PLA_2 activity. We found inverse associations of father's education with ICAM-1, TNFR2 and Lp-PLA_2 activity; strengths of association were reduced after adjusting for adulthood SEP and CHD risk markers, suggesting these may be mechanisms accounting for the association.

Cumulative SEP studies to date typically showed inverse associations between cumulative life course SEP with CRP and fibrinogen concentrations (Gimeno et al., 2008; Lawlor et al., 2005b; Pollitt et al., 2008; Tabassum et al., 2008). Our findings are consistent with other observed inverse associations of cumulative SEP with CRP and fibrinogen concentrations. Little prior information is availableon associations between cumulative life course SEP and concentrations of other inflammatory markers addressed in this report (i.e. IL-6, ICAM-1, TNFR2, Lp-PLA_2, P-selectin and MCP-1).

Furthermore, to our knowledge, there is very minimal information on associations between social mobility and most inflammatory marker concentrations reported here. In conjunction with findings from "accumulation of risk" and "sensitive periods" SEP frameworks discussed above, this paper's analyses found general evidence that low SEP at any time in the life course was associated with elevated inflammatory markers. For example, in social mobility analyses there were associations between declining life course SEP and elevated IL-6, ICAM-1 and

TNFR2 in age- and sex-adjusted analyses. Further, participants with low childhood SEP and high adulthood SEP had elevated ICAM-1, TNFR2 and Lp-PLA_2 activity; participants with low childhood SEP and low adulthood SEP had elevated CRP and TNFR2. Findings were not as consistent for social mobility analyses as for the other two SEP frameworks, likely in part because only father's education and offspring occupation were used in these analyses, rather than all three sensitive periods (including own education which was strongly associated with most inflammatory markers).

Mechanisms

For the observed associations between SEP and inflammatory markers in this study after adjusting for age and sex, further adjustment for CHD risk markers typically accounted for a substantial amount of the association. These factors may be substantial mediating pathways through which life course SEP influences inflammatory markers. There is evidence that SEP in childhood and adulthood may influence health behaviors and CHD risk markers, which could serve as intermediate mechanisms contributing to the emergence of altered concentrations of inflammatory markers. For example, childhood SEP is inversely associated with obesity in adult females (Senese et al., 2009) and smoking in adult males and females (Lawlor et al., 2005a). With regard to adulthood SEP, those with low SEP tend to have higher smoking rates (Gilman et al., 2008), blood pressure (Colhoun et al., 1998), diabetes (Maty et al., 2005), and in the case of women, obesity (McLaren, 2007). Cigarette smoking and obesity have been shown to be associated with inflammatory markers reported in this cohort and may be mechanisms by which childhood SEP influences inflammatory marker concentrations. An additional potential mechanism is through psychological distress, such as depression or anxiety. Childhood SEP is associated with depression in youth and adulthood (Gilman et al., 2003). Adulthood SEP is also related to depression (Muntaner et al., 2004). Reports have demonstrated that depression is associated with elevated inflammatory markers including C-reactive protein, IL-6, and ICAM-1 (Empana et al., 2005). The causal direction between depression and inflammation is still being elucidated (Almeida et al., 2009; Dantzer et al., 2008). Furthermore, low SEP is associated with chronic inflammatory conditions such as periodontal disease that can influence circulating levels of inflammatory markers including CRP (Borrell & Crawford, 2008; Linden et al., 2008).

Strengths and Weaknesses

Strengths of the present investigation include the well-characterized community-based cohort in which a wide range of CHD risk markers were routinely measured using high quality methods, enabling us to adjust for a large number of covariates. Furthermore, childhood SEP was obtained directly from parents, which can limit recall bias compared to studies that asked participants to estimate parents' SEP.

