# Visceral Fat Area Cutoff for the Detection of Multiple Risk Factors of Metabolic Syndrome in Japanese: The Hitachi Health Study

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**The relationships between metabolic risk factors and abdominal fat distribution determined using computed tomography (CT) are poorly defined in large populations. We investigated the cutoff values of the visceral fat area (VFA) to detect subjects with multiple risk factors of metabolic syndrome (MS) by sex and age groups, and attempted to examine whether sex- and age-specific cutoff values are needed. The subjects of this study were 11,561 Japanese men and women who participated in the Hitachi Health Study, received CT examination, and answered questionnaires on lifestyles between 2004 and 2009. VFA and waist circumference were measured using CT. The VFA cutoff values yielding an 80% sensitivity for the detection of multiple risk factors of MS were typically smaller among men under the age of 40 years (<40 years vs. ≥40 years; 86.4 $cm^2$ vs. 103.9 $cm^2$). The area under the receiver operator characteristic curve of VFA for the detection tended to decrease according to age ($P = 0.056$ and $P = 0.020$ for trends in men and women). Age- and sex-specific cutoff values are needed. The sensitivity of the subjects under the age of 40 years is relatively smaller (70.0% for men and 60.0% for women) compare to other age groups when the same cutoff value is used regardless of age (e.g., cutoff value calculated to correspond to 80% sensitivity for subjects of all ages). Therefore, a smaller VFA cutoff point should be used among men under the age of 40 years.**

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The prevalence of metabolic syndrome (MS), which is comprised of a cluster of factors such as obesity, high blood pressure, impaired lipid metabolism, and hyperglycemia, has been growing globally. Individuals with MS have a higher risk of cardiovascular disease and a subsequent increase in disease mortality or morbidity (1–3). For the detection of MS, waist circumference (WC) is almost always used as one criterion, and this measure is typically used as a simplified measure of the visceral fat area (VFA (4–7)). Fat tissue is regarded as an endocrine organ, secreting adipocytokines, and other vasoactive substances that can influence the risk of developing traits of MS (8). In a previous study, we analyzed the epidemiological impact of VFA, compared with that of the subcutaneous fat area, WC, and BMI, against the clustering of metabolic risk factors and its components and demonstrated a superior performance of VFA for predicting the clustering of metabolic risk factors compared with other anthropometric indexes (9). Despite it is reported that the anthropometric values are changed by age (10), we had a limitation that the sample size was not enough to analyze by age groups in the previous study.

In this study, we extended the surveillance period and increased the study subjects ($n$ = 11,561; which was approximately double in our previous study (9)). We investigated the cutoff values of the VFA to detect subjects with multiple risk factors of MS by sex and age groups, and attempted to examine whether sex- and age-specific cutoff values are needed for a Japanese population.

## METHODS AND PROCEDURES

The employees of a company in Ibaraki Prefecture and their spouses underwent health examinations between 2004 and 2009; all the health examinations were performed after more than 12 h of fasting. Of these participants, we analyzed the data for 11,561 Japanese subjects (9,867 men and 1,694 women) between the ages of 20–76 years who had undergone a computed tomography (CT) examination, answered a questionnaire on lifestyle and health, and did not have a current treatment of serious illness (cancer, cerebrovascular disease, myocardial infarction). The VFA and WC were measured using a CT scanner and calculated using the PC software application (fatPointer; Hitachi Medico, Tokyo,

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**Table 1 Areas under the curve of ROC for detecting multiple risk factors of metabolic syndrome**

| | | Anthropometric indexes | | Presence/absence for the metabolic risk factors | | | | | | | | $L_{pos}$ | | $L_{neg}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Mean | (s.d.) | *n* | Area under the curve | s.e. | Corresponding to 80% sensitivity | Specificity corresponding to 80% sensitivity (%) | Corresponding to maximal sensitivity plus specificity | Sensitivity (%) | Specificity (%) | Corresponding to 80% sensitivity | Corresponding to maximal sensitivity plus specificity | Corresponding to 80% sensitivity | Corresponding to maximal sensitivity plus specificity |
| Men | | | | | | | | | | | | | | | |
| VFA | under 40 years | 100.7 $cm^2$ | (49.0) | 366/994 | 0.741 | (0.015) | 86.4 $cm^2$ | 49.2 | 114.0 $cm^2$ | 64.2 | 72.9 | 1.58 | 2.37 | 0.41 | 0.49 |
| | 40s | 118.7 $cm^2$ | (51.8) | 1,041/1,727 | 0.722 | (0.010) | 103.6 $cm^2$ | 52.6 | 106.6 $cm^2$ | 78.2 | 55.4 | 1.69 | 1.75 | 0.38 | 0.39 |
| | 50s | 125.6 $cm^2$ | (53.9) | 1,429/1,897 | 0.697 | (0.009) | 104.5 $cm^2$ | 47.3 | 124.8 $cm^2$ | 67.6 | 62.6 | 1.52 | 1.81 | 0.42 | 0.52 |
| | 60s | 127.2 $cm^2$ | (57.0) | 858/1,029 | 0.678 | (0.012) | 102.1 $cm^2$ | 44.2 | 120.4 $cm^2$ | 68.4 | 57.6 | 1.44 | 1.61 | 0.45 | 0.55 |
| | 70s | 128.7 $cm^2$ | (57.4) | 242/284 | 0.706 | (0.022) | 109.4 $cm^2$ | 50.4 | 104.8 $cm^2$ | 83.1 | 49.3 | 1.61 | 1.64 | 0.39 | 0.34 |
| | all ages | 120.7 $cm^2$ | (54.2) | 3,936/5,931 | 0.712 | (0.005) | 102.4 $cm^2$ | 50.2 | 115.6 $cm^2$ | 72.1 | 59.8 | 1.61 | 1.79 | 0.40 | 0.47 |
| | over 40 years | 123.9 $cm^2$ | (54.3) | 3,570/4,937 | 0.702 | (0.006) | 103.9 $cm^2$ | 48.8 | 121.1 $cm^2$ | 68.9 | 61.3 | 1.56 | 1.78 | 0.41 | 0.51 |
| WC | Under 40 years | 85.9 cm | (10.0) | 366/994 | 0.729 | (0.015) | 83.4 cm | 51.9 | 85.6 cm | 72.1 | 62.0 | 1.66 | 1.90 | 0.39 | 0.45 |
| | 40s | 87.0 cm | (9.2) | 1,041/1,727 | 0.701 | (0.010) | 83.8 cm | 47.1 | 87.6 cm | 64.2 | 65.0 | 1.52 | 1.83 | 0.42 | 0.55 |
| | 50s | 86.4 cm | (8.4) | 1,429/1,897 | 0.680 | (0.009) | 83.1 cm | 43.4 | 85.5 cm | 68.7 | 58.1 | 1.42 | 1.64 | 0.46 | 0.54 |
| | 60s | 85.0 cm | (8.2) | 858/1,029 | 0.666 | (0.012) | 81.8 cm | 43.9 | 83.2 cm | 74.0 | 52.1 | 1.43 | 1.54 | 0.45 | 0.50 |
| | 70s | 85.3 cm | (8.8) | 242/284 | 0.677 | (0.023) | 82.0 cm | 46.5 | 81.9 cm | 80.6 | 46.1 | 1.49 | 1.50 | 0.44 | 0.42 |
| | All ages | 86.2 cm | (8.9) | 3,936/5,931 | 0.685 | (0.005) | 82.9 cm | 45.4 | 83.7 cm | 77.1 | 49.8 | 1.47 | 1.53 | 0.44 | 0.46 |
| | Over 40 years | 86.2 cm | (8.7) | 3,570/4,937 | 0.679 | (0.006) | 82.8 cm | 44.1 | 83.7 cm | 77.0 | 49.0 | 1.43 | 1.51 | 0.45 | 0.47 |
| BMI | Under 40 years | 24.3 $kg/m^2$ | (3.5) | 366/994 | 0.729 | (0.015) | 23.3 $kg/m^2$ | 49.8 | 25.3 $kg/m^2$ | 58.7 | 78.0 | 1.60 | 2.67 | 0.40 | 0.53 |
| | 40s | 24.4 $kg/m^2$ | (3.3) | 1,041/1,727 | 0.691 | (0.010) | 22.9 $kg/m^2$ | 44.8 | 24.6 $kg/m^2$ | 61.2 | 69.0 | 1.45 | 1.97 | 0.45 | 0.56 |
| | 50s | 23.9 $kg/m^2$ | (2.8) | 1,429/1,897 | 0.675 | (0.009) | 22.6 $kg/m^2$ | 43.3 | 23.8 $kg/m^2$ | 66.1 | 60.3 | 1.41 | 1.66 | 0.46 | 0.56 |
| | 60s | 23.6 $kg/m^2$ | (2.6) | 858/1,029 | 0.651 | (0.013) | 22.4 $kg/m^2$ | 41.4 | 22.8 $kg/m^2$ | 75.3 | 47.6 | 1.37 | 1.44 | 0.48 | 0.52 |
| | 70s | 23.5 $kg/m^2$ | (2.6) | 242/284 | 0.661 | (0.024) | 22.3 $kg/m^2$ | 38.7 | 23.9 $kg/m^2$ | 60.7 | 67.6 | 1.30 | 1.88 | 0.52 | 0.58 |
| | all ages | 24.0 $kg/m^2$ | (3.0) | 3,936/5,931 | 0.673 | (0.005) | 22.7 $kg/m^2$ | 43.1 | 24.2 $kg/m^2$ | 59.5 | 66.0 | 1.41 | 1.75 | 0.46 | 0.61 |
| | over 40 years | 24.0 $kg/m^2$ | (2.9) | 3,570/4,937 | 0.669 | (0.006) | 22.6 $kg/m^2$ | 42.1 | 23.8 $kg/m^2$ | 65.5 | 59.5 | 1.38 | 1.62 | 0.48 | 0.58 |
| Women | | | | | | | | | | | | | | | |
| VFA | under 40 years | 45.6 $cm^2$ | (33.1) | 10/123 | 0.759 | (0.015) | 36.5 $cm^2$ | 51.2 | 60.2 $cm^2$ | 70.0 | 80.5 | 1.64 | 3.59 | 0.39 | 0.37 |
| | 40s | 61.6 $cm^2$ | (41.6) | 40/251 | 0.823 | (0.032) | 66.4 $cm^2$ | 67.7 | 63.3 $cm^2$ | 85.0 | 66.1 | 2.48 | 2.51 | 0.30 | 0.23 |

