Published in final edited form as:

Int J Cardiol. 2011 August 4; 150(3): 247–252. doi:10.1016/j.ijcard.2010.04.011.

Association of obesity and biomarkers of inflammation and endothelial dysfunction in adults in Inner Mongolia, China

Angela M. Thompson^a, Yonghong Zhang^c, Weijun Tong^c, Tan Xu^c, Jing Chen^{a,b}, Li Zhao^d, Tanika N. Kelly^a, Chung-Shiuan Chen^a, Lydia A. Bazzano^{a,b}, and Jiang He^{a,b,*}

^a Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, USA

^b Department of Medicine, Tulane University School of Medicine, New Orleans, LA, USA

^c Department of Epidemiology, Soochow University School of Radiation Medicine and Public Health, Suzhou, Suzhou, China

^d Tongliao Center for Disease Prevention and Control, Tongliao, Inner Mongolia, China

Abstract

Background—Recent studies suggest that central obesity is an important predictor of cardiovascular disease (CVD) in addition to overall obesity. Both inflammation and endothelial dysfunction are associated with increased risk of CVD. We examined the association between body mass index (BMI) and waist circumference (WC) with plasma concentrations of biomarkers of inflammation and endothelial dysfunction.

Methods—We conducted a cross-sectional study of 2589 lean, moderately active participants aged 20 years and older in Inner Mongolia, China. Overnight fasting blood samples were obtained to measure the biomarkers including C-reactive protein (CRP), soluble inter-cellular adhesion molecule-1 (sICAM-1), soluble E-selectin (sE-selectin), and angiotensin II. Height, body weight, and WC were measured by trained staff and BMI was calculated (kg/m^2).

Results—In univariate analysis, CRP, sICAM-1, and sE-selectin were all significantly higher among individuals with a higher BMI and WC. In multivariate analysis, each standard deviation (SD) increase in WC (9.6 cm) was associated with about 46% higher risk (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.21–1.76) of elevated CRP but a 1 SD increase in BMI (3.5 kg/m^2) was not associated with the risk of elevated CRP (OR 0.96, 95% CI 0.80–1.16). However, each SD increase in BMI was associated with about 30% higher risk of having elevated E-selectin (OR 1.30, 95% CI 1.08–1.55).

© 2010 Elsevier Ireland Ltd. All rights reserved.

* Corresponding author. Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, 1430 Tulane Ave, SL18, New Orleans, LA 70112, USA. jhe@tulane.edu (J. He)..

Conflict(s) of interest/disclosure(s) statement

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijcard.2010.04.011.

Conclusions—WC is a stronger predictor of inflammation while BMI is a stronger predictor for endothelial dysfunction. These results suggest measuring both BMI and WC will help to assess the risk of CVD in the Chinese population.

Keywords

Inflammation; Endothelial dysfunction; C-reactive protein; Body mass index; Waist circumference

1. Introduction

Overweight and obesity constitute an important public health burden worldwide. In China it is estimated that over 25% of men and women 20 years of age and older are overweight or obese [1]. Assuming past trends, projections estimate that by the year 2030, more than 70% of the population of China (approximately 800 million people), will be overweight or obese [1]. Overall obesity is a well established risk factor for cardiovascular disease (CVD), diabetes, hypertension, and premature deaths [2–6]. Body mass index (BMI) is the most frequently reported measure of overall body fatness in epidemiological studies of obesity [2,3,5]. In recent years, several studies have suggested that the distribution of fat, specifically central body fat or visceral fat may be an important predictor of morbidity and mortality in addition to BMI [6–9]. However, the mechanisms whereby body fat or visceral fat impairs vascular function are not completely understood. Studies suggest that biomarkers of inflammation and endothelial dysfunction are associated with atherosclerosis, CVD, hypertension and insulin resistance [10–14].

In the early stages of atherosclerosis, angiotensin II may stimulate the expression of pro-inflammatory cytokines and adhesion molecules on the surface of endothelial cells and increase oxidative stress in plaques [15]. Increases in these biomarkers may play a role in the development of atherosclerotic plaques. C-reactive protein (CRP) is a commonly used and robust biomarker of inflammation associated with cardiovascular risk in various populations. The Centers for Disease Control and Prevention and the American Heart Association endorsed CRP as an independent marker of cardiovascular risk, especially among those at intermediate risk [16]. It has been suggested that CRP may simply be a marker of inflammation related to obesity and insulin resistance or it may mediate the effect of obesity on outcomes such as type II diabetes or coronary heart disease [17,18].

Most research related to inflammation, endothelial dysfunction and obesity has been conducted in American or European populations and there is a dearth of obesity related research in Asian populations. The purpose of our study is to assess which measure of adiposity, BMI or waist circumference (WC), is more strongly associated with elevated levels of selected biomarkers of inflammation and endothelial dysfunction in a Mongolian population.

