Determinants of C-Reactive Protein in Individuals with Very Low Socioeconomic Status

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Abstract

Background: Low socioeconomic (SE) status has been associated to inflammation and predictors of C-reactive protein (CRP) have been investigated by studies performed in developed countries.

Objective: This study aimed to identify predictors of CRP in individuals of very low SE level in a developing country and evaluate whether CRP is related to SE status in this scenario.

Methods: Eight-two individuals of very low SE level were recruited from a poor, semi-rural community in Brazil. Thirty-two individuals of high socioeconomic level comprised a comparison sample. High-sensitivity CRP was measured by nephelometry.

Results: In the low SE individuals, independent predictors of CRP were body mass index ≥ 25 Kg/m² (P<0.001), smoking (P=0.005) and acute infection conditions (P=0.049). The low SE group (median=2.02 mg/L; interquartile range 0.92 – 4.95 mg/dl) had higher CRP levels compared to the high SE group (1.16 mg/L, interquartile range 0.55 – 2.50 mg/dl, P=0.03). Body mass index tended to be higher (27 ± 4.9 Kg/m² *vs* 25.5 ± 3.2 Kg/m²; P=0.07) and the prevalence of acute infection greater (32% *vs* 3%, P=0.002) in the low SE group. After overweight individuals and those with infectious conditions were excluded, the CRP levels were similar between the groups with low and high SE levels (0.93 mg/L *vs* 1.08 mg/L, P=0.28).

Conclusion: Adiposity, infection conditions and smoking are predictors of CRP in individuals with very low SE level. The first two factors determine greater level of inflammation in low SE individuals when compared to the high SE counterparts.(Arq Bras Cardiol 2010;94(2): 202-208)

Key words: Protein C; inflammation; social class; risk; cardiovascular diseases.

Introduction

There are consistent gaps regarding the burden of atherosclerosis among groups of different socioeconomic (SE) status[1-3]. Economically unprivileged populations and developing countries have higher mortality from cardiovascular diseases, in comparison to the developed regions of the globe[4,5]. Lack of risk factors control and access to medical treatment are plausible causes for this social contrast. In addition, environmental conditions imposed by a low SE status might enhance subclinical inflammation[6], which is a risk factor for cardiovascular events[7-9].

C-reactive protein is the best validated inflammatory marker in terms of cardiovascular risk prediction[10]. Studies performed in developed countries have identified predictors of C-reactive protein (CRP) and have shown that groups with lower SE status have higher levels of inflammation[11,12]. However, it has not been evaluated in developing countries, where social conditions of the lower class are even worse. Therefore, the present study sought to identify the determinants of CRP in a population representative of the lowest social stratum in a developing country, Brazil. Moreover, to evaluate whether CRP is related to SE status, low SE level individuals were compared with a group of individuals with high SE level.

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Methods

Sample population

Selection criteria were targeted to a population of very low socioeconomic status, as frequently observed in regions of developing countries. Individuals were recruited in a semi-rural suburb of very low income, called Monte Gordo, in the city of Camacari, State of Bahia, Northeast of Brazil. A public high-school located in this city served as the cluster for the selection of individuals. All students' parents were invited to participate in the study and 82 who responded positively were recruited. Secondarily, individuals of high socioeconomic status were selected as a comparison sample. These subjects were recruited from a private medical school at the State

Capital, Salvador, which is approximately 100 km away from Camacari. All freshmen's parents were invited to participate in the study and 32 who responded positively were evaluated. Considering that individuals of the two socioeconomic levels were recruited from specific schools, both groups were defined as non-probabilistic samples.

Study protocol

The subjects underwent interview, physical examination, dental examination, blood collection, and stool examination, all on the same day. Demographic data collected were age, gender, race/ethnicity, socioeconomic status, educational level. Regarding risk factors for cardiovascular disease, collected data were history of diabetes, hypertension, blood pressure treatment, lipid disorders, cholesterol treatment, smoking status, alcohol use, menopausal status, postmenopausal hormone therapy use, parental history of myocardial infarction before age 55 in men and 65 years in women, physical inactivity, height, weight, waist and hip circumferences.

