

Correlates of C-reactive protein levels in young adults: a population-based cohort study of 3827 subjects in Brazil

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The socio-demographic, behavioral and anthropometric correlates of C-reactive protein levels were examined in a representative young adult Brazilian population. The 1982 Pelotas Birth Cohort Study (Brazil) recruited over 99% of births in the city of Pelotas that year (N = 5914). Individuals belonging to the cohort have been prospectively followed up. In 2004-2005, 77.4% of the cohort was traced, members were interviewed and 3827 individuals donated blood. Analyses of the outcome were based on a conceptual model that differentiated confounders from potential mediators. The following independent variables were studied in relation to levels of C-reactive protein in sex-stratified analyses: skin color, age, family income, education, parity, body mass index, waist circumference, smoking, fat/fiber/alcohol intake, physical activity, and minor psychiatric disorder. Geometric mean (95% confidence interval) C-reactive protein levels for the 1919 males and 1908 females were 0.89 (0.84-0.94) and 1.96 mg/L (1.85-2.09), respectively. Pregnant women and those using oral contraceptive therapies presented the highest C-reactive protein levels and all sub-groups of women had higher levels than men ($P < 0.001$). Significant associations between C-reactive protein levels were observed with age, socioeconomic indicators, obesity status, smoking, fat and alcohol intake, and minor psychiatric disorder. Associations were stronger at higher levels of C-reactive protein and some associations were sex-specific. We conclude that both distal (socio-demographic) and proximal (anthropometric and behavioral) factors exert strong effects on C-reactive protein levels and that the former are mediated to some degree by the latter.

Key words: C-reactive protein; Inflammation; Cohort studies; Prospective studies; Brazil

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Introduction

There has recently been increasing interest in identifying factors associated with inflammation, a fundamental process in atherogenesis. C-reactive protein (CRP) has received special attention not only due to its characteris-

tics as a highly specific marker for coronary events, but also because of its potential pathogenic role (1). While recent Mendelian randomization studies suggest that CRP does not have an independent role in causing coronary heart disease-related outcomes, its role as an atherogenic risk marker remains unchallenged (2).

Racial/ethnic, socioeconomic and demographic correlates have been studied as potential distal determinants of CRP levels. Proximal factors that have been examined include diet (3), alcohol intake (4), smoking (5), anthropometric indicators of body fat (6), physical activity (7), and stress (8). Results from these studies have not always been consistent, though age, female sex and poverty have been widely shown to be positively associated with CRP levels as have proximal factors including smoking, poor diet, higher body fat, lower levels of physical activity, and high stress.

Identifying factors associated with CRP levels could lead to strategies designed to combat the causes or long-term consequences of chronic inflammation. Identification of these factors in young adults would be particularly useful. There are few population-based studies on this topic in low- and middle-income countries, and none in Latin America, where nutrition and epidemiological transitions are already exerting a heavy toll. Thus, the purpose of this study was to examine the correlates of C-reactive protein levels in a young adult Brazilian population.

Material and Methods

The 1982 Pelotas Birth Cohort Study (Brazil) is one of the largest and longest-running prospective birth cohorts in the low- and middle-income countries. It enrolled 5914 live births to mothers who lived in the urban area of the city that year (population in 1982: 214,000), representing over 99% of total births. A questionnaire on socio-demographic and health factors was applied to the mothers soon after delivery. The cohort has been followed up numerous times throughout the years. More detailed information on methods, variables and sampling fractions has been published (9).

In 2004-2005, members of the 1982 cohort were sought using a variety of methods. Family income data were categorized into groups representing ≤ 1 , 1.1-3.0, 3.1-6.0, 6.1-10, and >10 minimum wage units. These groupings capture the wide income gaps common in Brazil more precisely than a division into, say, quintiles. The minimum wage at the time of the cohort visit was equivalent to approximately US\$180. Number of years of formal education completed by the participant was also collected and grouped into 0-4, 5-8, 9-11, and ≥ 12 years.

Self-described skin color of the participant was collected as white, black, and mulatto, others being excluded due to small numbers (76 Indigenous and 74 Asian). Current smoking was defined as smoking at least one cigarette per week and analyzed as a dichotomous variable.

A food frequency questionnaire was applied and relevant elements were used to calculate intake of fat and

fiber as suggested by Block et al. (10). Fat intake was grouped as "best low fat", "lower fat", "American diet", "high fat", and "very high fat" and analyzed as an ordinal variable. Fiber intake was dichotomized into "adequate/moderate" or "low fiber intake". An overall score for alcohol intake was calculated and categorized into three groups: "non-drinker", "one drink per day" (equivalent to 350 mL beer, 150 mL wine, or 30 mL liquor), or "more than one drink per day".