2. Methods

2.1. Study participants

This cross-sectional study was conducted between 2002 and 2003 in Inner Mongolia, an autonomous region in north China. The methods for selection of study participants and data collection have been described elsewhere [19]. Briefly, individuals aged 20 years and older were recruited from 32 villages in two adjacent townships located in Kezuohou Banner and Naiman Banner in Inner Mongolia. The majority of local residents were Mongolians who had lived there for many generations, their professions were farmers and herdsmen and they maintained a traditional diet that was high in fat and salt. A total of 2589 persons chose to participate in the study out of 3475 individuals aged 20 years and older who lived in the villages. This study was approved by the institutional review board at the Soochow University and other participating institutes in China as well as Tulane University Health Sciences Center. Written informed consent was obtained for all study participants.

2.2. Data collection

Trained staff administered a standard questionnaire to obtain data on demographic characteristics, lifestyle risk factors, family history of hypertension and personal medical history. Smoking was defined as having smoked at least 1 cigarette per day for 1 year or more. Heavy alcohol consumption was defined as drinking at least 50 g of alcohol per day for 1 year or more. Height and body weight were measured by trained staff using a balance beam scale after subjects removed their shoes and were wearing light clothing. BMI was calculated as weight in kilograms divided by the square of the height in meters. WC was measured at the level of 1 cm above the umbilicus. For this analysis, high BMI was defined as $\geq 24 \text{ kg/m}^2$ and high WC was defined as $\geq 85 \text{ cm}$ for men and as $\geq 80 \text{ cm}$ for women based on the recommendations of the Working Group on Obesity in China [20].

Blood samples were collected in the morning after at least 8 h of fasting. All plasma and serum samples were frozen at -80°C until laboratory testing. Plasma glucose was measured using a modified hexokinase enzymatic method. Concentrations of total cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides were assessed enzymatically on a Beckman Synchrony CX5 Delta Clinical System (Beckman Coulter, Fullerton, CA, USA) using commercial reagents. Low density lipoprotein (LDL) cholesterol concentration was calculated by means of the Friedewald equation for participants who had less than 400 mg/dL triglycerides [21]. Plasma CRP concentration was assessed using an immunoturbidimetric assay on a Beckman Synchron CX5 Delta Clinical System with commercial reagents. Soluble E-selectin (sE-selectin) and soluble inter-cellular adhesion molecule 1 (sICAM-1) were measured by an ELISA assay (R & D Systems, Minneapolis, MN) which employs the quantitative sandwich enzyme immunoassay technique [22,23]. Quantitative determination of immunoreactive angiotensin II was performed by a double antibody radioimmunoassay (RIA) after a reversed-phase sample extraction by means of phenylsilylsilica columns following the method previously reported by Emanuel et al. and a commercial RIA kit [24].

2.3. Statistical analysis

The 2589 participants were initially categorized into four mutually exclusive groups based on BMI and WC: low BMI/low WC, low BMI/high WC, high BMI/low WC and high BMI/high WC. The unadjusted means and standard deviations (SD) of continuous variables and prevalence of categorical variables were calculated for participants according to these groups. For normally distributed biomarkers (sICAM-1) the mean (SD) was calculated according to BMI and WC groups and *p* values were calculated using an age and gender-adjusted ANOVA model. CRP, sE-selectin, and angiotensin II had skewed distributions, therefore the median values and interquartile ranges (IQR) for each group were reported. *p* values were computed using rank order ANOVA calculations adjusted for age and gender.

In order to assess whether BMI or WC was a better predictor of inflammation and endothelial dysfunction, we used logistic regression to calculate the odds ratio (OR) for elevated plasma concentration of each biomarker associated with each standard deviation increase in BMI or WC. The outcome was binary and elevated plasma concentration of each biomarker was defined as a measurement in the upper quartile of values for this study population. BMI and WC were included in the models as continuous variables divided by their standard deviation. The first model included only BMI; in the second model, age and gender were added. In the third model, the following additional risk factors were also included: LDL cholesterol, systolic blood pressure, current smoking (yes/no), and fasting blood glucose. These analyses were repeated using WC instead of BMI. Finally, both BMI and WC were included in the multivariate-adjusted model.

The ORs were calculated for the elevated levels of biomarkers associated with each obesity subtype using individuals in the low BMI/low WC group as the reference population. Since the World Health Organization recommendation for the cut-point of elevated waist circumference among Chinese populations is 80 cm in women and 90 cm in men, we conducted a sensitivity analysis using this more conservative definition of elevated WC [25]. Since gender has been found to modify the association between obesity and inflammation in previous studies [7,26], the significance of this interaction was examined in this study. It has been suggested that a CRP concentration ≥ 3 mg/L is associated with the increased risk of adverse health outcomes [23], therefore a sensitivity analysis was conducted using the bivariate outcome CRP ≥ 3 mg/L. All *p* values were 2-tailed and statistical significance was defined as *p* ≤ 0.05 . Statistical analysis was conducted using SAS statistical software (version 9.1, Cary, North Carolina).

