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Change in waist circumference over 11 years and current waist circumference independently predict elevated CRP in Filipino women

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Abstract

C-reactive protein, a marker of chronic, low-grade inflammation, is strongly associated with current central adiposity, and has been linked to elevated risk of cardiovascular disease. Less is known about the contribution of longitudinal change in waist circumference to current inflammation. We evaluated the extent to which current waist circumference and change over an 11-year interval contribute independently to low-grade systemic inflammation measured in a group of 1,294 women, 35–69 years, participating in the Cebu Longitudinal Nutrition and Health Survey in the Philippines. Waist circumference was measured at the time of blood draw for CRP analysis in 2005 and during an earlier survey in 1994. A waist circumference delta variable was constructed by subtracting current circumference from past circumference. We used logistic regression models to predict having an elevated plasma CRP concentration (3 mg/L<CRP<10 mg/L). Waist circumference in 2005 was a strong predictor of elevated CRP (OR 1.10, 95% CI=1.08,1.12, P<0.001). In combined models, increase in circumference over 11 years was a significant and independent predictor of elevated CRP risk (OR=1.023, 95% CI=1.00,1.05, P<0.05). Considering the average increase over time, the cumulative risk of elevated CRP due to increased central adiposity was 20.1%. However, women who reduced their waist circumference between 1994 and 2005 had greatly reduced risk (6.2%), suggesting that even long-term inflammatory burden can be reversed by weight loss. Although current waist circumference is an important contributor to risk of elevated systemic inflammation in this as in other populations, history of central adiposity may be an independent phenomenon.

Introduction

Visceral adipose tissue (VAT), measured indirectly by waist circumference, is metabolically and hormonally distinct from subcutaneous fat (Weiss 2007) and is directly implicated in metabolic and cardiovascular disease (CVD) development (Schaffler and others 2006;

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Wajchenberg and others 2002). Visceral fat produces cytokines like TNF-α and IL-6 (Fain and others 2004) which stimulate hepatic production of C-reactive protein (CRP). High-sensitivity CRP is a marker of chronic, low-grade inflammation that has been linked to elevated risk of CVD (Danesh and others 2000), type-2 diabetes (Pradhan and others 2001), the metabolic syndrome (Ridker and others 2003), late-life disability (Kuo and others 2006), and mortality (Jenny and others 2007). Weight, body mass index, and waist circumference tend to be among the strongest predictors of high CRP (Paniagua and others 2008; Rexrode and others 2003), but measures of visceral fat may be the best single anthropometric predictor of elevated CRP (Lee and others 2008; Saijo and others 2004).

Many short-term intervention studies, ranging from 6 to 24 months, have examined the relationship between weight loss and CRP (Heilbronn and others 2001; Selvin and others 2007). Relatively modest decreases (~5 cm) in waist circumference improve lipid profiles and blood pressure (Brochu and others 2003) and lower serum adipocytokines including CRP (Esposito and others 2004; Valsamakis and others 2004). Reduction in CRP levels can be dramatic, reaching 32% in one recent study (Tchernof and others 2002). These studies demonstrate a causal relationship between excess body weight, and more specifically, visceral fat, and elevated CRP and other CVD risk factors. It is presently less clear whether a chronic history of being overweight is important independent of one's current adiposity. It has been proposed that long-term weight excess can lead to chronic dysregulation of physiologic systems, including inflammation (Seeman and others 2001). Recent longitudinal studies have confirmed a linear relationship between increases in weight and CRP measured over 9 years (Fogarty and others 2008), suggesting that long term weight profiles could be used to predict CRP prospectively. Barzilay et al. (Barzilay and others 2006) showed that elevated baseline CRP predicted weight gain over a 3-year period. One recent study found an association between prior adult weight gain and elevated CRP in a cohort of Japanese adults over 40 years old, independent of current adiposity (Saito and others 2003). Considering the specificity of visceral fat in systemic inflammation related to cardiovascular and metabolic disease risk, it is unclear what role longitudinal profiles of waist circumference play in driving inflammation. To date, no studies have explored the specific role of an individual's history of central adiposity deposition as a predictor of later CRP.