**Table 1 Continued on next page**

**Table 1 Continued**

| | | Anthropometric indexes | | Presence/absence for the metabolic risk factors | | | | | | | | $L_{pos}$ | | $L_{neg}$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age | Mean | (s.d.) | *n* | Area under the curve | s.e. | Corresponding to 80% sensitivity | Specificity corresponding to 80% sensitivity (%) | Corresponding to maximal sensitivity plus specificity | Sensitivity (%) | Specificity (%) | Corresponding to 80% sensitivity | Corresponding to maximal sensitivity plus specificity | Corresponding to 80% sensitivity | Corresponding to maximal sensitivity plus specificity |
| | 50s | 79.5 $cm^2$ | (41.6) | 146/449 | 0.746 | (0.023) | 68.3 $cm^2$ | 53.2 | 67.8 $cm^2$ | 82.9 | 53.0 | 1.71 | 1.76 | 0.37 | 0.32 |
| | 60s | 93.7 $cm^2$ | (46.7) | 205/381 | 0.694 | (0.023) | 75.7 $cm^2$ | 43.0 | 97.7 $cm^2$ | 65.9 | 65.7 | 1.40 | 1.92 | 0.46 | 0.52 |
| | 70s | 98.4 $cm^2$ | (48.0) | 31/58 | 0.672 | (0.061) | 77.3 $cm^2$ | 43.1 | 75.7 $cm^2$ | 87.1 | 43.1 | 1.42 | 1.53 | 0.45 | 0.30 |
| | all ages | 79.7 $cm^2$ | (45.8) | 432/1,262 | 0.754 | (0.014) | 69.0 $cm^2$ | 54.0 | 67.8 $cm^2$ | 82.9 | 53.5 | 1.74 | 1.78 | 0.37 | 0.32 |
| | over 40 years | 82.6 $cm^2$ | (45.6) | 422/1,139 | 0.743 | (0.014) | 69.2 $cm^2$ | 50.9 | 97.6 $cm^2$ | 60.4 | 74.5 | 2.37 | 1.63 | 0.53 | 0.39 |
| WC | under 40 years | 78.0 cm | (9.0) | 10/123 | 0.818 | (0.058) | 78.7 cm | 64.2 | 75.3 cm | 100.0 | 50.4 | 2.24 | 2.02 | 0.31 | 0.00 |
| | 40s | 81.1 cm | (10.0) | 40/251 | 0.759 | (0.035) | 80.7 cm | 55.0 | 79.5 cm | 92.5 | 49.8 | 1.78 | 1.84 | 0.36 | 0.15 |
| | 50s | 83.4 cm | (9.3) | 146/449 | 0.688 | (0.025) | 80.5 cm | 45.9 | 84.7 cm | 63.7 | 65.5 | 1.47 | 1.85 | 0.45 | 0.55 |
| | 60s | 84.6 cm | (9.6) | 205/381 | 0.658 | (0.024) | 79.8 cm | 34.6 | 88.9 cm | 46.8 | 79.5 | 1.22 | 2.29 | 0.58 | 0.67 |
| | 70s | 84.6 cm | (8.7) | 31/58 | 0.679 | (0.060) | 81.8 cm | 46.6 | 89.4 cm | 51.6 | 82.8 | 1.51 | 2.99 | 0.42 | 0.58 |
| | all ages | 83.0 cm | (9.6) | 432/1,262 | 0.701 | (0.014) | 80.2 cm | 45.7 | 84.1 cm | 66.4 | 63.2 | 1.47 | 1.46 | 0.44 | 0.40 |
| | over 40 years | 83.5 cm | (9.6) | 422/1,139 | 0.689 | (0.015) | 80.2 cm | 43.3 | 84.1 cm | 66.6 | 61.4 | 1.41 | 1.72 | 0.46 | 0.54 |
| BMI | under 40 years | 21.7 $kg/m^2$ | (3.5) | 10/123 | 0.869 | (0.056) | 22.1 $kg/m^2$ | 69.1 | 23.0 $kg/m^2$ | 80.0 | 80.5 | 2.59 | 4.10 | 0.29 | 0.25 |
| | 40s | 22.7 $kg/m^2$ | (3.6) | 40/251 | 0.774 | (0.037) | 22.2 $kg/m^2$ | 54.6 | 23.9 $kg/m^2$ | 70.0 | 74.9 | 1.76 | 2.79 | 0.37 | 0.40 |
| | 50s | 23.0 $kg/m^2$ | (3.4) | 146/449 | 0.689 | (0.025) | 21.6 $kg/m^2$ | 46.1 | 23.6 $kg/m^2$ | 57.5 | 70.8 | 1.49 | 1.97 | 0.43 | 0.60 |
| | 60s | 23.2 $kg/m^2$ | (3.2) | 205/381 | 0.664 | (0.024) | 21.7 $kg/m^2$ | 40.2 | 23.8 $kg/m^2$ | 54.6 | 71.1 | 1.34 | 1.89 | 0.50 | 0.64 |
| | 70s | 22.8 $kg/m^2$ | (3.2) | 31/58 | 0.715 | (0.056) | 21.6 $kg/m^2$ | 48.3 | 22.9 $kg/m^2$ | 71.0 | 65.5 | 1.56 | 2.06 | 0.40 | 0.44 |
| | all ages | 22.9 $kg/m^2$ | (3.4) | 432/1,262 | 0.704 | (0.014) | 21.7 $kg/m^2$ | 46.9 | 23.5 $kg/m^2$ | 58.6 | 71.7 | 1.51 | 2.07 | 0.42 | 0.58 |
| | over 40 years | 23.0 $kg/m^2$ | (3.4) | 422/1,139 | 0.692 | (0.015) | 21.7 $kg/m^2$ | 45.1 | 23.8 $kg/m^2$ | 56.2 | 72.3 | 1.46 | 2.02 | 0.44 | 0.61 |

Multiple risk factors: having two or more risk factors of metabolic syndrome defined by NCEP-ATPIII (2005).

VFA, visceral fat area; WC, waist circumference.

Japan) according to a protocol described elsewhere (11). Briefly, single slice imaging at the umbilical level was performed using a CT machine (Redix turbo; Hitachi Medico, Tokyo, Japan) while the subject was in a supine position. The imaging conditions were 120 kV, 50 mA, and a 5-mm slice thickness. Height, weight, and body fat were measured using an automated scale (BF-220; Tanita, Tokyo, Japan) with the patient wearing a light gown. The BMI was defined as the weight (kg) divided by the square of the height (m). The blood was collected from each subject after more than 12 h of fasting. The plasma glucose was measured using the glucose oxidase enzyme-electrode method (A&T, Tokyo, Japan) Triglyceride and high-density lipoprotein cholesterol levels were measured using the enzymatic colorimetric method (Cholestest TG; Sekisui Medical, Tokyo, Japan), the nonsettling enzymatic method (Choletest NHDL; Sekisui Medical, Tokyo, Japan), respectively. Blood pressure was measured using automated sphygmomanometer (Kentaro ADVANCE BP-203RV III A/B; Colin, Tokyo, Japan). Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. This study was approved by the ethics review committee of the National Center for Global Health and Medicine.

In this study, subjects with two or more of the four risk factors (high blood pressure, high triglyceride, low HDL-cholesterol, and hyperglycemia) defined according to the criteria of the National Cholesterol Education Program's Adult Treatment Panel III guidelines in 2005 (6) except for WC were defined as having the clustering of metabolic risk factors. Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of the biochemical values.

Receiver operator characteristic (ROC) analysis was used to develop a cutoff of each anthropometric value associated with the presence of two or more risk factors of MS, with the exception of WC. ROC analysis is a formal method that plots sensitivity against 1-specificity for assessing the trade-offs between sensitivity and specificity at various test cutoff points or thresholds, providing a measure of diagnostic accuracy called area under the curve (AUC). We drew the ROC curves for each anthropometric value, and calculated the corresponding AUC. To test for the equality of the AUCs, an algorithm suggested by DeLong, DeLong, and Clarke-Pearson was applied for each anthropometric value (12). Pairwise comparisons of VFA with WC and BMI were also performed, and the *P* values for multiple tests (two comparisons) were adjusted using the Bonferroni–Holm method. The AUC and the s.e. were calculated for each of the 10-year age groups. The decreasing trend in the AUCs according to age was statistically tested using a weighted regression analysis of AUC on age groups, where $1/s.e.^2$ was used as the weight and the age group was coded as the median age of the group. Sensitivity was plotted against 1-specificity for each segment of anthropometric value. Likelihood ratios were calculated as for positive results ($(L_{pos})$ = sensitivity/(1-specificity)), and negative results ($(L_{neg})$ = (1-sensitivity)/specificity) for each segment of anthropometric value. All analyses were performed using SPSS for Windows version 15.0 (SPSS, Chicago, IL) and Stata 10 (StataLP, College Station, TX).

## RESULTS

The mean age was 51.9 ± 10.4 years in men and 55.8 ± 9.8 years in women. The mean VFA was 120.7 ± 54.2 $cm^2$ in men and 79.7 ± 45.8 $cm^2$ in women. The mean WC was 86.2 ± 8.9 cm in men and 83.0 ± 9.6 cm in women. The mean BMI was 24.0 ± 3.0 $kg/m^2$ in men and 22.9 ± 3.4 $kg/m^2$ in women. The mean body fat percentage was 22.9 ± 5.0% in men and 29.1 ± 6.1% in women. The prevalence of the multiple risk factors of MS was 39.9% in men and 25.5% in women.

We plotted the ROC curve to determine the cutoff values of VFA, BMI, and WC in relation to the detection of multiple risk factors. **Table 1** shows the AUC values for VFA, BMI, and WC. The AUC values were greater in women than in men for all ages. The anthropometric measurement with the largest AUC value was the VFA for both men and women ($P < 0.001$; VFA vs. each anthropometric values). Given that a WC is used for the first screening of subjects as a prerequisite for the detection of multiple risk factors of MS, setting a cutoff level to obtain a high sensitivity of at least 80% may be justified, even if the specificity is reduced to some extent. The VFA, BMI, and WC cutoff values yielding an 80% sensitivity for the detection of multiple risk factors of MS for all ages were 102.4 $cm^2$, 22.7 $kg/m^2$, and 82.9 cm in men and 69.0 $cm^2$, 21.7 $kg/m^2$, and 80.2 cm in women, respectively. At an 80% sensitivity for all age group, men who had multiple risk factors were 1.61 times more likely to be above the criteria of VFA (102.4 $cm^2$), and were only 0.40 times more likely to be below it as compared to those who do not have. Both $L_{pos}$ and $L_{neg}$ had a monotonically increasing trend along with VFA. Therefore, we could not identify a cut off that simultaneously satisfied maximized $L_{pos}$ and minimized $L_{neg}$ ratios.

