Differences in Associations between Visceral Fat Accumulation and Obstructive Sleep Apnea by Sex

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Abstract

Rationale: Difference in mortality from obstructive sleep apnea (OSA) by sex is an important issue. Visceral fat, a significant risk factor for cardiovascular disease (CVD), was reported to be closely related to OSA.

Objectives: To assess the different associations between OSA and visceral fat area (VFA) by sex, which might account for the different prognosis in men and women with OSA.

Methods: Participants were 271 men and 100 women consecutively hospitalized for examination of OSA from October 2008 to December 2010. Among the 371 participants, relationships were analyzed between fat areas by computed tomography, comorbidity, polysomnographic data, arterial blood gas, pulmonary function and venous blood data. Multiple regression analyses were performed to identify variables independently associated with VFA and subcutaneous fat area (SFA) for each sex.

Measurements and Main Results: Despite similar body mass index (BMI) and waist circumference, men had larger VFA, more severe OSA and more severe dyslipidemia than women. Multiple regression analyses revealed that in men, not only age and BMI but also minimum oxygen saturation (contribution rate (R^2) = 4.6%) during sleep, and alveolar-arterial

oxygen difference (R^2 = 7.6%) were independently associated with VFA. Conversely, VFA was only associated with BMI in women.

Conclusions: Only in men OSA was independently associated with VFA. The lesser associations between OSA and visceral fat in women might account for OSA's lower impact on CVD or mortality in women.

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Introduction

Obstructive sleep apnea (OSA) was reported to be an important risk factor for cardiovascular diseases (CVD) and mortality (1, 2), especially in men (3). Visceral obesity, an important component of metabolic syndrome (4), also appears to be an important risk factor for CVD and all-cause mortality (5).

A relationship between OSA and visceral obesity was reported (6, 7). However, although a close relationship can be predicted between OSA and visceral obesity, the connection between OSA and visceral fat area (VFA), accurately measured by computed tomography (CT) in a large number of participants, has not been well investigated. Moreover, few studies assessed the relationships between OSA and VFA in men and women respectively, and, when assessed, the number of participants was small (8).

Recently, differences in morbidity and mortality by sex have become important issues (3, 9). A different pathophysiology of OSA between men and women also has been reported. The Sleep Heart Health Study revealed that OSA was associated with all-cause mortality or other fatal and nonfatal cardiovascular outcomes in men $\leq$ 70 years of age but not in older men or in women of any age (3, 10, 11), although Campos-Rodriguez et al. reported substantial mortality in women with untreated OSA (12).

Visceral obesity was proven to be a key factor in metabolic syndrome and CVD (4, 5), and the association between OSA and VFA may differ between men and women. Thus, we

hypothesized that the associations between OSA and visceral fat accumulation in men differed from those in women, which might account for the different prognosis in men and women with OSA and why OSA in women has less impact on CVD or mortality than in men.

Some of the results of these studies have been previously reported in the form of an abstract at the ATS 2013 International Conference in Philadelphia (13).

Methods

Participants

Participants were patients who were hospitalized in Kyoto University Hospital from October 2008 to December 2010 for a detailed examination of OSA and who agreed to undergo a CT scan to assess the distribution of abdominal fat. Excluded were those previously diagnosed with or treated for OSA or with central sleep apnea (CSA). We defined CSA as having a central apnea index (AI) $\geq$ 5 /h, with central AI accounting for more than half of the AI. Finally, 271 male and 100 female consecutive participants were included in the study (Figure E1). The study protocol was approved by the Kyoto University Graduate School and Faculty of Medicine Ethics Committee. The approval number was E-1452. Informed consent was obtained from all participants.

Body weight and height were measured with the patient wearing light clothing and no footwear. Body mass index (BMI) was calculated as weight in kilograms over height in meters squared. Waist circumference was measured midway between the lower costal margin and iliac crest. Pack years of smoking were calculated as the number of packs of cigarettes smoked per day × number of smoking years. The presence of hypertension, diabetes mellitus and dyslipidemia was based on a previous diagnosis or ongoing treatment.

Visceral and Subcutaneous Adipose Tissue Measurement

In this study, VFA was assessed by an Aquilion 64 CT system (Toshiba Medical Systems Corporation, Tochigi, Japan) running on 135 kVp, 440 mA, 0.5 second scan time and 10.0 mm slice thickness. CT scans were performed with participants in a supine position with arms outstretched above the head when breathing was stopped at the end of the respiratory phase. We used a single CT scan obtained at the level of the umbilicus (approximately at the level of L4 and L5) (14) for assessment of VFA and subcutaneous fat area (SFA). VFA and SFA were quantified using a specialized image analysis program (AZE Virtual Place 99, AZE of America, Ltd., Irvine, CA, USA). With this software, a histogram for fat tissue was automatically computed on the basis of mean Hounsfield attenuation ± 2 standard deviations (SD) and the attenuation interval to indicate fat was set. Then, by tracing the contour of the outermost aspect of the abdominal muscle on the scan, the SFA was defined as the area between the outermost aspect of the abdominal muscle wall and the skin and the VFA was defined by the innermost aspect of the oblique and abdominal wall musculature and the anterior aspect of the vertebral body.

Polysomnography

Diagnosis of OSA was confirmed by polysomnography (SomnoStar pro, Cardinal Health, Dublin, OH, USA) as previously reported (15). Sleep stages were defined according to the criteria of Rechtschaffen and Kales (16). Apnea was defined as the complete cessation of

airflow for at least 10 seconds and hypopnea as a decrease in airflow of 30% or more lasting for at least 10 seconds, accompanied by oxygen desaturation of ≥ 4% (17). All apnea-hypopnea index (AHI) values were expressed as the number of episodes of apnea and hypopnea per hour over the total sleep time. The minimum arterial oxygen saturation (SpO_2) during sleep was also calculated. The 4% oxygen desaturation index (ODI) was determined by the frequency of desaturations of ≥ 4% per hour.

Pulmonary Function

Pulmonary function tests were performed to determine vital capacity, forced vital capacity, and forced expiratory volume in 1 second using a standard spirometer, according to the recommended method (18).

Laboratory Analyses of Blood

Arterial blood for the analysis of gases under room air breathing was drawn just before polysomnography started at night with the participants in the supine position. Arterial oxygen pressure (PaO_2) and arterial carbon dioxide pressure ($PaCO_2$) was measured in a blood gas analyzer (Chiron Arterial Blood Gas Analyzers RL865, Chiron Corporation, Emeryville, CA, USA). Alveolar-arterial oxygen pressure difference ($A\text{-}aDO_2$) was calculated by the following formula; (760 - 47) × 0.21 - $PaCO_2$ (mmHg) / 0.8 - PaO_2 (mmHg). Venous blood

samples were taken in the fasting state in the morning after one-night polysomnography. Estimation of insulin resistance by the homeostasis model assessment (HOMA-R) was calculated by the following formula; fasting serum insulin (μU/ml) × fasting plasma glucose (mg/dl) / 405.

