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RESEARCH ARTICLE

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Life-course origins of social inequalities in adult immune cell markers of inflammation in a developing southern Chinese population: the Guangzhou Biobank Cohort Study

Douglas A West¹, Gabriel M Leung¹, Chao Q Jiang², Timothy M Elwell-Sutton¹, Wei S Zhang², Tai H Lam^{1*}, Kar K Cheng³ and C Mary Schooling¹

Abstract

Background: Socioeconomic position (SEP) throughout life is associated with cardiovascular disease, though the mechanisms linking these two are unclear. It is also unclear whether there are critical periods in the life course when exposure to better socioeconomic conditions confers advantages or whether SEP exposures accumulate across the whole life course. Inflammation may be a mechanism linking socioeconomic position (SEP) with cardiovascular disease. In a large sample of older residents of Guangzhou, in southern China, we examined the association of life course SEP with inflammation.

Methods: In baseline data on 9,981 adults (≥ 50 years old) from the Guangzhou Biobank Cohort Study (2006-08), we used multivariable linear regression and model fit to assess the associations of life course SEP at four stages (childhood, early adult, late adult and current) with white blood, granulocyte and lymphocyte cell counts.

Results: A model including SEP at all four life stages best explained the association of life course SEP with white blood and granulocyte cell count for men and women, with early adult SEP (education) making the largest contribution. A critical period model best explained the association of life course SEP with lymphocyte count, with sex-specific associations. Early adult SEP was negatively associated with lymphocytes for women.

Conclusions: Low SEP throughout life may negatively impact late adult immune-inflammatory status. However, some aspects of immune-inflammatory status may be sensitive to earlier exposures, with sex-specific associations. The findings were compatible with the hypothesis that in a developing population, upregulation of the gonadotropic axis with economic development may obscure the normally protective effects of social advantage for men.

Background

Socioeconomic position (SEP) throughout life is usually inversely associated with morbidity and mortality from cardiovascular disease, although the underlying biological pathway is not entirely clear [1,2]. Cardiovascular disease has been associated with higher levels of inflammatory molecules, perhaps as a consequence of exposure to pathogenic organisms [3], although it is unclear whether

pathogen burden mediates SEP differences in cardiovascular risk [3,4]. Poor early life conditions are usually associated with higher levels of inflammatory markers [5-11] and poorer adult immune function [12,13]. These associations are less clear, however, amongst men from middle income countries [10]. Furthermore, little is known about the association of SEP across the life course with immune function. The duration or number of exposures across the life course may be most important (the accumulation hypothesis) [14]. Alternatively, the timing of exposure to poor socioeconomic conditions may be crucial as a number of sensitive periods or simply as a single

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critical period (the critical period hypothesis). It is also possible that either inter- or intra-generational social mobility plays a part.

Developmental trade-offs between growth, maintenance, and reproduction may occur when there are competing demands for energy resources between biological systems [13,15,16], potentially at the expense of immune function in resource-poor environments. Alternatively, intergenerationally and environmentally driven up-regulation of the gonadotropic axis with economic development may obscure some of the normally protective effects of social advantage in the first few generations of men to experience better living conditions [17,18], thus generating epidemiologically stage specific associations between SEP and immune-related functions, such as pro-inflammatory states, among men [18,19].

Rapidly developing mega-cities of China may provide a sentinel for the changes in non-communicable diseases expected with economic development and inform effective interventions to reduce the disease burden. In a large sample of older residents from one of the most developed mega-cities in China, Guangzhou in southern China, we assessed the association of SEP at four life stages with proxies of inflammation (total white blood cell, granulocyte, and lymphocyte counts) and compared models representing the accumulation, sensitive periods and critical period hypotheses. Additionally, we hypothesise that 1) higher life course SEP is protective for adult inflammation, 2) the normal protective effect of social advantage is obscured in men experiencing rapid socioeconomic development.

Methods

Sources of data

The Guangzhou Biobank Cohort Study is a collaboration between the Guangzhou No. 12 Hospital (Guangzhou, China) and the universities of Hong Kong (Hong Kong, China) and Birmingham (Birmingham, United Kingdom). The study has been described previously in detail [20]. Participants were drawn from the Guangzhou Health and Happiness Association for the Respectable Elders (GHHARE), a community social and welfare association unofficially aligned with the municipal government, where membership is open to anyone aged 50 years or older for a nominal monthly fee of 4 yuan (US \$0.50). Approximately 7 percent of permanent Guangzhou residents aged 50 years or more are members of the GHHARE. Eleven percent of the members were included in this study, who were capable of consenting, were ambulatory, and were not receiving treatments which if discontinued might have resulted in immediate, life-threatening risk, such as chemotherapy, radiotherapy or dialysis. Those with less serious chronic illnesses or with acute illnesses were not specifically excluded from the

study though they may have been less likely to attend. Participants were recruited in three phases and this study includes participants recruited in phase 3 only (recruited between 2006 and 2008), because only phase 3 has detailed information on childhood socioeconomic position and inflammatory markers.

Participants underwent a detailed half-day medical interview, as well as a physical examination with fasting blood being sampled. Quantitative haematological analysis was performed using a SYSMEX KX-21 haematology analyser. The Guangzhou Medical Ethics Committee of the Chinese Medical Association approved the study and all participants gave written, informed, consent prior to participation.