The VFA cutoff values yielding an 80% sensitivity for the detection of clusters of multiple risk factors were typically smaller in subjects under the age of 40 years (<40 years vs. ≥40 years; 86.4 $cm^2$ vs. 103.9 $cm^2$ for men and 36.5 $cm^2$ vs. 69.2 $cm^2$ for women, respectively). The AUC of the body fat percentage was the smallest of all of anthropometric values (data not shown).

The mean VFA was larger in the higher age groups. The AUC of the ROC curve of VFA for the detection of multiple risk factors of MS tended to decrease according to age ($P = 0.056$ and $P = 0.020$ for trends in men and women, respectively). The cutoff values for maximal sensitivity and specificity differed according to age groups, yielding inconsistent sensitivity and specificities among the groups.

## DISCUSSION

In the present study, we proposed VFA cutoff points for the detection of multiple risk factors of MS of 103.9 $cm^2$ in men and 69.2 $cm^2$ in women over the age of 40 years, yielding a sensitivity of at least 80% for the prediction of clusters of multiple risk factors in a Japanese population. Among subjects under the age of 40 years, a smaller cutoff point should be used, i.e., 86.4 $cm^2$ in men. However, among the subjects under the age of 40 years for women, the number of subjects having multiple risk factors of MS was small; thus it may be difficult to detect the cutoff values of VFA.

A few studies have reported appropriate VFA cutoff points for the detection of multiple risk factors of MS (13,14). However, as age-specific cutoff values were not calculated, the present study is the first to examine whether age-specific cutoff values are needed.

Two methods have been reported for determining the cutoff point. One is calculating $L_{pos}$ and $L_{neg}$ and using the cutoff point that yields the highest value of $L_{pos}$ and the lowest value of $L_{neg}$ concurrently. If there is no cutoff point that corresponds to both the highest and lowest values, the cutoff point for highest value of $L_{pos}$ and that for the lowest value of $L_{neg}$ are shown, respectively. According to this method, a previous study indicated that intra-abdominal adipose tissue above 131 $cm^2$ was related to elevated multiple risk factors of cardiovascular

disease, and intra-abdominal adipose tissue below 71 $cm^2$ was associated with reduced multiple risk factors of cardiovascular disease in men (15). Similarly, another study showed the upper and lower cutoff points of intra-abdominal adipose tissue as 110 $cm^2$ and 40 $cm^2$ in female subjects who have multiple risk factors of cardiovascular disease (16). Another method to determine the cutoff point is calculating the Youden index (sensitivity + specificity −1) and using the maximal value of it (17,18). Incorporating this method, Oka *et al.* showed the optimal cutoff points of VFA for discriminating the subjects with multiple risk factors of MS as 132.6 $cm^2$ and 91.5 $cm^2$ for men and women, respectively (14). A separate study showed the cutoff points of it as 103.0 $cm^2$ and 69.0 $cm^2$ for men and women, respectively (19). Though there have been several studies before our own, our results show that both $L_{pos}$ and $L_{neg}$ tend to rise with an increase in VFA. Therefore, a cutoff point that simultaneously meets a requirement of both maximized $L_{pos}$ and minimized $L_{neg}$ ratios could not be determined in our study. When attempting to classify individuals based on anthropometric levels, it is always the intent to do so "optimally". However, the event of interest may intrinsically involve constraints that must be considered for ethical or fiscal reasons. These constraints commonly account for the prevalence of the event and the costs of misclassification, both monetary and physiological (20). The maximal value of the Youden index, used in previous studies to calculate the cutoff values, does not take these points into consideration. Our purpose was to screen individuals with multiple risk factors for MS; thus, the cost of false-positive results may not be a serious problem because the interventions, even among "false-positive" individuals, to improve lifestyles would have some benefits and would have a relatively low cost in the Japanese system. In Japan, the prevalence of MS is increasing because of the increasing prevalence of obesity; thus, the Ministry of Health, Labour and Welfare of Japan is making a strong effort to prevent MS. Therefore, for the first screening of subjects as a prerequisite for the diagnosis of MS, we set a cutoff level so as to obtain a relatively high sensitivity (80%) to increase the probability of identifying people with this disease.

The VFA cutoff point for the detection of multiple risk factors of MS yielding a sensitivity of 80% increased with age. This observation can likely be explained by the increase in the mean VFA values in older age groups given the relationship between VFA and having multiple risk factors does not differ among age groups. The cutoff values were typically smaller among subjects under the age of 40 years. If the same cutoff value (e.g., cutoff value corresponding to 80% sensitivity for all ages) is used regardless of age, the sensitivity under the age of 40 years is relatively smaller (70.0% for men and 60.0% for women, respectively) than that in other age groups. Thus, age-specific cutoff values are especially needed for this generation.

Furthermore, the AUC of the ROC curve of VFA for the detection of multiple risk factors of MS tended to decrease with age in both sexes. The effect of VFA on the detection of multiple risk factors of MS is thought to be stronger among young individuals and weaker among elderly individuals. In the elderly, MS may also be caused by risk factors other than VFA (such as age-related hyperglycemia and high blood pressure).

The AUC for women was larger than that for men in all the age groups. This finding can likely be explained by the fact that men tend to have more other risk factors of MS which are not used for the diagnostic criteria of MS (such as a smoking habit, and alcohol drinking habit, stress, hard work, etc (21)); thus, the contribution of VFA to the multiple risk factors of MS may be relatively smaller in men than it is in women.

The present study described the VFA cutoff values yielding a sensitivity of 80% according to age group. Further studies are needed to elucidate the most suitable and easy method of measuring VFA and the most appropriate cutoff point for use in clinical settings.

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### DISCLOSURE

The authors declared no conflict of interest.



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# Effect of Longitudinal Changes in Visceral Fat Area and Other Anthropometric Indices to the Changes in Metabolic Risk Factors in Japanese Men

## The Hitachi Health Study

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**OBJECTIVE**—The effects of longitudinal changes in the visceral fat area (VFA), and other anthropometric indices, on the risk factors of metabolic syndrome were not studied. We calculated the changes in metabolic risk factors in relation to changes in certain anthropometric indices in a large-scale study of Japanese men.

**RESEARCH DESIGN AND METHODS**—The subjects were 1,106 men participating in the Hitachi Health Study who received a computed tomography examination in both 2004 and 2007. VFA, subcutaneous fat area (SFA), and waist circumference were measured using the computed tomography. We examined how longitudinal changes in each anthropometric index over a 3-year period influenced the value of each metabolic risk factor.

**RESULTS**—Changes (Δ) over a 3-year period in body weight, SFA, and waist circumference strongly correlated, while the changes in body weight and VFA were weakly correlated. Changes in the VFA were associated with changes in metabolic risk factors, especially changes in triglyceride and HDL; we found these changes to be independent of the Δbody weight and Δwaist circumference.

**CONCLUSIONS**—Change in body weight is not a precise surrogate marker of ΔVFA, and repeated VFA measurements over time are useful. Adopting a lifestyle that does not increase the VFA is important in preventing metabolic syndrome.

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in the world (1). Previous reports have shown that obesity plays a significant role in increasing cardiovascular risk (2). Certain indicators of obesity, such as the visceral fat area (VFA), or visceral adipose tissue, are more strongly associated with the risk of CVD than other indicators of obesity, such as waist circumference, BMI (3), or the subcutaneous fat area (SFA) (2). A large VFA is strongly related to a higher prevalence of impaired fasting glucose levels (4,5), diabetes (4,6,7), insulin resistance (4,8–10), hypertension (11,12), abnormality of lipid metabolism (13–16), and metabolic risk factors (14,17,18). Previous studies have examined the relationship between baseline VFA and metabolic risk factors. In a previous intervention study of 54 postmenopausal women, an increase in VFA strongly correlated with changes in triglyceride and HDL cholesterol levels compared with changes in the blood pressure and fasting blood glucose levels (19). In the current study, we examined the relationships between changes in the VFA, SFA, body weight, and waist circumference and changes in CVD risk factors to determine the relative contributions of the longitudinal changes in these anthropometric indices to the changes in metabolic risk factors over a 3-year period. Determining the relationships between the anthropometric indices and metabolic risk factors would be useful for preventing CVD in clinical settings.

## RESEARCH DESIGN AND METHODS

Overall, a total of 13,971 male employees and their spouses, after ≥12 h of fasting, underwent health check-ups during a baseline survey performed in 2004 and 2005 at the Hitachi Health Care Center in Ibaraki Prefecture. Of these, 2,655 men received a computed tomography scan. The final analysis involved 1,106 men from the initial study who participated in a 3-year follow-up survey performed in 2007 and 2008 (aged 30–72 years in the baseline survey). The mean age of the men for whom follow-up data were available was younger than that of the men for whom follow-up data were not available. In addition, the mean age of the men who received a computed tomography examination in the baseline survey was greater than the mean age of the men who did not receive the computed tomography examination. No significant differences were seen between the other characteristics when age-adjusted comparisons were performed. Self-reporting questionnaires were used to investigate whether the subjects were currently receiving medical treatment for hyperlipidemia, hypertension, or diabetes

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at the time of both surveys. Body height and weight were measured using an automated scale (BF-220; Tanita), and the BMI was defined as the weight in kilograms divided by the square of the height in meters. VFA, SFA, and waist circumference were measured using a computed tomography scanner and protocols previously described (20). In brief, single-slice imaging was performed at the umbilical level in a spine position using a Redix turbo CT machine (Hitachi Medico). The imaging conditions were 120 kV, 50 mA, and a slice thickness of 5 mm. VFA, SFA, and waist circumference were calculated using fatPointer software (Hitachi Medico). Triglyceride and HDL cholesterol levels were measured using the oxygen method with a Hitachi 7600 device (Sekisui Medical). Blood glucose levels were measured using the glucose electrode technique with an ADAMS glucose GA-1170 device (Arkrey). Blood pressure was measured using an oscillometric method with a Kentaro ADVANCE BP-203RV III A/B device (Colin) while the patient was in a sitting position and after the patient had rested for 3 min. Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. The current study was approved by the ethics review committee of the National Center for Global Health and Medicine.