Environmental variables such as periodontal disease, infection conditions and intestinal parasitosis were assessed. In addition, alcohol intake and current use of statins or estrogen therapy were registered. All participants self-reported race/ethnicity as white, black, or other. To define the socioeconomic (SE) status of each participant, the questionnaire adopted by the Brazilian Society of Research Institutes was used, taking into account information regarding material properties and educational level of the family member responsible for the highest income. This classification defines SE level distributed in 5 classes, as A (the highest level), B, C, D and E (the lowest SE level). The amount of exercise a week was estimated by the International Physical Activity Questionnaire[13], which takes into account both recreational and non-recreational activities. Physical inactivity was defined as < 150 minutes/week of moderately intense exercise[14]. Smoking status was defined as current, past or never. Blood pressure was measured 3 times by an automatic digital system (OMRON, Shimogyo-ku, Kyoto, Japan) and the arithmetic mean was calculated as the final value. Periodontal evaluation was performed by trained dentists and periodontal disease was defined by attachment loss ≥ 3 mm of at least one tooth[15]. Overweight individuals were defined as those with body mass index ≥ 25 Kg/m^2. The presence of acute infection condition was assessed on the same day of CRP measurement and was defined by at least one of the following: (1) acute flu-like symptoms; (2) acute pharyngitis; (3) acute diarrhea; (4) acute urinary symptoms; (5) fever. Stool examination was performed for intestinal parasitosis by Baermann-Moraes' and Hoffman's methods[16]. Plasma samples were collected for measurement of glucose, plasma lipids and CRP as a measurement of systemic inflammation. Commercial enzymatic methods were used for the determination of total cholesterol, high density lipoprotein (HDL)-cholesterol and triglycerides (Dimension Clinical Chemistry System, Dade-Behring, Newark, Delaware, USA)[17]. Low density lipoprotein (LDL)-cholesterol was calculated by Friedewald's formula. High-sensitivity CRP was measured using a commercially available immunoenzymatic nephelometric method (Dade-Behring, Newark, Delaware, USA).

Data analysis

Demographic data, risk factors and environmental information were described as relative frequencies for categorical variables and mean ± standard deviation for continuous variables. Considering its non-normal distribution, C-reactive protein was described as median and interquartile range. In order to be treated as a parametric variable, CRP suffered *log*-transformation and assumed a normal distribution. Firstly, categorical variables were evaluated as CRP predictors in the univariate analysis by comparing CRP values between groups defined by the presence or absence of each independent variable. For example, CRP was compared between individuals of black ethnicity *versus* no black ethnicity, and so forth. For this analysis, Student's *t* test was utilized to compare *log*-transformed CRP. Numeric variables were evaluated as univariate predictors of *log*-transformed CRP by linear regression and Pearson's correlation coefficient. Secondly, in order to evaluate independent predictors of CRP, variables with a significance level $\leq 10\%$ in the univariate analysis were included in a multivariate approach by analysis of covariance, taking *log*-transformed CRP as the dependent variable. A backward technique was used to establish the variables independently associated with CRP.

Secondarily, as a means to evaluate whether the independent predictors of CRP in the low socioeconomic population have a role in determining a different inflammatory profile in these individuals, a sample of high socioeconomic level individuals was selected and *log*-transformed CRP was compared between the two by Student's *t* test. Then, variables found to be predictors of CRP in the multivariate analysis were compared between the two groups, in order to identify the factors that intermediate the relationship between socioeconomic level and inflammation. Finally, the difference in CRP between the groups was adjusted for intermediate variables (predictors of CRP that differed between these two groups) by analysis of covariance. SPSS version 10.0 (Chicago, Illinois, USA) was used for data analysis and a P value < 0.05 was considered statistically significant.