Socioeconomic position across the life course

We used indicators of SEP at four life stages: childhood, early adult, late adult and current SEP. Childhood SEP was measured by an index of notable parental possessions that were appropriate to China in the mid-20th century, based on sociologic accounts of life in southern China at that time [17]. The items selected were a watch, a sewing machine, and a bicycle. These items were categorized, as previously, as none or at least one [21]. As in other similar studies, we used education and longest-held occupation as proxies for early and late adult SEP [22]. Early adult SEP was assessed from the highest level of education (primary or less versus secondary or more). Occupation was categorised as manual (agricultural work, factory work, or sales and service) or non-manual (administrative/managerial, professional/technical, or military/police). Current SEP was assessed from household income per head. Household income was recorded in six categories (<5,000 Yuan, 5000-9,999 Yuan, 10,000-19,999 Yuan, 20,000-29,999 Yuan, 30,000-49,999 Yuan and ≥50,000 Yuan). Household income per head was estimated using the mid-point of each income category and assuming that those in the highest category had an annual income of 75,000 Yuan. The median household income per head was used as the cut-off point between low and high SEP.

Outcome measures

The primary outcome was total white blood cell count used, as in other studies, as a marker of a pro-inflammatory state [5], and less well functioning immune system. As we do not have a detailed breakdown of different white blood cell types, such as macrophages, we also considered granulocyte and lymphocyte counts as outcomes because these immune cell sub-populations largely relate to innate and adaptive immunity respectively. They have previously been used as markers of inflammation [23,24]. Other measures of inflammation (e.g. C-reactive protein) were not available.

Statistical analysis

Multivariable linear regression was used to assess the adjusted associations of SEP with the outcomes. Following Mishra et al. [25] we determined the most parsimonious representation of life course SEP by comparing models for three different life course hypotheses (the accumulation, sensitive periods and critical period hypotheses) to a 'fully saturated' model which represents all possible life course SEP trajectories. As in previous work [26], the accumulation hypothesis was represented by a model representing the number of life stages with high socioeconomic position, and the sensitive periods hypothesis by a model in which all four measures of SEP were considered as separate items in one model adjusted for all four measures of SEP. The critical period hypothesis was represented by models in which only one SEP exposure (the critical period) was included [25]. We used the Akaike Information Criterion (AIC) to compare models [27]. A smaller AIC indicates a better model.

We examined whether the outcomes had different associations with SEP by sex or age, from the heterogeneity across subgroups and the significance of an interaction term obtained from a model including all interaction terms with age or sex. All models were adjusted for age (in 5 year age groups) and sex. A second set of models was additionally adjusted for lifestyle factors (smoking, alcohol use, and physical activity categorized as in Table 1) as potential mediators and a third set of models additionally adjusted for body mass index (BMI) as a potential mediator

Proxies of SEP were unavailable or unclassifiable for 28.7% of the participants, mainly because information on household income or the longest-held occupation was missing. Alcohol use or smoking was not available for 2% of participants. We used multiple imputation for missing data [28,29]. Socioeconomic position at any stage, alcohol use and smoking were predicted based on a flexible additive regression model with predictive mean matching incorporating age, sex, leg length, seated height, alcohol use, smoking status, physical activity and SEP at the other three stages [28]. We imputed missing values 10 times and analysed each complete dataset separately, then summarized estimates with confidence intervals adjusted for missing data uncertainty [30]. As a sensitivity analysis, a complete case analysis without imputation was performed. We used STATA version 10.0 (STATA Corp., College Station, TX) and R version 2.12.2 for analysis, imputation and model estimation.

Results

Of the 10,088 phase 3 participants examined, 1.1% ($n = 107$) had missing data for total white blood cell, granulocyte or lymphocyte counts. Analysis was based on the remaining 9,981 participants. There were more women

($n = 7,445$) than men ($n = 2,536$) and the women were younger [mean age 59.2 years (S.D. 7.6)] than the men [mean age 63.1 years (S.D. 7.6)]. Overall the mean white blood cell and granulocyte counts were lower in women than men (Table 1).

The associations of SEP with white blood cell, granulocyte or lymphocyte counts did not vary with age (data not shown). However, associations of SEP with lymphocyte count varied with sex, so only sex stratified results have been presented for this outcome. For white blood cell count and granulocyte count, the sensitive periods model performed better than the fully saturated model, accumulation or critical period models (Table 2). The sensitive periods model shows that some life stages had stronger negative associations than others with white blood cell count and granulocyte count; the early adult stage had the strongest association for both outcomes.

The pattern for lymphocyte cell count was somewhat different. Associations varied by sex. Table 3 shows that for both sexes the accumulation and sensitive periods models did not perform as well as critical period models. The early adult life stage was a critical period for women, with a negative association between SEP and lymphocyte cell count. By contrast, for men, all estimates of association between SEP and lymphocyte cell count were positive, although all confidence intervals included zero.

Additional adjustment for lifestyle factors (smoking, alcohol use, and physical exercise) attenuated estimates slightly (see Appendix) but the pattern of associations generally remained the same. Smoking among men is associated with both low SEP and higher lymphocyte count, hence adjustment for smoking strengthened the positive association of SEP with lymphocyte count (Appendix). Further adjustment for BMI (Appendix) produced very similar results; estimates of association were little changed. All results were similar in a complete case analysis (Appendix).

Discussion

Consistent with other studies in developed and developing settings examining the association between SEP and inflammation [5-11], we found that SEP was negatively associated with adult immune cell numbers, particularly among women. Consistent with the only other study from a developing country setting, the advantage of higher SEP for adult inflammation was less marked among men [10]. In general, considering SEP at all four life stages was better than considering individual life stages (critical periods) except for lymphocyte cell counts.

