

Adiposity and Pathogen Exposure Predict C-Reactive Protein in Filipino Women^{1,2}

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Abstract

Obesity and infectious agents are both sources of inflammatory stimuli that result in increased production of C-reactive protein (CRP). Rates of overweight and obesity are increasing globally, but for many populations, gains in body fat are set against a backdrop of high levels of pathogen exposure. Our primary objective was to evaluate the extent to which adiposity and pathogenicity contribute to a double burden of inflammation in a population currently undergoing the nutrition transition. Measures of adiposity, pathogen exposure, and infectious disease symptoms were evaluated as predictors of high-sensitivity CRP concentration in plasma samples from 1875 women participating in the Cebu Longitudinal Health and Nutrition Survey in the Philippines. Proxy measures of pathogen exposure included household crowding and cleanliness, quality of water source, mode of waste disposal, and fecal exposure. A series of maximum likelihood logistic regression models were used to predict a plasma CRP concentration > 3 mg/L. Waist circumference was the strongest anthropometric predictor of elevated CRP [odds ratio (OR) = 2.29; 95% CI = 2.00, 2.62; $P < 0.001$]. Presence of infectious disease symptoms (OR = 2.51; 95% CI = 1.84, 3.44; $P < 0.001$) and level of pathogen exposure (OR = 1.56; 95% CI = 1.15, 2.12; $P < 0.01$) were also associated with elevated CRP. These associations were independent of socioeconomic status and other health behaviors. Overweight/obesity and infectious exposures are associated with elevated CRP in the Philippines; it is likely that other populations undergoing the nutrition transition are experiencing comparable double burdens of inflammatory stimuli. These results underscore the need for additional research on the contributions of pathogenicity, adiposity, and inflammation to global epidemics of cardiovascular and metabolic diseases. *J. Nutr.* 138: 2442–2447, 2008.

Introduction

Chronic degenerative diseases have recently superseded nutritional deficiencies and infectious diseases as the primary causes of morbidity and mortality worldwide (1,2). Whereas classic epidemiologic transition theory postulates that rising rates of communicable diseases are preceded by declines in infectious disease (3), many populations in less developed countries are now confronting a double burden of disease in which rapidly rising rates of obesity and associated metabolic conditions are supplementing rather than supplanting infectious diseases as contributors to morbidity and mortality (4–6). Obesity and pathogen exposure are both involved in activating proinflammatory pathways and we investigated these factors as predictors of plasma C-reactive protein (CRP)⁶ to evaluate whether women

in the Philippines are experiencing a double burden of inflammation as a result of the nutrition transition.

The development of high sensitivity assays has revealed that slight elevations in CRP, indicating chronic, low-grade inflammation, are associated with subsequent incidence of cardiovascular disease (7), type 2 diabetes (8), the metabolic syndrome (9), late-life disability (10), and mortality (11). This rapidly growing literature has drawn attention to the important role that inflammatory processes may play in the pathophysiology of a wide range of chronic diseases (12). Even as uncertainty remains about the causal role of CRP in the pathophysiology of chronic disease processes and outcomes, the value of CRP as a marker of risk has been widely demonstrated and it is increasingly being used in routine clinical practice (13).

In light of the roles played by infectious agents (14–17) as well as adipose tissue (18–20) in upregulating inflammatory pathways, populations undergoing the nutrition transition may be particularly vulnerable to metabolic and cardiovascular diseases linked to inflammation. The Philippines is a lower-middle income nation undergoing considerable economic, dietary, and lifestyle changes, and it exemplifies current trends toward rising prevalences of overweight, cardiovascular disease, and the metabolic syndrome globally (21,22). At the same time, infectious disease accounts for over 30% of all mortality in Southeast

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⁶ Abbreviations used: CRP, C-reactive protein; OR, odds ratio; SES, socioeconomic status; VAT, visceral adipose tissue.

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Asia, with pneumonia, diarrhea, and tuberculosis serving as major contributors (23). In the Philippines, respiratory infections rank beside ischemic heart disease as the top causes of mortality (24).