Sample size calculation was based on the multivariate analysis of CRP predictors. In order to provide 80% statistical power, it is established that 20 individuals are necessary for each covariate of the multivariate analysis[18]. Considering that 82 individuals were studied, a maximum of 4 covariates in the model yield adequate statistical power. The covariates entered in the analysis of covariance model were determined by the univariate analysis, so the ideal sample size was only known subsequently.

Results

Characteristics of the low socioeconomic sample population

Eight-two individuals from the Monte Gordo community were studied. As depicted in Table 1, this study population usually consisted of young adults (46 ± 10 years), predominantly females of black ethnicity. Educational level was very poor; 44% had no schooling at all and only 5% had reached high school level. Monthly income was no more than a minimal

wage for 71% of the subjects. Regarding traditional risk factors, the group usually had blood pressure, plasma lipids and plasma glucose within the normal range and there was a low prevalence of diabetes, smoking and alcohol consumption. Hypertension was present in 27% of the subjects. Mean body mass index was 27 ± 4.9 Kg/m^2 and 65% of the participants were overweight (> 25 Kg/m^2). Physical inactivity was identified in 28%. Regarding general health, there was a 35% prevalence of periodontal disease (evaluated in 54 individuals) and 32% prevalence of acute infectious conditions at the time of CRP evaluation. Among individuals with acute inflammation, 63% of the cases were identified as flu-like symptoms and 23% had urinary symptoms. Intestinal parasitosis, evaluated in 64 participants, was observed in only 6% of them. Thus, the study population consisted of individuals of very low SE level, body weight frequently above the normal range, and commonly observed infectious conditions. None of the individuals reported a history of myocardial infarction or stroke.

Determinants of inflammation in the low socio-economic sample population

The level of CRP had a median of 2.0 mg/L (interquartile range 0.92 – 4.95 mg/L). When the median of CRP was compared between groups, demonstrated by the presence or absence of clinical characteristics or risk factors (Table 2), overweight individuals (body mass index ≥ 25 Kg/m^2) showed higher levels (4.08 mg/L) in comparison with those of normal weight (1.22 mg/L, P < 0.001), as well as smokers (4.84 mg/L vs. 1.86 mg/L, P = 0.01) and hypertensive subjects (4.59 mg/L vs. 1.70 mg/L, P = 0.007). Individuals with acute inflammation had a trend towards higher CRP levels (3.60 mg/L vs. 1.79 mg/L, P = 0.10). In opposition, alcohol intake was associated with lower levels of CRP (0.94 mg/L vs. 2.35 mg/L, P = 0.02). C-reactive protein levels were not associated with gender, ethnicity, educational level, income, physical activity, parasitosis or diabetes. When linear association was tested between continuous variables and *log*-transformed CRP, body mass index (r = 0.51, P < 0.001), waist circumference (r = 0.47, P < 0.001), age (r = 0.23, P = 0.038) and LDL-cholesterol (r = 0.22, P = 0.047) had a positive correlation with CRP – Table 2.

The variables associated with CRP in the univariate analysis at ≤ 10% confidence level entered the multivariate analysis of covariance as independent variables (body mass index ≥ 25 Kg/m^2, hypertension, smoking, acute inflammation, alcohol consumption and LDL-cholesterol). Although waist circumference had a significant correlation with CRP, it was not included in the model, due to its intense colinearity with BMI (r = 0.89, P < 0.001). To determine which of these two variables were to be included in the model, a partial correlation was performed with body mass index and waist circumference, having *log*-CRP as the dependent variable. After adjusting for waist circumference, body mass index tended to maintain its association with CRP (r = 0.21, P = 0.07). On the contrary, waist circumference completely lost its association with log-CRP after adjustment for body mass index (r = 0.05, P = 0.67). Thus, BMI was chosen as the marker of adiposity in the present study.

