Associations between body mass index and serum levels of C-reactive protein

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Background. Obesity leads to increased risk of cardiovascular disease and glucose intolerance, which are phenomena of chronic inflammation. This study was performed to determine whether a higher body mass index (BMI) and central obesity are associated with low-grade inflammation.

Methods. An analysis of 8 453 adults aged ≥20 years was performed. Every subject completed a household interview and a questionnaire regarding personal health, and their BMI and serum C-reactive protein (CRP) level were measured. The BMI data were divided into quintiles, using multiple linear regression to estimate the relationship between CRP level and BMI quintiles. An extended-model approach was used for covariate adjustment. The association between central obesity and CRP level was examined by this method as well.

Results. After controlling for demographics, chronic diseases, health behaviours and levels of folate and vitamin B_{12}, the β coefficient (which represents the change of natural-log-transformed levels of CRP for each kg/m^2 increase in BMI) was 0.078 (p<0.001). The CRP levels also increased across increasing quintiles of BMI (p for trend <0.001). The β coefficient, representing the change of natural-log-transformed levels of CRP comparing subjects with central obesity to those without, was 0.876 (p<0.001).

Conclusion. Higher BMIs as well as central obesity are independently associated with higher levels of CRP.

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C-reactive protein (CRP) (an acute phase protein) has been thought to be synthesised in the liver, with a plasma half-life of 18 hours.[1] However, the extrahepatic expression of CRP has been detected in macrophages and smooth-muscle cells from atherosclerotic plaques.[2] It plays an important role in the inflammatory process and is recognised as a useful biochemical marker of inflammation. Increasing epidemiological evidence supports the notion that low-grade inflammation, as reflected by elevated levels of CRP, is associated with glucose intolerance[3] and various vascular diseases[4-7] including atherosclerosis, stroke, ischaemic heart disease, and peripheral vascular disease. Evidence-based systemic reviews have suggested that elevated CRP is related to an increased risk of stroke and cognitive impairment.[8]

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There is evidence for the presence of CRP in human adipose tissue[9,10] and growing evidence that adipose tissue can induce chronic low-grade inflammation by producing pro-inflammatory cytokines such as interleukin-6.[11] Overweight or obese individuals have an increased risk of developing cardiovascular diseases[12] and insulin resistance.[13] A certain degree of inflammatory process in subjects with obesity could be suspected, but data examining the direct association between body mass index (BMI) and CRP is sparse. This study aimed to evaluate whether higher BMI and central obesity are associated with low-grade systemic inflammation as measured by serum CRP levels, using data from the National Health and Nutrition Examination Survey (NHANES), 1999 - 2002.

Materials and methods

Participants

The National Health and Nutrition Examination Survey (NHANES) is a population-based survey to collect information on the health and nutrition of the USA's domestic population. NHANES used a stratified, multistage and cluster sampling design to obtain a representative sample of the non-institutionalised civilian USA population by conducting detailed home interviews and health examinations in a mobile examination centre. Since 1999, NHANES became a continuous annual survey rather than its past form of a periodic survey. Our study population comprised adults aged ≥20 years who participated in the NHANES 1999 - 2002. Detailed survey operations manuals, consent documents and brochures of NHANES 1999 - 2002 are available on its website.[14,15]

A total of 10 291 participants aged ≥20 years were included. Body measurements in some participants could not be obtained

because of safety concerns, refusals or physical limitations (such as the participant being confined to a wheelchair); of these, 1 402 were excluded from the analysis because of missing BMI values (*N*=1 227) and waist measurements (*N*=175), and 436 were excluded because of unavailable data on CRP. Therefore, the final sample comprised 8 453 adults who completed a household interview and laboratory and clinical examinations.

Body measurements

Generally, height and weight were not obtained for subjects using a wheelchair in the mobile examination centre. Height was measured with a stadiometer to the nearest 0.1 cm. Weight was measured with a Toledo digital scale and recorded to the nearest 0.01 kg. BMI was calculated as mass in kilograms divided by the square of height in metres. Waist circumference was measured on the horizontal plane at the level of the uppermost border of the bilateral iliac crests.