Information on physical activity (leisure time, transportation, occupation, and housework) was collected using long version of the International Physical Activity Questionnaire (www.ipaq.ki.se). Total and leisure time physical activity variables were dichotomized, defining as "sedentary" those with less than 150 min of moderate-intensity physical activity per week.

Interviewers applied the Self-Reported Questionnaire-20 (SRQ), which has been validated in Brazil, to evaluate mental health. SRQ score was dichotomized into sex-specific groups representing those without and those with an elevated score (≥ 6 for men and ≥ 8 for women). An elevated score was used in this study as a proxy for mental stress.

Individuals were weighed using the Seca (UNICEF) scale (100 g precision). A locally manufactured aluminum anthropometer (1 mm precision) was used to measure standing height. Body mass index (BMI) was calculated as kg/m^2 and categorized into WHO recommended groups: <18.5 (underweight), 18.5-24.9 (normal), 25.0-29.9 (overweight), and ≥ 30.0 (obese) (11).

Waist circumference was measured at the narrowest girth of the trunk or halfway between the costal margin and iliac crest using a fiberglass measuring tape (Cardiomed, Brazil, 1 mm precision). Central obesity was analyzed both as a continuous variable and dichotomous variable, using cutoffs of ≥ 94 cm for men and ≥ 80 cm for women (12).

Quality control measures throughout the 2004-2005 cohort visit included telephoning or re-visiting 10% of the interviewed participants by study supervisors to test reliability and double data input.

Non-fasting venous blood was collected from volunteers being interviewed. High sensitivity CRP assays were performed using the automated DPC (Siemens) Immulite chemiluminescent immunoassay (Los Angeles, CA, USA). The intra- and inter-assay coefficients of variation were 10 and 7%, respectively. Samples with results below the assay sensitivity threshold, which registered as <0.1 mg/L, were converted to 0.05 mg/L for statistical analysis.

Statistical analysis

Analyses of this 2004-2005 cohort visit were cross-sectional. Since the cohort had a fixed number, the mini-

minimum detectable differences in CRP values relative to independent variables were calculated using a two-tailed level of significance of 95 with 80% power. Sample size calculations were based on standard deviations of 1.0 and 3.0 mg/L CRP, reflecting the variations described in the literature. The minimum detectable differences between groups were thus calculated and ranged from 0.10 and 0.60 mg/L, depending on the exposure.

CRP values (mg/L) were natural log-transformed (\ln mg/L) for greater symmetry prior to undertaking statistical analyses (Figure 1). CRP values are presented in the text

as the geometric mean 95% confidence interval (95%CI), which were similar to median values. Linear and logistic regression were used, the former for continuous \ln CRP values and the latter for CRP >10 mg/L. Wald tests for trend and heterogeneity were used where appropriate. Analyses were stratified by gender. Statistical analyses were based on a conceptual framework based on a hierarchy of levels of determination (Table 1). Socio-demographic variables may be confounders for anthropometric and behavior variables, whereas the latter are potential mediators of the former. Socio-demographic factors were