Statistical Analysis

Baseline characteristics are expressed as mean ± SD or numbers (percent). Unpaired t-tests and chi-square tests were used to compare the backgrounds of the two groups. Relationships between two sets of continuous data were analyzed by Pearson's correlation coefficient tests and of dichotomous data were by Spearman rank correlation coefficient. *P* values < 0.05 were considered to be statistically significant. Multiple regression analyses, with a p value < 0.10 for entry into the models, were performed to identify variables that could be best associated with VFA, SFA, and AHI. To exclude the effects of co-linearity on the multiple regression analyses, we tested for co-linearity among the variables by Pearson's correlation coefficient tests. Then, of the variables with very strong co-linearity (correlation coefficient (r) ≥ 0.70), one was chosen. Statistical analyses were performed using Statview 5.0 (SAS Institute, Inc. Cary, NC, USA).

Results

Characteristics of Participants

Tables 1 and 2 show characteristics of the 371 participants (271 men, 100 women), sleep data, arterial blood gas analyses, pulmonary function and results of studies of venous blood samples. Although we could not determine whether 14% of the total women were premenopausal or postmenopausal, we ascertained that more than 74% of the women were postmenopausal. Although BMI and waist circumference did not differ between men and women, the men had a significantly larger waist-hip ratio, larger VFA and smaller SFA. Figure 1 shows a single CT scan obtained at the level of the umbilicus of a male participant and a female participant, showing very well the difference in fat distribution by sex. The men in the study had significantly more severe OSA ($P < 0.001$), higher triglyceride (TG), and lower high density lipoprotein cholesterol (HDL-Chol) values than the women.

Univariate Analyses of Relationships with VFA and SFA

As has been reported (6, 7), although values of r were small, VFA was significantly associated with AHI in men, in women, and also in the entire group of 371 participants (AHI; range, 0.0 - 113.0) (Figure E2). PaO_2 and A-aDO_2 were significantly associated with VFA and SFA only in men, with the association stronger with VFA (A-aDO_2, r = 0.39, $P < 0.001$) than with SFA (A-aDO_2, r = 0.17, $P = 0.007$) (Table E1).

Multiple Regression Analyses to Identify Independent Associations with VFA and SFA

Table 3 shows results of multiple regression analyses to identify those variables that were independently associated with VFA (Table 3A) and with SFA (Table 3B) in men and women.

We used variables with p values < 0.10 by univariate analyses of relationships with both VFA and SFA (Table E1) to identify independent associations with VFA and SFA in men and women, respectively. To exclude the effects of co-linearity, we tested for co-linearity among the variables. Then, of the variables with very strong co-linearity ($r \geq 0.70$), one was chosen. Correlation coefficients among each variable are shown in Tables E2 and E3. About OSA-related parameters, we chose 4% ODI because 4% ODI had the largest mean r value with VFA for men and women (Table E1). In addition, 4% ODI is a good marker for intermittent hypoxia and was reported to be independently associated with CVD (19). The parameters we used for analysis are shown in Table 3.

In the men, VFA had a significant and independent association not only with age and BMI (contribution rate (R^2) = 2.3% and 25.3%, respectively) but also with minimum SpO_2 (R^2 = 4.6%) and A-aDO_2 (R^2 = 7.6%) (Table 3A and Figure 2A). In contrast, SFA had the most significant association with BMI (R^2 = 63.6%) followed by age (R^2 = 4.8%) and HOMA-R (R^2 = 4.7%) (Table 3B and Figure 2B). SFA had no significant associations with OSA-related parameters.

On the other hand, in the women, VFA and SFA had a significant and independent

association with BMI (R^2 = 54.5% and 80.6%, respectively) (Table 3 and Figure 2). In the women, OSA-related parameters were not associated with either VFA or SFA.

Factors Independently Associated with VFA and SFA in OSA Patients and in Control Participants

We compared factors independently associated with VFA and SFA, respectively, in the OSA groups (defined as AHI ≥ 10 /h) and in the control groups (defined as AHI < 10 /h) by sex. The male OSA group was comprised of 206 men, and there were 65 men in the male control group. The female OSA group was comprised of 54 women, and the female control group consisted of 46 women.

Table 4 shows results of multiple regression analyses to identify those factors independently associated with VFA (Table 4A) and with SFA (Table 4B) in men and women in both OSA and control groups.

We used variables with p values < 0.10 by univariate analyses of relationships with both VFA and SFA (Tables E4 and E5) in each group. To exclude the effects of co-linearity, one variable was chosen among those with very strong co-linearity (r ≥ 0.70). Correlation coefficients among each variable are shown in Tables E6 and E7.

In the male OSA group (Table 4), almost the same results were obtained as for the entire group of male participants (Table 3). Also, in the female OSA group (Table 4), the results

were almost the same for the entire group of female participants (Table 3). On the other hand, in the male control group, regarding VFA, after multiple regression analyses, no significantly and independently associated factors remained (Table 4A), although VFA was significantly associated with 4%ODI in a univariate analyses (P = 0.005) (Table E5).

Then, although the number of control participants became smaller, when the control groups were defined as being comprised of those with AHI < 5 /h, in the male OSA group (AHI ≥ 5 /h) (n = 236), VFA had independent associations with BMI (R^2 = 21.9%), minimum SpO_2 (R^2 = 4.9%) and A-aDO_2 (R^2 = 9.0%). In the male control group (AHI < 5 /h) (n = 35), VFA had an independent association only with BMI (R^2 = 24.8%).

Multiple Regression Analyses to Identify Independent Associations with AHI

Next, we performed multiple regression analyses to identify those factors independently associated with AHI in men and women (Table 5). Table E8 shows univariate analyses of relationships with AHI in men and in women, respectively. Correlation coefficients among each variable with p values < 0.10 with AHI by univariate analyses are shown in Table E9. AHI had an independent association with VFA only in men (R^2 = 4.1%) (Table 5A). In contrast, in women, AHI had an independent association with age (R^2 = 6.8%) and $PaCO_2$ (R^2 = 9.3%), but not with VFA (Table 5B).

Discussion

In this study, we found differences in the associations between OSA and visceral obesity by sex. Multiple regression analyses revealed that in the men, not only age and BMI, but also minimum SpO_2 during sleep and A-aDO_2 were independently associated with VFA. On the other hand, in the women, OSA-related parameters were not associated with VFA, but BMI was.

Although previous studies have shown an association of OSA-related parameters with visceral fat, not subcutaneous fat, the number of participants in those studies was small (7, 8, 20). This study included a large dataset with both polysomnography and CT data to allow examination of the association between OSA and visceral obesity. Furthermore, we analyzed the associations between VFA and OSA in men and women separately and revealed differences by sex. We also confirmed that AHI had an independent association with VFA only in men, but not in women.

In our study, women were older and had less severe OSA than men despite similar BMI, which was compatible with the previous report showing that women with OSA had less severe OSA even though they were more obese than men with OSA (21). Furthermore, despite similar BMI and waist circumference, the men had a greater degree of visceral obesity. Figure 1 shows a clear example of differences in fat distribution between sexes. In addition, the men had significantly higher TG and lower HDL-Chol than the women (Tables 1 and 2).