This pathogen burden, in combination with the potential impact of recent increases in body weight, provides an opportunity to investigate the predictors of inflammation in a population confronting double burdens of disease. Furthermore, because overweight is positively related to socioeconomic status (SES) in Cebu (21) (unlike the US and other affluent nations) and because we expect exposure to pathogens to be negatively related to SES, we are in a better position to disentangle the independent roles that adiposity and pathogen exposure may play in predicting inflammation. Our specific objectives in this article are 3-fold: 1) to document concentrations of CRP in Filipino women undergoing the nutrition transition; 2) to investigate associations between CRP and both anthropometric measures of nutritional status as well as proxy measures of pathogen exposure; and 3) to evaluate the extent to which adiposity and pathogenicity contribute to a double burden of inflammation in this population.

Subjects and Methods

Participants and data collection. The Cebu Longitudinal Health and Nutrition Survey began in 1983 with the recruitment of 3327 pregnant women representative of the childbearing population in Cebu City (25). The women have been followed through multiple rounds of data collection since 1983 and the data for the present analyses come from the most recently completed survey, conducted in 2005, when the women were 35–69 y. Complete anthropometric, environmental, socio-demographic, and CRP data were available for 1875 women (6 women who were pregnant at the time of survey were excluded). Participants provided information on household demographics and income levels, economic activities and resources, environmental quality, and health behaviors in personal interviews conducted in their homes. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

We evaluated how our sample differed from the original cohort as assessed when the study started in 1983. Compared with those lost to follow-up, participants remaining in the study were significantly older (6.61 ± 2.50 mo), had less formal education (0.86 ± 0.13 y), lower household income (0.06 ± 0.01 log pesos) and number of household assets (0.19 ± 0.07 items), and lived in slightly more rural communities (3.65 ± 0.43 points on urbanicity scale, see below). Participants did not differ in height at baseline or in other household traits.

Body weight, height, waist and hip circumferences, and triceps, subscapular, and suprailiac skinfold thicknesses were measured using standard anthropometric techniques (26). The BMI was calculated as the ratio of weight (kg):height (m^2).

Following prior research in the Philippines and elsewhere (27–29), we collected multiple measures of environmental quality as proxies for the likelihood of exposure to infectious microbes. Measures included household crowding (number of persons per number of rooms), type of toilet (no toilet, pit, flush/water sealed), and source of drinking water (bottled, piped municipal supply, closed well with pump, open sources: uncovered well, spring, river, rain). We also constructed a pathogen exposure scale based on 5 variables, each scored on a 3-point scale (0 = low exposure, 1 = moderate, 2 = high): cleanliness of the food preparation area, means of garbage disposal, presence of excrement near the house, level of garbage, and excrement present in the neighborhood surrounding the household. Cronbach's α for the scale was 0.741, suggesting a relatively high degree of reliability. Low correlations between these variables and our measures of household density, toilet type, and water access precluded the construction of a single summary pathogenicity scale. Prior analyses in the Cebu Longitudinal Health and Nutrition Survey have documented significant associations between comparable measures of environmental quality and risk for infant diarrhea, attesting to their utility as proxies for pathogen exposure (29).

In addition to measures of pathogen exposure, at the time of blood collection, we asked participants if they were currently experiencing any symptoms of infection, consistent with prior research on CRP (30,31). Symptoms included runny nose, cough, fever, diarrhea, and sore throat, as well as the more general categories of flu, cold, and sinusitis. Responses were used to construct a summary variable indicating the presence or absence of any infectious symptoms at the time of blood collection. Participants were also asked to report any medications they were currently taking. Only 16% of the sample reported taking medications at the time of blood collection, and we considered 5 broad categories of medications with potential relevance to CRP: oral contraceptives, antihypertensives, antibiotics, cough and cold remedies, and antiinflammatory analgesics. No other types of medication were reported with sufficient frequency for analysis. Individuals reporting symptoms of infection were more likely to be taking antibiotics (Pearson $\chi^2 = 67.5$; $P < 0.001$) or cough/cold remedies (Pearson $\chi^2 = 359.6$; $P < 0.001$), suggesting that these reports were capturing the experience of infectious symptoms in this population.

In an attempt to capture other unmeasured aspects of environmental quality and lifestyle that may be related to CRP, we considered 4 measures of SES: highest grade completed, household income, household assets, and home ownership. We also used a previously validated measure of the degree of urban development in the community in which participants lived (32). This scale is based on population size and density, availability of communications (e.g. telephone, Internet), transportation infrastructure, and presence of educational facilities, health services, and markets for food and other consumer goods. Higher scores (range, 0–70) on the scale indicate a higher degree of urban development.