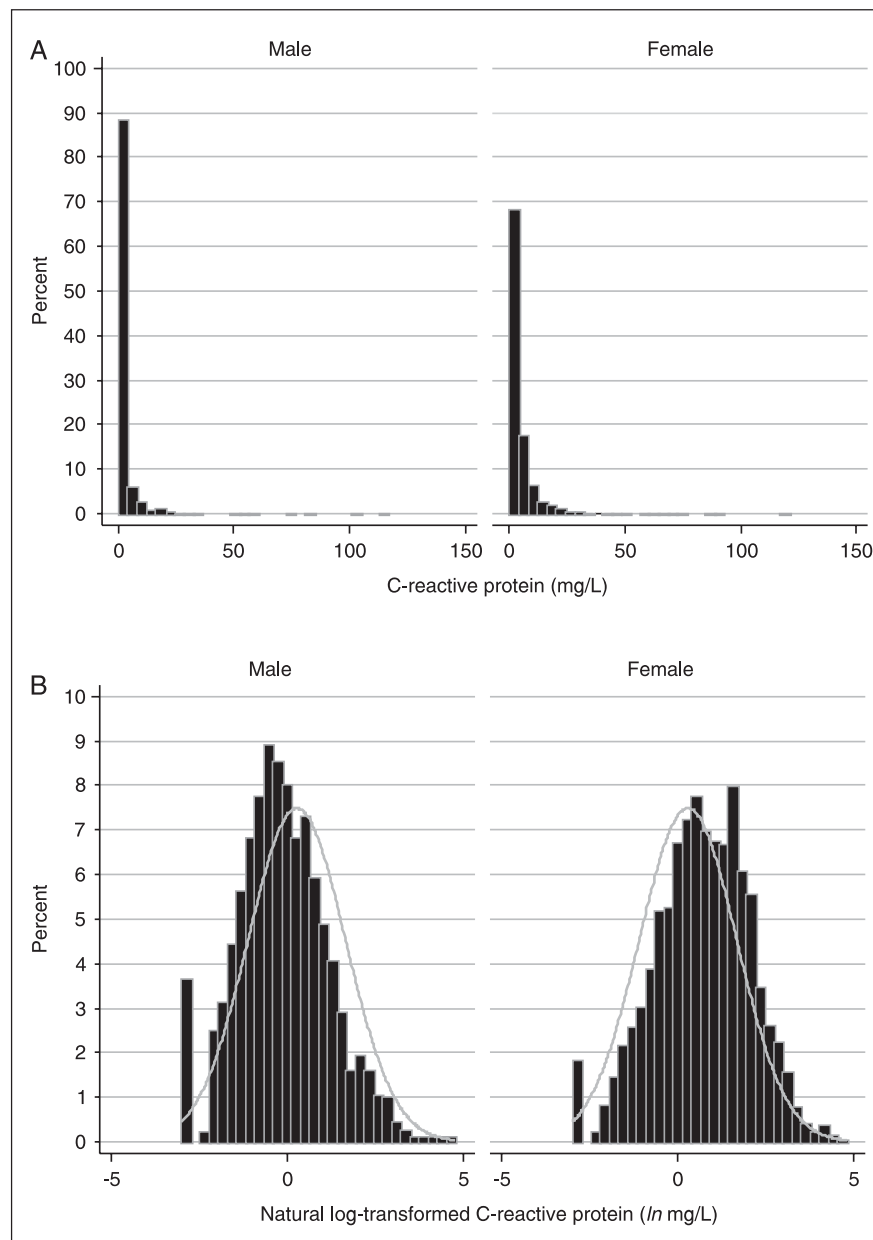


Figure 1. Raw (A) and natural log-normalized distribution (B) of C-reactive protein in men (N = 1919) and women (N = 1908) belonging to the 1982 Pelotas Birth Cohort (2004-2005). Values (in mg/L) that registered as “<0.1” were transformed to 0.05 prior to analysis; the gap in the normalized distributions reflects this transformation.

adjusted for one another (level 1), and behavioral/anthropometric factors were adjusted for each other and also for socio-demographic factors (level 2; Table 1). To investigate possible mediating factors, socio-demographic factors that were still significant after adjustment for one another were further adjusted for behavioral/anthropometric factors, and these analyses are mentioned in the text when relevant.

Adjusted β coefficients and their 95%CI from the analyses of geometric means are interpretable as ratios. Analyses were performed on Stata, version 8.

BMI and waist circumference - as continuous and categorical variables - were entered in the analyses individually and simultaneously in an attempt to disentangle the contributions of body mass versus fat distribution in influencing CRP levels.

The Federal University of Pelotas Ethics Committee approved all aspects of the 1982 Pelotas birth cohort study. Informed written consent was collected for the questionnaire and blood draw associated with the 2004-2005 cohort visit.

Results

From October 2004 to September 2005, 4297 individuals were traced, representing 77.4% of the original cohort (this percentage includes 282 individuals who died prior to 2004). The mean age was 22.8 years (range, 21.9-23.7). Those who donated blood for CRP tests (89.1% of those interviewed) tended to be poorer and less educated than those who did not, and those with black skin color were

Table 1. Proposed hierarchical model for the associations between socio-demographic, anthropometric and behavioral factors and C-reactive protein levels in young adulthood.

Level	Variable
1	Socio-demographic characteristics Age Skin color Family income Years of education Parity (women)
2	Anthropometric and behavioral factors Body mass index Waist circumference Smoking Fat and fiber intake Alcohol intake Physical activity Minor psychiatric disorder
Outcome	C-reactive protein level

over-represented in this follow-up (data not shown).