The Philippines is a lower-middle income nation undergoing significant economic, dietary and lifestyle changes, and it exemplifies current trends toward rising prevalence of overweight, cardiovascular disease, and the metabolic syndrome globally (Adair 2004; Tanchoco and others 2003). At the same time, infectious disease accounts for over 30% of all mortality in Southeast Asia (WHO 2004), leading to a dual burden of pro-inflammatory stimuli (McDade and others 2008). We (McDade and others 2008) recently demonstrated that waist circumference was the strongest anthropometric predictor of elevated CRP in a cohort of women from Cebu, Philippines, but this was a cross-sectional analysis, thus leaving unknown whether it is merely waist circumference in the present, or an individual's chronic history of abdominal fat deposition, that is most predictive of inflammatory status. In hopes of clarifying these issues, the current study takes advantage of the prospective design of the Cebu Longitudinal Health and Nutrition Survey (CLHNS) to model longitudinal risk factors for elevated CRP among women in the Philippines with the aims of characterizing changes in waist circumference over an 11-year period, and the degree to which current waist circumference, and change in waist circumference during the past 11-years, are predictive of current CRP status.

Methods

Participants and data collection

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) began in 1983 with the recruitment of 3327 pregnant women representative of the childbearing population in Cebu City. The women have been followed through several rounds of data collection every few years since 1983. Data for the current analyses of longitudinal adiposity come from 1994 and 2005. CRP was first measured in 2005, and we worked backward to 1994, to generate a timespan of approximately one decade. By 1994, all the women in the study were at least in their twenties to eliminate confounding due to growth-related effects on adiposity. Complete anthropometric and reproductive data from both 1994 and 2005 were available for 1613 of the 1892 women in which we had measured CRP in 2005. All data were collected under conditions of informed consent with institutional review board approval from the University of North Carolina, Chapel Hill.

Height and waist circumference were measured using standard anthropometric techniques (Lohman and others 1988). Change in waist circumference was calculated as the difference between 1994 and 2005 circumference, and three change categories were constructed using ±5 cm cutoffs, with maintenance of a stable waist circumference being defined within 5 cm of baseline. The cutoff of 5 cm was chosen because this level of waist circumference reduction has been associated with improvement of cardiovascular disease risk factors and thus may have potential interventional value (Han and others 1997). Categories of high and low waist circumference were determined by a median split of the sample; a WC greater than the median value in both 1994 and 2005 was considered to be a sustained history of high WC.

All other covariates were measured in 2005. The sample was divided into smokers and non-smokers on the basis of self-report data on the number of cigarettes smoked per day. Percentage of fat in the diet was assessed by dietary recall questionnaires and then log-transformed for regression analysis. We constructed a continuous reproductive history variable that totaled the number of months spent pregnant during the 11-year interval. To assess household pathogenicity, we constructed a pathogen exposure scale based on five variables, each scored on a three 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, and levels of garbage and excrement present in the neighborhood surrounding the household (McDade and others 2008).

Women who reported infectious disease symptoms such as runny nose, cough, fever, diarrhea, sore throat, as well as the more general categories of “flu,” “cold,” and “sinusitis”, at the time of blood draw in 2005 (n=267) were excluded from the analyses since infection is associated with acutely elevated CRP levels. To further screen elevated CRP due to acute, rather than chronic, inflammation, 48 women with CRP levels > 10 mg/L were excluded. This cut point was selected based on recommendations issued by a recent joint scientific statement from the American Heart Association and the Centers for Disease Control and Prevention (Pearson and others 2003). Concentrations of CRP above 10 mg/L are presumed to be the result of acute inflammatory processes (e.g., infectious disease), whereas elevations of CRP above 3 mg/L, but below 10 mg/L, indicate increased cardiovascular risk due to chronic, low-grade inflammation. Finally, 4 women who were pregnant at the time of data collection in either 1994 or 2005 were excluded, yielding a final sample of 1294.