With regard to weaknesses, because the historical design of the Framingham Offspring Study reflected the population of Framingham, Massachusetts at study onset in 1948, the Original and Offspring cohorts are largely composed of participants of European descent. Consequently, the generalizability of our findings to other races/ethnicities is uncertain. Additionally, excluded participants were more likely to be of low SEP, and have elevated CHD risk markers, certain inflammatory markers and CHD, compared with included participants. We expect this could have induced bias in the reported findings likely towards the null as the excluded participants tended to have extreme values for both the exposures and outcomes.Furthermore, our primary analyses on life course SEP included only 3 measures: father's education, own education and own occupation. Other studies that have additional measures of life course SEP (such as *in utero*SEP, or multiple measures of occupation throughout the life course) will provide richer data as to the potential contribution of sensitive periods, accumulation of risk and social mobility SEP frameworks to inflammatory marker concentrations as well as further

limit misclassification of SEP categories. Furthermore, education and occupation exposures were categorized as three-level variables, consequently socioeconomic misclassification is expected.In addition, for the measure of own occupation, the minimum age used for occupation assessment was 28 years in order to allow at least 10 years fromthe typical age of high school graduation to complete education, and obtain an occupation. Most participants were middle-aged or older when occupation was assessed. There was an approximately 40-year age range in participants at each measurement time, and approximately 20 years between Examinations 2 and 7 when occupation was assessed. Ideally all participants would be of similar ages when occupation was assessed, however these data were not available in this study. Given that occupation was categorized using only two or three broad categories, and that the mean age of assessment for the exam when participants were youngest (Examination 2) was 47.7 years, we felt this was a reasonable approximation of occupation. Misclassification of occupation is expected in this study, and other studies with occupation measured at narrower aged ranges will provide more precise information on the role of occupation in relation to inflammatory markers.Finally, the primary analyses represented potential risk for multiple statistical testing where there were 64 individual point estimates presented for age- and sex-adjusted regression analyses (**Tables** 2-4). Given an alpha of 0.05 used for the 95 percent confidence intervals, we would expect the reference categories' point estimates to be outside of comparison groups point estimates' 95 percent confidence intervals for 3 of the 64 tests simply due to chance. Given that the analyses demonstrated 35 of the 64 tests to have a reference category point estimates outside of the comparison groups point estimates' 95% confidence intervals, we feel that the overarching findings in this report are consistent with a relation between SEP and inflammation.

CONCLUSION

This study provides evidence that cumulative SEP across the life course is inversely associated with several inflammatory markers including CRP, IL-6, ICAM-1, TNFR2, LP-PLA_2 activity, MCP-1 and fibrinogen in age- and sex-adjusted analyses. Own education was associated with almost all studied inflammatory markers (CRP, IL-6, ICAM-1, TNFR2, P-selectin, MCP-1 and fibrinogen), while father's education, father's occupation and ownoccupation were associated with several but not all inflammatory markers in age- and sex-adjusted analyses (father's education: CRP, ICAM-1, TNFR2, Lp-PLA_2 activity; father's occupation: CRP, IL-6, ICAM-1, TNFR2 and MCP-1; offspring occupation: CRP, IL-6, ICAM-1 and TNFR2). There were few consistent trends between social mobility trajectories and most inflammatory markers, with general evidence that low SEP at any time in the life course conferred risk for elevated inflammatory markers. The strengths of association between the SEP measures and inflammatory markers were typically substantially accounted for by CHD risk markers, suggesting these may be important mechanisms that explain a reasonable amount of the association between SEP and the studied inflammatory markers. These data provide potential biological mechanistic evidence of inverse associations between life course SEP and CHD found in observational studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

Almeida OP, Norman PE, Allcock R, van Bockxmeer F, Hankey GJ, Jamrozik K, et al. Polymorphisms of the CRP gene inhibit inflammatory response and increase susceptibility to depression: the Health in Men Study. Int J Epidemiol 2009;38(4):1049–1059. [PubMed: 19433520]

Armstrong EJ, Morrow DA, Sabatine MS. Inflammatory biomarkers in acute coronary syndromes: part IV: matrix metalloproteinases and biomarkers of platelet activation. Circulation 2006;113(9):e382–385. [PubMed: 16520416]

Borrell LN, Crawford ND. Social disparities in periodontitis among United States adults 1999-2004. Community Dent Oral Epidemiol 2008;36(5):383–391. [PubMed: 18924254]

Brunner E, Davey Smith G, Marmot M, Canner R, Beksinska M, O'Brien J. Childhood social circumstances and psychosocial and behavioural factors as determinants of plasma fibrinogen. Lancet 1996;347(9007):1008–1013. [PubMed: 8606563]