This study has a number of strengths. To our knowledge, it is the first study to investigate the role of life course SEP in later adulthood inflammation in a non-western, developing setting. Moreover, we explicitly determined the most parsimonious representation of life

Table 1 Characteristics (mean value or percentage) of 9,981 Chinese adults (≥ 50 years) by socioeconomic position at four life stages in women and men from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008

	Socio-economic position in:															
	Childhood(Parental possession of a watch, sewing machine, and bicycle)				Early Adulthood (Education*)			Late Adulthood (Occupation)				Current (Household Income per Head)				
	No.	0 items	1+ items	Unknown	p †	Low	High	p †	Manual	Non-manual	Unknown	p †	Low	High	Unknown	p †
Women																
Number of participants	7445	4084	3123	238		3057	4386		5225	1211	1009		3025	3141	1279	
<i>Mean (SD)</i>																
White blood cells (10 ⁹ /L)	7445	6.38(1.5)	6.13(1.5)	6.36(1.4)	<0.001	6.52(1.6)	6.10(1.5)	<0.001	6.33(1.5)	6.04(1.4)	6.25(1.5)	<0.001	6.38(1.6)	6.12(1.5)	6.41(1.6)	<0.001
Granulocytes (10 ⁹ /L)	7445	3.79(1.2)	3.62(1.2)	3.71(1.1)	<0.001	3.89(1.2)	3.60(1.1)	<0.001	3.76(1.2)	3.53(1.1)	3.71(1.2)	<0.001	3.79(1.2)	3.60(1.1)	3.84(1.2)	<0.001
Lymphocytes (10 ⁹ /L)	7445	2.19(0.6)	2.15(0.6)	2.26(0.6)	<0.001	2.22(0.6)	2.14(0.6)	<0.001	2.18(0.6)	2.15(0.6)	2.18(0.6)	0.227	2.20(0.6)	2.16(0.6)	2.16(0.6)	0.008
Leg length (cm)	7430	69.7(3.8)	69.8(3.6)	69.8(4.3)	0.393	69.6(3.8)	69.8(3.7)	0.008	69.7(3.7)	69.9(3.6)	69.6(3.8)	0.202	69.6(3.8)	69.8(3.6)	69.6(3.8)	0.099
Sitting height (cm)	7431	83.7(3.6)	85.1(3.1)	84.1(3.7)	<0.001	83.1(3.6)	85.1(3.1)	<0.001	84.0(3.5)	85.0(3.3)	84.6(3.3)	<0.001	83.9(3.5)	85.0(3.2)	83.5(3.7)	<0.001
<i>Row%</i>																
Age group (years)																
50-54	2644	36.0	60.7	3.3		17.9	82.1		65.0	18.5	16.5		36.0	53.0	11.1	
55-59	1892	52.7	44.5	2.7		39.1	60.9		69.8	17.2	12.9		39.0	44.2	16.8	
60-64	1133	64.9	32.7	2.5		51.5	48.5		73.8	14.7	11.6		46.5	34.6	18.9	
65-69	833	74.5	21.5	4.0		63.5	36.4		76.1	13.8	10.1		46.2	29.7	24.1	
70-74	621	82.8	13.4	3.9		75.7	24.3		75.0	13.7	11.3		44.8	28.3	26.9	
75-79	228	82.0	14.5	3.5		81.1	18.4		75.9	10.5	13.6		49.1	25.0	25.9	
80+	94	80.9	12.8	6.4	<0.001	81.9	18.1	<0.001	81.9	5.3	12.8	<0.001	37.2	34.0	28.7	<0.001
Alcohol use																
Never	3981	57.9	39.1	3.1		45.9	54.1		71.7	15.2	13.1		43.8	37.8	18.4	
<1/week	2811	49.8	47.1	3.2		33.8	66.2		67.4	18.1	14.5		36.7	48.4	14.9	
1-4/week	162	53.1	40.7	6.2		35.2	64.8		72.8	16.7	10.5		35.8	47.5	16.7	
5+ /week	126	63.5	33.3	3.2		43.7	56.3		70.6	13.5	15.9		34.1	46.8	19.0	
Ex-drinker	196	62.8	34.7	2.6	<0.001	50.5	49.5	<0.001	78.1	11.2	10.7	0.001	44.4	35.2	20.4	<0.001
Unknown	169	54.4	40.8	4.7		41.4	57.4		68.6	17.8	13.6		36.1	43.2	20.7	
Smoking status																
Never	7192	54.5	42.4	3.1		40.1	59.9		70.0	16.4	13.5		40.4	42.5	17.1	
Ex-smoker	95	76.8	18.9	4.2		87.4	12.6		77.9	6.3	15.8		46.3	27.4	26.3	
Current	106	63.2	28.3	8.5	<0.001	65.1	34.9	<0.001	79.2	12.3	8.5	0.013	55.7	27.4	17.0	<0.001
Unknown	52	48.1	46.2	5.8		38.5	57.7		61.5	17.3	21.2		34.6	51.9	13.5	
Physical activity																
Inactive	626	55.4	40.7	3.8		42.8	56.9		71.4	15.8	12.8		40.3	38.0	21.7	
Minimally active	1848	54.9	42.0	3.1		41.5	58.5		70.1	17.4	12.6		41.7	41.3	16.9	
HEPA active [§]	4971	54.8	42.1	3.2	0.877	40.7	59.3	0.520	70.1	15.9	14.0	0.450	40.3	43.0	16.7	0.249

Table 1 Characteristics (mean value or percentage) of 9,981 Chinese adults (≥ 50 years) by socioeconomic position at four life stages in women and men from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008 (Continued)

