## Title

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# Adipokines and Body Fat Composition in South Asians: Results of the Metabolic syndrome and Atherosclerosis in South Asians Living in America (MASALA) Study

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## Abstract

**Objective—**To investigate whether leptin and adiponectin are associated with body fat composition in a South Asian population independent of metabolic variables.

**Design—**Cross-sectional study

**Subjects—**150 South Asian men and women, between the ages of 45–79 years, in the San Francisco Bay Area without pre-existing clinical cardiovascular disease.

**Measurements—**Blood samples were obtained to measure glucose metabolism variables, lipid profiles and adipokines. Total body fat was determined using dual-energy x-ray absorptiometry. Abdominal computed tomography was used to measure subcutaneous, visceral, and hepatic fat.

**Results—**Average body mass index (BMI) was overweight at 26.1±4.6 kg/m$^2$ and did not differ by sex. However, women had significantly more total body fat ($p<0.001$) and subcutaneous fat ($p<0.001$) than men, while men had significantly more visceral fat ($p<0.001$) and hepatic fat ($p=0.04$) than women. Women had significantly higher levels of adiponectin ($p<0.01$) and leptin ($p<0.01$). In sex-stratified analyses, leptin was strongly associated with all body composition measures in women ($p<0.05$) as well as in men ($p<0.05$ except for hepatic fat) while there was an insignificant trend towards an inverse association between adiponectin and body composition in both women and men which was significant in combined bivariate analyses. In multivariate analyses, leptin was strongly associated with all measures of adiposity, including BMI ($p<0.001$), total body fat ($p<0.001$), visceral fat ($p<0.001$), and hepatic fat ($p=0.01$). However, adiponectin's



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**Conflicts of interest:** None.

inverse association with adiposity was significantly attenuated by high-density lipoprotein (HDL), triglycerides, and insulin resistance. The association between adipokines and diabetes was markedly attenuated after adjusting for body composition.

**Conclusion—**Despite only modestly elevated BMI, South Asians have elevated levels of total and regional adiposity. Leptin is strongly associated with adiposity while adiponectin's association with adiposity is attenuated by metabolic variables in South Asians. Adipokines in association with adiposity play an important role in the development of diabetes.

### Keywords

South Asians; body composition; sex differences in adiposity; adiponectin and leptin; hepatic fat

## Introduction

South Asians, individuals from India, Pakistan, Bangladesh, Sri Lanka and Nepal; have a higher amount of total body fat for a given body mass index (BMI) compared to whites (1). At a given level of total body fat, South Asians also have a higher amount of total abdominal adipose tissue, subcutaneous abdominal adipose tissue, and visceral adipose tissue compared to white Europeans (2–3). Additionally, Asian Indians with central adiposity are more likely to have abnormal metabolic profiles and elevated blood pressure (4). South Asians are also predisposed to the development of hepatic steatosis which leads to further insulin resistance and inflammation (3). Adiposity has been linked to obesity-related diseases and increased mortality in developing countries, including India (5).

The link between adipose tissue and metabolic abnormalities is thought to be partially mediated by adipose tissue secreted factors known as adipokines (6). Two well-known adipokines are adiponectin and leptin. Adiponectin is known to have anti-inflammatory and insulin sensitizing effects (7–8) and is inversely related to the metabolic syndrome and type 2 diabetes mellitus (T2DM). On the other hand, leptin normally has insulin sensitizing and anorexigenic effects (9). However, obese people develop hyperleptinemia and become leptin resistant (10), and leptin is positively correlated with the metabolic syndrome in obese subjects (9, 11). Visceral adiposity is predictive of the development of insulin resistance since it appears to be a more active endocrine organ secreting more pro-inflammatory adipokines and less adiponectin (12). Studies of South Asians have shown that lower levels of adiponectin are correlated with insulin resistance and the metabolic syndrome while leptin levels appear to be positively correlated with impaired glucose tolerance and T2DM (13–14). However, studies assessing the relation between serum levels of adipokines and body composition (total and regional adiposity) have mainly been conducted in white populations, and such research in South Asians is limited and controversial.

In this study, we aimed to determine whether there is an association between serum levels of two adipokines, adiponectin and leptin, and body composition independent of metabolic parameters in a South Asian population.