3. Results

The characteristics of participants are presented by four exclusive categories of BMI and WC (Table 1). Overall, 694 participants (27%) had a BMI ≥ 24 kg/m² and 1065 (41%) had a WC ≥ 85 cm in men and ≥ 80 cm in women. Study participants with a high WC tended to be female, older, had higher fasting glucose, and had higher LDL cholesterol, triglyceride and total cholesterol levels. Individuals with a high BMI differed from individuals with low BMI on many of these same characteristics.

The median value (IQR) for CRP, sE-selectin, and angiotensin II and the mean (SD) of sICAM-1 are shown in Table 2. There is a graded relationship between the obesity groups and plasma concentrations of CRP, sICAM-1, and sE-selectin. Median plasma concentrations of CRP, sICAM-1 and sE-selectin were higher among individuals with high BMI or high WC and highest among individuals with both high BMI and high WC.

The ORs of elevated concentrations of biomarkers of inflammation and endothelial dysfunction associated with 1 SD of BMI (3.5 kg/m²) or WC (9.6 cm) are presented in Table 3. In the crude, age and gender-adjusted, and multivariable-adjusted models that did not include WC, BMI was associated with the increased risk of elevated CRP ($p<0.01$ for all models), sICAM-1 ($p<0.05$ for all models) and sE-selectin ($p<0.05$ for all models). Similarly, in all models that did not include BMI, WC was independently associated with the increased risk of elevated CRP ($p<0.001$ for all models), sE-selectin ($p<0.001$ for all models) and sICAM-1 ($p<0.05$ all models). In a multivariate model including both BMI and WC, each SD increase in WC was associated with about 46% higher risk (OR 1.46, 95% CI 1.21–1.76) of elevated CRP. Increases in BMI were not associated with the increased risk of elevated CRP (OR 0.96, 95% CI 0.80–1.16); however, it was associated with the increased risk of elevated sE-selectin. Each SD increase in BMI was associated with about 30% higher risk of elevated sE-selectin (OR 1.30, 95% CI 1.08–1.55).

Table 4 shows the odds of elevated inflammation and endothelial dysfunction associated with each obesity subtype compared to individuals in the low BMI/low WC group. The top quartile of the distribution corresponded to CRP of 11.4 mg/L. The proportion of participants with elevated CRP were 15.0%, 20.9%, 27.3% and 35.1% in among low BMI/low WC, low BMI/high WC, high BMI/low WC, and high BMI/high WC participants, respectively. Compared to the reference group, the risk of elevated CRP was 73% higher among individuals in the low BMI/high WC group and 2-fold higher among those with high BMI/high WC but there was no significant difference among those with high BMI/low WC. Soluble E-selectin was elevated in participants with high BMI/low WC and among those with high BMI/high WC but not among those with low BMI/high WC. Angiotensin II levels were not associated with WC or BMI. In order to determine if there was effect modification by BMI category, we examined inflammation and endothelial dysfunction in those with high WC compared to low WC in a multivariate model stratified by low or high BMI. High WC was associated with elevated CRP (OR 1.75, 95% CI 1.33–2.31) among participants with low BMI, however was not significant among those with high BMI (OR 1.48, 95% CI 0.77–2.82). There was no difference in risk for any of the other biomarkers.

We conducted a sensitivity analysis using the more conservative WHO definition of high WC (80 cm for women and 90 cm for men) and did not find marked changes in these associations (results available in the Supplemental Table). We tested interactions in the multivariate models and found that neither gender nor smoking status modified the association between BMI or WC and the biomarkers in this population. Additionally, in the multivariate model that employed the bivariate outcome CRP >3 or >3 mg/L and adjusted for both WC and BMI, only an increase in WC remained significantly associated with the risk of having a CRP level >3 mg/L (OR 1.65, 95% CI 1.30–2.10).

After excluding participants with a CRP concentration >10 mg/L (28% of study participants), the top quartile of CRP then corresponded to a concentration 6.36 mg/L. The proportion of participants with elevated CRP was 15.1%, 17.4%, 22.1% and 28.2% in the low BMI/low WC, low BMI/high WC, high BMI/low WC, and high BMI/high WC groups, respectively. Excluding participants with CRP value 10 mg/L did not significantly alter any of the results.

4. Discussion

This study of 2589 individuals is the largest study to have examined the association between BMI and WC and the risk of elevated biomarkers of inflammation and endothelial dysfunction in adults from Inner Mongolia, China. The primary findings of this study show that WC is a stronger predictor of inflammatory biomarkers however BMI may be a stronger predictor for endothelial dysfunction.