High TG and low HDL-Chol have been associated with the risk of CVD (22, 23) and are possibly associated with a higher risk of CVD in men with OSA. In many cases, visceral obesity has been assessed by waist circumference. However, the difference in visceral fat despite similar waist circumference in our study implies that waist circumference cannot accurately assess visceral obesity.

In the men, OSA was associated with VFA. The R^2 value of BMI for SFA was more than twice of that for VFA. Thus, a lower BMI may be an insufficient predictor of a lower VFA, but could be a good predictor of a lower SFA. Minimum SpO_2 due to OSA was independently associated with VFA, while no OSA-related parameters had an independent association with SFA, which was compatible with the report that minimum SpO_2 was significantly associated with VFA (6, 7). Although minimum SpO_2 may fluctuate slightly day by day, it changes according to the severity of OSA. Indeed, the relationships between minimum SpO_2 and AHI or 4% ODI were significant ($r = -0.55$, $P < 0.001$ and $r = -0.58$, $P < 0.001$, respectively) (Table E2). Additionally, A-aDO_2, which had a significant association with VFA, was independently associated with 4% ODI in men (Table E10, Model 2). Therefore, although minimum SpO_2 and A-aDO_2 remained statistically significant, other OSA-related parameters also possibly correlate with VFA.

It was reported that visceral obesity effected a restrictive respiratory impairment, which was associated with a reduction in PaO_2 (24, 25) and an elevated A-aDO_2, frequently

inducing daytime hypoxemia, even in eucapnic individuals with visceral obesity (26). In addition, A-aDO_2 was reported not only to imply daytime oxygenation but also to be a main predictor of nocturnal desaturation and to be related to sleep apnea (27, 28). Thus, both awake and sleep hypoxemia due to OSA were independently associated with VFA. Our study revealed the degree of independent contributions of OSA-related parameters to VFA.

In our study, only about 12% of VFA was explained by OSA-related parameters. This might be one reason for the different results among reports on the effects of continuous positive airway pressure (CPAP) treatment on VFA; that is, a reduction in VFA following CPAP treatment in two reports and no reduction of VFA in four reports (8, 29-33).

In women, not only SFA but also VFA were independently associated with BMI (R^2 = 80.6% and 54.5%, respectively) whereas OSA-related parameters were not associated with VFA or SFA. In addition, age and $PaCO_2$ were independently associated with AHI, but VFA was not. This finding implies that in women, the role of OSA in visceral fat accumulation is slight, which could be one reason for the lower risk of CVD or mortality in women than in men with OSA. This could indicate the importance of the effect of age in women.

Although obesity is said to be the most reliable risk factor for OSA both in Asian and Western populations, differences in craniofacial morphology could make it more likely for Asians to develop OSA at a relatively lower BMI. Asian patients with OSA were reported to have more severe disease but be less obese and have greater craniofacial restriction (34). It

has been noted that in the presence of increasing degrees of obesity, Asians were more prone to developing abdominal obesity than Western individuals (34, 35). Thus, our results might be modified somewhat when applying them to Western peoples. Therefore, future studies in Western countries are warranted.

Our study had some limitations. First, we cannot determine causality or the mechanisms for our findings because this was a cross-sectional observational study. This study was done at the time of the diagnosis of OSA, so the duration of OSA, which might have influenced VFA, was unclear. Second, the participants were not selected from the general population but were those who consulted our institution for examination of OSA. Third, we did not separately evaluate data on premenopausal and postmenopausal women. We did not have menopausal data on about 14 % of the female participants. However, at least 74% of the total women were postmenopausal. Therefore, we consider that the data on women in this study would very closely reveal the postmenopausal profiles of the participants. Fourth, as we included the participants consecutively, the severity of OSA differed significantly between men and women. However, the difference would not be a significant issue because we adjusted with 4% ODI when examining multiple regression analyses. Fifth, this was not a longitudinal study. Thus, to determine the future prevalence of CVD or mortality and changes after CPAP treatment, long-term studies are needed. Our findings could not reveal the mechanism for why OSA-related parameters affect visceral fat in men, but not in women.

This mechanism should be studied by both basic and clinical investigations in the future. Also it should be noted that analysis of fat was based on one CT slice in the L4 and L5 region. This might yield an inaccurate quantification of the VFA/SFA ratio, although we did not consider this a large problem because CT is considered the gold standard for determining the quantity of visceral and subcutaneous adipose tissues, and many studies have assessed fat areas in the same way as we did (14).

In conclusion, in men with OSA, awake and sleep hypoxemia, as shown by low minimum SpO_2 and elevated A-aDO_2 induced by OSA were significantly associated with VFA, independent of age, BMI and other factors. BMI was a major factor associated with SFA. On the other hand, in women with OSA, OSA-related parameters were not independently associated with VFA or SFA. Since it is said that VFA is a risk factor for CVD, the lesser association between OSA and VFA in women than in men might be one reason that OSA in women has less impact on CVD or mortality than in men.

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Figure legends

Figure 1. CT scan at the umbilicus level of a male participant (A) and a female participant (B).

Definition of abbreviations: CT = computed tomography; BMI = body mass index; VFA = visceral fat area; SFA = subcutaneous fat area.

Figure 2. Independent contribution rate of each component to visceral fat area (A) and subcutaneous fat area (B) in men and women.

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; BMI = body mass index; min SpO_2 = minimum arterial oxygen saturation; A-aDO_2 = alveolar-arterial oxygen pressure difference; HOMA-R = homeostasis model assessment of insulin resistance.

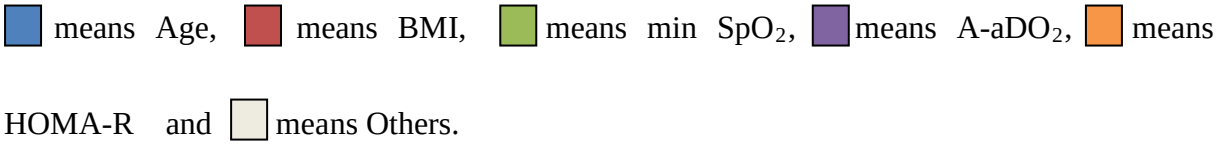


Table 1. Characteristics of participants

Variables	All participants	Men	Women	*P* Value
No. of participants (%)	371 (100.0)	271 (73.0)	100 (27.0)	
Age, yr	58 ± 13	57 ± 14	61 ± 12	0.014
Height, cm	164.3 ± 8.8	168.0 ± 6.5	154.4 ± 5.9	< 0.001
Weight, kg	72.2 ± 16.3	75.2 ± 14.9	63.8 ± 17.0	< 0.001
BMI, kg/m^2	26.6 ± 5.1	26.6 ± 4.6	26.6 ± 6.4	0.92
Neck circumference, cm	39.2 ± 4.1	40.4 ± 3.1	36.1 ± 4.6	< 0.001
Waist circumference, cm	94.7 ± 13.6	95.3 ± 12.9	93.1 ± 15.3	0.16
Hip circumference, cm	96.9 ± 10.7	96.6 ± 9.5	97.4 ± 13.5	0.53
Waist-hip ratio	0.98 ± 0.07	0.99 ± 0.07	0.95 ± 0.07	< 0.001
Smoking history (Never/Ex/Current)	159/165/45	82/148/39	77/17/6	< 0.001
Smoking, pack years	19.7 ± 29.1	25.5 ± 31.4	4.5 ± 12.9	< 0.001
Hypertension, n (%)	196 (52.8)	146 (53.9)	50 (50.0)	0.51
Diabetes mellitus, n (%)	101 (27.2)	72 (26.6)	29 (29.0)	0.64
Dyslipidemia, n (%)	201 (54.2)	139 (51.3)	62 (62.0)	0.078
Fat areas				
VFA, cm^2	118.3 ± 66.9	124.5 ± 68.5	101.5 ± 59.4	0.003
SFA, cm^2	161.8 ± 95.8	149.1 ± 84.9	196.1 ± 113.8	< 0.001
Total fat area, cm^2	280.1 ± 138.7	273.6 ± 129.9	297.5 ± 159.5	0.14
VFA/SFA ratio	0.83 ± 0.47	0.93 ± 0.48	0.55 ± 0.28	< 0.001