	Socio-economic position in															
	Childhood(Parental possession of a watch, sewing machine, and bicycle)					Early Adulthood (Education*)			Late Adulthood (Occupation)				Current (Household Income per Head)			
	No.	0 items	1+ items	Unknown	p †	Low	High	p †	Manual	Non-manual	Unknown	p †	Low	High	Unknown	p †
Men																
Number of participants	2536	1664	812	60		730	1803		1581	791	164		1131	1035	370	
<i>Mean (SD)</i>																
White blood cells (10 ⁹ /L)	2536	6.85(1.7)	6.86(1.7)	6.74(1.5)	0.878	7.01(1.7)	6.79(1.7)	0.010	6.87(1.7)	6.75(1.7)	7.15(1.9)	0.021	6.93(1.7)	6.73(1.7)	6.95(1.7)	0.012
Granulocytes (10 ⁹ /L)	2536	4.21(1.4)	4.14(1.4)	4.17(1.1)	0.439	4.38(1.4)	4.11(1.3)	<0.001	4.21(1.4)	4.10(1.3)	4.40(1.6)	0.018	4.27(1.4)	4.07(1.3)	4.27(1.4)	0.002
Lymphocytes (10 ⁹ /L)	2536	2.14(0.6)	2.23(0.7)	2.05(0.5)	0.002	2.10(0.6)	2.19(0.7)	0.006	2.16(0.7)	2.17(0.6)	2.23(0.6)	0.389	2.15(0.7)	2.18(0.6)	2.18(0.7)	0.619
Leg length (cm)	2519	75.2(3.8)	75.7(4.2)	75.3(3.7)	0.005	74.6(3.7)	75.6(4.0)	<0.001	75.2(3.9)	75.6(4.0)	75.6(3.9)	0.020	75.1(4.0)	75.7(3.8)	75.1(4.0)	0.003
Sitting height (cm)	2520	88.6(3.6)	89.8(3.4)	88.7(3.7)	<0.001	87.6(3.5)	89.6(3.4)	<0.001	88.8(3.6)	89.3(3.4)	89.7(4.0)	<0.001	88.5(3.5)	89.7(3.4)	88.6(3.8)	<0.001
<i>Row%</i>																
Age group (years)																
50-54	346	41.3	56.6	2.0		11.3	88.7		68.8	21.4	9.8		43.9	42.8	13.3	
55-59	568	57.0	41.0	1.9		23.6	76.4		67.3	25.4	7.4		44.9	43.0	12.1	
60-64	599	65.4	32.2	2.3		25.2	74.6		61.3	32.9	5.8		37.4	47.9	14.7	
65-69	470	76.0	22.3	1.7		30.6	69.1		56.8	38.5	4.7		48.5	37.0	14.5	
70-74	339	82.3	15.3	2.4		44.5	55.5		58.7	36.3	5.0		48.7	32.2	19.2	
75-79	156	78.2	16.0	5.8		51.3	48.1		60.9	32.1	7.1		48.1	35.9	16.0	
80+	58	81.0	13.8	5.2	<0.001	53.4	46.6	<0.001	56.9	37.9	5.2	<0.001	55.2	29.3	15.5	<0.001
Alcohol use																
Never	880	68.3	29.9	1.8		30.1	69.9		61.0	32.0	6.9		48.1	36.8	15.1	
<1/week	1068	63.2	34.7	2.1		24.4	75.6		61.5	32.0	6.5		41.5	44.4	14.1	
1-4/week	176	62.5	34.7	2.8		25.6	74.4		67.6	28.4	4.0		46.0	44.9	9.1	
5+/week	271	65.7	32.5	1.8		39.9	60.1		66.4	28.8	4.8		43.9	39.9	16.2	
Ex-drinker	93	71.0	21.5	7.5	0.046	37.6	62.4	<0.001	67.7	24.7	7.5	0.323	49.5	34.4	16.1	0.011
Unknown	48	70.8	18.8	10.4		33.3	60.4		52.1	33.3	14.6		39.6	37.5	22.9	
Smoking status																
Never	940	63.8	34.3	1.9		20.3	79.7		58.3	35.3	6.4		41.0	45.5	13.5	
Ex-smoker	675	69.0	28.1	2.8		33.5	66.5		62.2	31.3	6.5		46.2	40.4	13.3	
Current	900	65.1	32.9	2.0	0.039	34.3	65.7	<0.001	66.8	27.0	6.2	<0.001	47.6	36.2	16.2	<0.001
Unknown	21	57.1	19.0	23.8		19.0	66.7		57.1	23.8	19.0		28.6	38.1	33.3	
Physical activity																
Inactive	223	65.9	31.4	2.7		31.8	66.8		68.6	26.0	5.4		48.4	30.9	20.6	
Minimally active	866	61.1	36.4	2.5		29.1	70.9		58.8	33.9	7.3		44.3	40.9	14.8	
HEPA active [§]	1447	68.3	29.5	2.2	0.002	28.1	71.9	0.438	63.5	30.3	6.2	0.021	44.2	42.3	13.5	0.046

* Highest level of education was categorised as low (primary or less) and high (above primary)

Manual is agricultural worker, factory worker or sales and service, non-manual is administrator/manager, professional/technical or military/disciplined

† p value for linear trend for continuous variables and χ^2 p value for categorical variables

§ Health enhancing physical activity: vigorous activity at least 3 days a week achieving at least 1500 metabolically equivalent tasks (MET) minutes per week or activity on 7 days of the week achieving at least 3000 MET minutes per week

Table 2 Associations of high socioeconomic position (compared to low) at four life stages with white cell count and its differentials, adjusted for age^a and sex in 9,981 Chinese adults (≥ 50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008