CRP analysis. Venipuncture blood samples were collected using EDTA-coated vacutainer tubes in the participants' homes in the morning after an overnight fast. Blood samples were kept in coolers on ice packs for no more than 2 h and were then centrifuged to separate plasma prior to freezing at -70°C . Samples were express-shipped in a single batch to Northwestern University on dry ice and stored frozen at -80°C until analysis. CRP concentrations have been shown to remain stable under these transport and storage conditions (33). CRP concentrations were determined using a high sensitivity immunoturbidimetric method (Synchron LX20, lower detection limit: 0.1 mg/L).

Statistics. We performed a series of maximum likelihood logistic regression analyses to predict, first, the likelihood of CRP >10 mg/L and then CRP >3 mg/L, excluding those individuals with CRP >10 mg/L. These cut-off values were selected based on recommendations issued by a recent joint scientific statement from the AHA and the CDC (13). Concentrations of CRP >10 mg/L are presumed to be the result of acute inflammatory processes (e.g. infectious disease), whereas elevations of CRP >3 mg/L but <10 mg/L indicate increased cardiovascular risk due to chronic, low-grade inflammation. Recent research, however, has suggested that CRP concentrations >10 mg/L are also predictive of cardiovascular risk (34). We therefore conducted a final series of analyses predicting the likelihood of CRP >3 mg/L in the entire sample. In addition, we used Pearson product-moment correlation coefficients to investigate bivariate associations among BMI, SES, and pathogen exposure.

Analyses proceeded in 3 stages. First, we considered anthropometric measures of nutritional status as predictors of elevated CRP. We began with crude associations, followed by models that adjusted for additional factors known to influence CRP (age, smoking, alcohol consumption, medication use). Adjusted models also included measures of SES and urbanicity in an attempt to account for omitted variables related to lifestyle and/or environmental quality that might confound associations between CRP and our more proximate measures of nutritional status and pathogenicity. Second, in a separate set of models, we evaluated crude and adjusted associations with measures of pathogen exposure and infectious disease. Finally, we considered a combined model with significant nutritional status and pathogenicity variables to evaluate their independent and combined contributions to explaining elevated CRP. All statistical analyses were conducted with Stata for Windows, version 10 (StataCorp). We used $\alpha < 0.05$ as the criterion for significance. Values in the text are means \pm SEM or odds ratio (OR), 95% CI.

Results

The median CRP concentration was 0.9 mg/L (Table 1). Mean BMI was 24.3 kg/m², with 41.4% of the sample classified as overweight or obese according to WHO criteria [BMI ≥25; (35)]. Applying lower BMI cut-points recommended for Asian populations [≥23; (36–38)] increased the prevalence of overweight/obesity to 59.5%. As expected, measures of SES were positively associated with BMI, including household income ($r = 0.21$; $P < 0.001$), highest completed grade ($r = 0.16$; $P < 0.001$), and household assets ($r = 0.29$; $P < 0.001$). Similar associations were also found with other anthropometric measures of adiposity. Conversely, socioeconomic measures were negatively related to scores on our pathogen exposure scale, including household income ($r = -0.08$; $P < 0.001$), highest completed grade ($r = -0.10$; $P < 0.001$), and household assets ($r = -0.22$; $P < 0.001$).

Eighty-four women, or 4.5% of the sample, had concentrations of CRP >10 mg/L. Age (1.04, 1.00, 1.07; $P < 0.05$), the presence of infectious disease symptoms at the time of blood collection (2.66, 1.65, 4.26; $P < 0.001$), and living in a more urban environment all predicted CRP >10 mg/L (1.27, 1.01, 1.61; $P < 0.05$). No anthropometric, socioeconomic, or other pathogenicity variables approached significance as predictors of CRP >10 mg/L.

We next modeled the likelihood of CRP >3 mg/L, excluding the 84 women with CRP >10 mg/L. Twenty percent of the sample ($n = 352$) had CRP >3 mg/L and ≤10 mg/L. Each anthropometric measure of body composition was significantly associated with increased CRP, but waist circumference was the strongest predictor and the only one that remained significant when measures were considered simultaneously (Table 2, Model 1). This association was independent of age, smoking, household income, use of antiinflammatory analgesics, and neighborhood urbanicity, all of which were positively associated with elevated CRP. Other medication variables were not associated with CRP. The association between waist circumference and CRP was not substantially altered by the addition of these covariates. Controlling for these variables, each SD increase in waist circumference was associated with a >1-fold increase in risk of CRP >3 mg/L.