Geometric mean (95%CI) CRP levels for the 1919 males and 1908 females were 0.89 (0.84-0.94) and 1.96 mg/L (1.85-2.09), respectively. Seventy-nine (4.1%) men and 194 (10.2%) women had CRP levels >10 mg/L.

A total of 445 women were using oral contraceptive therapy (OCT) at the time blood was drawn and 93 others were pregnant. Women who were neither pregnant nor using OCT had the lowest CRP levels (1.66 mg/L (1.54-1.78)), followed by women using OCT (2.88 (2.58-3.22)), and pregnant women had the highest levels (3.90 (3.11-4.90)). Differences between men and all categories of women were significant ($P < 0.0001$), as were differences between each of the three groups of women ($P < 0.0001$). Men ($N = 1919$) and women who were neither pregnant nor using OCT ($N = 1370$) formed the sample for the main analyses.

The distribution of risk factors and their association with characteristics for the cohort and associations between CRP and the variables in the hierarchical model are reported in Tables 2 and 3 for men and women, respectively.

Skin color did not show any associations with CRP levels in either sex in unadjusted or adjusted analyses. In unadjusted analyses, age showed a strong direct association in women only, maintaining a significant association and consistent effect size, even when adjusted for all other variables in the model.

Family income distribution was similar between men and women. In unadjusted analyses and when adjusted for confounders, a significant and direct association between family income and CRP levels was observed in men, with the poorest at 65% the geometric mean CRP levels compared to the richest. When potential mediators (i.e., anthropometric and behavioral factors) were adjusted for, effect size and significance were lost (data not shown). In contrast, unadjusted analyses revealed an inverse trend between family income and CRP levels in women. This association lost significance with adjustment for confounders. In crude analyses, there was a significant interaction between sex and income.

On average, women had more years of education than men. Education was inversely associated with CRP levels in women but there was no association in men. When adjusted for confounders, this association disappeared in women.

Parity showed a significant and direct association with CRP levels in women such that those with three or more children had 30% higher geometric mean CRP levels than those with no children. When adjusted for socio-demographic factors, this association was no longer significant.

Similar distributions in BMI were observed between the

Table 2. Distribution and associations of C-reactive protein (CRP) levels with socio-demographic (level 1), anthropometric and behavioral (level 2) factors in a total of 1919 men.

Level	Independent variable	% in group	Geometric mean (95%CI)	Crude analyses		Adjusted analyses	
				β (95%CI)	P	β (95%CI)	P
1	Age (years)	-	-	1.03 (0.88-1.20)	0.7	1.05 (0.90-1.24)	0.5
	Skin color ^a				0.4*	1 (ref)	0.5*
	White	77.2	0.92 (0.86-0.98)	1 (ref)		1 (ref)	
	Mulatto	6.4	0.85 (0.67-1.07)	0.93 (0.73-1.18)		0.95 (0.74-1.21)	
	Black	16.4	0.82 (0.71-0.95)	0.90 (0.76-1.05)		0.91 (0.77-1.07)	
	Family income in 2004 (minimum wage units)				0.02		0.01
	≤ 1	4.6	0.78 (0.59-1.03)	0.71 (0.52-0.97)		0.65 (0.46-0.92)	
	1.1-3.0	31.6	0.87 (0.78-0.96)	0.79 (0.65-0.96)		0.77 (0.62-0.96)	
	3.1-6.0	34.1	0.85 (0.77-0.94)	0.78 (0.64-0.94)		0.75 (0.62-0.92)	
	6.1-10.0	16.7	0.91 (0.79-1.05)	0.78 (0.64-0.94)		0.83 (0.66-1.03)	
>10	12.9	1.10 (0.94-1.28)	1 (ref)		1 (ref)		
Education (years)				1.0		0.2	
0-4	9.4	0.94 (0.76-1.15)	0.88 (0.68-1.14)		1.04 (0.78-1.39)		
5-8	32.5	0.92 (0.83-1.02)	0.87 (0.71-1.06)		0.99 (0.79-1.23)		
9-11	46.7	0.83 (0.76-0.90)	0.78 (0.64-0.94)		0.85 (0.70-1.04)		
≥ 12	11.4	1.06 (0.90-1.25)	1 (ref)		1 (ref)		
2	BMI (kg/m ²) ^b				<0.001		<0.001
	<18.5	4.6	0.43 (0.32-0.58)	0.57 (0.43-0.75)		0.60 (0.42-0.85)	
	18.5-24.9	64.7	0.76 (0.71-0.82)	1 (ref)		1 (ref)	
	25.0-29.9	23.2	1.17 (1.06-1.29)	1.54 (1.34-1.76)		1.55 (1.31-1.84)	
	≥ 30.0	7.5	2.30 (1.91-2.78)	3.03 (2.44-3.76)		2.84 (1.88-4.28)	
	Central obesity ^{b,c}				<0.001		0.2
	No	89.8	0.81 (0.77-0.86)	1 (ref)		1 (ref)	
	Yes	10.2	1.90 (1.62-2.22)	2.33 (1.94-2.82)		1.23 (0.92-1.64)	
	Current smoking				0.05		0.02
	No	72.1	0.86 (0.80-0.92)	1 (ref)		1 (ref)	
	Yes	27.9	0.98 (0.88-1.09)	1.14 (1.00-1.30)		1.21 (1.03-1.42)	
	Fat intake category				0.2		0.3
	Best low fat	11.7	1.01 (0.83-1.23)	1 (ref)		1 (ref)	
	Lower fat	10.9	1.03 (0.85-1.25)	1.02 (0.77-1.35)		0.96 (0.73-1.27)	
	American diet	12.3	0.83 (0.68-1.00)	0.81 (0.62-1.07)		0.81 (0.62-1.06)	
High fat	14.1	0.80 (0.67-0.96)	0.79 (0.60-1.03)		0.78 (0.60-1.02)		
Very high fat	51.0	0.90 (0.81-0.99)	0.88 (0.71-1.10)		0.88 (0.71-1.09)		
Fiber intake ^b				0.7		1.0	
Moderate/adequate	30.5	0.92 (0.80-1.05)	1 (ref)		1 (ref)		
Low	69.5	0.89 (0.83-0.96)	1.03 (0.89-1.19)		1.01 (0.87-1.17)		
Alcohol intake				0.02*		0.5*	
Non-drinker	24.7	0.85 (0.75-0.96)	1.01 (0.87-1.17)		1.00 (0.84-1.18)		
Up to 1 drink/day	41.8	0.83 (0.77-0.91)	1 (ref)		1 (ref)		
More than 1 drink/day	33.5	1.00 (0.91-1.11)	1.20 (1.05-1.38)		1.09 (0.90-1.30)		