Cesari M, Penninx BW, Newman AB, Kritchevsky SB, Nicklas BJ, Sutton-Tyrrell K, et al. Inflammatory markers and onset of cardiovascular events: results from the Health ABC study. Circulation 2003;108(19):2317–2322. [PubMed: 14568895]

Colhoun HM, Hemingway H, Poulter NR. Socio-economic status and blood pressure: an overview analysis. J Hum Hypertens 1998;12(2):91–110. [PubMed: 9504351]

Danesh J, Wheeler J, Hirschfield G, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med 2004;350(14):1387–1397. [PubMed: 15070788]

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9(1):46–56. [PubMed: 18073775]

de Lemos JA, Morrow DA, Sabatine MS, Murphy SA, Gibson CM, Antman EM, et al. Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. Circulation 2003;107(5):690–695. [PubMed: 12578870]

Elliott P, Chambers JC, Zhang W, Clarke R, Hopewell JC, Peden JF, et al. Genetic Loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA 2009;302(1):37–48. [PubMed: 19567438]

Empana JP, Sykes DH, Luc G, Juhan-Vague I, Arveiler D, Ferrieres J, et al. Contributions of depressive mood and circulating inflammatory markers to coronary heart disease in healthy European men: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). Circulation 2005;111(18):2299–2305. [PubMed: 15867179]

Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). J Epidemiol Community Health 2006a;60(1):7–12. [PubMed: 16361448]

Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol 2006b;16(2):91–104. [PubMed: 16257232]

Garza CA, Montori VM, McConnell JP, Somers VK, Kullo IJ, Lopez-Jimenez F. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. Mayo Clin Proc 2007;82(2):159–165. [PubMed: 17290721]

Gilman SE, Abrams DB, Buka SL. Socioeconomic status over the life course and stages of cigarette use: initiation, regular use, and cessation. J Epidemiol Community Health 2003;57(10):802–808. [PubMed: 14573586]

Gilman SE, Martin LT, Abrams DB, Kawachi I, Kubzansky L, Loucks EB, et al. Educational attainment and cigarette smoking: a causal association? Int J Epidemiol. 2008

Gimeno D, Brunner EJ, Lowe GD, Rumley A, Marmot MG, Ferrie JE. Adult socioeconomic position, C-reactive protein and interleukin-6 in the Whitehall II prospective study. Eur J Epidemiol 2007;22(10):675–683. [PubMed: 17668278]

Gimeno D, Ferrie JE, Elovainio M, Pulkki-Raback L, Keltikangas-Jarvinen L, Eklund C, et al. When do social inequalities in C-reactive protein start? A life course perspective from conception to adulthood in the Cardiovascular Risk in Young Finns Study. Int J Epidemiol 2008;37(2):290–298. [PubMed: 18056120]

Gonzalez MA, Rodriguez Artalejo F, Calero JR. Relationship between socioeconomic status and ischaemic heart disease in cohort and case-control studies: 1960-1993. Int J Epidemiol 1998;27(3): 350–358. [PubMed: 9698119]

Hallqvist J, Lynch J, Bartley M, Lang T, Blane D. Can we disentangle life course processes of accumulation, critical period and social mobility? An analysis of disadvantaged socio-economic positions and myocardial infarction in the Stockholm Heart Epidemiology Program. Soc Sci Med 2004;58(8):1555–1562. [PubMed: 14759698]

Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol 1979;110(3):281–290. [PubMed: 474565]

Keaney JF Jr. Larson MG, Vasan RS, Wilson PW, Lipinska I, Corey D, et al. Obesity and systemic oxidative stress: clinical correlates of oxidative stress in the Framingham Study. Arterioscler Thromb Vasc Biol 2003;23(3):434–439. [PubMed: 12615693]

Keaney JF Jr. Massaro JM, Larson MG, Vasan RS, Wilson PW, Lipinska I, et al. Heritability and correlates of intercellular adhesion molecule-1 in the Framingham Offspring Study. J Am Coll Cardiol 2004;44(1):168–173. [PubMed: 15234428]

Keavney B, Danesh J, Parish S, Palmer A, Clark S, Youngman L, et al. Fibrinogen and coronary heart disease: test of causality by 'Mendelian randomization'. Int J Epidemiol 2006;35(4):935–943. [PubMed: 16870675]