Definition of abbreviations: BMI = body mass index; VFA = visceral fat area; SFA: = subcutaneous fat area.

Data are expressed as mean ± standard deviations (SD) or numbers (%).

Table 2. Data on sleep, arterial blood gas, pulmonary function and venous blood

Variables	All participants	Men	Women	*P* Value
No. of participants (%)	371 (100.0)	271 (73.0)	100 (27.0)	
Sleep data				
Slow wave sleep stage, %	5.2 ± 7.1	4.1 ± 5.8	8.3 ± 9.1	< 0.001
REM stage, %	14.7 ± 6.1	14.8 ± 6.1	14.4 ± 6.1	0.55
AHI, /hr	24.7 ± 20.8	27.5 ± 20.9	17.2 ± 18.6	< 0.001
Arousal index, /hr	20.3 ± 12.1	21.9 ± 12.2	16.1 ± 10.8	< 0.001
minimum SpO_2, %	79.9 ± 9.7	79.4 ± 9.8	81.5 ± 9.5	0.062
mean SpO_2, %	93.9 ± 3.1	93.5 ± 3.1	94.7 ± 3.1	0.001
4% ODI, /hr	23.2 ± 21.1	25.5 ± 21.1	16.9 ± 19.7	< 0.001
<90(TST)%, %	19.5 ± 21.2	23.9 ± 21.1	7.5 ± 16.0	< 0.001
Arterial blood gas				
PaO_2, mmHg	83.8 ± 10.6	84.0 ± 10.2	83.2 ± 11.8	0.53
$PaCO_2$, mmHg	41.3 ± 3.7	41.4 ± 3.5	41.1 ± 4.4	0.53
A-aDO_2, mmHg	14.2 ± 10.5	13.9 ± 10.5	15.1 ± 10.8	0.37
Pulmonary function				
%VC, %	110.8 ± 17.5	110.9 ± 16.9	110.6 ± 19.0	0.88
%FVC, %	108.3 ± 17.7	108.2 ± 17.3	108.5 ± 18.8	0.90
$FEV_{1.0}$% , %	77.4 ± 8.2	76.9 ± 8.5	78.9 ± 6.9	0.041
Blood data				
Glucose, mg/dl	105 ± 31	104 ± 28	107 ± 36	0.50
HbA1c, %	5.68 ± 1.01	5.65 ± 1.02	5.76 ± 0.98	0.33
Insulin, μU/ml	11.12 ± 11.26	11.41 ± 11.82	10.35 ± 9.57	0.43
HOMA-R	3.03 ± 3.54	3.02 ± 3.32	3.06 ± 4.13	0.92
TG, mg/dl	143 ± 101	153 ± 109	116 ± 66	0.002
T-Chol, mg/dl	195 ± 37	194 ± 37	198 ± 38	0.34
LDL-Chol, mg/dl	113 ± 31	113 ± 30	113 ± 32	0.99
HDL-Chol, mg/dl	50 ± 13	48 ± 12	55 ± 13	<0.001
BNP, pg/ml	36.4 ± 78.8	33.3 ± 52.0	44.8 ± 125.2	0.22

Definition of abbreviations: REM = rapid-eye-movement; AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; TST = total sleep time; PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; VC = vital capacity; FVC = forced vital capacity;

$FEV_{1.0}$ = forced expiratory volume in 1 second; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol = total cholesterol; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol = high density lipoprotein cholesterol; BNP = brain natriuretic peptide.

Data are expresses as mean ± SD or numbers (%). <90(TST)% means the percentage of the total sleep time with SpO_2 < 90%.

Table 3. Multiple regression analyses to reveal independently associated factors with VFA (A) and SFA (B) in men and in women

A. VFA

Men

	β	***P* Value**	**r**	**R^2 (%)**
Age, yr	0.21	< 0.001	0.11	2.3
BMI, kg/m^2	0.48	< 0.001	0.53	25.3
4%ODI, /hr	-0.02	0.79	-	-
minimum SpO_2 , %	-0.13	0.035	-0.36	4.6
A-aDO_2 , mmHg	0.19	< 0.001	0.41	7.6
HbA1c , %	0.03	0.55	-	-
HOMA-R	-0.03	0.61	-	-
TG , mg/dl	0.09	0.088	-	-
Cumulative R^2				39.8

Women

	β	***P* Value**	**r**	**R^2 (%)**
BMI, kg/m^2	0.68	< 0.001	0.80	54.5
pack years	-0.02	0.81	-	-
4%ODI, /hr	0.09	0.24	-	-
HbA1c , %	0.18	0.056	-	-
HOMA-R	-0.09	0.23	-	-
LDL-Chol, mg/dl	0.09	0.22	-	-
HDL-Chol, mg/dl	-0.06	0.39	-	-
Cumulative R^2				54.5

B. SFA

Men

	β	*P* Value	r	R^2 (%)
Age, yr	-0.13	< 0.001	-0.36	4.8
BMI, kg/m^2	0.78	< 0.001	0.81	63.6
4%ODI, /hr	-0.05	0.25	-	-
minimum SpO_2 , %	0.04	0.33	-	-
A-aDO_2 , mmHg	-0.02	0.59	-	-
HbA1c , %	-0.02	0.64	-	-
HOMA-R	0.11	0.004	0.41	4.7
TG , mg/dl	-0.04	0.35	-	-
Cumulative R^2				73.1

Women

	β	*P* Value	r	R^2 (%)
BMI, kg/m^2	0.92	< 0.001	0.88	80.6
pack years	-0.08	0.17	-	-
4%ODI, /hr	-0.08	0.20	-	-
HbA1c , %	0.01	0.86	-	-
HOMA-R	0.005	0.94	-	-
LDL-Chol, mg/dl	0.03	0.58	-	-
HDL-Chol, mg/dl	0.008	0.89	-	-
Cumulative R^2				80.6

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; BMI = body mass index; ODI = oxygen desaturation index; SpO_2 = arterial oxygen saturation; A-aDO_2 = alveolar-arterial oxygen pressure difference; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol= high density lipoprotein cholesterol.