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Table 2 continued.

Level	Independent variable	% in group	Geometric mean (95%CI)	Crude analyses		Adjusted analyses	
				β (95%CI)	P	β (95%CI)	P
2	Physical activity, total				0.07		0.4
	Not sedentary	92.3	0.88 (0.83-0.93)	1 (ref)		1 (ref)	
	Sedentary	7.7	1.08 (0.85-1.36)	1.23 (0.99-1.53)		1.11 (0.87-1.43)	
	Physical activity, leisure				0.8		-
	Not sedentary	50.4	0.90 (0.83-0.97)	1 (ref)		-	
	Sedentary	49.6	0.88 (0.81-0.96)	0.98 (0.87-1.10)		-	
	SRQ result ^b				0.8		0.4
	Normal	75.7	0.88 (0.83-0.94)	1 (ref)		1 (ref)	
	Elevated	24.4	0.90 (0.80-1.02)	1.02 (0.89-1.17)		1.07 (0.91-1.25)	

Crude analyses adjusted for skin color, age, family income, and years of education. Adjusted analyses included adjustment for all variables (except leisure time physical activity).

*Wald test for heterogeneity. ^aOther categories excluded due to small numbers (N = 43 Indigenous and 27 Asian). ^bDue to missing data, the numbers of observations for analyses were: body mass index (BMI) = 1916; central obesity = 1915; fiber intake = 1917; Self-Reported Questionnaire (SRQ, minor psychiatric disorder) = 1914. ^cDefined as waist circumference ≥ 94 cm (WHO, 2000). P values for trend by linear regression, *ln*CRP as dependent variable.

Table 3. Distribution and associations of C-reactive protein (CRP) levels with socio-demographic (level 1), anthropometric and behavioral (level 2) factors in a total of 1370 women.