## Materials and Methods

### Participants

We conducted a cross-sectional study of 150 South Asian Indians recruited from the San Francisco Bay Area between August 2006 and October 2007 called the Metabolic Syndrome and Atherosclerosis in South Asians Living in America (MASALA) study. The sampling strategy and recruitment procedures have been previously described (15). Briefly, this study was modeled on the Multi-Ethnic Study of Atherosclerosis (MESA) (16). To be eligible, participants had to be between 45 and 84 years old, self-identify as South Asian Indian, and have no existing clinical cardiovascular disease. Excluded were those under cancer treatment, with impaired cognitive ability, life expectancy <5 years, plans to move, or living in a nursing home. Also excluded were persons who could not speak or understand Hindi or English. We randomly sampled South Asian Indians using surname lists from a commercial marketing company (Genesys Marketing System Group, Washington, PA, USA) for a goal of recruiting 150 participants. Participants were invited to a single session to complete the laboratory tests and clinical measurements described below.

### Demographic Measurements

Participants completed face-to-face, interviewer-administered questionnaires to ascertain age, sex, medical history, and smoking status (current, never, former).

### Metabolic Measurements

To obtain a metabolic profile on each of the subjects, blood samples were obtained after a requested12-hour fast. These samples were used to measure plasma glucose, insulin, total cholesterol, triglycerides, HDL-cholesterol, dysfunctional HDL, and lipid subfractions. Fasting plasma glucose was measured using a glucose oxidase method (YSI 2300, Yellow Sprints, OH, USA) and insulin was measured using a radioimmunoassay (Millipore, St. Charles, MO, USA). Total cholesterol, triglycerides, and HDL-cholesterol were measured using enzymatic methods (Quest, San Jose, CA, USA). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. The insulin sensitivity index and homeostasis model of insulin resistance (HOMA-IR) (17), which are both measures of insulin resistance, were calculated using fasting glucose and fasting insulin. We performed an oral glucose tolerance test in which participants were administered a 75-g oral glucose with blood samples taken at 120 minutes for plasma glucose and insulin.

Participants were also assessed for traditional cardiovascular risk factors including hypertension, diabetes, and the metabolic syndrome. Three seated blood pressure measurements were obtained with an automated blood pressure monitor (Philips-Agilent V24C, Andover, MA, USA). Mean systolic and diastolic blood pressures were calculated from the second and third blood pressure measurement. Those with a systolic blood pressure ≥ 140 and/or a diastolic blood pressure ≥ 90 were defined as having hypertension. Individuals were categorized with normal glucose tolerance, prediabetes, or diabetes. Diabetes was defined by use of a hypoglycemic medication, or fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or 2-hour post-challenge glucose ≥ 11.1 mmol/L (18). Prediabetes was defined by FPG 5.5–6.9 mmol/L and/or a 2-hour post-challenge glucose between 7.8–11.0

mmol/L. Normal glucose tolerant participants had both FPG < 5.5 mmol/L and 2-hour glucose < 7.8mmol/L. Metabolic syndrome was determined using the modified ATP III guidelines for Asians with a waist circumference cut-off of ≥ 80cm for women and ≥ 90cm for men (19–21).

## Adipokine Measurements

From samples which were processed and stored at −80°C for batched assays, serum adiponectin levels (total and high molecular weight - HMW) were measured in duplicate via a radioimmunoassay (RIA; Linco, St. Charles, MO, USA). For total adiponectin, the intra-assay coefficient of variation (CV) was 4.7%. For HMW adiponectin, the intra-assay CV was 2.1% and the inter-assay CV was 12.6%. Serum leptin levels were measured in duplicate by RIA (Linco, St. Charles, MO, USA). For leptin, the intra-assay CV was 6.0%.

## Body Fat Composition Measurements

Participant weight (in kg) was measured on a digital scale and height (in cm) with a stadiometer. Body mass index (BMI) was determined using weight and height measurements. Waist circumference was measured (in cm) using a Gullick II tape at the site of maximum circumference midway between the lower ribs and the anterior superior iliac spine. Total lean and fat mass was assessed using dual-energy x-ray absorptiometry (Hologic Discovery-Wi; Waltham, MA, USA). Percent body fat was then determined using the measures of total lean and fat mass. Computed tomography (CT, Philips Medical Systems, Best, The Netherlands) was used to determine abdominal visceral and subcutaneous fat area. A trained radiology technician used a lateral scout image of the spine to establish the correct position (between the L4 and L5 vertebrae) for the abdominal CT using standardized protocols. Visceral and subcutaneous abdominal fat were measured at the L4–L5 level after participants were positioned supine. All CT scans were digitally recorded for batched readings by a trained research assistant. Intra- abdominal adipose tissue area was quantified by delineating the intra-abdominal cavity at the innermost aspect of the abdominal and oblique muscle walls surrounding the cavity. Subcutaneous adipose tissue area was quantified by highlighting of adipose tissue located between the skin and the outermost aspect of the abdominal muscle wall.