Table 1 - Demographic and clinical characteristics of the low socio-economic group

Categorical variables	Frequência
Sample size	82
Female gender	67 (82%)
Black ethnicity	69 (84%)
Educational level	
No education	36 (44%)
Elementary school	32 (39%)
High school	4 (5%)
Very low income	58 (71%)
BMI ≥ 25 Kg/m^2	53 (65%)
Hypertension	22 (27%)
Diabetes	6 (7%)
Smoking habit	8 (10%)
Physical inactivity	23 (28%)
Alcohol ≥ 2 days/week	8 (10%)
Statin therapy	1 (1%)
Estrogen therapy	5 (6%)
Periodontal disease	19/54 (35%)
Acute inflammation	26 (32%)
Intestinal parasitosis	4/64 (6%)
Numeric variables	**Mean ± SD**
Age (years)	46 ± 10
Body mass index (Kg/m^2)	27 ± 4,9
Waist circumference (cm)	88 ± 12
Systolic blood pressure (mmHg)	135 ± 21
Diastolic blood pressure (mmHg)	82 ±12
Total cholesterol (mg/L)	199 ± 42
HDL-cholesterol (mg/L)	50 ± 14
LDL-cholesterol (mg/L)	124 ± 34
Triglycerides (mg/L)	128 ± 130
Glucose (mg/dl)	85 ± 40
C-reactive protein (mg/L) - median	2.0

Very Low income: no more than 1 minimal wage a month (equivalent to 227.00 US dollars); Physical Inactivity: < 150 minutes a week of moderate exercise; BMI: body mass index; Acute Inflammation: possible acute infection on the day of blood sample collection for C-reactive protein measurement.

In the multivariate analysis, the variables which remained independent predictors of CRP were body mass index ≥ 25 Kg/m^2 (P < 0.001; β = 0.41, 95% CI = 0.20 - 0.61), smoking (P = 0.005; β = 0.48, 95% CI = 0.15 - 0.82) and acute inflammation (P = 0.049; β = 0.21, 95% CI = 0.001 - 0.42). On the other hand, age, hypertension, alcohol intake and LDL-cholesterol lost its statistical significance (Table 3).

Table 2 - Association between C-reactive protein and demographic/ clinical characteristics of the low socio-economic group

Clinical Characteristic	Median of C-Reactive Protein (mg/L)		P Value
	Variable Present	Variable Absent	
Female gender	2,27	1,77	0,70
Black ethnicity	1,87	3,05	0,47
No education	1,92	2,31	0,77
Very low income	1,94	4,34	0,33
Hypertension	4,59	1,79	0,007
Diabetes	3,52	1,92	0,16
Smoking habit	4,84	1,86	0,01
BMI ≥ 25 Kg/m^2	4,08	1,22	< 0,001
Physical inactivity	1,65	2,43	0,41
Alcohol ≥ 2 days/week	0,94	2,35	0,02
Estrogen therapy	2,35	1,96	0,48
Periodontal disease	2,50	1,73	0,32
Acute inflammation	3,60	1,79	0,10
Intestinal parasitosis	2,89	1,82	0,64

	Correlation with log-transformed C-reactive protein	
Clinical Characteristic	**Pearson's Coefficient (R)**	**P Value**
Age (years)	0.23	0.038
Body mass index (mg/L)	0.51	< 0.001
Waist circumference (cm)	0.47	< 0.001
Systolic BP (mmHg)	0.14	0.20
Diastolic BP (mmHg)	0.12	0.35
Total cholesterol (mg/L)	0.17	0.12
HDL-cholesterol (mg/L)	0.02	0.85
LDL-cholesterol (mg/L)	0.22	0.047
Triglycerides (mg/L)	- 0.01	0.62
Glucose (mg/dl)	< 0.001	1.0

Very Low income: no more than 1 minimal wage a month (equivalent to 227.00 US dollars); Physical Inactivity: < 150 minutes a week of moderate exercise; Acute Inflammation: acute infection on the day of blood sample collection for C-reactive protein measurement; BMI - body mass index; BP - blood pressure.