Level	Independent variable	% in group	Geometric mean (95%CI)	Crude analyses		Adjusted analyses	
				β (95%CI)	P	β (95%CI)	P
1	Age (years)	-	-	1.35 (1.11-1.65)	0.003	1.37 (1.12-1.67)	0.003
	Skin color ^a				0.8*		0.5*
	White	78.6	1.67 (1.54-1.82)	1 (ref)		1 (ref)	
	Mulatto	5.1	1.72 (1.25-2.36)	1.03 (0.73-1.44)		0.97 (0.69-1.37)	
	Black	16.3	1.56 (1.27-1.91)	0.93 (0.76-1.14)		0.88 (0.71-1.08)	
	Family income in 2004 (minimum wage units)				0.04		0.3
	≤ 1	7.0	1.46 (1.06-2.02)	1.13 (0.80-1.59)		1.01 (0.69-1.49)	
	1.1-3.0	33.5	1.83 (1.60-2.09)	1.42 (1.11-1.80)		1.30 (0.99-1.72)	
	3.1-6.0	32.1	1.72 (1.52-1.95)	1.33 (1.05-1.70)		1.31 (1.01-1.69)	
	6.1-10.0	14.9	1.58 (1.31-1.90)	1.22 (0.93-1.62)		1.19 (0.89-1.58)	
	>10	12.5	1.29 (1.07-1.56)	1 (ref)		1 (ref)	
	Education (years)				0.03		0.4
	0-4	6.4	1.75 (1.29-2.36)	1.34 (0.96-1.87)		1.19 (0.80-1.77)	
	5-8	22.9	1.76 (1.50-2.06)	1.35 (1.08-1.70)		1.20 (0.90-1.60)	
	9-11	52.3	1.74 (1.57-1.93)	1.34 (1.10-1.63)		1.28 (1.03-1.60)	
	≥ 12	18.4	1.30 (1.11-1.53)	1 (ref)		1 (ref)	
	Parity				0.01		0.2
	0	61.8	1.55 (1.42-1.71)	1 (ref)		1 (ref)	
	1	25.0	1.77 (1.53-2.05)	1.14 (0.96-1.35)		1.06 (0.88-1.28)	
2	9.0	1.82 (1.44-2.29)	1.17 (0.90-1.52)		1.05 (0.79-1.40)		
3+	4.2	2.30 (1.54-3.43)	1.48 (1.03-2.13)		1.44 (0.96-2.18)		

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Table 3 continued.

Level	Independent variable	% in group	Geometric mean (95%CI)	Crude analyses		Adjusted analyses	
				β (95%CI)	P	β (95%CI)	P
2	BMI (kg/m ²) ^b						
	<18.5	8.1	1.03 (0.77-1.39)	0.73 (0.56-0.96)	<0.001	0.75 (0.54-1.05)	0.001
	18.5-24.9	67.2	1.41 (1.29-1.54)	1 (ref)		1 (ref)	
	25.0-29.9	16.1	2.36 (2.01-2.77)	1.68 (1.37-2.05)		1.19 (0.88-1.62)	
	≥30.0	8.6	4.70 (3.75-5.87)	3.34 (2.56-4.34)		2.01 (1.29-3.12)	
	Central obesity ^{b,c}						
	No	77.4	1.37 (1.26-1.49)	1 (ref)	<0.001	1 (ref)	0.001
	Yes	22.6	3.15 (2.73-3.64)	2.29 (1.93-2.74)		1.63 (1.21-2.19)	
	Current smoking						
	No	76.4	1.63 (1.50-1.77)	1 (ref)	0.4	1 (ref)	0.6
	Yes	23.6	1.75 (1.51-2.03)	1.07 (0.90-1.27)		1.06 (0.84-1.33)	
	Fat intake category						
	Best low fat	10.3	1.63 (1.23-2.17)	1 (ref)	0.1	1 (ref)	0.06
	Lower fat	12.2	1.47 (1.14-1.89)	0.90 (0.63-1.29)		0.99 (0.68-1.43)	
	American diet	13.8	1.55 (1.25-1.92)	0.95 (0.66-1.35)		0.98 (0.69-1.41)	
	High fat	12.7	1.33 (1.05-1.70)	0.82 (0.57-1.17)		0.79 (0.55-1.15)	
	Very high fat	50.1	1.84 (1.63-2.07)	1.12 (0.84-1.51)		1.21 (0.90-1.64)	
	Fiber intake						
	Moderate/adequate	31.0	1.63 (1.41-1.88)	1 (ref)	0.8	1 (ref)	0.5
	Low	69.0	1.67 (1.50-1.85)	0.98 (0.81-1.18)		0.93 (0.77-1.12)	
Alcohol intake							
Non-drinker	41.3	1.63 (1.46-1.83)	0.98 (0.84-1.14)	1.0*	0.93 (0.77-1.13)	0.7*	
Up to 1 drink/day	46.7	1.67 (1.50-1.86)	1 (ref)		1 (ref)		
More than 1 drink/day	12.0	1.66 (1.37-2.01)	0.99 (0.78-1.26)		1.03 (0.77-1.37)		
Physical activity, total							
Not sedentary	91.9	1.66 (1.54-1.79)	1 (ref)	0.8	1 (ref)	0.5	
Sedentary	8.1	1.60 (1.24-2.07)	0.96 (0.74-1.26)		1.13 (0.82-1.56)		
Physical activity, leisure							
Not sedentary	19.8	1.59 (1.35-1.87)	1 (ref)	0.6	-	-	
Sedentary	80.2	1.67 (1.54-1.81)	1.05 (0.88-1.26)		-		
SRQ result ^b							
Normal	66.9	1.64 (1.50-1.80)	1 (ref)	0.6	1 (ref)	0.9	
Elevated	33.1	1.71 (1.50-1.94)	1.04 (0.89-1.21)		0.99 (0.81-1.20)		