We evaluated how our sample differed from the original cohort as assessed when the study started in 1983. Compared to those lost to follow up, participants remaining in this study had significantly fewer years of education (mean (s.e.) difference: 0.26 (0.13) years), and lived

in slightly more rural communities (2.5 (0.44) points on urbanicity scale). Participants did not differ with respect to age, height, weight, or BMI at baseline, household log income, or other household traits.

CRP analysis

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 hours and were then centrifuged to separate plasma prior to freezing at −70°C. Samples were express shipped to Northwestern University on dry ice and stored frozen at −80°C until analysis. CRP concentrations were determined using a high sensitivity immunoturbidimetric method (Synchron LX20, lower detection limit: 0.1 mg/L) with between-assay % coefficients of variation less than 7.6 across the assay range (McWhorter and others 2004).

Data analysis

Analyses of variance (ANOVA) and Pearson chi-square tests were used to compare household variables, anthropometric and other individual characteristics, and CRP levels women across the three waist change categories (loss, stable, gain). We then performed a series of logistic regression analyses to predict the likelihood of CRP>3 mg/L. Logistic analyses proceeded in three stages. Our first model considered only current waist circumference and height as predictors of elevated CRP (Model 1). This basic model was further adjusted by current household, individual, and behavioral factors including age, log income, household pathogenicity score, and smoking status (Models 2 and 3), factors known to influence CRP in this population (McDade and others 2008), as well as pregnancy history and log percent fat in the diet. Finally, we considered combined models that simultaneously evaluated the effects of current waist circumference and change between 1994 and 2005 (Model 4).

The findings presented here were broadly corroborated by similar analyses using BMI and weight as predictors (Rutherford et al., unpublished analyses). However, given the stronger association between CRP and central adiposity in this cohort (McDade and others 2008) and other studies (Lee and others 2008; Saijo and others 2004), we limit our analyses to waist circumference measures. Statistical analyses were conducted with Stata for Windows, version 10 IC (StataCorp, College Station, TX).

Results

Baseline and current characteristics of women across waist circumference change categories

Approximately 30% of the women in the sample maintained a stable waist circumference (WC) over the 11-year period, as defined by a ±5 cm circumference change between 1994 and 2005 (Table 1). Thirty-nine per cent of women had a reduced WC, while women who increased their WC comprised over 31% of the sample. The average change overall was −1 cm, with women who reduced WC losing an average of 8.8 cm, compared to women whose WC increased by an average of 7.9 cm.

Women who experienced a reduction in central adiposity over the 11-year period were significantly lighter and had lower BMI in 2005, and lost more weight, than women whose waist increased in circumference. However, they started at higher WC at baseline than women who went on to increase in WC. Women who experienced reductions in WC were significantly older and more likely to be postmenopausal in 2005 than were women whose waists increased in circumference. There were no significant differences across groups in

log percent fat calories, pathogen score, or smoking status. Median CRP differed significantly across the three change groups, with women who had reduced their WC (who were also significantly lighter than the other groups in 2005) having the lowest current CRP levels and women whose waists increased (who were currently the heaviest women) having the highest levels.

Current predictors of elevated CRP

We next investigated the predictors of elevated CRP using multiple logistic regression (Table 2). In the base model including only anthropometrics and age (Model 1), WC and height were independent predictors of elevated CRP. WC was a robust predictor, with each increase of 1 cm associated with a 10% increase in the risk of elevated CRP. Each cm increase in height was associated with a 4% reduction in the probability of elevated CRP. The significant associations between height and WC and elevated CRP were maintained when household variables were considered simultaneously (Model 2), with increases in WC predicting a 9.9% increase in CRP risk. In addition to the anthropometric predictors, current household pathogenicity was associated with significant increases in the risk of elevated CRP. Neither reproductive history, measured by the total number of months spent pregnant during the study interval, nor household income contributed significantly to an increased likelihood of CRP>3 mg/L. Further adjustment for behaviors that could influence inflammatory status, including dietary fat intake and smoking status, did not change the relationship between anthropometric characteristics and CRP (Model 3). Fat intake was weakly associated with CRP risk, whereas smoking status was unrelated to CRP.