Inflammation in low versus high socio-economic groups

To serve as a comparison group, 32 individuals of high SE status were selected according to study protocol. Differently from the low SE group, this opposite group had only 7% of individuals with no schooling and 97% had an income higher than minimal wage. When CRP levels were compared between the two samples, the low SE group (2.02 mg/L; interquartile range 0.92 – 4.95 mg/dl) had significantly higher levels than the high SE group (1.16 mg/L, interquartile range 0.55 – 2.50 mg/dl, P = 0.03) – Figure 1, Panel A. The low SE group was younger, had more females and individuals with black ethnicity. Regarding the predictors of CRP determined by the multivariate analysis in the low SE group, smoking was similar between the groups, but body mass index was higher and acute inflammation more frequent in the low socio-economic group – Table 4. Therefore, these two variables could be the explanation for the difference in CRP between the two groups. In order to test this hypothesis, an analysis of covariance model for prediction of *log*-CRP was utilized, taking the SE group, body mass index ≥ 25 Kg/m^2 and acute inflammation as covariates. In this analysis, the SE group lost statistical significance after adjustment for the other two

Table 3 - Multivariate analysis of log-transformed C-reactive protein prediction by analysis of covariance in the individuals of low socio-economic status (N = 82).

	Initial model	Final model	
Independent variable	**P value**	**Regression coefficient β (95% CI)**	**P value**
Hypertension	0.22		
Smoking habit	0.014	0.48 (0.15 - 0.82)	0.005
BMI ≥ 25 Kg/m^2	0.009	0.41 (0.20 - 0.61)	< 0.001
Alcohol ≥ 2 days/week	0.22		
Acute inflammation	0.056	0.21 (0.001 - 0.42)	0.049
Age	0.97		
LDL-cholesterol	0.52		

Final model contains only significant predictors of log-transformed C-reactive protein; BMI - Body Mass Index.

Table 4 - Comparison of demographic data and independent predictors of C-reactive protein between low and high socio-economic groups

	Low SE Group	High SE Group	P Value
Sample size	82	32	
Age (years)	48 ± 10	56 ± 7	0.001
Female gender	82%	57%	0.007
Black ethnicity	84%	50%	< 0.001
Very low income	72%	3%	< 0.001
No education	44%	7%	< 0.001
Body mass index (Kg/m^2)	27 ± 4.9	25.5 ± 3.2	0.07
Smoking habit	9.8%	10%	0.97
Acute infection	32%	3%	0.002

SE: Socio-economic; Very Low income: no more than 1 minimal wage a month (equivalent to 227.00 US dollars); Acute Inflammation: acute infection on the day of blood sample collection for C-reactive protein measurement; Periodontal Disease: 55 patients evaluated in the low SE group and 20 patients in the high SE group; Intestinal Parasitosis: 60 patients evaluated in the low SE group and 17 patients in the high SE group.