Findings from previous studies have been mixed with many cross-sectional studies showing an association between CRP and obesity. The Insulin Resistance Atherosclerosis Study (IRAS) reported a strong correlation between CRP and BMI, WC and adipose body mass and similar associations in persons with and without diabetes [13]. CRP was modestly correlated with adiposity in a cross-sectional study of 160 Korean adults. Visceral fat was the most important predictor of CRP which increased as tertiles of visceral fat increased [27]. Similarly, in a population based study of 3042 men and women in Greece, those with central fat had 53% higher levels of CRP [10]. Among a Turkish population, visceral adipose fat was associated with CRP in men but not women [28]. In the Third National Health and Nutrition Examination Survey (NHANES III), neither higher WC nor BMI were associated with inflammation among men, but among women higher quartiles of WC were associated with an elevated CRP [7]. Gender did not modify the association between BMI or WC and CRP in the present study where a higher WC was associated with an elevated CRP in multivariate-adjusted models. Regardless of BMI category, higher WC was a risk factor for inflammation.

Study data from NHANES III showed that elevated CRP levels, defined as the 85th percentile of the sex-specific distribution (4.4 mg/L among men and 7.0 mg/L among women) were associated with overweight and obesity [29]. They also reported that the proportion of persons with elevated CRP increased in a dose-response manner according to BMI, and were 8.7%, 8.8%, 15.3%, 25.9%, 38.0% and 51.3% among persons with BMI <18.5, 18.5 to <25, 25 to <30, 30 to <35, 35 to <40, and 40 kg/m², respectively [29]. In the current study, we defined elevated CRP as the top quartile of the distribution and also saw an increase in the proportion of elevated CRP with increasing levels of adiposity. Although this study population has a lower mean BMI than western populations, their risk of elevated CRP increased with increasing adiposity thereby indicating that they may still be at an increased risk of cardiovascular disease despite lower overall body fatness.

Our study also reported a positive association between BMI and levels of sE-selectin which is consistent with reports from other populations [30–32]. In a cross-sectional study of 664 men and women in the Wandsworth Heart and Stroke Study, sE-selectin had a positive

association with BMI ($p<0.001$) and waist-to-hip ratio ($p<0.001$) and sE-selectin had a 1.7% (95% CI 0.9–2.4) increase per unit increase in BMI [30]. Other recent studies assessed the contribution of visceral and subcutaneous adiposity to the production of adhesion molecules [31,32]. BMI was positively correlated with serum concentrations of sE-selectin but not with sICAM-1 [31,32]. Protein levels of sICAM-1 were significantly higher in the visceral adipose tissue of obese women compared to non-obese controls [31].

The median level of CRP in our study participants was higher than reported in other studies with Asian populations [27,33–37]. Ye et al. reported that median CRP levels were 0.60 mg/dL in men and 0.88 mg/L in women with diabetes aged 50 to 70 years in Beijing and Shanghai [33]. In a group of 1730 Chinese Han men and women, serum CRP concentration increased with increasing BMI and glycemic dysfunction however the measure of variance also increased. Among subjects with normal glucose tolerance, geometric mean CRP concentrations (standard deviation [SD]) were 0.85 mg/L (3.82), 1.42 mg/L (5.82) and 1.74 mg/L (11.87) corresponding to BMI 24.4 kg/m², 24.4–27.9 kg/m², and 27.9 kg/m², respectively [34]. For subjects with impaired glucose tolerance, the corresponding geometric mean CRP concentrations (SD) were 1.87 (4.83), 2.28 (5.72), and 2.61 (11.41) [34].

In a study of 6107 Japanese participants, CRP concentration ranged from 0.03 to 68.2 mg/L with the 75th percentile value of 0.3 mg/L. Due to the highly skewed distribution, the authors defined elevated CRP as a concentration ≥ 0.11 mg/L [35]. Although the measured levels of CRP were quite different from the current study, the increased risk for elevated CRP per standard deviation increase in BMI was similar. In multivariable logistic regression, the authors found an odds ratio of 1.52 (95% CI 1.40, 1.64) for a 1 standard deviation increase in BMI [35]. In a population of adults in Korea, the median CRP level was 0.06 mg/L and CRP increased as both percent body fat and visceral fat area increased. Visceral fat was found to be the most significant predictor of CRP concentrations [27].

The reason for the difference in the CRP concentration may include analytic sources of variability such as noncommutability of reference samples, differences in calibration procedures or significant intra-assay variability [38,39]. The mean coefficient of variation among manufacturers is highly variable and increases as CRP concentrations decrease [40]. Nephelometric and turbidimetric assay methods have been shown to be susceptible to a prozone effect at high CRP concentrations as well as at CRP concentrations as low as 12 mg/L and may result in falsely low results [41].

Additionally, we did not exclude participants with CRP <10 mg/L because the positive predictive value of CRP values for CVD events has been found to be linear without an upper threshold value; therefore even high concentrations of CRP are clinically useful [42]. In our study, even after excluding participants with CRP concentration <10 mg/L, the odds ratios for elevated CRP were not significantly altered.

Finally the reason for differences in CRP levels may have included pre-analytic sources of variability such as diet or subclinical disease. Our study population maintained a traditional diet high in fat and salt which may contribute to higher CRP levels. Studies have shown an

inverse relationship between CRP levels and a healthy diet high in fruits and vegetables and low in sodium and red meat intake [43].