We next considered whether there was an independent effect of longitudinal central adiposity on current CRP (Model 4). Adding the change variable to the model slightly strengthened the relationship between current waist circumference and CRP, increasing the risk of elevated CRP to 10.6%. In addition, increased WC over 11 years predicted current CRP independent of current WC (Model 4). Each cm increase in WC over the 11 year follow-up period was associated with a 2.3% increase in the probability of elevated CRP. As in previous models, pathogen score was a strong predictor of CRP>3 mg/L, with dietary fat being a weak predictor.

Once we generated odds ratios from the logistic models predicting the risk of elevated CRP, we wanted to determine the total risk associated with the average increase in waist circumference, which we illustrate below using an example of a WC increase of three cm from 85 cm to 88 cm. In linear regression the risk difference is the absolute change per unit increase in exposure and thus can be multiplied directly by the exposure variable (e.g. a risk difference of 2%/cm multiplied by an exposure variable of 3 cm = 6%). This is not the same with logistic regression, where the odds ratio is a relative measure of effect dependent on the reference category that is the odds associated with, in this case, 1 cm lower WC (e.g. odds for WC 85 = .20; odds for WC 86 = odds for WC 85 + [odds for WC 85*2%] =.2+[.20*2%] = .204; odds for WC 87 = odds for WC 86 + [odds for WC 86*2%] = .204 +[.204*2%] = . 2081; odds for WC 88 = odds for WC 87 + [odds for WC 87*2%] = .208+[.2081*2%] = . 2122.) For a three centimeter increase from 85 to 88 cm, the odds increase from .20 to .2122 which is a 6.08% change. The *lincom* command in Stata applies the appropriate formula to calculate the total odds ratio associated with the average waist circumference increase. Based on an odds ratio of 1.023 (Table 2, Model 4) and an average increase of 9.7 cm (Table 1), the total risk due to waist increase was 20.1%.

Interactions between current and past adiposity as a predictor of CRP

Figure 1 presents the adjusted probabilities of elevated CRP as a result of the interactive effects of past and current central adiposity. Women with high current WC generally had the

highest probabilities of having elevated CRP. The highest probability was experienced by women who had high WC both in 1994 and 2005 (30.2%); this level of risk was slightly larger than that for women who had increased their WC since 1994 (25.5%). For women who were currently in the low WC category, the probability of elevated CRP was relatively low, regardless of past central adiposity. Women who had larger waistlines in 1994 that decreased over time had a slightly increased risk of CRP > 3 mg/L compared to women who had maintained a low level of central adiposity over the 11-year period (6.2% v. 5.0%, respectively).

Discussion

History of excess central adiposity is a significant predictor of elevated CRP in this sample of Filipino women independent of their current adiposity. Previous work in this cohort of women had shown that current WC was the strongest anthropometric predictor of elevated CRP (McDade and others 2008). The current study supports the hypothesis that it is not merely current WC, but also the long-term history of central adiposity that influences inflammatory status as reflected by CRP. The increased risk of elevated CRP was 2.3% per centimeter increase over the 11-year period. Considering the average increase over time was 9.7 cm, the average total risk of elevated CRP due to increased central adiposity was 20.1%. This is a substantial increase in the risk of developing chronic low-grade inflammation.