β means standard regression coefficient, r means correlation coefficient, and R^2 means contribution rate.

Table 4. Multiple regression analyses to reveal independently associated factors with VFA (A) and SFA (B) in men and in women with OSA and in control groups

A. VFA

Male OSA Group

	β	***P* Value**	**r**	**R^2 (%)**
BMI, kg/m^2	0.42	< 0.001	0.54	22.4
4%ODI, /hr	-0.004	0.95	-	-
minimum SpO_2, %	-0.17	0.01	-0.35	6.1
A-aDO_2, mmHg	0.23	< 0.001	0.37	8.5
HbA1c, %	0.04	0.52	-	-
HOMA-R	-0.03	0.60	-	-
Cumulative R^2				36.9

Male Control Group

	β	***P* Value**	**r**	**R^2 (%)**
BMI, kg/m^2	0.28	0.11	-	-
minimum SpO_2, %	-0.001	0.99	-	-
mean SpO_2, %	-0.07	0.59	-	-
HOMA-R	0.09	0.58	-	-
TG, mg/dl	0.20	0.16	-	-
HDL-Chol, mg/dl	-0.07	0.62	-	-
Cumulative R^2				-

Female OSA Group

	β	***P* Value**	**r**	**R^2 (%)**
Age, yr	-0.04	0.70	-	-
BMI, kg/m^2	0.79	< 0.001	0.84	65.7
Pack years	-0.09	0.41	-	-
4%ODI, /hr	0.14	0.16	-	-
HbA1c, %	0.08	0.57	-	-
HOMA-R	-0.04	0.68	-	-
Cumulative R^2				65.7

Female Control Group

	β	*P* Value	r	R^2 (%)
BMI, kg/m^2	0.46	< 0.001	0.72	32.8
mean SpO_2, %	-0.13	0.28	-	-
HbA1c	0.23	0.035	0.42	9.7
LDL-Chol, mg/dl	0.28	0.012	0.38	10.7
HDL-Chol, mg/dl	-0.17	0.12	-	-
Cumulative R^2				53.2

B. SFA

Male OSA Group

	β	*P* Value	r	R^2 (%)
BMI, kg/m^2	0.81	< 0.001	0.80	65.0
4%ODI, %	0.01	0.85	-	-
minimum SpO_2, %	0.06	0.18	-	-
A-aDO_2, mmHg	-0.07	0.13	-	-
HbA1c, %	-0.05	0.24	-	-
HOMA-R	0.12	0.009	0.38	4.7
Cumulative R^2				69.7

Male Control Group

	β	*P* Value	r	R^2 (%)
BMI, kg/m^2	0.74	< 0.001	0.87	64.4
minimum SpO_2, %	-0.09	0.23	-	-
mean SpO_2, %	-0.05	0.51	-	-
HOMA-R	0.16	0.055	-	-
TG, mg/dl	-0.12	0.088	-	-
HDL-Chol, mg/dl	-0.05	0.46	-	-
Cumulative R^2				64.4

Female OSA Group

	β	***P* Value**	**r**	**R^2 (%)**
Age, yr	-0.07	0.34	-	-
BMI, kg/m^2	0.97	< 0.001	0.89	86.0
Pack years	-0.15	0.094	-	-
4%ODI, /hr	0.07	0.38	-	-
HbA1c, %	-0.11	0.33	-	-
HOMA-R	-0.01	0.91	-	-
Cumulative R^2				86.0

Female Control Group

	β	***P* Value**	**r**	**R^2 (%)**
BMI, kg/m^2	0.80	< 0.001	0.89	71.5
mean SpO_2, %	-0.06	0.46	-	-
HbA1c, %	0.11	0.15	-	-
LDL-Chol, mg/dl	0.16	0.032	0.39	6.4
HDL-Chol, mg/dl	0.05	0.52	-	-
Cumulative R^2				78.0

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; OSA = obstructive sleep apnea; BMI = body mass index; ODI = oxygen desaturation index; SpO_2 = arterial oxygen saturation; A-aDO_2 = alveolar-arterial oxygen pressure difference; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol= high density lipoprotein cholesterol.

β means standard regression coefficient, r means correlation coefficient, and R^2 means contribution rate.

Table 5. Multiple regression analyses to reveal factors independently associated with AHI in men (A) and in women (B)

A. Men

	β	*P* Value	r	R^2 (%)
VFA, cm^2	0.15	0.039	0.28	4.1
SFA, cm^2	0.07	0.32	-	-
A-aDO_2, mmHg	0.10	0.12	-	-
HbA1c, %	0.12	0.059	-	-
HOMA-R	0.05	0.42	-	-
TG, mg/dl	0.04	0.55	-	-
T-chol, mg/dl	0.10	0.13	-	-
Cumulative R^2				4.1

B. Women

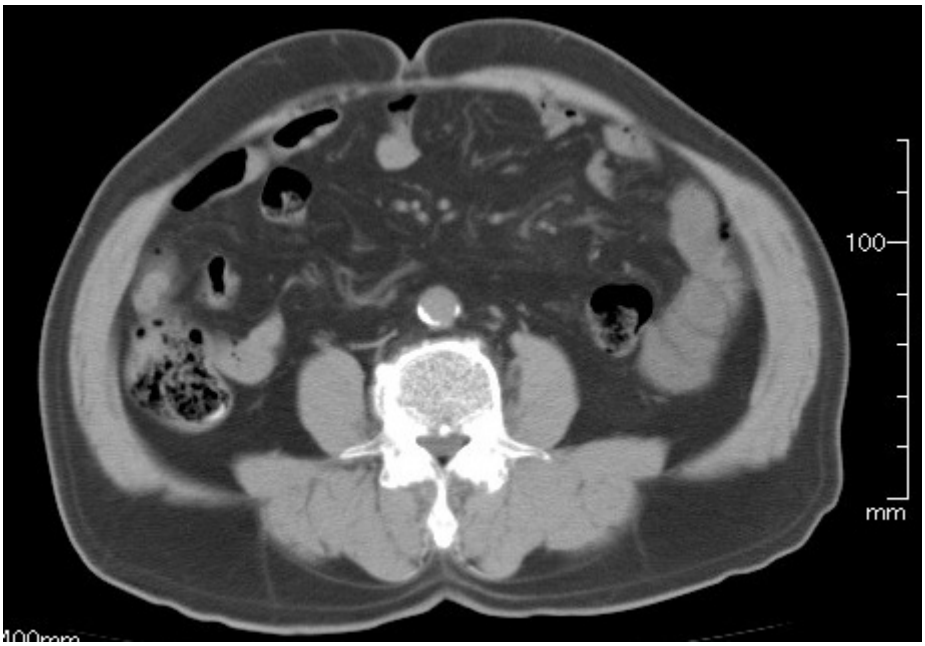
	β	*P* Value	r	R^2 (%)
Age, yr	0.30	0.007	0.22	6.8
Pack years	0.02	0.82	-	-
VFA, cm^2	0.20	0.16	-	-
SFA, cm^2	0.03	0.82	-	-
A-aDO_2, mmHg	0.03	0.75	-	-
$PaCO_2$, mmHg	0.29	0.007	0.33	9.3
%FVC, %	-0.13	0.24	-	-
HbA1c, %	0.11	0.43	-	-
HOMA-R	0.12	0.26	-	-
Cumulative R^2				16.1

Definition of abbreviations: AHI = apnea-hypopnea index; VFA = visceral fat area; SFA = subcutaneous fat area; A-aDO_2 = alveolar-arterial oxygen pressure difference; $PaCO_2$ = arterial carbon dioxide pressure; FVC = forced vital capacity; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol

=total cholesterol. β means standard regression coefficient, r means correlation coefficient, and R^2 means contribution rate.