Crude analyses adjusted for skin color, age, family income, years of education, and parity. Adjusted analyses included adjustment for all variables (except leisure time physical activity).

*Wald test for heterogeneity. ^aOther categories excluded due to small numbers (N =30 Indigenous and 15 Asian). ^bDue to missing data, the numbers of observations for analyses were: body mass index (BMI) = 1369; central obesity = 1368; Self-Reported Questionnaire (SRQ, minor psychiatric disorder) = 1366. ^cDefined as waist circumference ≥80 cm (WHO, 2000). Excludes pregnant women (N = 93) and those using oral contraceptive therapy (N = 445) at the time of the 2004-2005 cohort visit. BMI and central obesity categories exclude those up to 6 months post-partum (N = 62). P values for trend by linear regression, *ln*CRP as dependent variable.

sexes, but more women (23%) than men (10%) were centrally obese. All analyses in both sexes showed strong direct associations between BMI and CRP levels. Men and women in the obese category of BMI (≥ 30.0 kg/m²) had approximately five times higher geometric mean CRP levels than those in the underweight category (< 18.5 kg/m²). Similarly, the centrally obese had more than double the CRP levels of those without central obesity. When analyses were repeated using the continuous variable, even after adjustment for BMI, waist circumference was associated with higher CRP for men and women (1.02 and 1.03 times the CRP per cm of waist circumference, $P = 0.004$ and $P < 0.001$, respectively).

The distribution of smoking was similar between men and women, and showed a significant positive association with CRP levels in men only. This association was maintained when adjusted for confounders.

About half of both sexes had diets very high in fat and almost 70% consumed insufficient fiber. Women in the highest category of fat consumption showed higher but non-significant levels of CRP. When adjusted for confounders, this association reached the borderline level (P for trend = 0.06). In men, there was no association between dietary indicators and CRP levels. Fiber intake showed no association in either sex.

Men drinking more than one unit of alcohol per day were at higher risk for elevated CRP than those who did not drink, but this association was no longer significant after adjusting for all other variables. No association was observed for women.

Half of the men and 80% of the women were sedentary during leisure time, whereas only about 8% of each were sedentary during total time that included transportation, housework and occupational activities. In men, but not in women, those classified as sedentary had somewhat higher levels of CRP, although statistical significance was borderline. In adjusted analyses, this association lost significance.

SRQ scores indicated that 25% of men and 33% of women had minor psychiatric disorders. This variable was not associated with geometric mean CRP levels.

All analyses were repeated using CRP > 10 mg/L (acute-level inflammation) as a cut-off. Results were consistent with those using geometric means, with a few exceptions. Whereas obesity remained a risk factor, there was some indication that underweight (BMI < 18.5) was also associated with acute levels of CRP in both sexes (1.86 (95%CI = 0.90-3.85) and 1.25 mg/L (0.43-3.61) for men and women, respectively). Finally, minor psychiatric illness in men, assessed through elevated SRQ, was associated with a prevalence of acute level CRP that was 1.79 times (95%CI = 1.14-2.82, $P = 0.01$) higher than individuals with normal SRQ.

Discussion

CRP levels tended to be similar to some representative samples among comparable age groups from the USA (13,14) and New Zealand (15), but higher than those from Japan (16,17). Females tended to have higher levels than males in numerous population-based studies (18,19), although not all investigators observed a significant difference (20). Almost a third (27%) of non-pregnant women not using OCT from our sample - compared to only 13% of the men - were in the highest relative risk category (> 3.0 and < 10.0 mg/L CRP) for cardiovascular disease risk according to CDC/AHA guidelines, suggesting sex-independent criteria may be inadequate (21).