Current circumference and change in circumference over time were independent predictors of CRP when modeled simultaneously. These independent associations reflect separate phenomena. First, current central fat deposition, regardless of history, is a strong risk factor for elevated CRP. The probability of elevated CRP in women who have a high current WC is five times as high as that for women who are in the low WC category. Second, regardless of current central adiposity, increases in WC over time increase the risk of high CRP. It is important to note that the women in the sample most likely to have increased WC over the 11-year period started in 1994 with significantly smaller WC compared to women who maintained a steady WC (Table 1). This suggests that not only weight gain generally, but centile shifting in adiposity characteristics in particular may be an important screening tool (Liese and others 2001). Further, overall risk was much higher for women who had increased their waistlines over time than for women who experienced a decrease in WC (25.5% versus 6.2% respectively). A sustained history of high WC is associated with the greatest risk of elevated CRP (30.2%), with an 18% increase in the probability compared to women whose high WC is a more recent phenomenon.

The fact that women who decreased WC over the 11-year period significantly reduced their CRP risk suggests that while a history of sustained or increased central obesity may be an important risk factor, the long-term inflammatory effects of prior high circumference can be reversed. Prior studies in Western populations have shown that short-term weight loss programs are effective interventions for reducing CRP (Brochu and others 2003). In this sample, reductions in WC were associated with the lowest median CRP levels. The finding that long-term central adiposity increases the probability of developing elevated CRP above the risk associated with current central adiposity in the Philippines suggests that screening for central obesity earlier in adulthood and implementing reduction interventions will have important long term protective consequences. This potential for earlier intervention may be particularly important in contexts like the Philippines, where pathogen burden partners with adiposity as a potent inflammatory agent (McDade and others 2008; McDade and others 2009).

Some Asian populations may be more likely to deposit fat centrally, independent of body mass index, thus placing them at higher risk for the development of cardiovascular and

metabolic disease (Chandalia and others 2003; Forouhi and others 2001; Pi-Sunyer 2004). At each level of body mass index, a sample of Filipino-American women had higher levels of visceral adipose tissue, as measured by computed tomography, than women of European or African descent (Araneta and Barrett-Connor 2005). This significant difference in visceral adipose deposition is accompanied by higher triglycerides and higher ratio of total cholesterol to HDL cholesterol (Araneta and Barrett-Connor 2004). The rise in the prevalence of obesity, cardiovascular disease, and the metabolic syndrome in the Philippines (Adair 2004; Tanchoco and others 2003) may be underscored in part by the longitudinal profiles of increasing individual central obesity and attendant rises in CRP in this study. At the same time, it is important to note that CRP levels among this population are much lower than those reported for European-Americans in various studies (Albert and others 2004; McDade and others 2008), perhaps reflecting population differences in the factors that influence CRP levels. We have previously shown in the younger generation at Cebu that exposure to inflammatory stimuli reflecting an unhygienic environment during infancy predicts a reduced risk of elevated CRP in early adulthood independent of adiposity (McDade and others 2009), suggesting that an ecologically-focused life course approach will be helpful in clarifying population variation in CRP and its relationship to adiposity.

In summary, in this sample of Filipino women current waist circumference is associated with a high risk of elevated CRP, but increases over time pose an independent and cumulatively substantial risk. This risk is exacerbated for women who have had chronically high waist circumference compared to those experiencing more recent increases. However, the risk associated with a prior history of excessive central obesity may be reversible through weight loss.