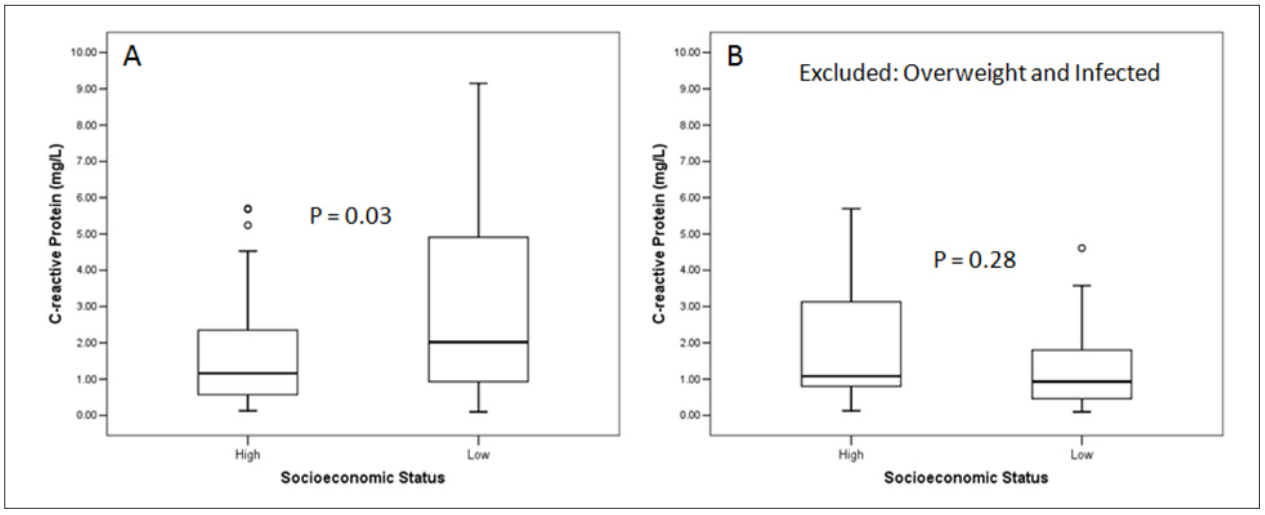

Figure 1 - Panel A compares C-reactive protein values between individuals of low socioeconomic status versus those of high socioeconomic status. Panel B makes the same comparison with the 34 individuals with body mass index < 25 kg/m2 and no acute inflammatory condition (21 of low socioeconomic status and 13 of high socioeconomic status). Upper scale level was set at 10 mg/L, although some values were above this limit.

variables (P = 0.17). Accordingly, when the subgroup of 34 individuals with normal body mass index and no infection condition was analyzed, CRP levels were similar between the groups of low (0.93 mg/L) and high (1.08 mg/L, P = 0.28) SE levels – Figure 1, Panel B.

Discussion

The present study indicates that adiposity, smoking and acute infection conditions are the independent predictors of CRP in individuals with very low SE status in a developing country, Brazil. Clinical and social predictors of CRP in the general population have been described in studies that took place in developed countries, such as the United States of America[12,19], Finland[20], Germany[21], England[11], Italy[22], Belgium[22]. Thus, the novelty of the present work consists in the investigation of environmental predictors of CRP in individuals of much lower SE conditions, in relation to what has been presented in the literature. Moreover, a sample of high SE status was compared with the low SE individuals in order to test the hypothesis that SE status influence low-grade inflammation. Indeed, CRP was higher in the low SE group, and this difference was statistically explained by greater body mass index and higher prevalence of acute infections at the time of evaluation.

Adiposity has been consistently described as the single most important determinant of CRP levels in the general population, in line with experimental evidence that adipocytes secrete interleukin-6[23], the main stimulus for CRP biosynthesis, and human subcutaneous adipose tissue expresses CRP mRNA[24]. In the present study, being overweight was the main independent predictor of CRP in low SE individuals. Thus, the data indicates that the great importance of adiposity observed in studies of developed countries remains a phenomenon of similar magnitude in lower SE realities. Interestingly, body mass index tended to be higher in the low SE group and this variable was a predictor of CRP in these individuals. The reason for the body mass index disparity between SE levels was not assessed by the study, but one can speculate that the amount of fat and high energy carbohydrates are possibly higher in the low SE individuals, as opposed to the more balanced diet in the high SE group[25].

Two measures of adiposity have been utilized in epidemiological studies: body mass index, a measure of total adiposity, and waist circumference, a measure of central adiposity. In our study, both measures were associated with C-reactive protein, but when body mass index and waist circumference were entered in the same model, the first was revealed as the independent predictor. Previous data has shown that, in women, body mass index is a stronger predictor than waist circumference, while in men waist circumference is the most important[22]. Thus, the predominance of women in our sample might be the reason for the stronger association with body mass index.

Following adiposity, smoking was the second most important determinant of C-reactive protein. This is in line with previous literature studies that demonstrated this risk factor as CRP predictor[26,27]. This phenomenon might be mediated by subclinical atherosclerosis, which is more prevalent in smokers. However, the prevalence of smoking did not vary according to the SE status, thus, not being responsible for the CRP heterogeneity between the SE groups.