**Table 1—*Anthropometric and CVD risk variables at baseline and changes during the 3-year follow-up period* (n = *1,106*)**

| | Baseline | | Changes in 3-year period | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | P* |
| Height (cm) | 169.0 | 6.1 | 0.3 | 0.5 | <0.001 |
| Weight (kg) | 67.6 | 9.4 | 0.0 | 3.1 | 0.61 |
| BMI (kg/m$^2$) | 23.6 | 2.7 | 0.1 | 1.1 | 0.018 |
| VFA (cm$^2$) | 120.0 | 52.2 | 0.0 | 32.5 | 0.99 |
| SFA (cm$^2$) | 122.6 | 52.2 | 4.2 | 24.7 | <0.001 |
| VFA/SFA | 1.03 | 0.54 | −0.03 | 0.48 | 0.055 |
| WC (cm) | 85.6 | 8.1 | −0.2 | 4.6 | 0.088 |
| SBP (mmHg) | 121.5 | 11.7 | −1.1 | 10.8 | 0.001 |
| DBP (mmHg) | 76.9 | 8.2 | −0.1 | 7.1 | 0.62 |
| TG (mg/dL) | 137.6 | 92.6 | −9.0 | 80.0 | <0.001 |
| HDL cholesterol (mg/dL) | 56.4 | 14.2 | −1.8 | 7.9 | <0.001 |
| Fasting glucose (mg/dL) | 105.2 | 13.0 | −1.5 | 8.7 | <0.001 |

TG, triglyceride; WC, waist circumference. *Paired *t* test between values at baseline and at the 3-year follow-up.

### Definition of the state of risk factor clustering

Subjects with two or more of the following four factors, defined by the National Cholesterol Education Program's Adult Treatment Panel III guidelines (21), with the exception of waist circumference, were defined to have clustering of metabolic risk factors: *1*) triglyceride ≥150 mg/dL (1.69 mmol/L), 2) HDL cholesterol <40 mg/dL (1.03 mmol/L), 3) systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥85 mmHg, or 4) fasting plasma glucose ≥110 mg/dL (6.11 mmol/L). Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factor, regardless of the biochemical value.

### Statistical analyses

The baseline data and the 3-year changes (Δ) in CVD risk-related variables (i.e., BMI, VFA, SFA, VFA/SFA, waist circumference, SBP, DBP, triglyceride, HDL cholesterol, and glucose) were calculated for subjects who had not received a medical treatment in both surveys. The *P* value between baseline and the 3-year follow-up period was calculated using a paired *t* test. Pearson correlation coefficients for the changes in the anthropometric and CVD risk variables were calculated. To establish the independent contribution of each anthropometric variable, multiple linear regression analyses were used to obtain the standardized partial regression coefficients, where the change in the CVD risk variable was the dependent variable and the changes in the anthropometric indices were the independent variables; a stepwise procedure was used to select significant variables. All analyses were performed using SPSS (version 15.0; SPSS, Chicago, IL).

**RESULTS**—The anthropometric and CVD risk variables at the baseline survey and changes at the 3-year follow-up period are shown in Table 1. The mean (SD) age of the subjects was 52.7 (8.4)

**Table 2—*Pearson correlations coefficients among changes in anthropometric and CVD risk variables* (n = *1,106*)**

| | ΔVFA | ΔSFA | ΔBody weight | ΔWaist circumference | ΔBMI | ΔSBP | ΔDBP | ΔFasting glucose | ΔLog triglycerides | ΔHDL |
|---|---|---|---|---|---|---|---|---|---|---|
| ΔVFA | 1 | 0.632 | 0.672 | 0.756 | 0.671 | 0.138 | 0.162 | 0.188 | 0.197 | −0.234 |
| ΔSFA | 0.632 | 1 | 0.738 | 0.765 | 0.738 | 0.174 | 0.177 | 0.187 | 0.171 | −0.238 |
| ΔBody weight | 0.672 | 0.738 | 1 | 0.722 | 0.989 | 0.155 | 0.210 | 0.203 | 0.222 | −0.252 |
| ΔWaist circumference | 0.756 | 0.765 | 0.722 | 1 | 0.718 | 0.140 | 0.156 | 0.168 | 0.196 | −0.233 |
| ΔBMI | 0.671 | 0.738 | 0.989 | 0.718 | 1 | 0.150 | 0.203 | 0.204 | 0.225 | −0.253 |
| ΔSBP | 0.138 | 0.174 | 0.155 | 0.140 | 0.150 | 1 | 0.627 | 0.055 | 0.096 | −0.003 |
| ΔDBP | 0.162 | 0.177 | 0.210 | 0.156 | 0.203 | 0.627 | 1 | 0.093 | 0.097 | −0.004 |
| ΔFasting glucose | 0.188 | 0.187 | 0.203 | 0.168 | 0.204 | 0.055 | 0.093 | 1 | 0.039 | 0.041 |
| ΔLog triglycerides | 0.288 | 0.280 | 0.350 | 0.295 | 0.353 | 0.109 | 0.117 | 0.079 | 1 | −0.288 |
| ΔHDL cholesterol | −0.234 | −0.238 | −0.252 | −0.233 | −0.253 | −0.003 | −0.004 | 0.041 | −0.250 | 1 |

The absolute value of a correlation coefficient >0.06 was statistically significant at $P < 0.05$. The correlation coefficients were essentially unchanged after adjustments for age (data not shown).

years at baseline. The mean BMI was 23.6 (2.7) kg/m$^2$, the mean VFA was 120.0 (52.2) cm$^2$, and the mean waist circumference was 85.6 (8.1) cm at baseline. The 3-year changes in each of these parameters were relatively small.

Pearson correlation coefficients for the changes in the anthropometric measurements and CVD risk variables are shown in Table 2. Strong correlations among the changes in the four adiposity indices were observed, with a colinearity observed among the indices. Correlations among the Δbody weight, ΔSFA, and Δwaist circumference were also strong, but the correlation between the Δbody weight and ΔVFA was weak. These findings suggested that the Δbody weight was not an exact surrogate marker of ΔVFA. We also analyzed correlations among the changes in anthropometric measurements and CVD risk variables. Significant correlations between the Δlog triglyceride and ΔVFA, the Δlog triglyceride and Δbody weight, the ΔSBP and ΔSFA, the ΔSBP and Δbody weight, and the Δglucose and Δbody weight were observed. The correlation coefficients were essentially unchanged after adjustments for age (data not shown).

Multiple linear regression analyses showed that the changes in VFA, SFA, body weight, and waist circumference were independently associated with the changes in CVD risk factors during the 3-year follow-up period (Table 3). The ΔDBP, Δglucose, Δlog triglyceride, and ΔHDL cholesterol were significantly affected by both the ΔVFA and ΔSFA. In contrast, the ΔSBP was only significantly affected by the ΔSFA. The Δlog triglyceride and ΔHDL cholesterol values were more strongly affected by the ΔVFA than by the ΔSFA. These results suggest that the ΔVFA and ΔSFA contribute differently to the ΔCVD risk variables. A multiple regression analysis showed that the ΔVFA were significantly related to the Δlog triglyceride and ΔHDL cholesterol and were independent of the Δbody weight and Δwaist circumference.

**Table 3—*Independent associations of changes in VFA, SFA, body weight, and waist circumference with changes in the CVD risk factors during the 3-year follow-up period according to multiple linear regression analyses***

| | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|
| Dependent variable | Independent variables | Standardized partial β | *P* | Standardized partial β | *P* |
| ΔSBP | ΔVFA | 0.056 | 0.115 | — | — |
| | ΔSFA | 0.161 | <0.001 | 0.194 | <0.001 |
| | Age | 0.034 | 0.216 | — | — |
| ΔDBP | ΔVFA | 0.093 | 0.008 | 0.093 | 0.008 |
| | ΔSFA | 0.135 | <0.001 | 0.135 | <0.001 |
| | Age | −0.105 | <0.001 | −0.105 | <0.001 |
| ΔFasting glucose | ΔVFA | 0.100 | 0.002 | 0.100 | 0.002 |
| | ΔSFA | 0.127 | <0.001 | 0.127 | <0.001 |
| | Age | −0.071 | 0.005 | −0.071 | 0.005 |
| ΔLog triglycerides | ΔVFA | 0.207 | <0.001 | 0.206 | <0.001 |
| | ΔSFA | 0.141 | <0.001 | 0.143 | <0.001 |
| | Age | −0.026 | 0.295 | — | — |
| ΔHDL cholesterol | ΔVFA | −0.154 | <0.001 | −0.154 | <0.001 |
| | ΔSFA | −0.134 | <0.001 | −0.134 | <0.001 |
| | Age | −0.082 | 0.001 | 0.082 | 0.001 |
| ΔSBP | ΔVFA | 0.031 | 0.480 | — | — |
| | ΔSFA | 0.121 | 0.011 | 0.128 | 0.002 |
| | ΔBody weight | 0.084 | 0.067 | 0.089 | 0.031 |
| | ΔWaist | −0.009 | 0.866 | — | — |
| | Age | 0.041 | 0.142 | — | — |
| ΔDBP | ΔVFA | 0.055 | 0.203 | — | — |
| | ΔSFA | 0.070 | 0.139 | — | — |
| | ΔBody weight | 0.157 | 0.001 | 0.220 | <0.001 |
| | ΔWaist | −0.035 | 0.507 | — | — |
| | Age | −0.092 | 0.001 | −0.088 | 0.001 |
| ΔFasting glucose | ΔVFA | 0.080 | 0.040 | — | — |
| | ΔSFA | 0.085 | 0.045 | — | — |
| | ΔBody weight | 0.158 | <0.001 | 0.223 | <0.001 |
| | ΔWaist | −0.082 | 0.070 | — | — |
| | Age | −0.053 | 0.037 | — | — |
| ΔLog triglycerides | ΔVFA | 0.112 | 0.003 | 0.127 | <0.001 |
| | ΔSFA | 0.008 | 0.846 | — | — |
| | ΔBody weight | 0.229 | 0.000 | 0.248 | <0.001 |
| | ΔWaist | 0.031 | 0.483 | — | — |
| | Age | −0.006 | 0.813 | — | — |
| ΔHDL cholesterol | ΔVFA | −0.105 | 0.004 | −0.112 | 0.001 |
| | ΔSFA | −0.065 | 0.106 | −0.073 | 0.043 |
| | ΔBody weight | −0.116 | 0.003 | — | — |
| | ΔWaist | −0.017 | 0.684 | −0.119 | 0.002 |
| | Age | −0.092 | <0.001 | −0.093 | <0.001 |

Model 1: All independent variables were entered into the model. Model 2: Significant variables were selected using the stepwise method. β, regression coefficient

**CONCLUSIONS**—This study investigated the change in metabolic risk factors between a baseline examination and a 3-year follow-up examination, measured using computed tomography. The changes in body weight, SFA, and waist circumference strongly correlated. The changes in body weight and VFA showed weak correlation, suggesting that changes in body weight are not an exact surrogate marker of changes in VFA. A multiple regression analysis showed that the ΔVFA was significantly related to Δtriglyceride and ΔHDL cholesterol independently of Δbody weight and Δwaist circumference, suggesting the importance of monitoring VFA over time.