Variables representing pathogen exposure and symptoms of infection were significantly associated with elevated CRP, even though individuals with CRP >10 mg/L were eliminated from the analyses. The presence of symptoms of infectious disease at the time of blood collection was a strong predictor of CRP >3 mg/L, as was our pathogen exposure scale (Table 2, Model 2). Similar patterns of association were found for each of the variables comprising the summary scale. Household density and the presence of a flush toilet were not associated with CRP.

TABLE 1 Descriptive statistics for study participants¹

Age, y	47.7 (6.1)
Household income, pesos/wk	574.4 (1200.1)
Highest grade of school completed	7.2 (3.8)
Household assets, 0–11	5.2 (1.9)
BMI, kg/m ²	24.3 (4.4)
Waist circumference, cm	81.1 (10.9)
Pathogen exposure scale, 0–2	0.6 (0.4)
Symptoms of infection, %	16.8
Current smoker, %	16.1
CRP, mg/L	0.9 (0.3, 2.8)

¹ Values are mean ± SD, median (25th percentile, 75th percentile) or %, $n = 1875$.

Our measure of water quality was also associated with elevated CRP. Compared with women whose households used bottled water for consumption, those that relied on open sources (uncovered well with bucket, spring, river, or rain) were less likely to have elevated CRP. This association was contrary to expectation and was attenuated slightly with the addition of household income to the model. Associations between other measures of pathogen exposure/infection and CRP remained unchanged with the addition of covariates.

Finally, we evaluated simultaneously measures of adiposity and pathogen exposure as predictors of elevated CRP (Table 2, Model 3). Waist circumference, symptoms of infectious disease, and pathogen exposure remained as strong, independent predictors of elevated CRP. The addition of waist circumference (which is positively associated with SES) eliminated the association between CRP and water quality. Household income was not significantly associated with elevated CRP in the full model. Smoking, as well as residence in neighborhoods with a higher degree of urban development, was also positively associated with elevated CRP.

Results were very similar when models were rerun including women with CRP >10 mg/L (results not shown). Smoking was an exception and was not significantly associated with CRP >3 mg/L when all women were considered.

We calculated the predicted probability of CRP >3 mg/L based on regression coefficients (Table 2, Model 3) to evaluate the magnitude of the independent associations among CRP, waist circumference, and pathogen exposure (Fig. 1A). Variables were set to low and high levels and individual values were retained for other covariates. For women with waist circumference 1 SD above average, the predicted probability of CRP >3 mg/L was 0.30 compared with 0.08 for women 1 SD below average. Living in a high-pathogen household environment or having symptoms of infection were associated with similarly high probabilities of elevated CRP.

We next considered 4 scenarios representing the double burden of inflammation (Fig. 1B). Our model (Table 2, Model 3) predicted that the probability of elevated CRP was 0.08 for women in Cebu who live in low-pathogen environments and who are 1 SD below average for waist circumference. For women with low pathogen exposure but high waist circumference, the probability of elevated CRP more than tripled to 0.29. This scenario is roughly comparable to that common for many women in affluent western settings and, indeed, approximately one-third of women in the US have CRP concentrations >3 mg/L (and <10 mg/L) (39). For women in Cebu with low waist circumference but high pathogen exposure, a scenario common in Cebu until the onset of the nutrition transition, the predicted probability of elevated CRP was 0.12. Double burdens of inflammatory stimuli, represented by high waist circumference and high pathogen exposure, increased the probability of elevated CRP to 0.42. This scenario may be more common as rates of overweight and obesity increase, whereas levels of environmental contamination remain high. In this sample, nearly 40 percent of all women resided in households where moderate or high levels of excrement were visible near the house.

Discussion

Dual burdens of chronic degenerative as well as infectious diseases are increasingly common in many populations around the world. In this study, we found that measures of body fat and pathogen exposure were significant, independent predictors of elevated CRP in women in the Philippines. These results suggest

TABLE 2 Results of maximum likelihood models predicting the likelihood of CRP >3 mg/L, excluding individuals with CRP >10 mg/L