We also obtained non-enhanced CT images of liver and spleen density to quantify hepatic fat content. CT measurements included minimal, maximal, and mean attenuation at a minimum of two liver sites and one spleen measurement. The presence of fatty liver was defined by a liver-to-spleen attenuation ratio (L:SAR) of < 1 and lower values represent higher amounts of hepatic fat (22–24).

## Statistical Analysis

For the bivariate analyses, adiponectin and leptin were treated as both continuous variables and also divided into tertiles. We performed both sex-stratified analyses and overall group analyses. Chi-squared or analysis of variance (ANOVA) analyses were performed to assess the relationship between tertiles of the adipokines and demographic, metabolic, and body composition variables. We created correlation matrices between individual body composition variables to avoid collinearity of variables.

We specified sequential multivariate models to assess the relationship between leptin (per standard deviation (SD)) and adiponectin (per SD) with body composition measures. We used linear regression models with a stepwise approach to adjust for covariates. For leptin, the models adjust for the following in a stepwise manner: first for age, sex, and ever smoking history; then adjusting for hypertension; next for both HDL-cholesterol and triglycerides; and finally adjusting for HOMA-IR. For adiponectin, the models adjust for the following in a stepwise manner: first for age and sex; then for hypertension; next for HDL separately from triglycerides; and finally adjusting for HOMA-IR. We also tested for a sex interaction in all of these models. To assess the association between leptin and diabetes, we performed logistic regression, adjusting for age, sex, hypertension, ever smoking history, and one body fat composition parameter (BMI, total body fat, and visceral fat area) in separate models. Similarly, to ascertain an association between adiponectin and diabetes, we performed logistic regression, adjusting for age, sex, hypertension, and one body composition parameter (total body fat, visceral fat, and hepatic fat – L:SAR) in separate models.

We used STATA (version 10 College Station, TX, USA) and SAS Version 9.1 (SAS Institute, Cary, NC, USA) for our analyses.

## Results

Of the 150 South Asians enrolled in the MASALA study, half of each sex, the average age was 57 ± 8 years and the average BMI was 26.1 ± 4.6 kg/m$^2$. While BMI did not differ by sex, women had a higher percentage of body fat (40.7 ± 5.5% vs. 29.5 ± 6.0%, $p < 0.001$), higher amount of total body fat (26.4 ± 8.3 kg vs. 22.7 ± 7.5 kg, $p < 0.01$), and a higher amount of subcutaneous fat area by CT (287.0 ± 123.6 cm$^2$ vs. 216.3 ± 89.0 cm$^2$, $p < 0.001$). (Figure 1) However, men had a larger visceral fat area (155.6 ± 56.3 cm$^2$ vs. 111.1 ± 47.8 cm$^2$, $p < 0.001$, Figure 1) and a higher amount of hepatic fat (liver-to-spleen attenuation ratio of 1.2 ± 0.2 vs. 1.3 ± 0.3, p=0.04). Women had higher serum levels of both leptin (21.6 ± 11.6 vs. 9.1 ± 6.3 ng/ml, $p < 0.01$) and adiponectin (9.0 ± 5.8 vs. 5.7 ± 3.3 μg/ml, $p < 0.01$).

In sex-stratified analyses, leptin was inversely associated with age among men only. In women, leptin was associated with HOMA-IR and triglycerides and showed a trend towards inverse association with HDL. In men, there was a similar trend towards association with HOMA-IR and inverse association with HDL. In both men and women, leptin was associated with metabolic syndrome but not with hypertension or diabetes. In women, leptin was strongly associated with all measures of both total and regional adiposity. In men, leptin was strongly associated with all measures of total adiposity and most measures of regional adiposity but not hepatic fat. (Table 1)

Adiponectin was associated with age in men but not in women. Furthermore, in women, adiponectin was associated with HDL, inversely associated with triglycerides and with HOMA-IR; whereas in men, adiponectin was inversely associated with triglycerides only. Adiponectin was not associated with diabetes, hypertension, or metabolic syndrome in either women or men. In women, adiponectin was not associated with any measures of total

adiposity but was inversely associated with visceral fat and hepatic fat. On the other hand, adiponectin was not associated with any measure of body composition in men. (Table 2) However, in combined analyses with both sexes, adiponectin was inversely associated with all measures of total and regional adiposity: BMI ($p < 0.001$), percent body fat ($p < 0.001$), total body fat ($p < 0.001$), waist circumference ($p < 0.001$), subcutaneous fat ($p < 0.01$), visceral fat ($p < 0.001$), and hepatic fat ($p = 0.01$). (Data not shown.)