This study was cross-sectional therefore a causal relationship between BMI, WC and biomarkers could not be established. In addition, changes in weight (i.e. weight loss or weight gain) were not measured in our study due to cross-sectional design. In other studies weight change has been associated with a decrease in plasma concentrations of CRP [44], and angiotensin II [45]. About one-quarter eligible individuals chose not to participate because they were not available or refused to respond which may have introduced some selection bias. However we believe this bias is minimal because it is unlikely that participants chose not to participate due to their BMI, WC or biomarker levels which they did not know. Finally, it should be mentioned that several important biomarkers, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) were not measured in this study.

This study has numerous strengths that should be mentioned. To our knowledge, it is the largest study to examine the association between the biomarkers of inflammation and endothelial dysfunction and obesity in an Asian population. The study participants were homogeneous regarding their genetic background and environmental exposures and the study data were collected with rigid quality control and important co-variables were measured and controlled in the analysis.

Understanding the mechanisms by which the distribution of fat increases inflammation or endothelial dysfunction may be important for better understanding CVD risk even in normal weight or lean individuals. The increased presence of large or hypertrophic adipocytes is characteristic of obesity. Adipose tissue is an active metabolic organ that produces vasodilatory substances (nitric oxide, NO) and vasoconstricting substances (reactive oxygen species (ROS) and angiotensinogen, a precursor to angiotensins I and II) [18,46]. Reduced NO and increased ROS have been associated with endothelial dysfunction. The macrophages around the large adipocytes release chemoattractant proteins (MCP) and pro-inflammatory cytokines (TNF- α , IL-6, IL-1 β , etc.) which upregulate the hepatic production of CRP. Selectins and adhesion molecules are upregulated in obese individuals and promote adhesion of monocytes [11,46–49]. Abdominal adiposity particularly may increase liver deposits of portal fatty acids, cytokines, and hormones and distort hepatic metabolism [9].

In conclusion, in this study of 2589 individuals from Inner Mongolia in China, we found that individuals with a high WC have an increased risk of inflammation independent of BMI. Those with high BMI may have increased risk for endothelial dysfunction. These study findings suggest that even in a relatively lean and active population, high BMI or high WC contribute to inflammation and endothelial dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are deeply appreciative of the participants in the study, and thank Kezuohouqi Banner Center for Disease Prevention and Control, and Naiman Banner Center for Disease Prevention and Control for their support and assistance. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [50].

Sources of funding

This study was supported by the National Natural Science Foundation of China (Grant No. 30471484) and partially supported by Tulane University School of Public Health and Tropical Medicine.

References

1. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. *Int J Obes*. 2008; 32:1431–7.
2. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006; 355:763–78. [PubMed: 16926275]
3. Jee SH, Sull JW, Park J, et al. Body-mass index and mortality in Korean men and women. *N Engl J Med*. 2006; 355:779–87. [PubMed: 16926276]
4. Hu D, Xie J, Fu P, et al. Central rather than overall obesity is related to diabetes in the chinese population: the InterASIA study**. *Obesity*. 2007; 15:2809–16. [PubMed: 18070772]
5. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2007; 298:2028–37. [PubMed: 17986696]
6. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008; 359:2105–20. [PubMed: 19005195]
7. Menke A, Muntner P, Wildman RP, Reynolds K, He J. Measures of adiposity and cardiovascular disease risk factors*. *Obesity*. 2007; 15:785–95. [PubMed: 17372330]
8. Reis JP, Araneta MR, Wingard DL, Macera CA, Lindsay SP, Marshall SJ. Overall obesity and abdominal adiposity as predictors of mortality in U.S. white and black adults. *Ann Epidemiol*. 2009; 19:134–42. [PubMed: 19185808]
9. Haslam DW, James WPT. Obesity. *Lancet*. 2005; 366:1197–209. [PubMed: 16198769]
10. Panagiotakos DB, Pitsavos C, Yannakoulia M, Chrysohou C, Stefanadis C. The implication of obesity and central fat on markers of chronic inflammation: the ATTICA study. *Atherosclerosis*. 2005; 183:308–15. [PubMed: 16285994]
11. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. *Basic Res Cardiol*. 2008; 103:398–406. [PubMed: 18600364]
12. Wang C-H, Li S-H, Weisel RD, et al. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation*. 2003; 107:1783–90. [PubMed: 12665485]
13. Festa A, D'Agostino Jr R, Williams K, et al. The relation of body fat mass and distribution to markers of chronic inflammation. *Int J Obes Relat Metab Disord*. 2001; 25:1407. [PubMed: 11673759]
14. Meigs JB, Hu FB, Rifai N, Manson JE. Biomarkers of endothelial dysfunction and risk of type 2 diabetes mellitus. *JAMA*. 2004; 291:1978–86. [PubMed: 15113816]
15. Libby P, Ridker PM. Inflammation and atherothrombosis: from population biology and bench research to clinical practice. *J Am Coll Cardiol*. 2006; 48:A33–46.
16. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003; 107:499–511. [PubMed: 12551878]
17. Wexler DJ, Hu FB, Manson JE, Rifai N, Meigs JB. Mediating effects of inflammatory biomarkers on insulin resistance associated with obesity**. *Obesity*. 2005; 13:1772–83.
18. Mathieu P, Poirier P, Pibarot P, Lemieux I, Despres J-P. Visceral obesity: the link among inflammation, hypertension, and cardiovascular disease. *Hypertension*. 2009; 53:577–84. [PubMed: 19237685]