	Model 1				Model 2				Model 3	
	Crude		Adjusted		Crude		Adjusted			
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI		
Waist circumference, standardized	2.29***	2.01, 2.61	2.22***	1.94, 2.53					2.29***	2.00, 2.62
Pathogen scale, 0–2					1.48**	1.12, 1.94	1.49**	1.10, 2.00	1.56**	1.15, 2.12
Infectious symptoms, 0, 1					2.18***	1.64, 2.89	2.23***	1.67, 2.99	2.51***	1.84, 3.44
Water source ¹										
Piped municipal supply					0.70*	0.51, 0.96	0.67*	0.47, 0.94		
Closed well with pump					0.55**	0.39, 0.78	0.64*	0.45, 0.93		
Open sources					0.29***	0.17, 0.49	0.47*	0.27, 0.85		
Age, <i>y</i>			1.03*	1.01, 1.05			1.03*	1.01, 1.05	1.03**	1.01, 1.05
Current smoker, 0, 1			1.59**	1.14, 2.23					1.48*	1.05, 2.09
Antiinflammatory analgesics, 0, 1			2.55*	1.09, 5.95			2.94*	1.27, 6.77	2.45*	1.05, 5.72
Household income, <i>log pesos</i>							1.54*	1.07, 2.21		
Urbanicity, 0–70			1.02**	1.01, 1.03			1.02**	1.01, 1.03	1.01*	1.00, 1.02
Model <i>P</i> -value			<0.001				<0.001		<0.001	

¹ Bottled water is the reference group.
* *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

that a double burden of inflammatory stimuli may be an important component of the nutrition transition in similar populations, with potential implications for understanding patterns of chronic degenerative disease globally.

In Cebu, SES is positively associated with overweight/obesity but negatively associated with pathogen exposure. Socioeconomic factors were not strong predictors of CRP in this population, likely due to the opposing influences that as SES increases, higher levels of overweight/obesity can be expected to promote CRP production, whereas cleaner household and neighborhood environments should reduce CRP production. These results confirm that Cebu is an advantageous setting in which to disentangle the independent contributions of adiposity and pathogenicity to variation in CRP, complementing findings from more affluent settings where exposure to pathogens and excess body fat are both likely to be concentrated in lower socioeconomic strata.

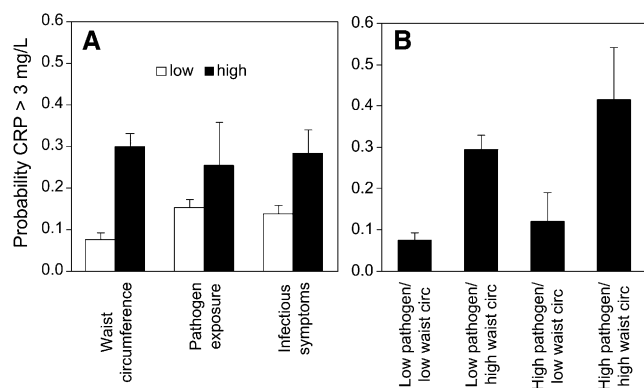


FIGURE 1 Probability of elevated CRP in relation to inflammatory stimuli: independent associations with waist circumference, pathogen exposure, and infectious symptoms (A) and cumulative associations representing double burdens of inflammatory stimuli (B). Values are predicted probability of CRP >3 mg/L for the entire sample (excluding individuals with CRP >10 mg/L) based on coefficients from Table 2, Model 3, with upper bound of 95% CI, *n* = 1791. Low and high values for predictors were set as follows: waist circumference (± 1 SD); pathogen exposure (≤ 1 , > 1); infectious symptoms (0, 1).

Using a BMI cut-off of 25 kg/m², 41.4% of women in Cebu were overweight or obese compared with 50.7% of European-American women in the US according to recent estimates from the NHANES (40). However, median CRP concentrations were substantially lower among women in Cebu than in their U.S. counterparts. For example, the median CRP concentration for European-American participants in the Women's Health Study (*n* = 24,455) was 2.02 mg/L (41) compared with 0.9 mg/L in Cebu. Interestingly, median CRP concentrations for Asian-American women in this U.S. sample were significantly lower (1.12 mg/L) and similar to the values reported here. Low CRP concentrations in Asian-American women in the Women's Health Study were explained largely by the relatively lower BMI in this group (mean = 23.4 kg/m²).

Similar to prior findings from a wide range of populations (20,42–44), waist circumference was the strongest anthropometric predictor of elevated CRP and among the strongest predictors of all the variables considered. These results are consistent with the established importance of visceral adipose tissue (VAT) as a source of proinflammatory cytokines. Although we did not measure VAT directly, waist circumference provides a more specific measure of central adiposity than do measures such as weight or BMI. VAT may be a particularly important source of inflammatory stimuli in this population, because prior research suggests that Filipino women have a higher proportion of VAT compared with European- or African-American women with the same level of waist circumference (45).