C-reactive protein measurements

Blood specimens were collected at the mobile examination centres and analysed at the Department of Laboratory Medicine, University of Washington. CRP was analysed by a highly sensitive assay technique. Standard phlebotomy techniques were used to obtain specimens, which were held at –20°C until used for laboratory analysis. CRP was quantified by utilising latex-enhanced nephelometry with a Behring nephelometer (Deerfield, USA). Results were reported to the nearest hundredth (0.01) unit. The lowest reportable CRP result is approximately 0.02 mg/dl; this varies slightly with different calibrator lots. The assay does not have a maximum reportable limit since the instrument automatically prepares a higher dilution and retests specimens with results above the linearity of the assay to obtain reactions within the linear range for the assay. Detailed specimen collection and processing instructions are discussed in the NHANES Laboratory Procedures Manual.

Covariates

Age, sex, race/ethnicity, and smoking status were self-reported. Diabetes was defined by the self-reporting of a physician's diagnosis, or random plasma glucose ≥200 mg/dl, or the use of diabetic medications (including insulin injection or oral hypoglycaemic agents). Three, and sometimes four, blood pressure (BP) tests were done, using a mercury sphygmomanometer, by a NHANES physician. BP was measured via the right arm unless specific conditions prohibited its use. Average systolic and diastolic BPs were obtained. The presence of hypertension was defined by a self-reported doctor's diagnosis, the use of antihypertensive medications, or average blood pressure ≥140/90 mmHg. Medical histories of myocardial infarction (>6 weeks), congestive heart failure, angina, chronic bronchitis, emphysema and arthritis were ascertained by self-report. Alcohol intake was determined by the question: 'In any one year, have you had ≥12 drinks of any type of alcohol beverage?' Serum folate levels were measured using a commercially available radioprotein binding assay kit, the Quantaphase II Folate/vitamin B_{12} radio-assay kit (Bio Rad Laboratories, Hercules, CA, USA). Detailed specimen collection and processing instructions are in the NHANES Laboratory Procedures Manual and on their website.[15]

Statistical analysis

The distributions of CRP serum levels in the population were right-skewed. Therefore, the values of CRP were natural-log-transformed, providing a best-fitting model for analysis in which the serum CRP levels were treated as a continuous variable. We used multiple linear regression to determine the change of natural-log-transformed levels of CRP for each kg/m^2 increase in BMI, and quintile-based analysis by dividing BMI into quintiles with the subjects in the lowest BMI quintile as the reference group. The cut-off levels for BMI quintiles were: Q1 – BMI <23.32 kg/m^2; Q2 – BMI ≥23.32 - 26.07 kg/m^2; Q3 – BMI ≥26.08 - 28.73 kg/m^2; Q4 – BMI ≥28.74 - 32.53 kg/m^2; Q5 – BMI >32.53 kg/m^2. The β coefficients were interpreted as the differences in mean natural-log-transformed CRP levels comparing subjects in the upper four BMI quintiles with those in the lowest quintile. Central obesity was defined as waist circumference >102 cm in males, and >88 cm in females. The β coefficients were interpreted as the differences in mean natural-log-transformed CRP levels comparing subjects with central obesity with those without. An extended-model approach was used for covariate adjustment: model 1= age, gender, race; model 2 = model 1 plus levels of vitamin B_{12} and folate; model 3 = model 2 plus chronic diseases (hypertension, diabetes mellitus, heart disease, stroke) and health behaviours (smoking status and alcohol consumption). All analyses were conducted using STATA version 8.0 (Stata Corporation, College Station, TX, USA).

Results

The characteristics of the study subjects are summarised in Table I. Concerning chronic diseases, 38.9% of the subjects were hypertensive and 11.4% had diabetes mellitus; 49.1% were non-Hispanic Caucasian; and participants with higher BMIs tended to have a high level of CRP.

In the linear model, CRP levels positively correlated with BMI. After adjusting for age, gender and race (model 1), the β coefficient, representing the change of natural-log-transformed levels of CRP for each kg/m^2 increase in BMI, was 0.080 (p<0.001) (Table II). The correlation remained unchanged after additionally adjusting for other covariates in models 2 and 3 (Table II). The results of BMI quintile-based multiple linear regression analysis are shown in Table III. From model 1 to model 3, we observed positive correlations between BMI and