Acute infection was another predictor of CRP level in the multivariate analysis and this finding is closely related to SE status, because environmental factors associated to a low SE condition leads to higher vulnerability to common infections. Indeed, acute infection at the time of the laboratory evaluation was 10 times more prevalent in the low SE group, compared to the high SE group of individuals. This might be a finding limited to very low SE conditions, because when the Multiethnic Study of Atherosclerosis (MESA) compared different SE status in the United States, there was no difference regarding recent infection[12]. Indeed, our population had a much worse SE

condition compared with that of the MESA population: 71% had a monthly income ≤ 227 US dollars, compared with a median of 3.125 US dollars in the MESA population. While in our sample only 5% had completed high school (nine years of education), the MESA study showed a median of 14 years of education. Thus, only under very poor conditions found in the developing world, acute infection is found as one of the responsible factors for the inverse association between SE level and low-grade inflammation. According to clinical guidelines, individuals with acute infection should not have cardiovascular risk assessed by C-reactive protein. However, the objective of the present study was not to assess cardiovascular risk. The aim was to evaluate the real inflammatory status of the two types of populations. Therefore, this exclusion criterion was not applied.

Risk factors such as hypertension, aging and LDL-cholesterol had a significant association with elevated CRP in the univariate analysis, but not in the multivariate model, suggesting that traditional risk factors were indirectly associated with CRP, via a primary relation with adiposity, as demonstrated before[19]. In addition, this is the first analysis to evaluate the effect of periodontal disease and parasitosis in a study that takes into account SE status. Unexpectedly, these inflammatory factors were not related to CRP, but we cannot rule out type II error as the justification for this lack of association. This issue needs to be clarified by future studies.

Limitations of the present study must be recognized. Firstly, in relation to the sample selection: the groups of SE status were non-probabilistic samples, what limits the generalizability of the present data. To avoid further selection bias, all parents were invited and all who responded positively were studied. Thus, there was no investigators' influence on patient's selection. In addition, our sample had a large predominance of females and the external validity of our conclusions to males is limited. Finally, the samples of high and low SE levels were not similar in terms of age, gender and ethnicity. This heterogeneity resulted from the fact that the samples were obtained from two different environments. However, since these variables did not have association with C-reactive protein levels, they did not act as confounders in the comparison of inflammation between the two SE groups. The sample size is another important issue which has to be discussed. To compute seven covariates in the multivariate analysis, 140 individuals would be necessary to yield an ideal statistical power. Therefore, the actual sample size may have missed additional independent predictors of inflammation due to insufficient statistical power.

Secondly, there is consistent evidence that CRP is influenced by psychological conditions, such as cynical distrust or lack of prestige[28-30]. These psychological factors, which are associated with SE level, might be causally related to cardiovascular disease. Thus, the fact that this study did not assess psychological conditions should be seen as a limitation to be resolved by future research. Thirdly, due to the cross-sectional nature of the study, one cannot guarantee that the relationship between CRP and its predictors are causally in nature. However, several scientific criteria of causation (such as consistency with previous literature, dose-response relationship regarding BMI, statistical strength, lack of alternate explanation and biological plausibility) suggest that it is adiposity, smoking and infection that cause CRP increase and not the contrary.

The clinical relevance of the present data relies on some observations: firstly, the burden of cardiovascular disease is greater in developing countries[4,5], justifying continuous efforts towards the understanding of this epidemiological phenomenon; secondly, inflammation has been established as a risk factor for cardiovascular disease in longitudinal studies, indicating independent association with cardiovascular events[8] and by randomized trials showing that reduction of inflammation is related to clinical benefit[9]; thirdly, by suggesting alternative mechanisms of increasing inflammation in low SE societies, our study indicates a potential pathway in prevention of cardiovascular disease. Regarding this last observation, we should recognize that this study is hypothesis-generating. It remains to be demonstrated that a decrease in inflammatory activity and cardiovascular risk will result from improving SE conditions of poor populations.

Therefore, the present study suggests that adiposity, smoking and common infections are associated with the inflammatory burden in poor societies. Further studies should focus on the anti-inflammatory impact of controlling traditional risk factors and improving living conditions of poor communities.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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