In previous cross-sectional studies, positive correlations between VFA and SBP and between VFA and serum triglyceride were reported to be significant when VFA was measured by computed tomography (14). In previous longitudinal studies, the effects of changes in BMI (22), weight (23), and waist circumference (24,25) on metabolic risk factors were examined. One such report showed a strong linear trend between increasing BMI and a worsening of various variables of metabolic risk factors, including blood pressure and lipid

profiles (24). Likewise, another report showed that weight changes were linearly related to all measurements of each component of the metabolic risk factors (23). Other studies have shown that a reduction in the waist circumference and the VFA achieved through lifestyle modifications is closely linked to an improvement in metabolic risk factors (19,25). These studies suggest that the changes in BMI, weight, waist circumference, and VFA are related to risk factors for CVD. However, the impact of the change in the VFA (measured twice in the same person), which is regarded as the strongest indicator of CVD risk among the anthropometric variables, has remained uncertain. To our knowledge, this is the first study to analyze the relationships between changes in VFA and changes in metabolic risk factors, compared with other anthropometric variables, in a large population. Our findings clearly showed that the ΔVFA were significantly related to the Δlog triglyceride and ΔHDL cholesterol and were independent of the Δbody weight and Δwaist circumference.

In previous studies (22), the mean value of each component of metabolic risk factors or the prevalence of metabolic risk factors and its components were compared according to changes in BMI, body weight, and waist circumference. This is the first study that compared the strength of the association of metabolic risk factors with the change in VFA in a large population.

The current study has the following strengths: the study had a longitudinal design and examined the relationships between metabolic risk factors and the change in VFA using computed tomography scans performed twice on the same subject. The number of subjects was relatively large, with >1,000 subjects being followed over a 3-year period. Our study is thought to have a small measurement bias because VFA and SFA were measured using the same computed tomography machine, in the same region, and at the same state of expiration during both the baseline examination and the 3-year follow-up examination. A random measurement error could have diluted the relationship between ΔVFA and the metabolic risk factors. Thus, the real relationship may be stronger than the observed one. Nevertheless, the current study also has a limitation. The study subjects were limited to men, and further studies in women are needed.

In conclusion, the current study of Japanese men showed that changes in the VFA were associated with changes in metabolic risk factors. The ΔVFA was significantly related to Δlog triglyceride and ΔHDL cholesterol and was independent of Δbody weight and Δwaist circumference, suggesting the importance of measuring the VFA repeatedly over time. The adoption of a lifestyle that does not result in an increase in VFA is important in preventing metabolic syndrome.

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Y.M. was the principal investigator, researched data, contributed to discussions, wrote the manuscript, and reviewed and edited the manuscript. T.N. researched data, contributed to discussions, and reviewed and edited the manuscript. S.Y. research data and reviewed and edited the manuscript. Y.T. contributed to discussions. T.Y., T.M., and M.N. contributed to discussions and reviewed and edited the manuscript. Y.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Original Article
EPIDEMIOLOGY/GENETICS

Obesity

# Effect of Longitudinal Changes in Visceral Fat Area on Incidence of Metabolic Risk Factors: the Hitachi Health Study

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**Objective:** To examine the incidences of metabolic risk factors according to changes in visceral fat area (VFA) in a large Japanese population.

**Design and Methods:** The subjects were 973 men who received a computed tomography (CT) examination in health checkups twice (2004-2005 and 2007-2008), and not having two or more of metabolic risk factors (except for the waist circumference) in 2004-2005. VFA was measured using CT. To assess the potential influence of changes in VFA for the 3-year incidences of each metabolic risk factor and clustering metabolic risk factors, logistic regression analyses were used.

**Results:** A significant association was observed between the change in VFA and the components of the metabolic risk factors. Incidences of the components of the metabolic risk factors were significantly higher among subjects with a larger increase in VFA and were significantly lower among subjects with a larger decrease in VFA (trend $P < 0.001$). Significant increases in the odds ratios for the incidences of high triglycerides and low high-density lipoprotein cholesterol level were observed among subjects with $\geq 50$ cm$^2$ VFA increase.

**Conclusions:** The adoption of a lifestyle that does not increase the VFA is important for preventing metabolic syndrome.

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## Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality in the world (1). Previous reports have shown that obesity plays a significant role in increasing cardiovascular risk (2). Some indicators of obesity, such as the visceral fat area (VFA), or visceral adipose tissue, are more strongly associated with the risk of CVD than other indicators of obesity, such as waist circumference, body mass index (BMI) (3,4), or subcutaneous fat area (SFA) (2,3). A larger VFA is strongly related to a higher prevalence of impaired fasting glucose levels (5), diabetes (5), insulin resistance (5), hypertension (6), abnormality of lipid metabolism (7), and metabolic risk factors (7,8). Several cross sectional and other types of studies have examined the association between VFA and metabolic risk factors. For instance, in some prospective studies, VFA was measured at baseline and its correlation between risk factors for diabetes (plasma insulin level, homeostasis model assessment for insulin resistance, etc.) was evaluated (9-11). However, no study has measured the longitudinal change in VFA among the same subjects twice, at baseline and at follow-up, to examine its relation to the incidences of metabolic risk factors in a large cohort study. Thus, whether an increase in VFA leads to an increase in the risk of CVD or whether a decrease in VFA leads to a decrease in the risk of CVD remain uncertain. Clarifying this point could be useful for preventing CVD in clinical settings.

Therefore, we examined the incidences of the clustering of metabolic risk factors and its components among subjects who did not have each of the risk factors or the clustering of metabolic risk factors at baseline according to the aforementioned changes in VFA.

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## Methods and Procedures

Overall, a total of 13,965 male employees and their spouses who, after more than 12 h of fasting, underwent health checkups during the baseline survey performed in 2004 and 2005 at the Hitachi Health Care Center in Ibaraki Prefecture. Of them, 3,119 men received a computed tomography (CT) scan. We studied 1,106 men who also participated in a 3-year follow-up survey performed in 2007 and 2008 (aged 30-72 years in 2004 and 2005) in the final analysis. Subjects without each metabolic risk factor (except for the waist circumference) or clustering of risk factors were included into the analysis of the incidence. Numbers of subjects in each group are shown in Table 1. Informed consent was obtained from each examinee regarding the use of his or her data for research purposes. The present study was approved by the ethics review committee of the National Center for Global Health and Medicine.

In this study, subjects with two or more of the four risk factors (high blood pressure, high triglyceride, low high-density lipoprotein (HDL) cholesterol, and hyperglycemia) defined in the criteria of the National Cholesterol Education Program's Adult Treatment Panel III guidelines in 2005 (12), except for waist circumference, were defined as having the clustering of metabolic risk factors. Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of the biochemical values. Subjects with metabolic risk factor and/or who were screened for diabetes, hypertension, hyperlipidemia, and obesity at the health check received brief recommendation on life style modification verbally and/or were advised to consult a doctor, if necessary.

**TABLE 1 Characteristics of subjects at baseline**

| | Subjects with 0–1 metabolic risk factor | Subjects with ≥2 metabolic risk factors |
|---|---|---|
| n | 973 | 659 |
| Age (years) | 52.7[a] (8.4) | 55.1[a] (7.8) |
| Height (cm) | 168.9[a] (6.2) | 168.2[a] (5.9) |
| Weight (kg) | 66.7[a] (9.1) | 70.4[a] (9.2) |
| BMI (kg/m$^2$) | 23.3[a] (2.6) | 24.8[a] (2.7) |
| VFA (cm$^2$) | 113.2[a] (52.1) | 149.1[a] (50.5) |
| SFA (cm$^2$) | 118.2[a] (51.9) | 136.8[a] (50.4) |
| VFA/SFA | 1.0[a] (0.4) | 1.2[a] (0.6) |
| Waist circumference (cm) | 84.6[a] (7.8) | 89.2[a] (8.3) |
| SBP (mmHg) | 120.1[a] (11.7) | 130.6[a] (10.0) |
| DBP (mmHg) | 76.1[a] (8.3) | 82.7[a] (7.2) |
| Triglycerides (mg/dL) | 113.4[a] (62.3) | 193.6[a] (133.5) |
| HDL-cholesterol (mg/dL) | 59.1[a] (13.6) | 51.8[a] (14.7) |
| Fasting glucose (mg/dL) | 103.2[a] (16.1) | 121.2[a] (27.9) |
| High blood pressure | 261[b] (26.8) | 520[b] (78.9) |
| Hyperglycemia | 132[b] (13.6) | 458[b] (69.5) |
| High triglycerides | 154[b] (15.8) | 451[b] (68.4) |
| Low HDL cholesterol | 17[b] (1.7) | 142[b] (21.5) |
| VFA ≥ 100cm$^2$ | 584[b] (60.0) | 549[b] (83.3) |

[a]Values are mean (SD)
[b]Values are number (percentage)

The 3-year change in the participants' VFA (designated as ΔVFA) was categorized into seven groups (Group 1, ≤ −50 cm$^2$; Group 2, > −50 cm$^2$ and ≤ −30 cm$^2$; Group 3, > −30 cm$^2$ and ≤ −10 cm$^2$; Group 4, > −10 cm$^2$ and <10 cm$^2$; Group 5, ≥ 10 cm$^2$ and < 30 cm$^2$; Group 6, ≥ 30 cm$^2$ and < 50 cm$^2$; Group 7, ≥ 50 cm$^2$). Odds ratios (95% confidence intervals (CI)) of the 3-year incidence of each metabolic risk factor and/or clustering of metabolic risk factors according to the seven groups of ΔVFA were estimated with the use of a multiple logistic regression analysis, where adjustments were made for the following potential confounders: age, VFA, and each parameter of the metabolic risk factors (high blood pressure, hyperglycemia, high triglycerides, or low HDL cholesterol) at baseline. *P* value for trend across the seven groups was calculated by applying consecutive integers to the categories in the logistic regression model. Similarly, odds ratios for incidences of four risk factors for metabolic syndrome were calculated. All analyses were performed using SPSS (Version 15.0, SPSS, IL).