	White Blood Cell Count (10 ⁹ /L)			Granulocyte Cell Count (10 ⁹ /L)		
	Δ	95% CI	AIC	Δ	95% CI	AIC
Men and Women						
Critical period Model ^b						
Childhood	-0.14	(-0.20, -0.07)	8995	-0.10	(-0.15, -0.04)	4095
Early Adult	-0.35	(-0.42, -0.29)	8909	-0.26	(-0.31, -0.21)	4018
Late Adult	-0.21	(-0.29, -0.13)	8980	-0.17	(-0.23, -0.11)	4074
Current	-0.22	(-0.29, -0.15)	8965	-0.16	(-0.22, -0.11)	4064
Accumulation Model ^c						
0	0		8905	0		4012
1	-0.19	(-0.29, -0.09)		-0.14	(-0.22, -0.06)	
2	-0.32	(-0.42, -0.22)		-0.23	(-0.31, -0.16)	
3	-0.48	(-0.58, -0.38)		-0.35	(-0.43, -0.27)	
4	-0.51	(-0.65, -0.38)		-0.40	(-0.50, -0.29)	
Sensitive Periods Model ^d						
Childhood	-0.06	(-0.13, 0.01)	8892	-0.03	(-0.09, 0.02)	4000
Early Adult	-0.28	(-0.36, -0.20)		-0.20	(-0.26, -0.14)	
Late Adult	-0.08	(-0.17, 0.002)		-0.08	(-0.14, -0.01)	
Current	-0.12	(-0.19, -0.05)		-0.09	(-0.15, -0.04)	
Fully Saturated Model ^e						
			8905			4015

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

* Test for interaction with sex significant at p < 0.05 level

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age and sex but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age and sex. ^dMutually adjusted for SEP at other life stages and adjusted for age and sex. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age and sex

Table 3 Associations of high socioeconomic position (compared to low) at four life stages with lymphocyte cell count (10⁹/L) by sex, adjusted for age^a in 9,981 Chinese adults (≥ 50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008

	Women (n = 7,445)			Men (n = 2,536)		
	Δ	95% CI	AIC	Δ	95% CI	AIC
Critical period Model ^b						
Childhood	-0.04	(-0.07, -0.01)	-7874	0.03	(-0.03, 0.08)	-2277
Early Adult	-0.08	(-0.11, -0.05)	-7894	0.03	(-0.02, 0.09)	-2277
Late Adult	-0.03	(-0.07, 0.01)	-7871	0.04	(-0.01, 0.10)	-2279
Current	-0.04	(-0.07, -0.01)	-7874	0.01	(-0.05, 0.07)	-2277
Accumulation Model ^c						
0	0		-7885	0		-2274
1	-0.02	(-0.07, 0.02)		0.02	(-0.07, 0.11)	
2	-0.05	(-0.10, -0.01)		0.05	(-0.03, 0.13)	
3	-0.10	(-0.14, -0.05)		0.04	(-0.05, 0.12)	
4	-0.09	(-0.15, -0.03)		0.10	(-0.01, 0.21)	
Sensitive Periods Model ^d						
Childhood	-0.02	(-0.05, 0.01)	-7891	0.02	(-0.03, 0.08)	-2274
Early Adult	-0.07	(-0.10, -0.04)		0.02	(-0.04, 0.08)	
Late Adult	0.00	(-0.04, 0.04)		0.04	(-0.02, 0.10)	
Current	-0.01	(-0.05, 0.02)		0.00	(-0.06, 0.06)	
Fully Saturated Model ^e						
			-7882			-2262

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age. ^dMutually adjusted for SEP at other life stages and adjusted for age. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age

course SEP. The large sample size allowed sex-specific analysis. Nevertheless, there are limitations. First, it is a cross-sectional study with recalled SEP, which may be imprecise, although most likely non-differential. Second, in a cross-sectional design reverse causality must be considered although it is unlikely that inflammation has a causal effect on life course SEP. Third, there may have been gender bias in the allocation of resources within families, most likely favouring boys and men, which may have mitigated the disadvantages of low SEP. However it is unclear why this should have mitigated the effect of SEP for lymphocytes but not for white blood cells and granulocytes. Fourth, our cohort may not be fully population representative. However, prevalence of certain morbidities, such as diabetes, were similar to those in a representative sample of urban Chinese [31]. Fifth, survivor bias is possible, which may have limited participants' socioeconomic and health diversity, biasing results towards the null. If survivorship were an issue we would have expected differences in associations by age, of which there was no evidence. Sixth, we did not explicitly consider the life course effects of social mobility since these are particularly hard to define and test clearly. Inter- and intra-generational mobility, upward and downward mobility are all potential risk factors.

Seventh, a single measurement of white blood cells and differential cell counts may not accurately reflect long-term immune function or inflammation. However, white blood cell count is used as a marker of immune status in clinical settings and is a well-established and routinely-used marker of systemic inflammation [32]. White blood cell count is associated with disease risk and predicts disease outcome [33,34]. Eighth, although we report associations between SEP and differential white blood cell counts, clinical significance remains to be determined. Within the normal range, elevated white blood cell counts are associated with risk factors for chronic diseases, such as cardiovascular disease [32,35]. White blood cell counts can be conceptualised as a mixed marker of exposure and response, even a relatively small shift towards a healthier inflammation-immunological profile might have significant public health benefits at the population level [33,34]. Ninth, acute infection, trauma and underlying chronic disease or medication could be mediators. There is no evidence to suggest that participants were experiencing infection during the assessment process, nor significant trauma. Although only those with life-threatening illness were specifically excluded, those experiencing significant acute infection or trauma were less likely to attend this study, which should have minimized any bias from this source. We also performed descriptive analysis of the data to detect and exclude outliers, which may have

resulted from unknown underlying disease, medication, or recording error.