Koster A, Bosma H, Penninx BW, Newman AB, Harris TB, van Eijk JT, et al. Association of inflammatory markers with socioeconomic status. J Gerontol A Biol Sci Med Sci 2006;61(3):284–290. [PubMed: 16567379]

Kuh, D.; Ben-Shlomo, Y. Introduction: a life course approach to the aetiology of adult chronic disease. In: Kuh, D.; Ben-Shlomo, Y., editors. A life course approach to chronic disease epidemiology. 2nd edition. Oxford University Press; New York: 2004. p. 3-14.

Kuh D, Ben-Shlomo Y, Lynch J, Hallqvist J, Power C. Life course epidemiology. J Epidemiol Community Health 2003;57(10):778–783. [PubMed: 14573579]

Lawlor DA, Batty GD, Morton SM, Clark H, Macintyre S, Leon DA. Childhood socioeconomic position, educational attainment, and adult cardiovascular risk factors: the Aberdeen children of the 1950s cohort study. Am J Public Health 2005a;95(7):1245–1251. [PubMed: 15983276]

Lawlor DA, Smith GD, Rumley A, Lowe GD, Ebrahim S. Associations of fibrinogen and C-reactive protein with prevalent and incident coronary heart disease are attenuated by adjustment for confounding factors. British Women's Heart and Health Study. Thromb Haemost 2005b;93(5):955–963. [PubMed: 15886815]

Libby P. Inflammation and cardiovascular disease mechanisms. Am J Clin Nutr 2006;83(2):456S–460S. [PubMed: 16470012]

Linden GJ, McClean K, Young I, Evans A, Kee F. Persistently raised C-reactive protein levels are associated with advanced periodontal disease. J Clin Periodontol 2008;35(9):741–747. [PubMed: 18647204]

Loucks EB, Sullivan LM, Hayes LJ, D'Agostino RB Sr. Larson MG, Vasan RS, et al. Association of educational level with inflammatory markers in the Framingham Offspring Study. Am J Epidemiol 2006;163(7):622–628. [PubMed: 16421236]

Malik I, Danesh J, Whincup P, Bhatia V, Papacosta O, Walker M, et al. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and meta-analysis. Lancet 2001;358(9286): 971–976. [PubMed: 11583751]

Maty SC, Everson-Rose SA, Haan MN, Raghunathan TE, Kaplan GA. Education, income, occupation, and the 34-year incidence (1965-99) of Type 2 diabetes in the Alameda County Study. Int J Epidemiol 2005;34(6):1274–1281. [PubMed: 16120636]

McLaren L. Socioeconomic status and obesity. Epidemiol Rev 2007;29:29–48. [PubMed: 17478442]

McNamara JR, Schaefer EJ. Automated enzymatic standardized lipid analyses for plasma and lipoprotein fractions. Clin Chim Acta 1987;166(1):1–8. [PubMed: 3608193]

Mendall MA, Patel P, Asante M, Ballam L, Morris J, Strachan DP, et al. Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. Heart 1997;78(3):273–277. [PubMed: 9391290]

Muntaner C, Eaton WW, Miech R, O'Campo P. Socioeconomic position and major mental disorders. Epidemiol Rev 2004;26:53–62. [PubMed: 15234947]

Nazmi A, Victora CG. Socioeconomic and racial/ethnic differentials of C-reactive protein levels: a systematic review of population-based studies. BMC Public Health 2007;7:212. [PubMed: 17705867]

Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351(25):2599–2610. [PubMed: 15602020]

Panagiotakos DB, Pitsavos C, Manios Y, Polychronopoulos E, Chrysohoou CA, Stefanadis C. Socio-economic status in relation to risk factors associated with cardiovascular disease, in healthy individuals from the ATTICA study. Eur J Cardiovasc Prev Rehabil 2005;12(1):68–74. [PubMed: 15703509]

Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G. Early-life and adult socioeconomic status and inflammatory risk markers in adulthood. Eur J Epidemiol 2007;22(1):55–66. [PubMed: 17225957]

Pollitt RA, Kaufman JS, Rose KM, Diez-Roux AV, Zeng D, Heiss G. Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood. J Epidemiol Community Health 2008;62(6):484–491. [PubMed: 18477746]