Age was strongly associated with CRP levels in women, even within the cohort's narrow age range. Other studies, including samples with similarly restricted age ranges, found direct associations, although both sexes were affected in most studies (22,23). Notably, the effect of age in women persisted even when adjusted for all socioeconomic, anthropometric and behavioral variables.

Skin color was not associated with CRP levels in either sex in this group. A recent systematic review of population-based studies, nearly all from high-income countries, showed higher risk for Africans, South Asians and Hispanics compared to those of European descent, and lower risk for Chinese and Japanese (24). Correct classification of race is complex in a highly miscigenated society such as Brazil but this has not precluded authors from detecting associations between African descent and higher risk of several chronic conditions (25,26).

In women, income and education were inversely associated with CRP levels in unadjusted analyses, but the confounding effects of age and skin color largely accounted for these associations. For men, CRP levels increased with income, even when adjusted for confounders. Other studies in Brazil have reported that overweight and obesity are directly related to socioeconomic factors in men and inversely related in women, but this has not been shown with respect to inflammatory markers (27,28).

We found that body mass and distribution of body fat strongly influence CRP levels. Similar β coefficient values between the sexes for BMI and waist circumference suggest that the inflammatory consequences of adipose tissue are comparable in men and women. Higher BMI tended to have stronger inflammatory effects in men whereas the effects of central obesity were more pronounced in women. Our findings on fatness and CRP levels are consistent with the notion that excess adipose tissue contributes to a chronic inflammatory state through a range of metabolic pathways (29). In the present study, only those with BMI

>30 kg/m² (obese) were at increased risk for acute inflammation (CRP >10 mg/L), suggesting that more extreme levels of obesity may be directly associated with “chronic acute” inflammation.

Most studies that examined smoking in relation to CRP levels found strong direct associations (30) and as observed here, some authors detected an association in men only (31,32). It is possible that sex-specific smoking behaviors - such as inhalation patterns - may impact health outcomes (33).

Healthier dietary profiles are associated with lower levels of CRP and other inflammatory markers (34,35). When adjusted for all other variables including potential mediators such as BMI, we found that women with a very high fat intake showed elevated CRP levels but the overall significance for linear trend was borderline ($P = 0.06$). These findings suggest that fat intake *per se* may be involved in pathways that impact inflammation independently of those associated with paracrine activity attributable to adipose tissue. Recent studies indicate that metabolic signals in response to various nutrients differ, making it feasible that certain metabolites exert specific inflammatory effects (36).

Our finding that moderate alcohol intake is associated with lower CRP levels has been reported previously, but not among younger adults (37,38). The literature describes a U-shaped curve of cardiovascular disease according to alcohol intake, but in our adjusted model, this pattern did not maintain significance (39).

It has been proposed that repeated psychological stressors chronically activate the innate immune response, driving an inflammatory stimulus and contributing to the progression of atherosclerosis (40). This is supported by observations that stress is a powerful risk factor for the onset and outcome of cardiovascular-related outcomes. In

the logistic regression analysis, elevated SRQ score was a significant risk factor for acute CRP levels in men, although this result was not apparent in the linear regression of geometric means. This finding underscores the importance of investigating psychosocial risk factors, even relatively early in life, for cardiovascular disease risk.

Individuals with ongoing inflammatory conditions were not excluded, which is a potential limitation of this study. However, given the young age of the cohort, it is likely that few individuals had chronic disorders and therefore this is unlikely to distort the results. Moreover, exclusion of individuals with CRP >10 mg/L did not significantly impact the findings in either sex. We did not utilize direct measurements of body fat and fat distribution, though the indirect methods of BMI and waist circumference are adequate for large samples and widely used in the literature. Nonetheless, this study was unique because it investigated a novel inflammatory biomarker in a representative sample of young Latin American adults. The fact that the sample is part of a prospective birth cohort opens possibilities for longitudinal and lifecourse analyses as the cohort ages.

We have shown that CRP levels in young adults are affected by demographic, socioeconomic, anthropometric, and behavioral factors and that many effects are sex-specific. Associations were observed with age, socioeconomic indicators, obesity status, smoking, fat and alcohol intake, and minor psychiatric disorder. We conclude that both distal and proximal factors exert strong effects on CRP levels and that the former are mediated to some degree by the latter. This is supported by the fact that many associations lost significance when mediators such as indicators of adiposity, smoking and dietary factors were included in statistical models. The identification of factors that, among young adults, are amenable to intervention reinforces the need for population-based preventive strategies.

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