19. Li H, Xu T, Tong W, Liu Y, Zhao L, Zhang Y. Comparison of cardiovascular risk factors between prehypertension and hypertension in a Mongolian population, Inner Mongolia, China. *Circulation J*. 2008; 72:1666–73.
20. Zhou B-F. The Cooperative Meta-analysis Group of the Work Group on Obesity in China. Conference Proceedings: predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults: study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Asia Pac J Clin Nutr*. 2002; 11:S685–93.
21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972; 18:499–502. [PubMed: 4337382]
22. Haber E, Koerner T, Page L, Kliman B, Purnode A. Application of a radioimmuno-assay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. *J Clin Endocrinol Metab*. 1969; 29:1349–55. [PubMed: 4311082]
23. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol*. 2007; 49:2129–38. [PubMed: 17531663]
24. Emanuel RL, Cain JP, Williams GH. Double antibody radioimmunoassay of renin activity and angiotensin II in human peripheral plasma. *J Lab Clin Med*. 1973; 81:632–40. [PubMed: 4348744]
25. Regional Office for the Western Pacific (WPRO), World Health Organization. The International Association for the Study of Obesity, The International Obesity Task Force. The Asia-Pacific perspective: redefining obesity and its treatment. World Health Organization; Australia, Melbourne: 2000. p. 1-56.
26. Thorand B, Baumert J, Döring A, et al. Sex differences in the relation of body composition to markers of inflammation. *Atherosclerosis*. 2006; 184:216–24. [PubMed: 15993885]
27. Kim K, Valentine RJ, Shin Y, Gong K. Associations of visceral adiposity and exercise participation with C-reactive protein, insulin resistance, and endothelial dysfunction in Korean healthy adults. *Metabolism*. 2008; 57:1181–9. [PubMed: 18702942]
28. Onat A, Can G, Hergenc G. Serum C-reactive protein is an independent risk factor predicting cardiometabolic risk. *Metab Clin Exp*. 2008; 57:207–14. [PubMed: 18191050]
29. Ford ES, Cappuccio FP. Body mass index, diabetes, and C-reactive protein among U. S. adults. *Diabetes Care*. 1999; 22(12):1971–7. [PubMed: 10587828]
30. Miller MA, Cappuccio FP. Cellular adhesion molecules and their relationship with measures of obesity and metabolic syndrome in a multiethnic population. *Int J Obes*. 2006; 30:1176–82.
31. Bošanská L, Michalský D, Lacinová Z, et al. The influence of obesity and different fat depots on adipose tissue gene expression and protein levels of cell adhesion molecules. *Physiol Res*. 2010; 59(1):79–88. [PubMed: 19249917]
32. Ponthieux A, Herbeth B, Droesch S, Haddy N, Lambert D, Visvikis S. Biological determinants of serum ICAM-1, E-selectin, P-selectin and -selectin levels in healthy subjects: the Stanislas study. *Atherosclerosis*. 2004; 172:299–308. [PubMed: 15019540]
33. Ye X, Franco OH, Yu Z, et al. Associations of inflammatory factors with glycaemic status among middle-aged and older Chinese people. *Clin Endocrinol*. 2009; 70:854–62..
34. Lin J, Zhang M, Song F, et al. Association between C-reactive protein and pre-diabetic status in a Chinese Han clinical population. *Diabetes Metab Res Rev*. 2009; 25:219–23. [PubMed: 19116941]
35. Yamada S, Gotoh T, Nakashima Y, et al. Distribution of serum C-reactive protein and its association with atherosclerotic risk factors in a Japanese population. *Am J Epidemiol*. 2001; 153:1183–90. [PubMed: 11415953]
36. Otsuka T, Kawada T, Katsumata M, Ibuki C, Kusama Y. High-sensitivity C-reactive protein is associated with the risk of coronary heart disease as estimated by the Framingham Risk Score in middle-aged Japanese men. *Int J Cardiol*. 2008; 129:245–50. [PubMed: 17997174]
37. Sung KC, Suh JY, Kim BS, et al. High sensitivity C-reactive protein as an independent risk factor for essential hypertension. *Am J Hypertens*. 2003; 16:429–33. [PubMed: 12799089]
38. National Institute of Standards and Technology. Development of a reference measurement procedure for C-reactive protein in human serum. Gaithersburg, MD, USA: 2009.