Ramsay S, Lowe GD, Whincup PH, Rumley A, Morris RW, Wannamethee SG. Relationships of inflammatory and haemostatic markers with social class: results from a population-based study of older men. Atherosclerosis 2008;197(2):654–661. [PubMed: 17395187]

Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352(1):20–28. [PubMed: 15635109]

Senese LC, Almeida ND, Kittler Fath A, Smith BT, Loucks EB. Associations between childhood socioeconomic position and adulthood obesity. Epidemiologic Reviews. 2009

Tabassum F, Kumari M, Rumley A, Lowe G, Power C, Strachan DP. Effects of Socioeconomic Position on Inflammatory and Hemostatic Markers: A Life-Course Analysis in the 1958 British Birth Cohort. Am J Epidemiol. 2008

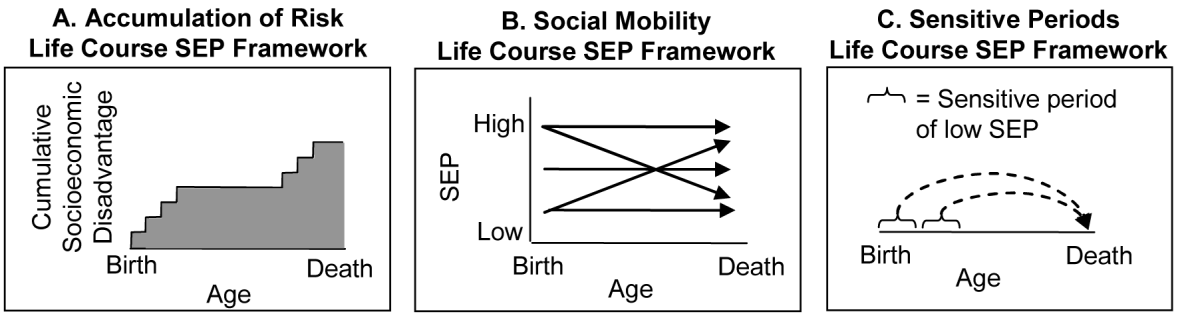

Figure 1.
Conceptual frameworks for three different frameworks to conceptualize socioeconomic position (SEP) across the life course: (**A**) Accumulation of Risk, (**B**) Social Mobility, and (**C**) Sensitive Periods.

Table 1

Age and sex-adjusted characteristics (95% confidence intervals for the mean) according to cumulative socioeconomic position (SEP) score

	Cumulative SEP score		
	0-1 (n=343)	**2-3 (n= 553)**	**4-6 (n=617)**
Clinical Characteristics			
Age, years	63.7(62.8,64.6)	58.8(58.1,59.4)	57.9(57.3,58.6)
Female, %	56.6(51.1,61.9)	59.9(55.6,64.0)	46.0(42.0,50.1)
Current Smoker, %	20.1(16.1,24.9)	14.0(11.4,17.1)	8.4(6.5,10.8)
Body Mass Index, kg/m^2	29.0(28.4,29.5)	28.5(28.1,28.9)	27.7(27.3,28.1)
Systolic Blood Pressure, mmHg	128(126,129)	125(124,126)	125(124,126)
Total:HDL* Cholesterol Ratio	4.1(4.0,4.3)	4.2(4.1,4.3)	4.0(3.9,4.1)
Fasting Glucose, mg/dL	105(102,108)	104(102,106)	102(100,104)
Taking Cholesterol-Lowering Medication, %	23.9(19.7,28.6)	16.4(13.5,19.7)	15.7(131,18.8)
Taking Anti-Hypertensive Medication, %	32.8(28.0,38.0)	31.3(27.6,35.4)	27.1(23.7,30.9)
Depressive Symptoms, CES-D* Score	5.7(5.1,6.4)	5.8(5.3,6.3)	4.6(4.1,5.1)
Prevalent Cardiovascular Disease, %	5.0(3.2,7.6)	3.5(2.3,5.3)	2.3(1.5,3.7)
Inflammatory Markers			
CRP, mg/L*	2.57(2.29,2.88)	2.26(2.06,2.47)	1.90(1.74,2.07)
IL-6, pg/mL*	3.10(2.89,2.33)	2.88(2.72,3.04)	2.69(2.55,2.83)
ICAM-1, ng/mL*	252(246,259)	249(244,253)	236(233,240)
TNFR2, pg/mL*	2074(2013,2136)	2064(2016,2112)	1937(1894,1980)
Lp-PLA_2 activity, nmol/min/mL*	140(137,143)	140(138,143)	136(133,138)
P-Selectin, ng/mL*	34.7(33.4,36.0)	36.5(35.4,37.6)	34.8(33.8,35.8)
MCP-1, pg/mL*	316(305,327)	304(296,313)	299(291,307)
Fibrinogen, g/L*	382(374,389)	371(365,376)	367(362,372)