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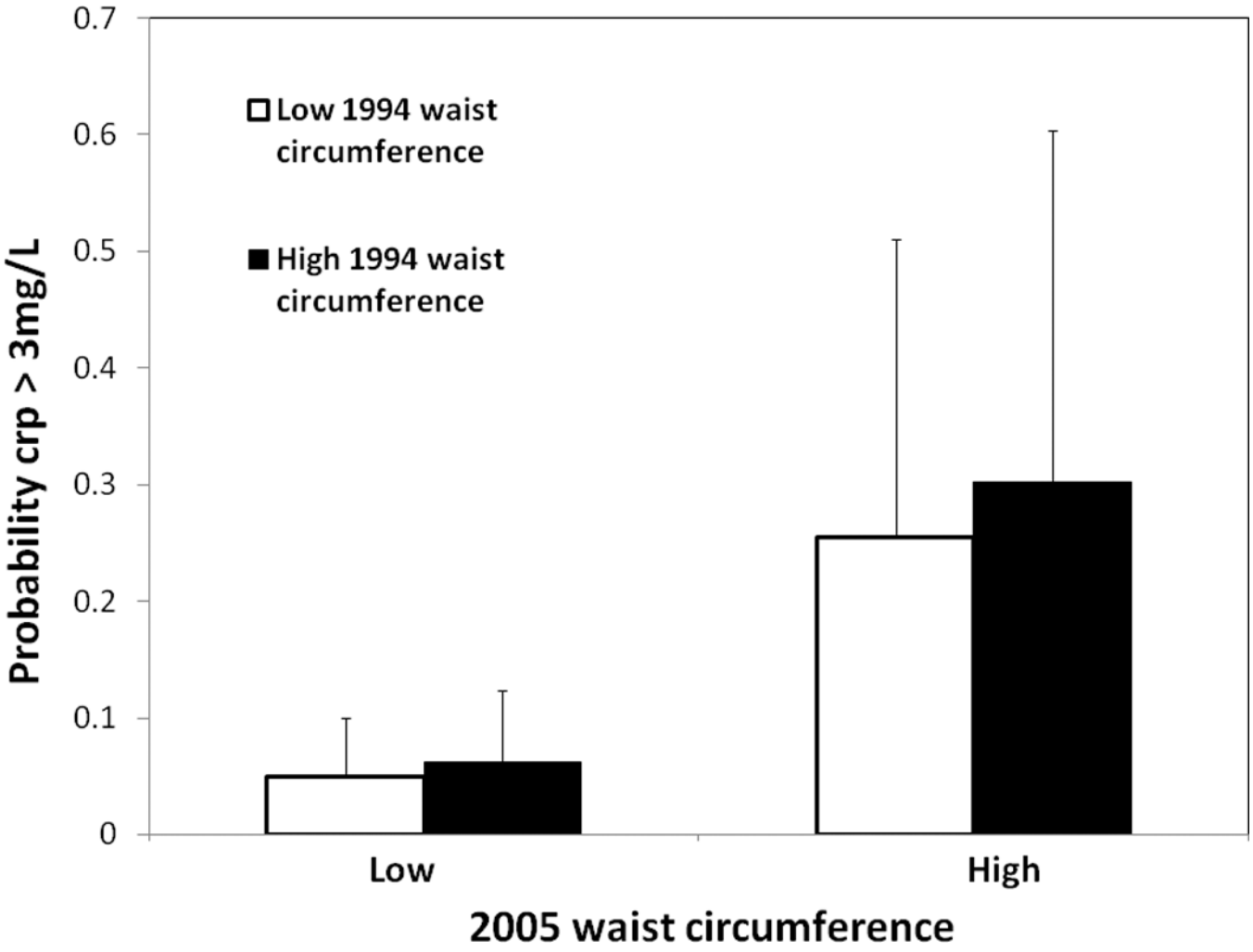

Figure 1.
Probability of elevated CRP in relation to past and current adiposity. Values are predicted probability of CRP>3 mg/L adjusted by variables listed in Table 2, Model 3, with upper bound of 95% CI. Low and high values for predictors were set as mean waist circumference ± 1 SD.