39. Kimberly MM, Vesper HW, Caudill SP, et al. Standardization of immunoassays for measurement of high-sensitivity C-reactive protein. Phase I: evaluation of secondary reference materials. *Clin Chem*. 2003; 49(4):611–6. [PubMed: 12651814]
40. Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clin Chem*. 2003; 49(8): 1258–71. [PubMed: 12881440]
41. Roberts WL, Moulton L, Law TC, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Part 2. *Clin Chem*. 2001; 47(3):418–25. [PubMed: 11238291]
42. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk scores. *Circulation*. 2004; 109:1955–9. [PubMed: 15051634]
43. Hickling S, Hung J, Knuiman M, Divitini M, Beilby J. Are the associations between diet and C-reactive protein independent of obesity? *Prev Med*. 2008; 47:71–6. [PubMed: 18329089]
44. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med*. 2007; 167:31–9. [PubMed: 17210875]
45. Kurukulasuriya LR, Stas S, Lastra G, Manrique C, Sowers JR. Hypertension in obesity. *Endocrinol Metab Clin North Am*. 2008; 37:647–62. [PubMed: 18775357]
46. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol*. 2004; 15:1983–92. [PubMed: 15284284]
47. Hotamisligil G, Arner P, Caro J, Atkinson R, Spiegelman B. Increased adipose tissue expression of tumour necrosis factor- α in human obesity and insulin resistance. *J Clin Invest*. 1995; 95:2409–15. [PubMed: 7738205]
48. Mohamed-Ali V, Goodrick S, Rawesh A, et al. Subcutaneous adipose tissue releases interleukin-6, but not tumor necrosis factor- α , in vivo. *J Clin Endocrinol Metab*. 1997; 82:4196–200. [PubMed: 9398739]
49. Lionetti L, Mollica MP, Lombardi A, Cavaliere G, Gifuni G, Barletta A. From chronic overnutrition to insulin resistance: the role of fat-storing capacity and inflammation. *Nutr Metab Cardiovasc Dis*. 2009; 19:146–52. [PubMed: 19171470]
50. Coats AJ. Ethical authorship and publishing. *Int J Cardiol*. 2009; 131:149–50. [PubMed: 19046787]

Table 1

Characteristics of 2589 participants according to waist circumference and body mass index, Inner Mongolia, China.

	Low BMI, <24 kg/m²		High BMI, ≥24 kg/m²		p value		
	Low WC, <85/80 cm	High WC, ≥85/80 cm	Low WC, <85/80 cm	High WC, ≥85/80 cm	BMI	WC	BMI*WC
<i>N</i>	1464	431	60	634			
Age, yr	45.0 (12.8)	51.9 (11.9)	42.8 (11.0)	46.6 (10.9)	0.55	<0.001	0.08
Female, %	52.3	69.4	55.0	67.5	<0.001	<0.001	<0.001
Alcohol consumption, %	35.5	33.9	30.0	28.9	0.003	0.02	0.005
Current cigarette smoking, %	50.2	44.3	33.3	32.2	<0.001	<0.001	<0.001
Family history of hypertension, %	12.1	13.9	15.0	14.3	0.20	0.14	0.25
Systolic blood pressure, mm Hg	126.0 (23.5)	133.8 (27.4)	131.6 (21.4)	135.7 (24.6)	0.04	<0.001	0.30
Diastolic blood pressure, mm Hg	82.3 (12.2)	85.8 (13.2)	85.3 (9.9)	88.9 (13.3)	<0.001	<0.001	0.99
Fasting glucose, mg/dL	87.2 (19.3)	90.2 (20.9)	89.9 (13.8)	95.6 (26.9)	<0.001	<0.001	0.38
HDL cholesterol, mg/dL	46.2 (12.7)	45.4 (11.9)	42.4 (11.7)	43.3 (13.3)	<0.001	<0.001	0.38
LDL cholesterol, mg/dL	82.0 (36.9)	96.5 (38.2)	86.8 (43.4)	101.3 (43.4)	<0.001	<0.001	0.99
Triglycerides, mg/dL	94.0 (76.4)	125.6 (118.2)	99.1 (85.5)	145.5 (166.9)	<0.001	<0.001	0.37
Total cholesterol, mg/dL	136.5 (40.3)	152.8 (441.3)	137.8 (45.9)	157.3 (48.4)	<0.001	<0.001	0.62
Body mass index, kg/m ²	20.1 (1.8)	22.2 (1.4)	24.9 (1.1)	26.7 (2.5)	<0.001	<0.001	0.99
Waist circumference, cm	74.4 (4.9)	85.2 (4.5)	78.0 (5.5)	92.6 (7.5)	<0.001	<0.001	<0.001

All values are means (SD) unless otherwise noted. Low waist circumference was defined as <85 cm for men and <80 cm for women; high waist circumference was defined as ≥85 cm for men and ≥80 cm for women. WC=waist circumference; BMI = body mass index.