## Results

Characteristics of subjects at baseline are shown in Table 1. The mean values of age, the waist circumference, VFA, SFA, and BMI of the subjects who were without clustering of metabolic risk factors at baseline were 52.7 ± 8.4 years, 84.6 ± 7.8 cm, 113.2 ± 52.1 cm$^2$, 118.2 ± 51.9 cm$^2$, and 23.3 ± 2.6 kg/m$^2$, respectively. The incidences of the metabolic risk factors at the 3-year follow-up survey are shown in Figure 1. The odds ratios for the incidences of the clustering of metabolic risk factors according to the ΔVFA groups were 0.45, 0.63, 0.74, 1.00 (ref.), 0.70, 1.04, and 3.91, respectively (trend $P < 0.001$). These results did not change after further adjustments for lifestyle factors (smoking and alcohol drinking) or lifestyle factors and ΔSFA. The odds ratios (95% CI) of the incidences of hyperglycemia, high triglycerides, and low HDL cholesterol for the group with the largest increase in ΔVFA (50 cm$^2$ or more) were 2.98 (1.33-6.68), 4.88 (2.51-9.47), and 3.36 (1.26-8.91), respectively. The odds ratios (95% CI) of the incidences of high blood pressure, hyperglycemia, high triglycerides, and low HDL cholesterol for the group with the largest decrease in ΔVFA (−50 cm$^2$ or less) were 0.83 (0.34-2.04), 1.16 (0.42-3.15), 0.19 (0.06-0.59), and 0.42 (0.13-1.39), respectively. In subjects with a decrease in ΔVFA, the incidences were low for high triglycerides and low HDL cholesterol, but did not change for high blood pressure and hyperglycemia. Of the components of the metabolic syndrome, especially the incidences of high triglycerides and low HDL-cholesterol paralleled with ΔVFA (trend $P < 0.05$).

## Discussion

This study investigated the change in metabolic risk factors between a baseline examination and a 3-year follow-up examination among subject groups divided according to the change in VFA, as measured using CT. We calculated the odds ratios for the incidences of metabolic risk factors and found that the risks of hyperglycemia, high triglycerides, low HDL cholesterol, and clustering of metabolic risk factors were significantly greater for the ΔVFA ≥ 50 cm$^2$ group, compared with the stable ΔVFA groups. For subjects with a decrease in ΔVFA, the incidences of high triglycerides and low HDL cholesterol levels were low, but the incidences of high blood pressure and hyperglycemia did not change.

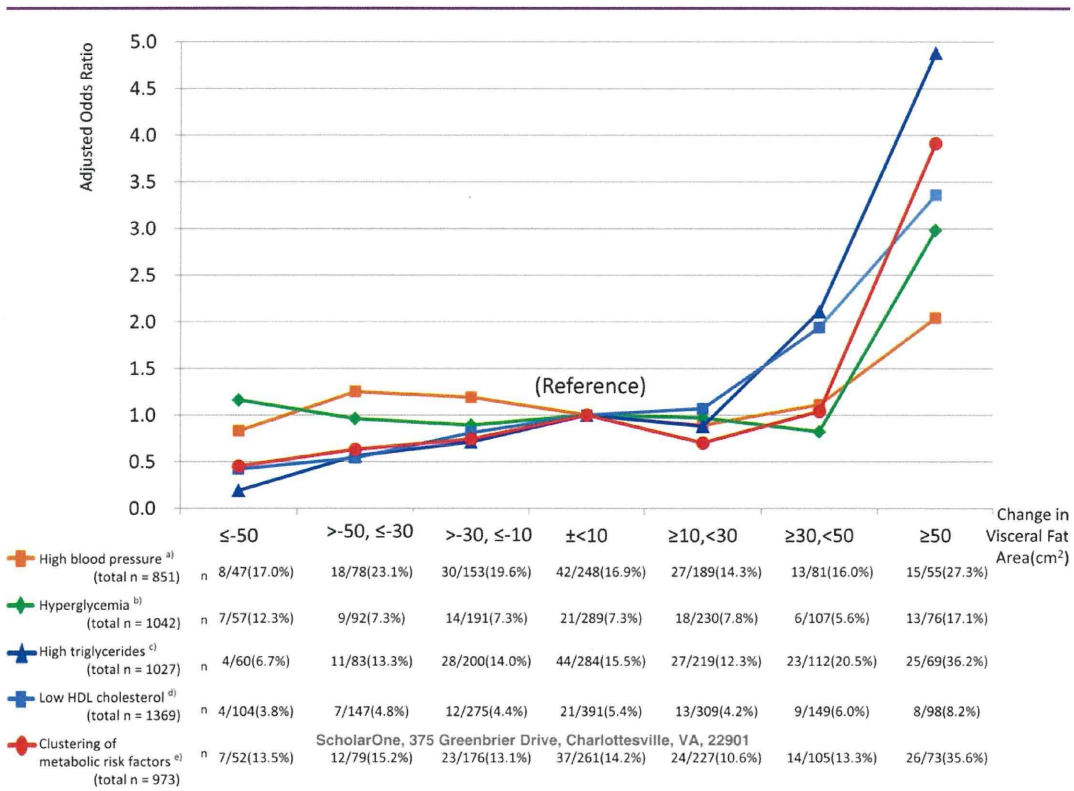


**FIGURE 1** Odds ratio of metabolic risk factors (defined by NCEP-ATPIII) at the 3-year follow-up survey. Values are odds ratio (95% CI) adjusted for age, visceral fat area at baseline in 2004 and 2005, and the baseline value of each risk factor, i.e., (**a**) mean blood pressure ((systolic blood pressure + diastolic blood pressure × 2)/3), (**b**) glucose levels, (**c**) triglyceride levels, (**d**) HDL-cholesterol levels, and (**e**) mean blood pressure, glucose, triglyceride, and HDL-cholesterol in 2004 and 2005. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

In previous cross-sectional studies, significant and positive correlations between VFA measured using CT and systolic blood pressure, serum triglycerides were shown (7). In previous longitudinal studies, the effects of changes in VFA (13), BMI (14), weight (15), and waist circumference (16-18) on the metabolic risk factors have been examined. One of those reports studied 1,106 men and showed that changes in the VFA were associated with changes in metabolic risk factors (13). Another report showed a strong linear trend between increasing BMI and a worsening of various variables of metabolic risk factors, including blood pressure and lipid profiles (14). Similarly, another report showed that weight changes were linearly related to all measurements of each component of metabolic risk factors (15). Other studies have shown that a reduction in waist circumference achieved through lifestyle modifications is closely linked to an improvement in metabolic risk factors (17,18). These studies suggest that the changes in VFA, BMI, weight, and waist circumference are related to risk factors for CVD. However, the impact of the change in VFA (measured twice in the same person), which is regarded as the strongest indicator of a risk of CVD, has remained uncertain. To our knowledge, this is the first study to analyze the relationship between the incidences of metabolic risk factors and changes in VFA by measuring VFA twice.

Our findings clearly showed that changes in VFA were significantly associated with the incidences of metabolic risk factors.

When the odds ratios of the incidences of the metabolic risk factors for the $\Delta$VFA $\geq$ 50 cm$^2$ were compared with those for the stable $\Delta$VFA group ($\Delta$VFA $>$ $-10$ cm$^2$, $<$ 10 cm$^2$) as a reference group, the highest odds ratio was seen for a high triglycerides level. The odds ratios for the incidences of high triglycerides and low HDL cholesterol levels, which are indicators of hyperlipidemia, were significantly higher among subjects with a larger increase in VFA and were significantly lower among subjects with a larger decrease in VFA (trend $P < 0.05$). In previous studies (14), the mean value of each component of metabolic risk factors or the prevalence of metabolic risk factors and its components were compared according to changes in BMI, body weight, and waist circumference. To our knowledge, however, no other studies have compared the strength of the association among metabolic risk factors to the change in VFA. Our study is the first to clarify the risk of each disease by calculating comparable odds ratios.

In conclusion, this study of Japanese men showed that changes in VFA were associated with the incidences of metabolic risk factors, with a significant increase in the odds ratios observed with a $\Delta$VFA $\geq$ 50 cm$^2$. This association was most pronounced for the risk of high triglycerides and low HDL cholesterol levels. The adoption of a lifestyle that does not result in an increase in VFA is important for preventing metabolic syndrome.O

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Original Article
EPIDEMIOLOGY/GENETICS

Obesity

# Adiponectin and Visceral Fat Associate with Cardiovascular Risk Factors

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**Objective:** To examine the combined effect of CT-measured visceral fat area (VFA) and adiponectin level against the clustering of metabolic risk factors.
**Design and Methods:** The subjects were 6,996 Japanese. The subjects were divided according to the combinations of VFA and adiponectin level quartiles and the odds ratio for multiple risk factors of metabolic syndrome were calculated (adjusted for age and lifestyle factors using logistic regression analyses). Group with the lowest VFA and the highest adiponectin level was used as a reference. The correlation between adiponectin level and each metabolic risk factor was evaluated.
**Results:** The strongest correlation was observed between adiponectin level and high-density lipoprotein cholesterol levels ($r$ = 0.369 and 0.439 for men and women). Both VFA and adiponectin level were independently associated with the clustering of metabolic risk factors (interaction $P$ = 0.58 and 0.11 for men and women). The odds ratio for the clustering of metabolic risk factors in the group with the highest VFA and the lowest adiponectin level, compared with the group with the lowest VFA and the highest adiponectin level, was 12.7 (9.7-16.6) for men and 13.5 (6.0-30.2) for women.
**Conclusion:** The ability to detect metabolic syndrome could be improved by examining adiponectin level in conjunction with VFA.

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## Introduction

The prevalence of metabolic syndrome has been growing globally with clusters of obesity, high blood pressure, impaired lipid metabolism, and hyperglycemia. Individuals with metabolic syndrome have a higher risk of cardiovascular disease and a subsequent increase in disease mortality or morbidity (1-3). Several criteria for the diagnosis of metabolic syndrome are used worldwide. The visceral adipose tissue is regarded as an endocrine organ, partly because it secretes adipocytokines and other vasoactive substances that can influence the risk of developing traits of metabolic syndrome (4). We recently demonstrated that measuring the visceral fat area (VFA) is superior in predicting the accumulation of multiple risk factors, compared with the subcutaneous fat area (SFA), BMI, and waist circumference (WC) measurements (5). Regarding the multiple risk factors of metabolic syndrome, the odds ratios for the VFA quintiles were 1.0 (ref.), 2.4, 3.4, 5.0, and 9.7 for men and 1.0 (ref.), 1.5, 2.6, 4.6, and 10.0 for women ($P$ < 0.001 for trends in both sexes) (5).