Table I. Characteristics of study participants

Characteristic	Quintile of BMI (kg/m^2) Q1 (<23.32)	Q2 (23.32 - 26.07)	Q3 (26.08 - 28.73)	Q4 (28.74 - 32.53)	Q5 (>32.53)	Total
Continuous variables*						
Age (yrs)	45.5 (19.9)	49.2 (19.5)	50.7 (18.5)	50.7 (17.4)	47.9 (16.6)	
Blood pressure (mmHg)						
Systolic	121.0 (21.7)	124.5 (21.1)	126.1 (20.6)	127.5 (19.9)	128.3 (19.3)	
Diastolic	69.2 (13.6)	69.2 (14.4)	71.2 (14.1)	72.2 (13.8)	73.8 (13.4)	
Waist (cm)	79.1 (7.3)	89.2 (6.9)	96.3 (7.2)	102.9 (7.5)	116.2 (12.1)	
C-reactive protein (mg/dl)†	0.11 (0.04 - 0.29)	0.17 (0.07 - 0.39)	0.22 (0.1 - 0.46)	0.29 (0.14 - 0.57)	0.5 (0.26 - 0.93)	
Vitamin B_{12} (pg/ml)†	482 (373 - 647)	482 (348 - 636)	459 (348 - 610)	459 (350 - 591)	441 (336 - 581)	
Folate (ng/ml)†	13.4 (9.3 - 18.9)	13.6 (9.6 - 18.9)	13.2 (9.4 - 18.4)	12.8 (9.3 - 17.8)	11.7 (8.6 - 16.9)	
Categorical variables‡						
Male	718 (42.4)	872 (51.6)	917 (54.3)	873 (51.5)	607 (36.0)	3 987 (47.2)
Race						
Mexican	311 (18.4)	414 (24.5)	465 (27.5)	464 (27.4)	406 (24.1)	2 060 (24.4)
Hispanic	83 (4.9)	86 (5.1)	111 (6.6)	85 (5.0)	81 (4.8)	446 (5.3)
Non-Hispanic white	940 (55.5)	871 (51.6)	815 (48.2)	792 (46.7)	736 (43.7)	4 154 (49.1)
Non-Hispanic black	285 (16.8)	258 (15.3)	245 (14.5)	318 (18.8)	418 (24.8)	1 524 (18.0)
All others	75 (4.4)	60 (3.6)	54 (3.2)	36 (2.1)	44 (2.6)	269 (3.2)
Diabetes mellitus	72 (4.3)	137 (8.1)	194 (11.5)	232 (13.7)	330 (19.6)	965 (11.4)
Hypertension	439 (25.9)	554 (32.8)	670 (39.6)	755 (44.5)	876 (52.0)	3 294 (38.9)
Current smoker	537 (31.7)	390 (23.1)	368 (21.8)	344 (20.3)	297 (17.6)	1 936 (22.9)
Ever had diagnosis of						
Stroke	26 (1.5)	41 (2.4)	56 (3.3)	53 (3.1)	57 (3.4)	233 (2.8)
Heart attack	49 (2.9)	62 (3.7)	73 (4.3)	70 (4.1)	75 (4.5)	329 (3.9)
Congestive heart failure	23 (1.4)	44 (2.6)	54 (3.2)	49 (2.9)	56 (3.3)	226 (2.7)
Coronary heart disease	41 (2.4)	65 (3.9)	78 (4.6)	81 (4.8)	65 (3.9)	330 (3.9)
Alcohol consumption						
≥12 drinks per year	1 119 (66.1)	1 129 (66.8)	1 121 (66.3)	1 130 (66.7)	957 (56.8)	5 456 (64.6)

*Values in the continuous variables were expressed as mean (standard deviation) unless otherwise specified.

†Values were expressed as median (interquartile range) owing to right skewness.

‡Values in the categorical variables were expressed as number (%).

Table II. Association between BMI and levels of C-reactive protein

Models*	β (SE)†	*p*-value
Model 1	0.080 (0.002)	<0.001
Model 2	0.080 (0.002)	<0.001
Model 3	0.078 (0.002)	<0.001

*Adjusted covariates: model 1 = age, gender, race; model 2 = model 1 + serum level of folate, vitamin B_{12}; model 3 = model 2 + chronic diseases and health behaviours.

†β coefficient was interpreted as change of natural-log-transformed levels of C-reactive protein for each kg/m^2 increase in BMI.
SE = standard error.

CRP levels. Subjects in the higher quintiles of BMI tended to have higher CRP levels (Fig. 1). The trends of CRP levels across BMI quintiles were all statistically significant.