* Mean inflammatory concentrations were obtained using linear regression on log-transformed variables, and then back-transformed to obtain estimates of the mean concentrations.

Table 2

Multivariable regression analyses demonstrating associations of *cumulative life course* socioeconomic position (SEP) score with inflammatory marker concentrations

			Model Adjustment	
			Age, Sex	Age, Sex, CHD Risk Markers*
Marker	**Cumulative SEP Score**	**N**	**β (95% CI)**	**β (95% CI)**
CRP, ln mg/L	0-1	343	**0.289(0.140,0.439)**	0.117(−0.021,0.254)
	2-3	553	**0.179(0.051,0.307)**	0.064(−0.050,0.177)
	4-6	617	0.00	0.00
IL-6,ln pg/mL	0-1	342	**0.135(0.044,0.227)**	0.042(−0.047,0.131)
	2-3	553	0.072(−0.011,0.156)	0.013(−0.067,0.092)
	4-6	615	0.00	0.00
ICAM-1, lnng/mL	0-1	343	**0.067(0.033,0.100)**	0.030(−0.002,0.062)
	2-3	552	**0.047(0.020,0.075)**	0.025(−0.000,0.051)
	4-6	614	0.00	0.00
TNFR2, ln pg/mL	0-1	338	**0.070(0.033,0.107)**	**0.050(0.013,0.086)**
	2-3	538	**0.062(0.030,0.093)**	**0.046(0.015,0.077)**
	4-6	596	0.00	0.00
Lp-PLA_2, lnnmol/min/mL	0-1	342	**0.037(0.006,0.068)**	0.018(−0.010,0.045)
	2-3	553	**0.032(0.006,0.058)**	0.012(−0.012,0.037)
	4-6	616	0.00	0.00
P-Selectin, lnng/mL	0-1	343	0.004(−0.046,0.055)	−0.031(−0.081,0.019)
	2-3	553	**0.048(0.007,0.090)**	0.029(−0.012,0.070)
	4-6	616	0.00	0.00
MCP-1, ln pg/mL	0-1	338	**0.051(0.006,0.096)**	0.035(−0.011,0.081)
	2-3	542	0.020(−0.020,0.061)	0.010(−0.031,0.051)
	4-6	609	0.00	0.00
Fibrinogen, ln g/L	0-1	344	**0.035(0.010,0.060)**	0.015(−0.009,0.038)
	2-3	553	0.013(−0.008,0.035)	−0.005(−0.025,0.016)
	4-6	614	0.00	0.00

*CHD risk markers include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, cholesterol-lowering medication use, anti-hypertensive medication use and depressive symptomatology.

Table 3

Multivariable regression analyses demonstrating the association of the *social mobility* framework of life course socioeconomic position (SEP) with inflammatory marker concentrations