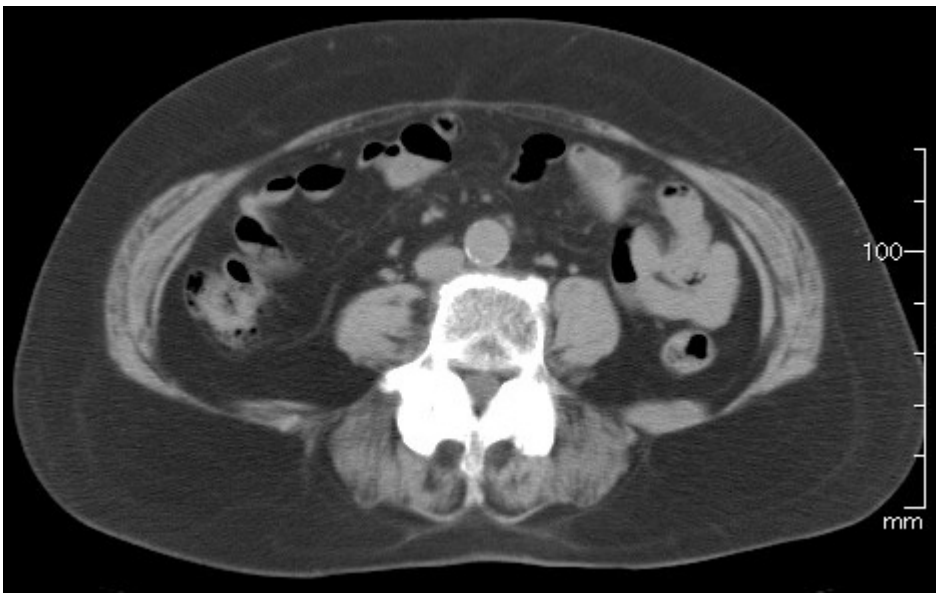
Figure 1.

A A male participant



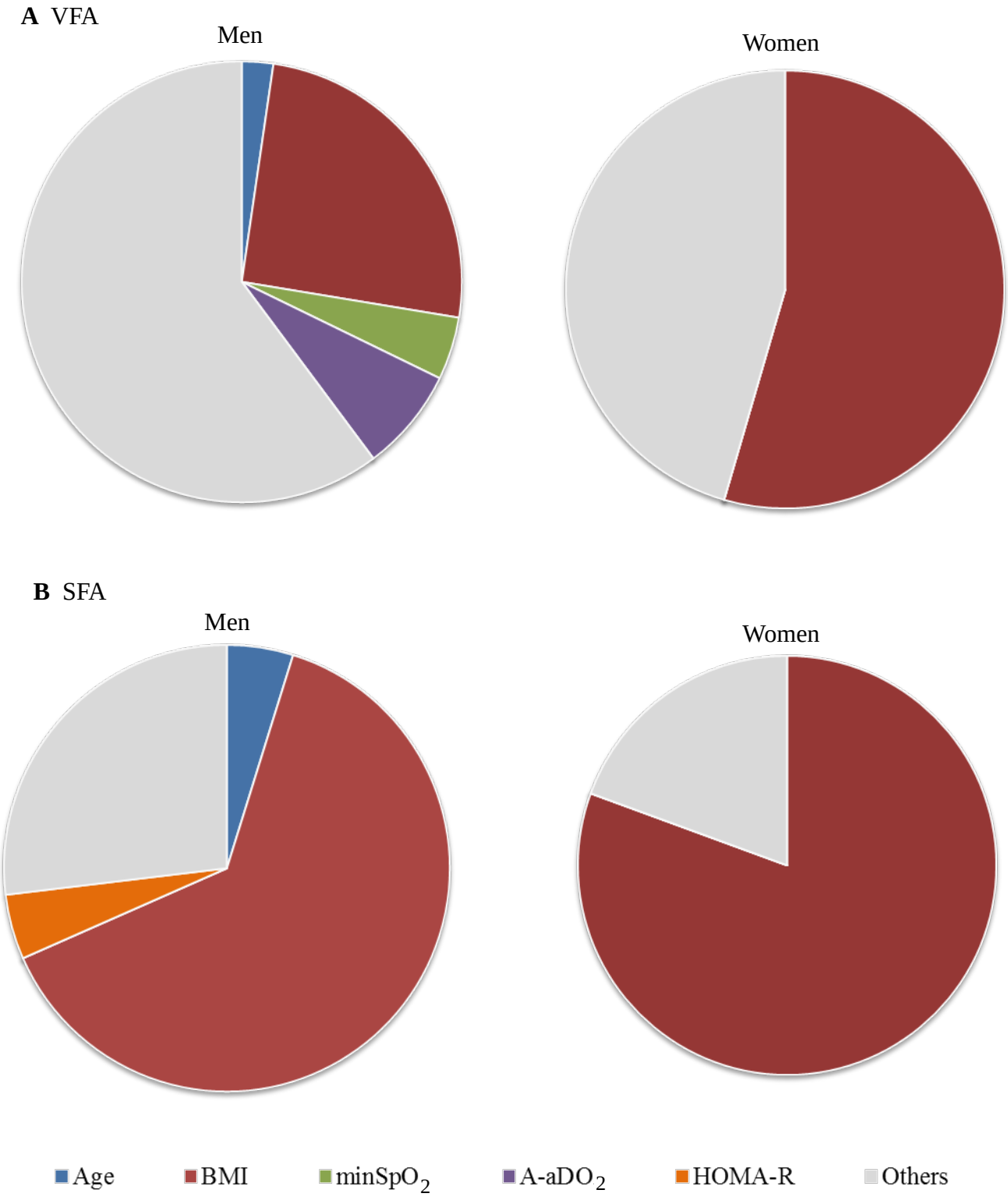
BMI 27.2 kg/m^2, VFA 179.5 cm^2, SFA 139.9 cm^2

B A female participant



BMI 27.2 kg/m^2, VFA 107.0 cm^2, SFA 264.3 cm^2

Figure 2.