CRP levels were higher in subjects with central obesity (Fig. 2). After controlling for age, gender and race, the β coefficient, reflecting the change of natural-log-transformed levels of CRP comparing subjects with central obesity with those without, was 0.876 (p<0.001). Additional adjustment of covariates did not change the correlation (Table IV).

Discussion

This study demonstrates a positive correlation between BMI and serum CRP, supporting and extending previous studies showing that elevated plasma levels of CRP are associated with obesity.[16, 17] Unlike this study, previous studies had weaknesses in terms of weight categorisation, with strikingly uneven subject numbers among different weight groups.[16,17] Stratifying the BMIs into quintiles, we tried to quantify the correlation between BMI and inflammation, and to investigate whether fat distribution, especially abdominal girth, is independently associated with CRP levels. Our finding that subjects with central obesity seemed to have higher CRP levels is compatible with other reports suggesting that a high waist-to-hip ratio and increased abdominal visceral fat have links with insulin resistance, hypertriglyceridaemia, hypertension, dyslipidaemia[18] and chronic low-grade inflammation.[16,18] Combining our observations with those in previous reports, it can be concluded that the high prevalence of chronic diseases among overweight and obese subjects – including insulin resistance, diabetes and cardiovascular disease – may be

Table III. Association between BMI quintiles and levels of C-reactive protein

Models*	BMI quintiles†	β (SE)‡	*p*-value	*p* for trend
Model 1	Q2 v. Q1	0.407 (0.039)	<0.001	
	Q3 v. Q1	0.666 (0.039)	<0.001	<0.001
	Q4 v. Q1	0.914 (0.039)	<0.001	
	Q5 v. Q1	1.395 (0.039)	<0.001	
Model 2	Q2 v. Q1	0.406 (0.039)	<0.001	
	Q3 v. Q1	0.663 (0.039)	<0.001	<0.001
	Q4 v. Q1	0.913 (0.039)	<0.001	
	Q5 v. Q1	1.393 (0.039)	<0.001	
Model 3	Q2 v. Q1	0.426 (0.039)	<0.001	
	Q3 v. Q1	0.674 (0.039)	<0.001	<0.001
	Q4 v. Q1	0.912 (0.039)	<0.001	
	Q5 v. Q1	1.357 (0.040)	<0.001	

*Adjusted covariates: model 1 = age, gender, race; model 2 = model 1 + serum level of folate, vitamin B_{12}; model 3 = model 2 + chronic diseases and health behaviours.
†Subjects in the lowest BMI quintiles were the reference group.
‡β coefficients can be interpreted as differences in mean natural-log-transformed C-reactive protein levels comparing subjects in the upper four BMI quintiles with those in the lowest quintile.
SE = standard error.

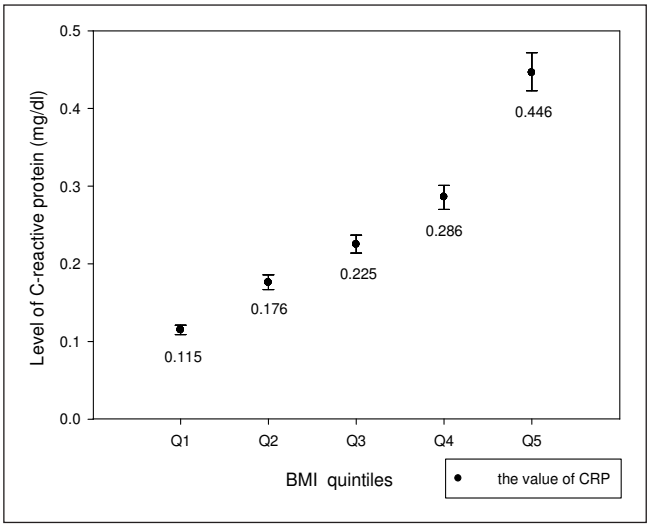

Fig. 1. Association between BMI quintiles and levels of C-reactive protein. With an increase in BMI, the levels of CRP increased. Q1 (<23.32 kg/m²), Q2 (23.32 to ≤26.07 kg/m²), Q3 (26.08 to ≤28.73 kg/m²), Q4 (28.74 to ≤32.53 kg/m²) and Q5 (>32.53 kg/m²). Each value of CRP was reversed from the natural-log-transformed CRP of each BMI quintile. The upper and lower bars indicate the 95% confidence interval (CI) reversed from the 95% CI of natural-log-transformed CRP in each BMI quintile.