To further investigate the association between adipokines and adiposity, we conducted multivariate analyses adjusting for age, sex, smoking history, hypertension, HDL, triglycerides, and HOMA-IR in a stepwise manner. (Table 3) After full adjustment, leptin remained strongly correlated to BMI, total body fat, and abdominal visceral fat ($p < 0.001$ for each), as well as hepatic fat ($p = 0.01$). However, the inverse association between adiponectin and all body composition measures which we saw in our combined analyses no longer remained significant after adjusting for HDL and triglycerides; these metabolic covariates completely attenuated the association between adiponectin and BMI, total body fat, and hepatic fat. There remained a trend towards association between adiponectin and visceral fat after full adjustment. The associations between each adipokine and adiposity did not vary by sex (p-for-interaction >0.15 for each adiposity outcome with both leptin and adiponectin).

We conducted similar analyses to assess the association between high molecular weight adiponectin and body fat composition parameters. The results were essentially the same as those seen with total adiponectin; no significant association was seen after adjusting for covariates. (Data not shown.)

Lastly, we investigated the association between the adipokines and diabetes. In unadjusted models, leptin (per SD) was not associated with diabetes (OR 0.88, 95% CI 0.60–1.28, $p = 0.50$). After adjusting for age, sex, hypertension, and smoking, there was a trend towards increased odds of diabetes with leptin (OR 1.48, 95% CI 0.91–2.42, $p = 0.12$). Further adjusting for any measure of adiposity significantly attenuated this association. For adiponectin (per SD), there was a weak trend towards association with diabetes in unadjusted analyses (OR 0.73, 95% CI 0.47–1.14, $p = 0.17$). After adjusting for age, sex, and hypertension, the association was further attenuated (OR 0.81, 95% CI 0.50–1.30, $p = 0.38$). Adding any measure of adiposity further nullified the association. (Data not shown.)

## Discussion

South Asian Indians had high levels of total and regional adiposity despite a modest BMI. Though both men and women had identical BMI, there were important sex differences in measured adiposity and fat distribution with women having higher amounts of total and subcutaneous body fat and less visceral and hepatic fat than men. In sex-stratified analyses, leptin was associated with total and regional body fat measures while there was a trend towards an inverse association between adiponectin and all body composition measures that was more evident in women than men. In combined bivariate analyses, the inverse association between adiponectin and all body composition measures became significant. After adjustment for demographic and metabolic covariates, leptin was positively associated

with all measures of adiposity, while the relationship between adiponectin and all adiposity measures was attenuated.

Our study demonstrated significant differences between men and women in body composition and adipokine levels. Ramachandran et al demonstrated that women had higher subcutaneous fat while men had higher visceral fat (25), similar to our findings. We also demonstrated that men had more hepatic fat, another ectopic fat store, than women. As in previous studies (13, 25), women had higher levels of leptin and adiponectin. While body fat patterns differ significantly between the two sexes, the biologic mechanisms explaining these differences remain elusive.

A few prior studies have evaluated differences in adipokine profiles and body composition measures among different ethnic groups simultaneously. Chandalia et al found that while BMI did not differ between South Asian and Caucasian men, South Asian men had significantly more total body fat and subcutaneous abdominal fat and less lean body mass (26). This is consistent with our results which show that while BMI is only modestly elevated, South Asians have high levels of total and regional adiposity. This study also found that South Asian men have higher leptin levels and lower adiponectin levels compared to white men, and that larger subcutaneous adipocyte cell size correlated with lower adiponectin levels (26). Furthermore, in Mauritius, both Asian Indian men and women have higher levels of leptin after adjustment for body composition compared to Creoles and Europids (27). In a more recent study, compared to Europeans, Chinese, and Aboriginal people, South Asians had the least favorable adipokine profile (28). The high levels of adiposity and unfavorable adipokine profiles are thought to cause metabolic disturbances in South Asians (13–14, 26–29).

Studies investigating leptin and body composition have been performed in South Asians. In prior studies, leptin levels have correlated with total and subcutaneous adipose tissue but not with visceral adipose tissue (25, 28, 30). On the contrary, our study results showed that leptin levels were correlated with all measures of adiposity in multivariate analyses, including visceral fat area and hepatic fat, independent of metabolic variables. However, these prior studies have included a much younger population which may account for some of these differences.

Some studies investigating adiponectin and body composition have been performed in South Asians. Two studies did not find an association between serum adiponectin and body composition measures (14, 28). Mohan et al (13) found that adiponectin was negatively associated with BMI and waist circumference after adjusting for age and sex in an Asian Indian population. However, our study demonstrated that the association between adiponectin and BMI was slightly attenuated by age and sex. They also demonstrated that while adiponectin values were lower in those with abdominal obesity (defined by waist circumference) it was not statistically significant (13) while our study showed that a more specific measure of abdominal obesity, visceral fat area, was no longer associated with adiponectin after adjustment for covariates.