			Model Adjustment	
			Age, Sex	Age, Sex, CHD risk markers*
Marker	**SEP Level in Childhood/Adulthood**	**N**	**β (95% CI)**	**β (95% CI)**
CRP, ln mg/L	Low/Low	167	**0.241(0.050,0.432)**	0.116(−0.067,0.299)
	High/Low	90	0.246(−0.008,0.499)	0.162(−0.046,0.369)
	Low/High	538	0.146(0.018,0.275)	0.005(−0.109,0.120)
	High/High	718	0.00	0.00
Interleukin-6, ln pg/mL	Low/Low	166	0.067(−0.050,0.183)	−0.002(−0.114,0.111)
	High/Low	90	**0.214(0.052,0.376)**	0.123(−0.021,0.267)
	Low/High	538	0.047(−0.035,0.129)	−0.016(−0.094,0.062)
	High/High	716	0.00	0.00
ICAM-1, lnng/mL	Low/Low	167	0.039(−0.002,0.080)	0.013(−0.027,0.053)
	High/Low	90	**0.097(0.040,0.154)**	**0.057(0.008,0.106)**
	Low/High	537	**0.031(0.001,0.061)**	0.010(−0.018,0.038)
	High/High	715	0.00	0.00
TNFR2, ln pg/mL	Low/Low	161	**0.087(0.039,0.135)**	**0.067(0.020,0.115)**
	High/Low	87	**0.102(0.046,0.159)**	**0.087(0.029,0.145)**
	Low/High	532	**0.035(0.001,0.069)**	0.009(−0.024,0.042)
	High/High	692	0.00	0.00
Lp-PLA_2,activity ln nmol/min/mL	Low/Low	166	0.035(−0.006,0.075)	0.026(−0.011,0.062)
	High/Low	90	0.015(−0.035,0.065)	0.019(−0.029,0.067)
	Low/High	538	**0.030(0.001,0.059)**	0.002(−0.025,0.028)
	High/High	717	0.00	0.00
P-Selectin, lnng/mL	Low/Low	166	−0.010(−0.073,0.053)	−0.042(−0.102,0.019)
	High/Low	90	0.025(−0.041,0.090)	0.007(−0.056,0.070)
	Low/High	539	−0.021(−0.065,0.023)	−0.042(−0.085,0.001)
	High/High	717	0.00	0.00
MCP-1, ln pg/mL	Low/Low	165	0.015(−0.046,0.077)	0.001(−0.062,0.064)
	High/Low	87	0.051(−0.019,0.121)	0.033(−0.039,0.106)
	Low/High	531	0.002(−0.040,0.044)	−0.006(−0.048,0.037)
	High/High	706	0.00	0.00
Fibrinogen, ln g/L	Low/Low	167	0.016(−0.016,0.048)	0.004(−0.026,0.034)
	High/Low	90	0.034(−0.006,0.074)	0.022(−0.014,0.057)
	Low/High	539	0.012(−0.010,0.034)	−0.009(−0.030,0.012)

			Model Adjustment	
			Age, Sex	Age, Sex, CHD risk markers*
Marker	SEP Level in Childhood/Adulthood	N	β (95% CI)	β (95% CI)
	High/High	715	0.00	0.00

*CHD risk markers include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, cholesterol-lowering medication use, anti-hypertensive medication use and depressive symptomatology.

Table 4

Multivariable regression analyses for the association of the *sensitive periods*framework of life course socioeconomic position with concentrations of inflammatory markers