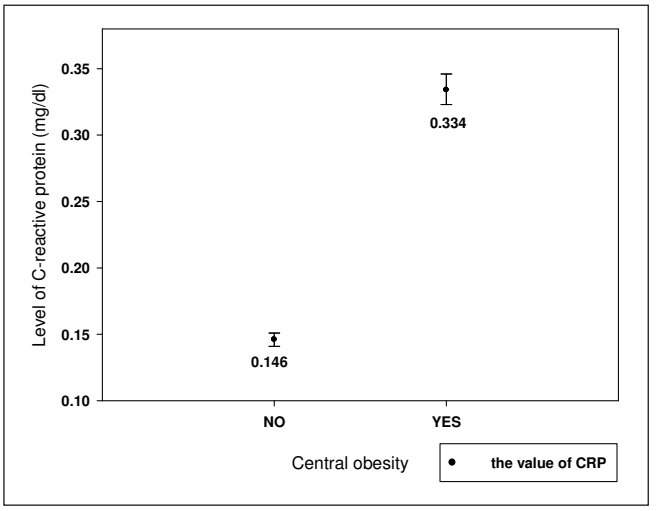

Fig. 2. Association between central obesity and levels of C-reactive protein. Subjects with central obesity had higher levels of CRP. Each value of CRP was reversed from the natural-log-transformed CRP of each category. The upper and lower bars indicate the 95% confidence interval (CI) reversed from the 95% CI of natural-log-transformed CRP in each category.

explained by the finding of higher CRP levels, indicating that a certain degree of inflammation is present in these populations.

Subjects with obesity tend to have more abdominal visceral adipocytes, which are supposed to produce almost 25% of systemic interleukin-6 *in vivo*;[19] and CRP could be stimulated by cytokines such as interleukin-1-beta, interleukin-6 and tumor necrosis factor-α. Consequently, adipose tissue could play a role in the regulation of circulating CRP levels via interleukin-6 production; this may partially explain our study's findings of why subjects with central obesity have higher serum levels of CRP.

Table IV. Association between central obesity* and levels of C-reactive protein

Models†	β (SE)‡	*p*-value
Model 1	0.876 (0.026)	<0.001
Model 2	0.874 (0.026)	<0.001
Model 3	0.825 (0.027)	<0.001

*Central obesity was defined as waist circumference in males >102 cm, in females >88 cm.
†Adjusted covariates: model 1 = age, gender, race; model 2 = model 1 + serum level of folate, vitamin B_{12}; model 3 = model 2 + chronic diseases and health behaviours.
‡β coefficient was interpreted as change of natural-log-transformed levels of C-reactive protein comparing subjects with central obesity with those without.
SE = standard error.

Our study has the following implications: firstly, subjects with a higher BMI tend to have higher CRP levels, indicating that overweight or obese adults are vulnerable to adverse outcomes of chronic inflammation such as myocardial infarction and stroke. Weight reduction has been demonstrated to reduce CRP[20] or interleukin-6 levels.[21] Aggressive weight control could potentially minimise the threat of cardiovascular diseases. Further prospective studies to investigate the influence of weight reduction, lifestyle modifications and weight control agents on inflammatory markers are necessary. The second implication is that a strong correlation exists between central obesity and CRP levels, after adjusting for possible confounding factors. Abdominal girth is viewed as one of the criteria for metabolic syndrome, and reduction of waist circumference is considered to be crucial in reducing the risk of inflammation.

There are some limitations to our study. Because of the cross-sectional design, causality between obesity and serum CRP level could not be established. Additional data regarding interleukin-6 or tumour necrosis factor-α is absent from NHANES. Since these factors play major roles in the inflammatory process, a concrete association between interleukin-6, tumour necrosis factor-α and weight status could possibly be obtained from further examination.

Conclusion

Higher BMIs are associated with higher CRP levels in this population-based cross-sectional study. Subjects with central obesity tend to have higher levels of CRP independent of major confounding variables. Aggressive weight reduction could be a worthwhile intervention to reduce inflammation-associated adverse outcomes in overweight and obese subjects.

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