A VFA
Men
Women
B SFA
Men
Women
Age
BMI
minSpO2
A-aDO2
HOMA-R
Others

Data Supplement

Differences in Associations between Visceral Fat Accumulation and Obstructive Sleep Apnea by Sex

Yuka Harada[1], Toru Oga[2], Yuichi Chihara[1], Masanori Azuma[1], Kimihiko Murase[1], Yoshiro Toyama[1], Kensaku Aihara[1], Kiminobu Tanizawa[2], Chikara Yoshimura[2], Takefumi Hitomi[2], Tomohiro Handa[1], Tomomasa Tsuboi[3], Michiaki Mishima[1], and Kazuo Chin[2]

Table E1. Univariate analyses of relationships between variables and VFA or SFA in men and in women

Variables	Men (n = 271)			Women (n = 100)		
	VFA	**r**	***P* Value**	**VFA**	**r**	***P* Value**
	SFA	**r**	***P* Value**	**SFA**	**r**	***P* Value**
Age, yr	0.10		0.092	-0.14		0.18
	-0.36		< 0.001	-0.38		< 0.001
BMI, kg/m^2	0.53		< 0.001	0.78		< 0.001
	0.82		< 0.001	0.87		<0.001
Waist circumference, cm	0.60		< 0.001	0.76		< 0.001
	0.72		< 0.001	0.84		< 0.001
pack years	0.21		< 0.001	0.32		0.001
	-0.06		0.30	0.24		0.019
Slow wave sleep stage, %	-0.05		0.47	0.079		0.44
	0.01		0.84	0.16		0.12
REM stage, %	-0.14		0.023	-0.080		0.44
	0.02		0.71	0.092		0.37
AHI, /hr	0.27		< 0.001	0.34		< 0.001
	0.19		0.002	0.21		0.042
Arousal index, /hr	0.22		< 0.001	0.18		0.086
	0.07		0.25	0.04		0.67
minimum SpO_2, %	-0.35		< 0.001	-0.13		0.21
	-0.21		< 0.001	-0.06		0.53
mean SpO_2, %	-0.33		< 0.001	-0.32		0.001
	-0.28		< 0.001	-0.26		0.009
4% ODI, /hr	0.31		< 0.001	0.37		< 0.001
	0.22		< 0.001	0.25		0.015
<90(TST)%, %	0.32		< 0.001	0.23		0.022
	0.23		< 0.001	0.12		0.24
PaO_2, mmHg	-0.32		< 0.001	-0.11		0.30
	-0.16		0.010	-0.12		0.23
$PaCO_2$, mmHg	-0.20		< 0.001	-0.03		0.79
	-0.03		0.58	0.03		0.78
A-aDO_2, mmHg	0.39		< 0.001	0.13		0.20
	0.17		0.007	0.12		0.24
Glucose, mg/dl	0.19		0.002	0.37		< 0.001

HbA1c, %	0.12	0.054	0.24	0.021
	0.23	< 0.001	0.52	< 0.001
	0.14	0.029	0.37	< 0.001
Insulin, μU/ml	0.23	< 0.001	0.29	0.004
	0.45	< 0.001	0.36	< 0.001
HOMA-R	0.24	< 0.001	0.25	0.015
	0.41	< 0.001	0.27	0.009
TG, mg/dl	0.24	< 0.001	0.33	0.001
	0.14	0.023	0.14	0.18
T-Chol, mg/dl	0.08	0.23	0.04	0.74
	0.004	0.95	0.08	0.43
LDL-Chol, mg/dl	0.03	0.67	0.24	0.022
	0.07	0.29	0.27	0.009
HDL-Chol, mg/dl	-0.10	0.13	-0.23	0.028
	-0.21	< 0.001	-0.19	0.072
BNP, pg/ ml	0.03	0.68	-0.01	0.93
	0.05	0.46	-0.15	0.13

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; BMI = body mass index; REM = rapid eye movement; AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; TST = total sleep time; PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol = total cholesterol; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol = high density lipoprotein cholesterol; BNP = brain natriuretic peptide.

r means correlation coefficient. <90(TST)% means the percentage of the total sleep time with SpO_2 < 90%.

Table E2. Correlation coefficients among variables significantly associated with VFA and SFA in men

	Age	BMI	WC	AHI	minSpO_2	meanSpO_2	4%ODI	<90(TST)%	PaO_2	$AaDO_2$	Glu	HbA1c	insulin	HOMA-R	TG
Age	-	-0.27	-0.14	0.06.	-0.03	-0.04	0.05	0.05	-0.11	0.20	0.04	0.02	-0.10	-0.06	-0.10
BMI	-	-	0.81	0.34	-0.37	-0.41	0.37	0.38	-0.29	0.29	0.22	0.23	0.41	0.40	0.23
WC	-	-	-	0.23	-0.35	-0.31	0.26	0.28	-0.24	0.27	0.18	0.20	0.33	0.33	0.18
AHI	-	-	-	-	-0.55	-0.74	0.97	0.94	-0.24	0.22	0.17	0.24	0.15	0.16	0.20
minSpO_2	-	-	-	-	-	0.55	-0.58	-0.57	0.22	-0.20	-0.13	-0.16	-0.13	-0.15	-0.19
meanSpO_2	-	-	-	-	-	-	-0.80	-0.81	0.38	-0.34	-0.17	-0.24	-0.20	-0.23	-0.24
4%ODI	-	-	-	-	-	-	-	0.97	-0.27	0.25	0.16	0.24	0.18	0.19	0.23
<90(TST)%	-	-	-	-	-	-	-	-	-0.27	0.25	0.12	0.22	0.16	0.16	0.18
PaO_2	-	-	-	-	-	-	-	-	-	-0.92	-0.18	-0.24	-0.25	-0.28	-0.18
A-aDO_2	-	-	-	-	-	-	-	-	-	-	0.21	0.25	0.26	0.29	0.18
Glu	-	-	-	-	-	-	-	-	-	-	-	0.71	0.09	0.28	0.30
HbA1c	-	-	-	-	-	-	-	-	-	-	-	-	0.05	0.17	0.34
Insulin	-	-	-	-	-	-	-	-	-	-	-	-	-	0.96	0.09
HOMA-R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.13
TG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; BMI = body mass index; WC = waist circumference; AHI = apnea-hypopnea index; min SpO_2 = minimum arterial oxygen saturation; ODI = oxygen desaturation index; TST = total sleep time; PaO_2 = arterial oxygen pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; Glu = glucose; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride.

<90 (TST)% means the percentage of the total sleep time with SpO_2 < 90%.

Table E3. Correlation coefficients among variables significantly associated with VFA and SFA in women

	BMI	WC	Pack years	AHI	meanSpO_2	4%ODI	Glucose	HbA1c	insulin	HOMA-R	LDL	HDL
BMI	-	0.91	0.37	0.28	-0.34	0.31	0.35	0.48	0.39	0.31	0.26	-0.24
WC	-	-	0.41	0.26	-.040	0.30	0.38	0.50	0.37	0.31	0.24	-0.28
Pack years	-	-	-	0.29	-0.53	0.35	0.34	0.50	0.12	0.13	0.08	-0.15
AHI	-	-	-	-	-0.72	0.97	0.26	0.43	0.11	0.19	0.03	-0.03
meanSpO_2	-	-	-	-	-	-0.79	-0.31	-0.55	-0.14	-0.20	-0.03	0.27
4%ODI	-	-	-	-	-	-	0.31	0.51	0.14	0.22	0.02	-0.07
Glucose	-	-	-	-	-	-	-	0.80	0.51	0.72	0.15	-0.25
HbA1c	-	-	-	-	-	-	-	-	0.35	0.46	0.03	-0.23
Insulin	-	-	-	-	-	-	-	-	-	0.92	0.25	-0.29
HOMA-R	-	-	-	-	-	-	-	-	-	-	0.26	-0.29
LDL	-	-	-	-	-	-	-	-	-	-	-	0.08
HDL	-	-	-	-	-	-	-	-	-	-	-	-

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; BMI = body mass index; WC = waist circumference; AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; LDL = low density lipoprotein cholesterol; HDL = high density lipoprotein cholesterol.