Interestingly, our study showed that adiponectin and leptin levels were not associated with diabetes after adjusting for age, sex, hypertension and any measure of adiposity. Prior studies have demonstrated that adiponectin is inversely associated with diabetes (13) and that adiponectin levels decrease across the glycemic spectrum (28) while leptin levels increase (14). However, these studies have not adjusted for various body composition parameters. Soderberg et al. (29) demonstrated that leptin predicts development of diabetes in South Asian men in Mauritius independent of waist circumference and BMI. Therefore, it appears that adipokines in association with adiposity influence the development of diabetes.

We had several radiographic measures of body composition in this study but were limited to a small sample which raises the possibility of lack of power to observe sex-specific differences in diabetes and smaller associations between adiponectin and body fat composition or diabetes. Questions that arise from this study include how adiponectin's influence on metabolic parameters, particularly lipids, affects body composition and also through what mechanisms does leptin cause fatty liver, which is known to lead to an adverse metabolic profile. Finally, further studies investigating the mechanisms that lead to different body composition profiles in men and women are warranted.

In conclusion, our study demonstrated that South Asians have high levels of adiposity despite only mildly elevated BMI and marked differences exist in body composition between men and women. We also found a strong association between leptin and body composition while the association between adiponectin and body composition was attenuated by metabolic variables. Our study emphasizes the importance of variation in regional adiposity and significance of adipokines in adiposity in South Asians which need to be investigated further given the adverse effects of obesity on this population.

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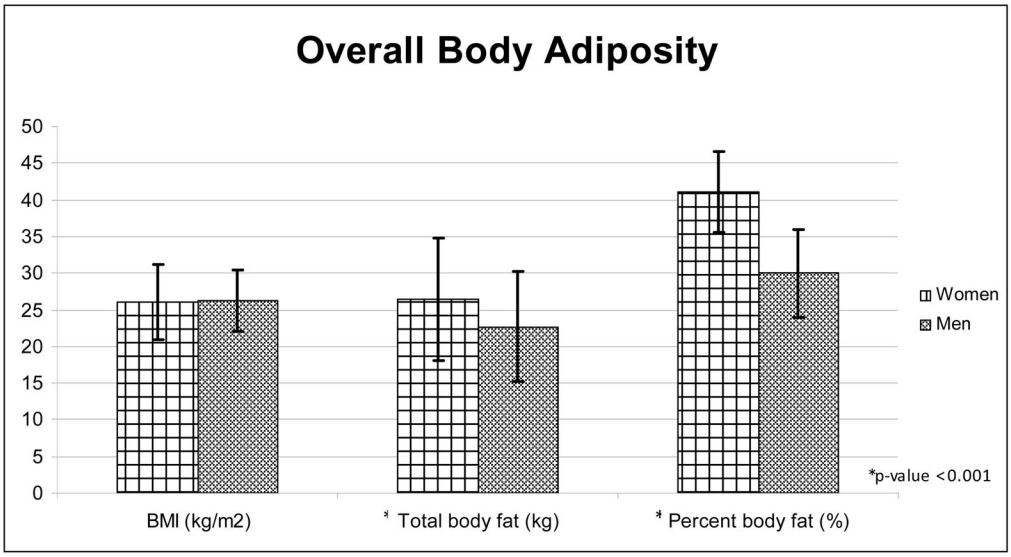
a)

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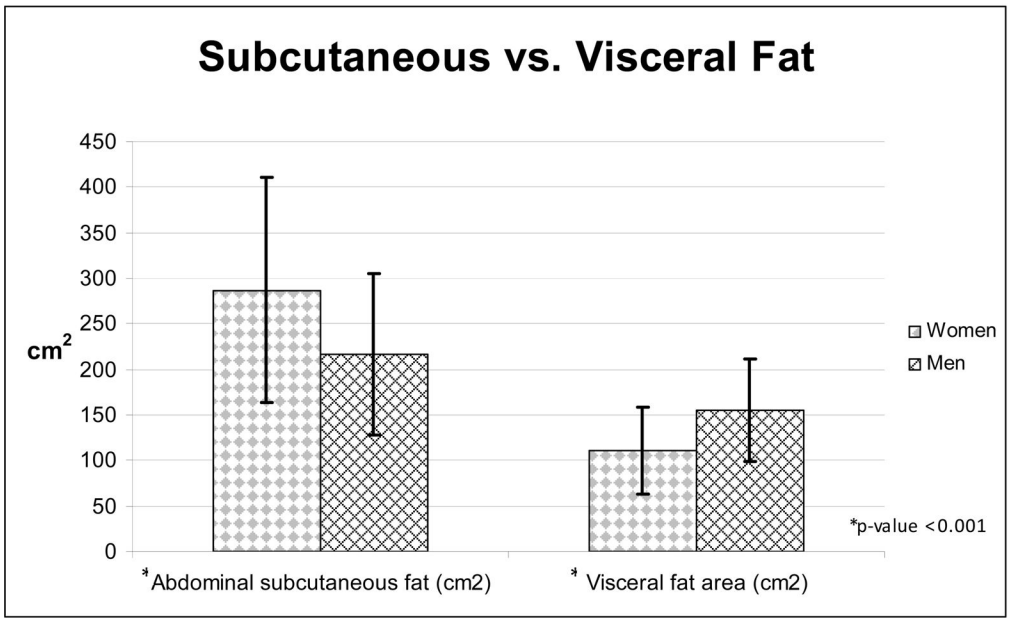