	Model Adjustment			
	Age, sex	**Age, Sex, Other SEP Measures†**	**Age, Sex, CHD Risk Markers‡**	**Age, Sex, Other SEP Measures†, CHD Risk Markers‡**
Inflammatory Marker	**β ***	**β**	**β**	**β**
Father's Education				
CRP,ln mg/L	**0.163(0.023,0302)**	0.098(−0.048,0.244)	0.017(−0.108,0.142)	−0.008(−0.138,0.121)
IL-6,ln pg/mL	0.067(−0.021,0.155)	0.031(−0.060,0.123)	−0.002(−0.086,0.082)	−0.015(−0.102,0.072)
ICAM-1, lnng/mL	**0.038(0.006,0.070)**	0.020(−0.014,0.055)	0.009(−0.021,0.039)	0.002(−0.030,0.033)
TNFR2, ln pg/mL	**0.055(0.018,0.093)**	**0.044(0.004,0.084)**	0.028(−0.009,0.064)	0.019(−0.020,0.058)
Lp-PLA_2, lnnmol/min/mL	**0.036(0.005,0.068)**	0.030(−0.003,0.063)	0.004(−0.025,0.032)	0.000(−0.030,0.030)
P-Selectin, lnng/mL	0.003(−0.044,0.050)	−0.014(−0.063,0.036)	−0.027(−0.074,0.020)	−0.033(−0.082,0.015)
MCP-1, ln pg/mL	0.016(−0.029,0.061)	−0.009(−0.058,0.039)	−0.003(−0.043,0.049)	−0.015(−0.064,0.034)
Fibrinogen, ln g/L	0.017(−0.007,0.041)	0.010(−0.014,0.035)	−0.005(−0.027,0.017)	−0.008(−0.031,0.015)
Own Education				
CRP,ln mg/L	**0.336(0.179, 0.494)**	**0.249(0.072,0.426)**	**0.149(0.010,0.288)**	0.111(−0.063,0.286)
IL-6,ln pg/mL	**0.148(0.051, 0.245)**	0.102(−0.010,0.214)	0.049(−0.045,0.142)	0.028(−0.081,0.137)
ICAM-1, lnng/mL	**0.064(0.030, 0.098)**	**0.040(0.002,0.079)**	0.027(−0.005,0.058)	0.013(−0.023,0.049)
TNFR2, ln pg/mL	**0.048(0.009, 0.088)**	0.012(−0.032,0.056)	0.025(−0.014,0.064)	−0.004(−0.048,0.040)
Lp-PLA_2, lnnmol/min/mL	0.024(−0.008, 0.055)	0.010(−0.027,0.046)	−0.000(−0.030,0.029)	−0.013(−0.048,0.022)
P-Selectin, lnng/mL	**0.073(0.023, 0.123)**	**0.071(0.014,0.128)**	0.034(−0.016,0.084)	0.037(−0.019,0.093)
MCP-1, ln pg/mL	**0.062(0.013, 0.111)**	**0.071(0.018,0.124)**	0.039(−0.012,0.089)	0.052(−0.002,0.106)
Fibrinogen, ln g/L	**0.037(0.012, 0.062)**	**0.031(0.003,0.060)**	0.015(−0.009,0.039)	0.014(−0.013,0.042)
Own Occupation				
CRP,ln mg/L	**0.221(0.066, 0.375)**	0.123(−0.049,0.296)	**0.167(0.028,0.307)**	0.150(−0.004,0.304)
IL-6,ln pg/mL	**0.124(0.026, 0.223)**	0.087(−0.024,0.198)	0.065(−0.027,0.158)	0.065(−0.040,0.170)
ICAM-1, lnng/mL	**0.057(0.022, 0.093)**	0.039(−0.001,0.079)	0.032(−0.001,0.066)	0.029(−0.008,0.066)
TNFR2, ln pg/mL	**0.076(0.037, 0.114)**	**0.064(0.023,0.106)**	**0.070(0.031,0.109)**	**0.069(0.026,0.111)**
Lp-PLA_2, lnnmol/min/mL	0.019(−0.013, 0.050)	0.008(−0.027,0.0432)	0.027(−0.003,0.057)	0.030(−0.004,0.064)
P-Selectin, lnng/mL	0.029(−0.020, 0.077)	0.012(−0.040,0.064)	0.017(−0.030,0.063)	0.017(−0.033,0.067)
MCP-1, ln pg/mL	0.024(−0.025, 0.073)	−0.006(−0.056,0.045)	0.007(−0.045,0.058)	0.015(−0.067,0.038)
Fibrinogen, ln g/L	0.020(−0.006, 0.046)	0.009(−0.020,0.038)	0.013(−0.011,0.038)	0.012(−0.016,0.039)

* For father's education, regression coefficients (β) represent the relative logarithmic change in biomarker units (95% confidence intervals) for participants with father's education of <high school, versus father's education of >high school. Multivariable regressions included category of high school education (results not shown). For own education, regression coefficients (β) represent the relative logarithmic change in biomarker units (95% confidence intervals) for participants with own education of ≤12 years, versus own education of >16 years. For ownoccupation, regression coefficients (β) represent the relative logarithmic change in biomarker units (95% confidence intervals) for laborers versus participants with supervisory/technical/professional/executive jobs.

† Other SEP measures correspond to the two SEP variables other than the independent variable. For example, if father's education is the independent variable, other SEP measures would include own education and occupation.

‡ CHD risk markers include smoking, body mass index, systolic blood pressure, total:HDL cholesterol ratio, fasting glucose, cholesterol-lowering medication use, anti-hypertensive medication use and depressive symptomatology.