One possible explanation for the association of low SEP with inflammation is via current health behaviour linked to inflammation [5,36-38]. Although we did not perform formal tests of mediation, we did adjust for smoking, alcohol consumption, physical activity and BMI in separate models (Appendix), which had little effect among women, but among men, this attenuated the negative association of early adult SEP with white blood cell and granulocyte counts and strengthened the positive association of early adult SEP with lymphocyte counts. This suggests that any associations are unlikely to be driven by adult health behaviour in women, though these may obscure negative associations of early adult SEP with inflammatory markers in men.

Low SEP may increase exposure to pro-inflammatory agents, such as microbial pathogens, pollutants or adverse work conditions. Mechanisms for increased exposure or vulnerability to pathogens in low SEP groups include earlier and/or greater lifetime exposure due to adverse living conditions, such as overcrowding, and increased susceptibility to primary infection through nutritional deficiencies, or stress-related immune dysfunction [3]. A gender bias may have protected low SEP men from such exposures and adverse work conditions, although it is not clear why the effects should be most obvious for lymphocytes. Lower birth weight amongst those with low childhood SEP is another possible explanation, but birth weight is not available for our participants. Birth weight is inversely associated with inflammatory markers [6,39]. However, birth weight appears to be less relevant in developing country settings such as ours [40], and there is no reason why birth weight should have sex-specific effects on some white cell sub-types.

An alternative explanation is that better early life conditions would be expected to promote development of the adaptive immune system, particularly of the thymus, [41] whose development takes place in early life [41] and which is sensitive to malnutrition, micro-nutrient deficiencies and infections during growth and development [42-44]. Moreover, the same exposure would also allow upregulation of the gonadotropic axis resulting in sex-specific effects on some immune cell sub-populations [45-47], particularly those relating to adaptive immunity. Consistent with this mechanism we have previously observed similar sex-specific associations, in the Guangzhou Biobank Cohort Study, of childhood stress with white cell count [48] and of childhood diet with lymphocytes but not granulocytes [19]. However, we do not have measurements that would allow proof of this mechanism.

Table 4 Associations of high socioeconomic position compared to low at four life stages with white cell count and granulocyte count, adjusted for age^a, sex and lifestyle factors in 9,981 Chinese adults (≥50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008

	White Blood Cell Count (10 ⁹ /L)			Granulocyte Cell Count (10 ⁹ /L)		
	Δ	95% CI	AIC	Δ	95% CI	AIC
Men and Women						
Critical Period Model ^b						
Childhood	-0.13	(-0.19, -0.06)	8789	-0.09	(-0.14, -0.04)	3967
Early Adult	-0.31*	(-0.38, -0.24)	8725	-0.23	(-0.29, -0.18)	3907
Late Adult	-0.18*	(-0.27, -0.10)	8779	-0.16	(-0.22, -0.09)	3951
Current	-0.18	(-0.25, -0.12)	8769	-0.15	(-0.20, -0.09)	3944
Accumulation Model ^c						
0	0		8722	0		3901
1	-0.17	(-0.27, -0.07)		-0.13	(-0.21, -0.05)	
2	-0.28	(-0.37, -0.18)		-0.21	(-0.28, -0.13)	
3	-0.42	(-0.52, -0.32)		-0.32	(-0.40, -0.24)	
4	-0.46	(-0.59, -0.32)		-0.37	(-0.47, -0.26)	
Sensitive Periods Model ^d						
Childhood	-0.06	(-0.13, 0.01)	8713	-0.04	(-0.09, 0.02)	3892
Early Adult	-0.24	(-0.32, -0.17)		-0.18	(-0.24, -0.12)	
Late Adult	-0.08	(-0.16, 0.01)		-0.07	(-0.14, -0.01)	
Current	-0.10	(-0.18, -0.03)		-0.08	(-0.14, -0.02)	
Fully Saturated Model ^e						
			8725			3907

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs * Test for interaction with sex significant at p < 0.05 level

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age, sex, smoking, alcohol use, and physical activity but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age, sex, smoking, alcohol use, and physical activity. ^dMutually adjusted for SEP at other life stages and adjusted for age, sex, smoking, alcohol use, and physical activity. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age, sex, smoking, alcohol use, and physical activity

Table 5 Associations of high socioeconomic position (compared to low) at four life stages with lymphocyte cell count (10⁹/L) by sex, adjusted for age^a and lifestyle factors in 9,981 Chinese adults (≥50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008

	Women (n = 7,445)			Men (n = 2,536)		
	Δ	95% CI	AIC	Δ	95% CI	AIC
Critical period Model ^b						
Childhood	-0.03	(-0.06, -0.01)	-7876	0.03	(-0.02, 0.09)	-2354
Early Adult	-0.08	(-0.11, -0.05)	-7894	0.07	(0.02, 0.13)	-2360
Late Adult	-0.03	(-0.07, 0.01)	-7873	0.06	(0.003, 0.11)	-2358
Current	-0.03	(-0.06, -0.001)	-7876	0.03	(-0.02, 0.09)	-2355
Accumulation Model ^c						
0	0		-7885	0		-2357
1	-0.02	(-0.07, 0.02)		0.04	(-0.05, 0.12)	
2	-0.05	(-0.10, -0.01)		0.08	(0.004, 0.16)	
3	-0.09	(-0.13, -0.04)		0.08	(0.001, 0.17)	
4	-0.09	(-0.14, -0.03)		0.15	(0.03, 0.26)	
Sensitive Periods Model ^d						
Childhood	-0.02	(-0.05, 0.01)	-7891	0.02	(-0.03, 0.08)	-2357
Early Adult	-0.07	(-0.10, -0.03)		0.06	(-0.01, 0.12)	
Late Adult	0.00	(-0.04, 0.04)		0.04	(-0.02, 0.10)	
Current	-0.01	(-0.04, 0.02)		0.01	(-0.05, 0.07)	
Fully Saturated Model ^e						
			-7881			-2345