**Figure 1.**
Differences in Body Composition Between Men and Women

## Table 1

Sex-stratified characteristics of the MASALA participants by tertiles of leptin*

| | Leptin (ng/ml) – Women (n = 74) | | | | Leptin (ng/ml) – Men (n = 73) | | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Tertile 1 (4.1–14.8) n = 25** | **Tertile 2 (15.2–24.6) n = 26** | **Tertile 3 (25.2–58.1) n = 23** | **P-value** | **Tertile 1 (0.7–6.2) n = 25** | **Tertile 2 (6.3–9.8) n = 24** | **Tertile 3 (10.1–37.6) n = 24** | **P-value** |
| Mean age, years | 55.3 ± 7.8 | 57.3 ± 6.4 | 57.8 ± 8.2 | 0.46 | 61.0 ± 9.7 | 54.8 ± 7.0 | 57.2 ± 8.5 | 0.04 |
| History of ever smoking | 2 (8) | 1 (4) | 1 (4) | 0.78 | 7 (28) | 7 (29) | 7 (29) | 0.99 |
| **Metabolic variables:** | | | | | | | | |
| Log-transformed HOMA-IR | 1.9 ± 0.7 | 2.4 ± 1.2 | 4.2 ± 3.6 | 0.002 | 2.5 ± 1.4 | 6.0 ± 8.6 | 5.0 ± 3.1 | 0.07 |
| Total cholesterol, mmol/L | 4.8 ± 0.9 | 4.9 ± 0.9 | 5.1 ± 0.8 | 0.44 | 4.9 ± 0.9 | 4.8 ± 0.8 | 4.7 ± 1.0 | 0.68 |
| Triglycerides, mmol/L | 1.3 ± 0.5 | 1.2 ± 0.5 | 1.6 ± 0.6 | 0.03 | 1.4 ± 0.8 | 1.8 ± 0.8 | 1.8 ± 0.8 | 0.11 |
| HDL, mmol/L | 1.5 ± 0.4 | 1.4 ± 0.3 | 1.3 ± 0.3 | 0.07 | 1.3 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 0.06 |
| LDL, mmol/L | 2.7 ± 0.7 | 2.9 ± 0.8 | 3.1 ± 0.8 | 0.3 | 3.0 ± 0.8 | 2.9 ± 0.8 | 2.8 ± 0.9 | 0.61 |
| Hypertension | 9 (36) | 4 (15) | 7 (30) | 0.23 | 17 (68) | 13 (54) | 12 (50) | 0.41 |
| Diabetes | 3 (12) | 3 (13) | 3 (13) | 0.17 | 9 (38) | 9 (38) | 13 (54) | 0.35 |
| Metabolic syndrome | 7 (28) | 4 (15) | 11 (48) | 0.05 | 11 (44) | 18 (75) | 21 (88) | < 0.01 |
| **Body fat composition:** | | | | | | | | |
| BMI, kg/m$^2$ | 22.6 ± 2.4 | 25.6 ± 3.4 | 30.4 ± 5.8 | < 0.001 | 23.4 ± 2.8 | 26.4 ± 3.1 | 28.8 ± 4.1 | < 0.001 |
| Waist circumference, cm | 84.2 ± 8.0 | 93.8 ± 11.2 | 106.2 ± 15.1 | < 0.001 | 89.9 ± 5.9 | 98.8 ± 7.2 | 104.6 ± 8.2 | < 0.001 |
| Total body fat, kg | 19.7 ± 3.8 | 26.1 ± 5.9 | 34.3 ± 7.7 | < 0.001 | 15.9 ± 3.8 | 23.0 ± 3.9 | 28.4 ± 5.4 | < 0.001 |
| Percent body fat, % | 35.6 ± 4.1 | 41.2 ± 4.0 | 45.6 ± 3.1 | < 0.001 | 23.8 ± 4.4 | 29.7 ± 2.9 | 34.4 ± 3.8 | < 0.001 |
| Abdominal subcutaneous fat, cm$^2$ | 200 ± 46 | 278 ± 95 | 393 ± 135 | < 0.001 | 146 ± 52 | 213 ± 48 | 281 ± 83 | < 0.001 |
| Abdominal visceral fat area, cm$^2$ | 79 ± 32 | 111 ± 36 | 148 ± 50 | < 0.001 | 115 ± 43 | 160 ± 51 | 186 ± 44 | < 0.001 |
| Liver-to-spleen attenuation ratio | 1.32 ± 0.19 | 1.32 ± 0.28 | 1.15 ± 0.28 | 0.04 | 1.22 ± 0.20 | 1.18 ± 0.16 | 1.15 ± 0.23 | 0.51 |