Table 1

Characteristics of Filipino women across three categories of waist circumference change

	All women (n=1294)	Decreasing waist circumference (change >−5cm) (n=504)	Stable waist circumference (n=386)	Increasing waist circumference (change >5 cm) (n=404)	P-value
Age (years)	48.4 (6.1)	59.6(6.2)	48.0(5.8)	47.4(5.9)	<0.001
Postmenopausal (%)	37.0	43.5	33.4	32.4	0.001
Smoker (%)	11.9	14.1	10.9	10.1	0.145
Log income (pesos)	6.0 (0.86)	6.0 (0.8)	6.0 (0.9)	6.0 (1.0)	0.446
Percent fat calories	15.2 (10.9)	14.7 (10.7)	15.1 (10.9)	16.1 (11.1)	0.148
Pathogen score	0.39	0.42 (0.41)	0.37 (0.40)	0.37 (0.40)	0.071
Anthropometric characteristics					
2005 height (cm)	150.7 (5.0)	150.4 (5.0)	150.8 (4.9)	150.9 (5.2)	0.257
1994 weight (kg)	52.5 (9.6)	52.8 (9.7)	52.1 (9.4)	52.6 (9.5)	0.578
2005 weight (kg)	55.5 (10.7)	51.9 (10.1)	55.5 (10.3)	59.9 (10.2)	<0.001
Weight Δ (kg)	2.7 (5.9)	−0.9 (4.9)	3.4 (4.3)	7.4 (4.9)	<0.001
1994 waist circum. (cm)	82.3 (10.1)	85.5 (10.1)	81.3 (9.6)	79.4 (9.6)	<0.001
2005 waist circum. (cm)	81.3 (10.7)	76.7 (9.7)	81.2 (9.6)	87.3 (10.1)	<0.001
Waist circum. Δ (cm)	−0.99 (8.0)	−8.8 (4.7)	0.04 (1.8)	9.7 (4.4)	<0.001
1994 BMI	23.1 (3.7)	23.3 (3.8)	22.9 (3.7)	23.1 (3.7)	0.232
1994 BMI category (%) - (25–30) - (>30)	24.3 4.6	26.4 4.6	20.7 4.4	25.2 5.0	0.357
2005 BMI	24.4 (4.3)	22.9 (4.0)	24.4 (4.1)	26.3 (4.0)	<0.001
2005 BMI category (%) - (25–30) - (>30)	33.2 9.6	25.0 4.6	31.1 9.6	45.5 15.8	<0.001
Median CRP(mg/L) (25th, 75th percentile)	0.7 (0.2, 2.2)	0.6 (0.2,1.7)	0.6 (0.2, 1.9)	1.1 (0.4, 2.8)	<0.001

Table 2

Multiple logistic regression models predicting CRP >3 mg/L

	Model 1: 2005 anthropometrics	Model 2: 2005 adding household and intrinsic factors	Model 3: 2005 adding behavioral factors	Model 4: 2005 adding change in waist circumference
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
2005 Waist circumference (cm)	1.100 (1.08,1.12) ***	1.099 (1.08,1.12) ***	1.097 (1.08,1.12) ***	1.106 (1.09–1.13) ***
2005 Height (cm)	0.955 (0.92,0.99) *	0.956 (0.93,0.99) **	0.954 (0.92,0.99) **	0.951 (0.92,0.98) **
Months pregnant 1994–2005 (months)		0.979 (0.95, 1.01)	0.981 (0.96,1.01)	0.981 (0.96,1.01)
Pathogen score		1.756 (1.21,2.56) **	1.799 (1.23,2.63) **	1.763 (1.21,2.58) **
Income (log pesos)		1.175 (0.97,1.43) +	1.118 (0.92,1.37)	1.106 (0.90,1.35)
Dietary fat intake (log %)			1.239 (0.99,1.56) ++	1.232 (0.98,1,55) ++
Current smoker			0.767 (0.44,1.33)	0.763 (0.98,1.55)
1994–2005 Δ waist circumference (cm)				1.023 (1.00, 1.05) *
Model r²	*0.138*	*0.148*	*0.152*	*0.156*

+ p≤ 0.15;

++ p ≤ 0.10;

* p ≤ 0.05;

** p ≤ 0.01;

*** p ≤ 0.001

Models adjusted by age.