Intensity of pathogen exposure and symptoms of infectious disease were independent predictors of elevated CRP, consistent with the hypothesis that Filipino women are currently experiencing double burdens of inflammatory stimuli. The presence of excreta, unsanitary means of garbage disposal, and an unhygienic food preparation area were all associated with increased risk for elevated CRP. Further, prior research has associated proxy measures of sanitation/pathogen exposure with elevated concentrations of CRP (46, T. W. McDade, S. T. Lindau, and K. Kasza, unpublished results), although few studies using high sensitivity CRP as an indicator of chronic, low-grade inflammation consider such measures. Rather, most prior work has followed recent guidelines (13) and excluded individuals

with CRP >10 mg/L in an effort to control for acute inflammatory conditions.

Contrary to expectations, household consumption of bottled water was associated with elevated CRP. Bottled water is costly and the pattern of results suggests that our water source measure was functioning primarily as a proxy for SES rather than pathogen exposure. This interpretation is supported by the fact that Table 2 shows a graded association between water source and odds of elevated CRP that parallels the association between water source and SES. In addition, prior microbiological analyses of water quality in Cebu suggest that moderate levels of bacterial contamination are not associated with increased prevalence of infant diarrhea compared with low levels of contamination and that other routes of pathogen transmission are likely to be more important in this area (47).

Recent analyses of NHANES data have shown that symptoms of infection increased the likelihood of CRP >10 mg/L by 77% (30). Infectious symptoms explained a substantial portion of the association between poverty and high CRP in this analysis, although infection was not a strong predictor of more modest elevations of CRP (>3 but ≤10 mg/L). This pattern of results underscores the importance of pathogen pressure and infectious disease as determinants of variation in CRP and suggests that cut-off points based on Western reference populations may not be appropriate for populations experiencing double burdens of inflammatory stimuli. It also suggests that investigators need to consider carefully whether individuals with CRP >10 mg/L should be eliminated from their analyses and that serious attention should be given to quantifying pathogen exposure in epidemiological analyses of inflammation.

To the extent that inflammation contributes to the pathophysiology of cardiovascular or metabolic disease, CRP may be an important mediator of the link between the recent increase in obesity prevalence in the Philippines and rising rates of chronic degenerative diseases (21,48). It remains an open question whether upregulation of inflammatory pathways due to pathogen exposure or infection acts independently or synergistically with adiposity in the etiology of cardiovascular disease in Cebu. Indeed, it is possible that increased production of CRP in response to pathogen exposure is part of a distinct inflammatory process that does not contribute to cardiovascular disease. High levels of pathogen exposure early in life shape the regulation of immune and inflammatory pathways (49,50) and may have implications for the association between CRP and cardiovascular disease later in life. However, studies demonstrating associations among infectious agents, elevated CRP concentration, and atherosclerosis suggest the possibility of causal links between pathogen-induced inflammation and the development of disease (14,17). Additional prospective research on the implications of infectious exposures as well as overweight/obesity for the development of cardiovascular disease in populations like the Philippines will be required to address this issue.

A limitation of this study is our use of a single CRP result to indicate chronic, low-grade inflammation. Whereas serial CRP measurements have reported a relatively high degree of intra-individual consistency that is comparable to other serum markers of cardiovascular disease risk, multiple measures as well as measures of other biomarkers of inflammation would provide a more complete and accurate assessment of individual differences in inflammatory activity (13,51,52). In addition, our symptom recall method for assessing current infection lacks specificity that may be relevant to CRP; latent infections, with no overt symptoms, may increase concentrations of CRP, whereas

symptoms associated with allergic reactions may lead to the appearance of infection without increasing CRP production.

This study casts new light on the dynamics of inflammation by focusing on a location where the ecology differs significantly from the relatively affluent settings in which most research on high sensitivity CRP is conducted. Pathogen exposure and adiposity are both important predictors of CRP in Cebu and other populations undergoing the nutrition transition are likely experiencing similar double inflammatory burdens. Our results suggest that caution is in order when generalizing findings across these settings and underscore the need for additional research on the contributions of pathogenicity, adiposity, and inflammation to the global epidemic of cardiovascular and metabolic diseases.

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