* values reported represent n (%) unless otherwise stated

**Table 2**

Sex-stratified characteristics of the MASALA participants by tertiles of adiponectin*

| | Adiponectin (ug/ml) – Women (n=74) | | | | Adiponectin (ug/ml) – Men (n=75) | | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Tertile 1 (2.5–6.3) n = 26** | **Tertile 2 (6.4–9.6) n = 24** | **Tertile 3 (9.7–37.9) n = 24** | **P-value** | **Tertile 1(0.9–4.1) n = 27** | **Tertile 2(4.3–5.7) n = 23** | **Tertile 3(6.2–17) n = 25** | **P-value** |
| Mean age, years | 56.3 ± 8.2 | 56.6 ± 5.9 | 57.5 ± 8.3 | 0.85 | 52.7 ± 5.4 | 57.0 ± 8.0 | 63.5 ± 8.8 | < 0.001 |
| History of ever smoking | 1 (4) | 2 (8) | 1 (4) | 0.74 | 6 (22) | 4 (17) | 11 (44) | 0.09 |
| **Metabolic variables:** | | | | | | | | |
| Log-transformed HOMA-IR | 3.4 ± 2.7 | 3.1 ± 2.7 | 1.9 ± 1.0 | 0.06 | 5.1 ± 3.7 | 5.3 ± 8.5 | 3.2 ± 2.3 | 0.32 |
| Total cholesterol, mmol/L | 4.9 ± 0.8 | 4.9 ± 0.7 | 5.1 ± 1.0 | 0.73 | 5.0 ± 0.9 | 4.7 ± 0.9 | 4.6 ± 0.9 | 0.19 |
| Triglycerides, mmol/L | 1.6 ± 0.6 | 1.4 ± 0.5 | 1.1 ± 0.4 | 0.02 | 1.9 ± 0.8 | 1.8 ± 0.9 | 1.3 ± 0.6 | 0.03 |
| HDL, mmol/L | 1.2 ± 0.3 | 1.4 ± 0.3 | 1.6 ± 0.3 | < 0.001 | 1.1 ± 0.2 | 1.1 ± 0.3 | 1.2 ± 0.4 | 0.29 |
| LDL, mmol/L | 3.0 ± 0.7 | 2.9 ± 0.6 | 2.9 ± 1.0 | 0.93 | 3.1 ± 0.9 | 2.8 ± 0.7 | 2.8 ± 0.8 | 0.32 |
| Hypertension | 7 (27) | 5 (21) | 8 (33) | 0.62 | 17 (63) | 13 (57) | 13 (52) | 0.72 |
| Diabetes | 4 (16) | 2 (9) | 3 (13) | 0.10 | 16 (59) | 6 (26) | 9 (38) | 0.15 |
| Metabolic syndrome | 11 (42) | 5 (21) | 6 (25) | 0.21 | 22 (82) | 14 (61) | 15 (60) | 0.17 |
| **Body fat composition:** | | | | | | | | |
| BMI, kg/m$^2$ | 27.0 ± 5.6 | 26.7 ± 5.5 | 24.5 ± 3.7 | 0.17 | 26.2 ± 3.3 | 27.4 ± 4.1 | 25.3 ± 5.0 | 0.22 |
| Waist circumference, cm | 97.2 ± 13.9 | 95.1 ± 17.5 | 90.8 ± 11.6 | 0.29 | 97.5 ± 7.5 | 99.2 ± 10.2 | 97.5 ± 11.3 | 0.77 |
| Total body fat, kg | 27.7 ± 9.1 | 27.2 ± 9.0 | 24.5 ± 6.3 | 0.34 | 22.0 ± 4.7 | 23.7 ± 7.1 | 22.6 ± 10.2 | 0.73 |
| Percent body fat, % | 40.8 ± 6.0 | 40.6 ± 5.1 | 40.6 ± 5.7 | 0.99 | 28.6 ± 4.4 | 30.0 ± 4.9 | 30.0 ± 8.2 | 0.63 |
| Abdominal subcutaneous fat, cm$^2$ | 315 ± 139 | 284 ± 133 | 261 ± 93 | 0.31 | 213 ± 66 | 226 ± 88 | 211 ± 111 | 0.83 |
| Abdominal visceral fat area, cm$^2$ | 129 ± 37 | 113 ± 58 | 91 ± 40 | 0.02 | 153 ± 41 | 167 ± 53 | 149 ± 72 | 0.51 |
| Liver-to-spleen attenuation ratio | 1.16 ± 0.34 | 1.33 ± 0.23 | 1.29 ± 0.18 | 0.07 | 1.18 ± 0.19 | 1.14 ± 0.24 | 1.22 ± 0.17 | 0.41 |