Adiponectin is predominantly secreted by adipocytes, and the adiponectin level is reduced in individuals with obesity, insulin resistance, and type 2 diabetes (6-10). Low plasma adiponectin levels have recently been shown to predict the risk of developing type 2 diabetes in humans (9,11). The adiponectin level is also inversely associated with other traditional cardiovascular risk factors, such as blood pressure, total and low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) levels (12,13), and is positively related to high-density lipoprotein (HDL) cholesterol levels (12,14).

Some previous studies reported the impact of adiponectin levels on metabolic syndrome and its components (15); however, the sample sizes were insufficient. In addition, the combined effect of the VFA and adiponectin level has not been examined in an epidemiological study. Thus, we have examined the combined effect of the VFA and adiponectin level on the clustering of metabolic risk factors.

## Methods and Procedures

### Survey

Among the 17,606 employees of the same company and their spouses who underwent a health examination in Japan between 2008 and 2009, we analyzed 6,996 subjects ranging in age from 25 to 75 years (6,221 men and 775 women) who had undergone a computed

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**TABLE 1 Characteristics of the subjects**

| | Men | | Women | |
|---|---|---|---|---|
| | Mean | (SD) | Mean | (SD) |
| *N* | 6,221 | | 775 | |
| Age, years | 52.8 | (10.2) | 57.4 | (9.7) |
| Body mass index, kg/m$^2$ | 24.1 | (3.0) | 23.0 | (3.4) |
| Visceral fat area, cm$^2$ | 121.7 | (53.4) | 81.6 | (46.3) |
| Subcutaneous fat area, cm$^2$ | 133.6 | (56.4) | 182.8 | (76.9) |
| Adiponectin, log μg/mL | 0.83 | (0.20) | 1.05 | (0.21) |
| High blood pressure, % | 38.9 | | 34.1 | |
| High triglyceride, % | 35.4 | | 23.7 | |
| Low HDL cholesterol, % | 11.0 | | 17.8 | |
| Hyperglycemia, % | 57.8 | | 40.8 | |
| Multiple risk factors of metabolic syndrome, % | 45.5 | | 34.2 | |

tomography (CT) examination and answered a questionnaire on lifestyle factors and current treatments for metabolic conditions (hyperlipidemia, hypertension, or diabetes). The VFA was measured using a CT scanner and was calculated using a software application (fatPointer; Hitachi Medico, Tokyo, Japan) according to a protocol described elsewhere (11). Briefly, single slice imaging at the umbilical level was performed using a CT machine (Redix turbo; Hitachi Medico) while the subject was in a supine position. The imaging conditions were 120 kV, 50 mA, using a 5 mm thick slice. Height, weight, and body fat were measured using an automated scale (BF-220; Tanita, Tokyo, Japan) with the patient wearing a light gown. The BMI was defined as the weight (kg) divided by the square of the height (m$^2$). A blood sample was collected from each subject after more than 12 hours of fasting. The glucose level was measured using the glucose oxidase enzyme-electrode method (A&T, Tokyo, Japan). TG and HDL cholesterol levels were measured using an enzymatic colorimetric method (Cholestest TG; Sekisui Medical, Tokyo, Japan) and a nonsettling enzymatic method (Cholestest NHDL; Sekisui Medical), respectively. Adiponectin levels were measured using an immunoturbidimetric method (Adiponectin Latex Kit for humans; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). Blood pressure was measured using an automated sphygmomanometer (Kentaro ADVANCE BP-203RV III A/B; Colin, Tokyo, Japan). This study was approved by the ethics review committee of the National Center for Global Health and Medicine. Written informed consent was obtained from all the subjects.

## Definition of the state of risk factor clustering

In this study, subjects were defined using the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines (6) published in 2005: [1] high TG (TG $\geq$ 150 mg/dL), [2] low HDL cholesterol (HDL cholesterol <40 mg/dL in men and <50 mg/dL in women), [3] high blood pressure (systolic blood pressure $\geq$130 mm Hg or diastolic blood pressure $\geq$85 mm Hg), [4] hyperglycemia (fasting glucose $\geq$100 mg/dL), and [5] multiple risk factors (having two or more of components [1-4] listed above). Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factor, regardless of the biochemical value.

## Statistical analyses

We calculated the Pearson's correlation coefficients between the adiponectin level and each metabolic risk factor. We divided the subjects according to quartiles of the adiponectin level and calculated the odds ratio for multiple risk factors of metabolic syndrome. We adjusted for age, smoking habits (never, past, current), alcohol consumption (nondrinker, drinker consuming less than 2 go per day [the go is a conventional unit of alcohol intake in Japan and contains approximately 23 g of ethanol], or drinker consuming more than 2 go per day), and regular fitness habit (based on a single yes/no question in the questionnaire) using a logistic regression analysis, with the highest adiponectin level group used as a reference. We calculated the odds ratio for the multiple risk factors of metabolic syndrome for a +1 SD increment in the quintile categories of VFA and a +1 SD increment in the quintile categories of adiponectin levels. Furthermore, we divided the subjects according to combinations of VFA and adiponectin level quartiles and calculated the odds ratio for multiple risk factors of metabolic syndrome adjusted for the above-mentioned variables, using the category with the lowest VFA and the highest adiponectin level as the reference. VFA, adiponectin levels, and their interaction term (VFA $\times$ adiponectin levels) were included as independent variables in the logistic regression model to examine the interaction effect between VFA and adiponectin levels on the risk of clustering of metabolic risk factors. The stepwise procedure was used to select variables in the multiple logistic regression model with $P < 0.1$ for entry and $P < 0.05$ for removal. All the analyses were performed using SPSS for Windows, Version 15.0 (SPSS Inc., Chicago. IL, USA).

# Results

The characteristics of the subjects are shown in Table 1. The mean (SD) age of the subjects was 52.8 $\pm$ 10.2 years for men and 57.4 $\pm$ 9.7 years for women. The mean VFA was 121.7 $\pm$ 53.4 cm$^2$ in men and 81.6 $\pm$ 46.3 cm$^2$ in women. The mean BMI was 24.1 $\pm$ 3.0 kg/m$^2$ in men and 23.0 $\pm$ 3.4 kg/m$^2$ in women. The mean log adiponectin level was 0.83 $\pm$ 0.20 μg/mL in men and 1.05 $\pm$ 0.21 μg/mL in women. The prevalence of multiple risk factors of metabolic syndrome was 45.5% in men and 34.2% in women.

Table 2 shows the partial correlations between adiponectin level and each metabolic risk factor. The HDL cholesterol level positively correlated with adiponectin level ($P < 0.001$). Other metabolic risk factors negatively correlated with the adiponectin level ($P < 0.001$).

The odds ratios for each component of metabolic syndrome according to the adiponectin level are shown in Figure 1. The odds ratios for a high TG level, a low HDL cholesterol level, high blood pressure, and hyperglycemia decreased with increasing quartile categories of adiponectin levels. For the multiple risk factors of metabolic syndrome, the odds ratios (95% confidence intervals [CI]) of the Q1, Q2, Q3, and Q4 adiponectin level categories were 3.4 (3.0-4.0), 2.1 (1.8-2.5), 1.5 (1.3-1.7), and 1.0 (ref.) for men and 4.3 (2.7-6.9), 2.5 (1.6-4.1), 1.5 (0.9-2.4), and 1.0 (ref.) for women. The odds ratio (95% CI) of the lowest (Q1) adiponectin level category for a high TG level was 3.9 (3.4-4.6) in men and that for a low

**TABLE 2** Partial correlation between adiponectin level and each metabolic risk factor

| | Men | Women |
|---|---|---|
| VFA | −0.364 | −0.428 |
| SFA | −0.220 | −0.234 |
| BMI | −0.281 | −0.237 |
| log TG | −0.340 | −0.342 |
| HT | −0.104 | −0.153 |
| HDL cholesterol | 0.369 | 0.439 |
| FG | −0.103 | −0.177 |

VFA, visceral fat area; SFA, subcutaneous fat area; BMI, body mass index; TG, triglyceride; HT, hypertension; FG, fasting glucose.
*P*-values are all less than 0.001.
Values are partial correlation coefficients adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no).

HDL cholesterol level was 5.8 (4.4-7.8) in men and 9.9 (4.8-20.1) in women.

In Table 3, the odds ratios of adiponectin and VFA levels for the clustering of multiple risk factors of metabolic syndrome are shown according to the VFA and adiponectin quartiles, respectively. For men, the increased adiponectin levels were significantly related to reduced clustering of metabolic risk factors, regardless of the VFA category ($P = 0.58$ for interaction VFA × adiponectin). For women, however, the odds ratio for a +1 SD in the VFA slightly weakened according to the increment of adiponectin level category ($P = 0.11$ for interaction of VFA × adiponectin). The odds ratio for multiple risk factors of metabolic syndrome according to combined groups of VFA and adiponectin are depicted in Figure 2. The odds ratio for the multiple risk factors of metabolic syndrome in the category with the highest VFA and the lowest adiponectin levels were 12.7 (9.7-16.6) for men and 13.5 (6.0-30.2) for women. We conducted stepwise logistic regression analyses among the largest quartile group of VFA, with hypoadiponectinemia (lowest vs. highest quartile group) as the independent variable. The result revealed that smoking, high TG, low HDL cholesterol, and older age were associated with hypoadiponectinemia in men. Low HDL cholesterol and age were associated with hypoadiponectinemia in women (data not shown).

## Discussion

We observed a strong association between the combined effect of an increasing VFA and a decreasing adiponectin level and the prevalence of multiple risk factors of metabolic syndrome. Both the VFA and the adiponectin level were independently associated with the clustering of metabolic risk factors. Among the components of metabolic syndrome, the adiponectin level had a particularly strong impact on a high TG level in men and a low HDL cholesterol level in both men and women.

Only one previous report, studying 68 obese Korean subjects, demonstrated an association between the adiponectin level and VFA. The adiponectin level was inversely correlated with the VFA ($r = -0.691$, $P = 0.009$ in men, $r = -0.319$, $P = 0.002$ in women). Levels of a high molecular weight adiponectin also negatively correlated with the VFA ($r = -0.650$, $P = 0.016$ in men, $r = -0.370$, $P = 0.005$ in women) but not with the BMI or SFA, suggesting hypoadiponectinemia may represent a dysfunction of adipose tissue during obesity (16).