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age, smoking, alcohol use, and physical activity but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age, smoking, alcohol use, and physical activity. ^dMutually adjusted for SEP at other life stages and adjusted for age, smoking, alcohol use, and physical activity. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age, smoking, alcohol use, and physical activity

Table 6 Associations of high socioeconomic position (compared to low) at four life stages with white cell count and granulocyte count, adjusted for age^a, sex and lifestyle factors and body mass index in 9,981 Chinese adults (≥50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008

	White Blood Cell Count (10 ⁹ /L)			Granulocyte Cell Count (10 ⁹ /L)		
	Δ	95% CI	AIC	Δ	95% CI	AIC
Men and Women						
Critical period Model ^b						
Childhood	-0.13	(-0.19, -0.06)	8248	-0.09	(-0.14, -0.04)	3675
Early Adult	-0.31	(-0.38, -0.24)	8206	-0.24	(-0.29, -0.18)	3631
Late Adult	-0.20	(-0.27, -0.12)	8239	-0.17	(-0.23, -0.10)	3659
Current	-0.20	(-0.27, -0.14)	8223	-0.16	(-0.21, -0.11)	3646
Accumulation Model ^c						
0	0		8186.0	0		3611
1	-0.19	(-0.29, -0.09)		-0.14	(-0.22, -0.06)	
2	-0.28	(-0.37, -0.18)		-0.21	(-0.29, -0.14)	
3	-0.40	(-0.50, -0.30)		-0.31	(-0.39, -0.23)	
4	-0.42	(-0.56, -0.29)		-0.35	(-0.45, -0.24)	
Sensitive Periods Model ^d						
Childhood	-0.06	(-0.13, 0.01)	8185.9	-0.04	(-0.09, 0.02)	3608
Early Adult	-0.18	(-0.25, -0.10)		-0.14	(-0.20, -0.08)	
Late Adult	-0.08	(-0.16, 0.00)		-0.08	(-0.14, -0.02)	
Current	-0.12	(-0.20, -0.05)		-0.10	(-0.15, -0.05)	
Fully Saturated Model ^e						
			8198			3624

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age, sex, smoking, alcohol use, and physical activity and body mass index but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age, sex, smoking, alcohol use, and physical activity and body mass index. ^dMutually adjusted for SEP at other life stages and adjusted for age, sex, smoking, alcohol use, and physical activity and body mass index. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age, sex, smoking, alcohol use, and physical activity

Table 7 Associations of high socioeconomic position (compared to low) at four life stages with lymphocyte cell count (10⁹/L) by sex, adjusted for age^a, lifestyle factors and body mass index in 9,981 Chinese adults (≥50 years) from the Guangzhou Biobank Cohort Study, phase3, 2006-2008

	Women (n = 7,445)			Men (n = 2,536)		
	Δ	95% CI	AIC	Δ	95% CI	AIC
Critical period Model ^b						
Childhood	-0.03	(-0.06, -0.01)	-8283	0.03	(-0.02, 0.09)	-2438
Early Adult	-0.08	(-0.11, -0.05)	-8288	0.07	(0.02, 0.13)	-2443
Late Adult	-0.03	(-0.06, 0.01)	-8278	0.05	(0.00, 0.11)	-2440
Current	-0.03	(-0.06, -0.01)	-8281	0.03	(-0.02, 0.09)	-2438
Accumulation Model ^c						
0	0*		-8284	0*		-2439
1	-0.03	(-0.08, 0.01)		0.02	(-0.06, 0.10)	
2	-0.04	(-0.08, 0.002)		0.07	(-0.01, 0.15)	
3	-0.07	(-0.12, -0.02)		0.07	(-0.02, 0.15)	
4	-0.06	(-0.12, -0.0003)		0.13	(0.02, 0.24)	
Sensitive Periods Model ^d						
Childhood	-0.02	(-0.05, 0.01)	-8285	0.02	(-0.04, 0.08)	-2440
Early Adult	-0.04	(-0.07, -0.01)		0.06	(0.002, 0.12)	
Late Adult	0.01	(-0.03, 0.05)		0.03	(-0.03, 0.09)	
Current	-0.01	(-0.04, 0.02)		0.00	(-0.06, 0.06)	
Fully Saturated Model ^e						
			-8274			-2428

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age, sex, smoking, alcohol use, and physical activity and body mass index but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age, sex, smoking, alcohol use, and physical activity and body mass index. ^dMutually adjusted for SEP at other life stages and adjusted for age, sex, smoking, alcohol use, and physical activity and body mass index. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age, sex, smoking, alcohol use, and physical activity

Table 8 Associations of high socioeconomic position (compared to low) at four life stages with white cell count and its differentials, adjusted for age^a and sex Chinese adults (≥50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008 including complete cases only