* values reported represent n (%) unless otherwise stated

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**Table 3**

Sequentially adjusted associations between leptin (per 11 ng/ml)* and adiponectin (per 5 μg/ml)** and body fat composition measures

| | BMI (per kg/m$^2$) | | Total body fat (per kg) | | Visceral fat area (per cm$^2$) | | Liver-to-Spleen attenuation ratio(per unit) | |
|---|---|---|---|---|---|---|---|---|
| **Leptin models:** | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** | **β (95% CI)** | ***p*-value** |
| 1: Unadjusted | 2.65 (2.07–3.24) | < 0.001 | 5.83 (5.02–6.64) | < 0.001 | 10.33 (1.76 – 18.91) | 0.02 | −0.03 (−0.07 – 0.00) | 0.08 |
| 2: + age, sex, ever smoke | 3.84 (3.24–4.45) | < 0.001 | 6.77 (5.84–7.70) | < 0.001 | 31.13 (22.82–39.44) | < 0.001 | −0.08 (−0.12 – −0.04) | < 0.001 |
| 3: + hypertension | 3.84 (3.24–4.44) | < 0.001 | 6.77 (5.84–7.69) | < 0.001 | 31.11 (22.81–39.41) | < 0.001 | −0.08 (−0.12 – −0.04) | < 0.001 |
| 4: + HDL and triglycerides | 3.72 (3.10–4.34) | < 0.001 | 6.60 (5.64–7.56) | < 0.001 | 27.25 (18.90–35.60) | < 0.001 | −0.06 (−0.11 – −0.02) | < 0.01 |
| 5: + HOMA-IR | 3.56 (2.93–4.18) | < 0.001 | 6.36 (5.39–7.33) | < 0.001 | 22.89 (15.00–30.79) | < 0.001 | −0.05 (−0.10 – −0.01) | 0.01 |
| **Adiponectin models:** | | | | | | | | |
| 1: Unadjusted | −0.81 (−1.56 – −0.07) | 0.03 | −0.62 (−0.19 – 0.69) | 0.36 | −19.8 (−28.5 – −11.2) | < 0.001 | 0.05 (0.01–0.09) | 0.01 |
| 2: + age, sex | −0.79 (−1.61 – 0.03) | 0.06 | −1.32 (−2.72 – 0.08) | 0.07 | −15.0 (−24.1 – −5.9) | <0.01 | 0.03 (−0.01 – 0.08) | 0.14 |
| 3: + hypertension | −0.84 (−1.66 – −0.01) | 0.05 | −1.36 (−2.77 – 0.05) | 0.06 | −15.5 (−24.6 – −6.3) | <0.001 | 0.04 (0.00 – 0.08) | 0.07 |
| 4: +HDL | −0.37 (−1.25 – 0.51) | 0.41 | −0.61 (−2.12 – 0.89) | 0.42 | −10.6 (−20.3 – −0.82) | 0.03 | 0.03 (−0.01 – 0.08) | 0.18 |
| 5: + triglycerides | −0.34 (−1.22 – 0.54) | 0.45 | −0.54 (−2.05 – 0.96) | 0.48 | −9.5 (−19.1 – 0.2) | 0.05 | 0.02 (−0.02 –0.07) | 0.34 |
| 6: + HOMA-IR | −0.23 (−1.07 – 0.62) | 0.60 | −0.35 (−1.80 – 1.10) | 0.63 | −7.6 (−16.3 – 1.1) | 0.09 | 0.02 (−0.03–0.06) | 0.46 |

* Model 1 is unadjusted; model 2 is adjusted for age, sex, and history of ever smoking; model 3 further adjusts for hypertension; model 4 adjusts for HDL and triglycerides; model 5 adjusts for HOMA-IR

** Model 1 is unadjusted; model 2 is adjusted for age and sex; model 3 further adjusts for hypertension; model 4 adjusts for HDL; model 5 adjusts for triglycerides; model 6 adjusts for HOMA-IR