It was unknown whether adiponectin levels were correlated with disease, even when the VFAs were the same. Therefore, we compared the prevalence of multiple risk factors of metabolic syndrome with combinations of the VFA and adiponectin level. We found a markedly increased risk of clustering of metabolic syndrome among individuals who had a low adiponectin level and a high VFA. It was revealed that even when VFAs were the same, hypoadiponectinemia was associated with older age, smoking, and lipid metabolism (high TG and low HDL cholesterol) in men. In women, hypoadiponectinemia was associated with older age and low HDL cholesterol. Thus, it was confirmed that adiponectin correlated with lipid metabolism independent of VFA; from this, we concluded that adiponectin correlated with the clustering of metabolic risk factors. However, even

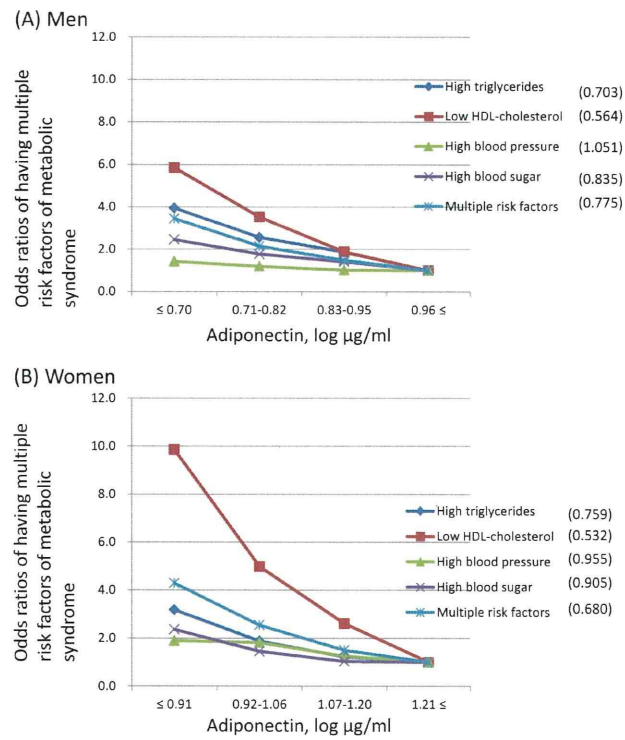


**FIGURE 1** Odds ratios for clustering of metabolic risk factors according to the quartiles of adiponectin. The definition of metabolic risk factors is based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines published in 2005. Subjects with two or more of the metabolic risk factors (except for waist circumference) were defined as having multiple risk factors. Odds ratios for clustering of metabolic risk factors according to the quartiles (Q1-Q4) of adiponectin adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no). Values in the case arcs are odds ratios for +1 SD increments of adiponectin. (Multiple risk factors; multiple risk factors of metabolic syndrome.) [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

**TABLE 3** Odds ratios for clustering of metabolic risk factors

| | | *n* | | Odds ratios of +1 SD increment of adiponectin | |
|---|---|---|---|---|---|
| **Men** | | | | | |
| VFA ($cm^2$) | ≤84.80 | 1,557 | Q1 | 0.8 | (0.7-0.9) |
| | 84.81-120.10 | 1,559 | Q2 | 0.8 | (0.7-0.9) |
| | 120.11-156.90 | 1,553 | Q3 | 0.8 | (0.7-0.9) |
| | 156.91≤ | 1,552 | Q4 | 0.8 | (0.7-0.9) |
| **Women** | | | | | |
| VFA ($cm^2$) | ≤44.30 | 194 | Q1 | 0.7 | (0.4-1.2) |
| | 44.31-77.90 | 195 | Q2 | 0.5 | (0.3-0.9) |
| | 77.91-113.10 | 193 | Q3 | 0.8 | (0.6-1.2) |
| | 113.11≤ | 193 | Q4 | 0.6 | (0.4-0.9) |
| | | n | | Odds ratios of +1 SD increment of VFA | |
| **Men** | | | | | |
| Adiponectin (log μg/mL) | ≤0.70 | 1,620 | Q1 | 2.1 | |
| | 0.71-0.82 | 1,556 | Q2 | 2.2 | (1.8-2.3) |
| | 0.83-0.95 | 1,518 | Q3 | 1.9 | (1.9-2.5) |
| | ≤0.96 | 1,527 | Q4 | 2.1 | (1.7-2.2) |
| **Women** | | | | | (1.9-2.4) |
| Adiponectin (log μg/mL) | ≤0.91 | 198 | Q1 | 2.6 | (1.7-3.9) |
| | 0.92-1.06 | 191 | Q2 | 2.5 | (1.6-3.8) |
| | 1.07-1.20 | 193 | Q3 | 2.1 | (1.3-3.3) |
| | 1.21≤ | 193 | Q4 | 1.7 | (1.1-2.5) |

VFA, visceral fat area.
Odds ratios of multiple risk factors of metabolic syndrome according to 1 SD increment of VFA or adiponectin adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no).

if the adiponectin levels were the same, weight gain led to a worsening of metabolic risk factors, including lipid. In the largest VFA group, adiponectin itself was related to lipid metabolism and smoking status. Therefore, it was shown that the ability to detect metabolic syndrome would be improved by examining the adiponectin level in conjunction with the VFA, as adiponectin correlated with metabolic risk factors independent of VFA and the correlation was most pronounced between lipid metabolism.

In a case–control study, high plasma adiponectin levels were associated with a lower risk of myocardial infarction (MI) over a follow-up period of 6 years among men without previous cardiovascular disease. After adjustment for matched variables, participants in the highest quintile, compared with the lowest quintile, of adiponectin levels had a significantly decreased risk of MI (relative risk [RR], 0.39; 95% confidence interval [CI], 0.23-0.64; *P* for trend <0.001). Further adjustment for the hemoglobin A1c or C-reactive protein levels had little impact, but additional adjustment for LDL and HDL cholesterol levels modestly attenuated this association (RR, 0.56; 95% CI, 0.32-0.99; *P* for trend =0.02) (17). A multiple logistic regression analysis revealed that hypoadiponectinemia was significantly and independently correlated with coronary artery disease (CAD) ($P < 0.0088$) among 450 Japanese men. The multivariate-adjusted odds ratios for CAD in the first, second, third, and fourth quartiles (95% confidence) were 2.051 (1.288-4.951), 1.221 (0.684-2.186), 0.749 (0.392-1.418), and 1.000, respectively (18). Furthermore, another study showed that BMI, serum TG concentration, and the presence of diabetes or CAD remained significantly related to the plasma adiponectin concentration. Weight reduction significantly elevated the plasma adiponectin levels in diabetic obese Japanese subjects (six men and seven women) and nondiabetic obese Japanese subjects (six men and three women). However, the sample size was very small in this study (6).

This study has several strengths and limitations. As one of its strengths, we directly assessed abdominal fat accumulation using CT scanning. This allowed the role of fat deposition in the development of metabolic syndrome and its components to be examined more closely. Secondly, the sample size of our study was sufficiently large (almost 7,000 subjects), and both sexes were included. Thirdly, we adjusted for alcohol consumption and physical activity, which may confound the association between abdominal fat accumulation and metabolic risk factors. However, the study was limited because of its cross-sectional design, and changes in the metabolic risk profile were not monitored.

In this study, we demonstrated a strong association between the combined effect of an increasing VFA and a decreasing adiponectin level with multiple risk factors of metabolic syndrome. Both the VFA and the adiponectin level were independently associated with the clustering of metabolic risk factors in a large Japanese population, which has a relatively low BMI compared with other

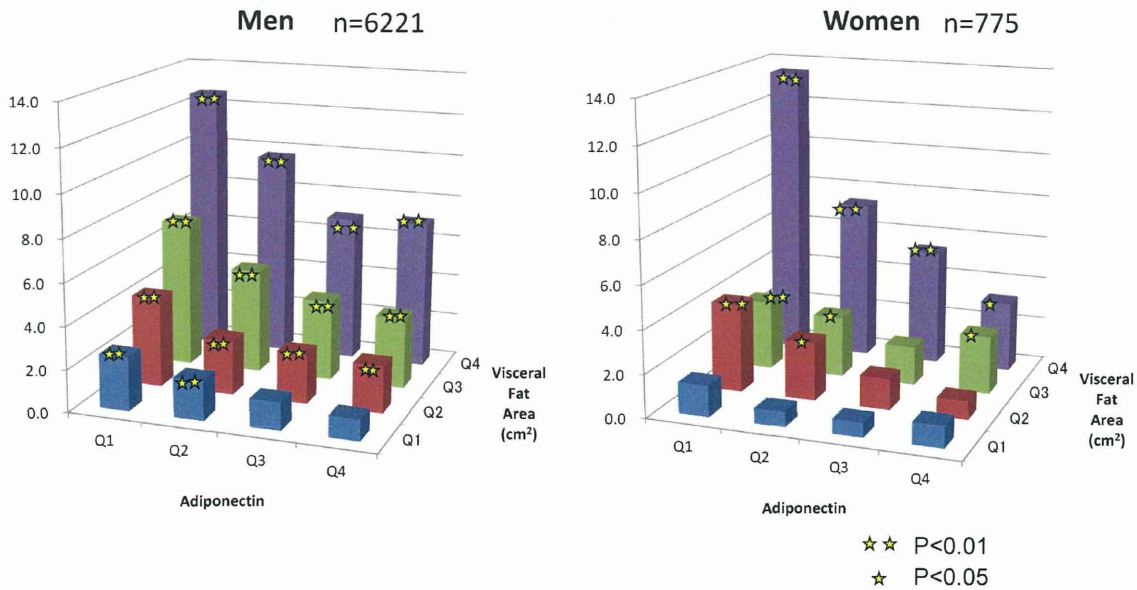


**FIGURE 2** Odds ratios for multiple risk factors of metabolic syndrome according to combined groups of VFA and adiponectin. The definition of metabolic risk factors is based on the criteria of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines published in 2005. Subjects with two or more of the metabolic risk factors (except for waist circumference) were defined as having multiple risk factors. Odds ratios for multiple risk factors of metabolic syndrome are shown according to combined groups of VFA and adiponectin adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming 2 go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than 2 go per day), and regular fitness habit (yes/no). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ethnicities. The present findings have important implications for the prevention of metabolic syndrome. Further prospective studies are needed to assess the impact of the VFA and adiponectin level on the incidence of metabolic syndrome or cardiovascular diseases.

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