	White Blood Cell Count (10 ⁹ /L)				Granulocyte Cell Count (10 ⁹ /L)			
	N	Δ	95% CI	AIC	N	Δ	95% CI	AIC
Men and Women								
Critical period Model ^b								
Childhood	9683	-0.14	(-0.21, -0.07)	8769	9683	-0.10	(-0.15, -0.04)	4038
Early Adult	9976	-0.35	(-0.42, -0.29)	8906	9976	-0.26	(-0.31, -0.21)	4018
Late Adult	8808	-0.23	(-0.31, -0.15)	7901	8808	-0.19	(-0.25, -0.12)	3575
Current	8332	-0.23	(-0.30, -0.16)	7446	8332	-0.17	(-0.23, -0.12)	3362
Accumulation Model ^c								
0	7117	0		6327	7117	0.00		2872
1	7117	-0.19	(-0.31, -0.07)		7117	-0.18	(-0.28, -0.08)	
2	7117	-0.38	(-0.50, -0.26)		7117	-0.30	(-0.40, -0.21)	
3	7117	-0.54	(-0.66, -0.42)		7117	-0.43	(-0.52, -0.33)	
4	7117	-0.53	(-0.69, -0.38)		7117	-0.42	(-0.55, -0.30)	
Sensitive Periods Model ^d								
Childhood	7112	-0.05	(-0.13, 0.03)	6299	7112	-0.03	(-0.09, 0.04)	2851
Early Adult	7112	-0.35	(-0.44, -0.26)		7112	-0.25	(-0.32, -0.18)	
Late Adult	7112	-0.07	(-0.16, 0.02)		7112	-0.07	(-0.14, -0.002)	
Current	7112	-0.12	(-0.20, -0.05)		7112	-0.10	(-0.16, -0.03)	
Fully Saturated Model ^e								
	7112			6310	7112			2864

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

* Test for interaction with sex significant at p < 0.05 level

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age and sex but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age and sex. ^dMutually adjusted for SEP at other life stages and adjusted for age and sex. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age and sex

Table 9 Associations of high socioeconomic position (compared to low) at four life stages with lymphocyte cell count (10⁹/L) by sex, adjusted for age^a in 9,981 Chinese adults (≥50 years) from the Guangzhou Biobank Cohort Study, phase 3, 2006-2008 including complete cases only

	Women (n = 7,445)				Men (n = 2,536)			
	N	Δ	95% CI	AIC	N	Δ	95% CI	AIC
Critical period Model ^b								
Childhood	7207	-0.04	(-0.07, -0.01)	-7619	2476	0.03	(-0.03, 0.08)	-2206
Early Adult	7443	-0.08	(-0.11, -0.05)	-7893	2533	0.03	(-0.02, 0.09)	-2274
Late Adult	6436	-0.03	(-0.07, 0.01)	-6835	2372	0.04	(-0.02, 0.09)	-2118
Current	6166	-0.04	(-0.07, -0.01)	-6589	2166	0.01	(-0.05, 0.06)	-1982
Accumulation Model ^c								
0		0.00		-5520	1981	0.00		-1783
1	5136	0.02	(-0.04, 0.07)		1981	0.03	(-0.08, 0.13)	
2	5136	-0.04	(-0.10, 0.01)		1981	0.07	(-0.03, 0.16)	
3	5136	-0.10	(-0.15, -0.04)		1981	0.08	(-0.02, 0.17)	
4	5136	-0.07	(-0.14, -0.002)		1981	0.07	(-0.05, 0.20)	
Sensitive Periods Model ^d								
Childhood	5131	-0.03	(-0.06, 0.01)	-5512	1981	0.03	(-0.03, 0.09)	-1782
Early Adult	5131	-0.08	(-0.12, -0.04)		1981	-0.01	(-0.08, 0.06)	
Late Adult	5131	0.02	(-0.03, 0.06)		1981	0.03	(-0.03, 0.09)	
Current	5131	-0.01	(-0.05, 0.02)		1981	-0.01	(-0.06, 0.05)	
Fully Saturated Model ^e								
	5131			-7222	1981			-7222

Abbreviations: CI Confidence Interval; AIC Akaike Information Criterion

Bold numbers indicate P < 0.05 for coefficients or best fitting model for AICs

^aAge in five year age groups. ^bEstimates for SEP at each individual life stage adjusted for age but unadjusted for SEP at other life stages. ^cNumber of periods in high SEP adjusted for age. ^dMutually adjusted for SEP at other life stages and adjusted for age. ^eIncludes SEP at all four life stages and all possible interactions between all four measures of SEP. Also adjusted for age

Conclusions

Socioeconomic position was inversely associated with white blood cell differential counts, as a marker of inflammation, with a clearer and more consistent association among women than men. Environmentally and inter-generationally driven changes to the gonadotropic axis may obscure the normally protective effect of social advantage in the first few generations of men, but not women, to experience better living conditions. Given the links between the immune system, inflammation and chronic disease, this provides a biological mechanism between SEP and the pathophysiological genesis of chronic disease. Understanding such mechanisms for populations experiencing the epidemiological transition is of public health significance.

Appendix

Associations of socioeconomic position with markers of inflammation, additionally adjusted for lifestyles factors (smoking, alcohol use and physical exercise), are shown below: associations with white cell counts and granulocyte counts are shown in Table 4 and sex-specific associations with lymphocyte counts are shown in Table 5. Associations further adjusted for body mass index are shown in Table 6 (for white cell count and granulocyte count) and Table 7 (lymphocyte count). Results from the complete case analysis are shown in below in Table 8 (white cell count and granulocyte count) and Table 9 (lymphocyte count).

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Authors' contributions

DA West carried out the statistical analyses and wrote the article. TM Elwell-Sutton performed additional analysis and reviewed drafts of the manuscript. CM Schooling and GM Leung helped conceptualize ideas, interpret findings and review drafts of the manuscript. TH Lam, CQ Jiang and KK Cheng initiated and oversee the Guangzhou Biobank Cohort Study and WS Zhang assisted in the planning and co-ordination of the study. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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