Table 2

Plasma concentrations of inflammation and endothelial biomarkers according to body mass index and waist circumference.

	Low BMI, <24 kg/m²		High BMI, ≥24 kg/m²		<i>p</i> value		
	Low WC, <85/80 cm	High WC, ≥85/80 cm	Low WC, <85/80 cm	High WC, ≥85/80 cm	BMI	WC	BMI*WC
CRP, mg/L	5.32 (3.56-9.32)	6.01 (4.21-13.02)	5.92 (3.94-10.47)	7.57 (4.86-16.00)	<0.001	< 0.001	< 0.001
sICAM-1, ng/mL	325.1 (96.2)	319.8 (98.0)	320.7 (87.4)	344.8 (101.1)	<0.001	0.02	0.04
sE-selectin, ng/mL	17.6 (14.2-23.5)	19.2 (15.0-24.1)	19.7 (15.0-26.6)	20.8 (16.1-27.6)	<0.001	<0.001	<0.001
Angiotensin II, pg/mL	48.5 (40.0-71.0)	50.0 (40.0-73.3)	49.0 (39.5-73.4)	49.0 (39.0-71.4)	0.97	0.44	0.87

For normally distributed variables (sICAM-1), values are presented as means (SD) and *p* values were computed with an age and gender-adjusted ANOVA test; for non-normally distributed variables (CRP, sE-selectin, and angiotensin II), values are presented as medians (interquartile range) and *p* values were computed using rank order ANOVA test for the difference in medians adjusted for age and gender. Low WC was defined as <85 cm for men and as <80 cm for women; high WC was defined as ≥85 cm for men and as ≥80 cm for women. BMI = body mass index; WC = waist circumference; CRP = C-reactive protein; sICAM-1 = soluble inter-cellular adhesion molecule-1; sE-selectin = soluble E-selectin.

Table 3

Odds ratio of elevated biomarkers associated with one standard deviation of BMI and waist circumference.

	<u>C-reactive protein</u>		<u>Soluble ICAM-1</u>		<u>Soluble E-selectin</u>		<u>Angiotensin II</u>	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
<i>Body mass index (SD =3.47 kg/m²)</i>								
BMI alone	1.43	(1.31, 1.56)	1.22	(1.11, 1.33)	1.29	(1.18, 1.41)	0.98	(0.89, 1.07)
BMI, age, and sex	1.49	(1.36, 1.63)	1.24	(1.13, 1.35)	1.32	(1.21, 1.45)	0.99	(0.90, 1.08)
BMI, age, sex and other risk factors ^a	1.31	(1.19, 1.45)	1.11	(1.01, 1.23)	1.41	(1.27, 1.56)	0.96	(0.87, 1.05)
BMI, WC, age, sex and other risk factors ^a	0.96	(0.80, 1.16)	1.11	(0.92, 1.33)	1.30	(1.08, 1.55)	0.82	(0.69, 0.99)
<i>Waist circumference (SD =9.59 cm)</i>								
WC alone	1.66	(1.52, 1.82)	1.26	(1.15, 1.38)	1.34	(1.22, 1.47)	1.06	(0.97, 1.16)
WC, age, and sex	1.61	(1.47, 1.76)	1.24	(1.13, 1.36)	1.32	(1.20, 1.45)	1.04	(0.95, 1.14)
WC, age, sex and risk factors ^a	1.41	(1.27, 1.56)	1.10	(0.99, 1.21)	1.37	(1.24, 1.52)	1.01	(0.92, 1.12)
WC, BMI, age, sex and risk factors ^a	1.46	(1.21, 1.76)	1.01	(0.84, 1.21)	1.10	(0.92, 1.32)	1.19	(1.00, 1.43)

BMI = body mass index; WC = waist circumference.

^aRisk factors included: low density lipoprotein cholesterol, smoking, systolic blood pressure, and fasting blood glucose.

Table 4

Odds ratio of elevated biomarkers associated with low or high waist circumference or BMI.

	<u>C-reactive protein</u>		<u>Soluble ICAM-1</u>		<u>Soluble E-selectin</u>		<u>Angiotensin II</u>	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Low BMI/low WC	1.00		1.00		1.00		1.00	
Low BMI/high WC	1.73	(1.32, 2.26)	0.87	(0.66, 1.16)	1.22	(0.92, 1.61)	1.08	(0.83, 1.41)
High BMI/low WC	1.33	(0.71, 2.52)	0.90	(0.46, 1.76)	1.87	(1.01, 3.44)	1.02	(0.55, 1.87)
High BMI/high WC	1.99	(1.57, 2.52)	1.19	(0.94, 1.51)	2.40	(1.90, 3.04)	1.01	(0.80, 1.27)

BMI = body mass index; WC = waist circumference; the multivariate model included BMI/WC groups, age, gender, low density lipoprotein cholesterol, smoking, systolic blood pressure and fasting blood glucose.