Table E4. Univariate analyses of relationships between variables and VFA or SFA in the male OSA group and in the female OSA group

Variables	Male OSA Group (n = 206)			Female OSA Group (n = 54)		
	VFA	**r**	***P* Value**	**VFA**	**r**	***P* Value**
	SFA	**r**	***P* Value**	**SFA**	**r**	***P* Value**
Age, yr		0.07	0.32		-0.38	0.004
		-0.38	< 0.001		-0.46	< 0.001
BMI, kg/m^2		0.54	< 0.001		0.81	< 0.001
		0.81	< 0.001		0.89	<0.001
Waist circumference, cm		0.59	< 0.001		0.77	< 0.01
		0.69	< 0.001		0.86	< 0.001
pack years		0.18	0.010		0.36	0.006
		-0.05	0.46		0.28	0.043
Slow wave sleep stage, %		-0.005	0.95		0.14	0.32
		0.03	0.64		0.32	0.018
REM stage, %		-0.11	0.12		-0.14	0.33
		0.07	0.30		0.10	0.48
AHI, /hr		0.26	< 0.001		0.37	0.005
		0.30	0.002		0.25	0.070
Arousal index, /hr		0.20	0.005		0.21	0.12
		0.13	0.075		0.05	0.72
minimum SpO_2, %		-0.35	< 0.001		-0.20	0.15
		-0.21	0.003		-0.11	0.44
mean SpO_2, %		-0.32	< 0.001		-0.29	0.033
		-0.32	< 0.001		-0.23	0.096
4% ODI, /hr		0.30	< 0.001		0.42	0.002
		0.31	< 0.001		0.32	0.019
<90(TST)%, %		0.31	< 0.001		0.22	0.11
		0.32	< 0.001		0.12	0.38
PaO_2, mmHg		-0.29	< 0.001		-0.06	0.66
		-0.17	0.017		-0.12	0.39
$PaCO_2$, mmHg		-0.17	0.013		-0.13	0.35
		-0.007	0.92		0.07	0.64
A-aDO_2, mmHg		0.36	< 0.001		0.15	0.29
		0.16	0.021		0.10	0.48
Glucose, mg/dl		0.17	0.016		0.37	0.008

	0.12	0.081	0.27	0.062
HbA1c, %	0.20	0.005	0.54	< 0.001
	0.13	0.068	0.40	0.004
Insulin, μU/ml	0.20	0.005	0.33	0.018
	0.40	< 0.001	0.34	0.017
HOMA-R	0.22	0.002	0.26	0.072
	0.38	< 0.001	0.25	0.084
TG, mg/dl	0.21	0.003	0.29	0.038
	0.12	0.10	0.08	0.58
T-Chol, mg/dl	0.09	0.19	-0.09	0.56
	0.01	0.89	0.009	0.95
LDL-Chol, mg/dl	0.04	0.58	0.14	0.34
	0.04	0.61	0.17	0.24
HDL-Chol, mg/dl	-0.03	0.69	-0.15	0.29
	-0.11	0.12	-0.13	0.37
BNP, pg/ ml	-0.04	0.56	-0.12	0.40
	-0.003	0.97	0.001	0.99

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; OSA = obstructive sleep apnea; BMI = body mass index; REM = rapid eye movement; AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; TST = total sleep time; PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol = total cholesterol; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol = high density lipoprotein cholesterol; BNP = brain natriuretic peptide.

r means correlation coefficient. <90(TST)% means the percentage of the total sleep time with SpO_2 < 90%.

Table E5. Univariate analyses of relationships between variables and VFA or SFA in the male control group and in the female control group

Variables	Male Control Group (n = 65)		Female Control Group (n = 46)	
	VFA r	***P* Value**	**VFA r**	***P* Value**
	SFA r	***P* Value**	**SFA r**	***P* Value**
Age, yr	0.07	0.57	-0.05	0.75
	-0.36	0.003	-0.42	0.004
BMI, kg/m^2	0.49	< 0.001	0.69	< 0.001
	0.89	< 0.001	0.87	<0.001
Waist circumference, cm	0.61	< 0.001	0.72	< 0.001
	0.85	< 0.001	0.84	< 0.001
pack years	0.24	0.054	0.23	0.14
	-0.10	0.44	0.18	0025
Slow wave sleep stage, %	-0.14	0.28	-0.08	0.61
	-0.04	0.79	-0.08	0.63
REM stage, %	-0.18	0.15	0.12	0.46
	-0.11	0.40	0.11	0.46
AHI, /hr	0.17	0.17	-0.003	0.98
	-0.06	0.64	0.43	0.003
Arousal index, /hr	0.07	0.59	-0.25	0.096
	-0.12	0.33	-0.05	0.77
minimum SpO_2, %	-0.22	0.086	0.10	0.53
	-0.52	< 0.001	0.01	0.95
mean SpO_2, %	-0.22	0.078	-0.32	0.032
	-0.27	0.029	-0.47	0.001
4% ODI, /hr	0.35	0.005	0.02	0.91
	0.05	0.70	0.28	0.061
<90(TST)%, %	0.24	0.060	0.13	0.42
	0.05	0.71	0.30	0.046
PaO_2, mmHg	-0.38	0.002	-0.15	0.34
	-0.15	0.27	-0.12	0.45
$PaCO_2$, mmHg	-0.39	0.002	0.14	0.36
	-0.11	0.39	-0.06	0.73
A-aDO_2, mmHg	0.52	< 0.001	0.10	0.53
	0.19	0.15	0.14	0.37
Glucose, mg/dl	0.23	0.067	0.32	0.034

	0.12	0.36	0.22	0.16
HbA1c, %	0.36	0.004	0.42	0.005
	0.15	0.25	0.35	0.022
Insulin, μU/ml	0.36	0.004	0.24	0.12
	0.74	< 0.001	0.39	0.009
HOMA-R	0.38	0.002	0.22	0.16
	0.69	< 0.001	0.35	0.021
TG, mg/dl	0.38	0.002	0.42	0.005
	0.26	0.038	0.20	0.20
T-Chol, mg/dl	-0.05	0.70	0.28	0.073
	-0.02	0.90	0.19	0.23
LDL-Chol, mg/dl	-0.01	0.93	0.38	0.011
	0.15	0.24	0.39	0.009
HDL-Chol, mg/dl	-0.32	0.011	-0.38	0.011
	-0.41	< 0.001	-0.26	0.099
BNP, pg/ ml	0.25	0.046	0.06	0.69
	0.19	0.14	-0.22	0.16

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; BMI = body mass index; REM = rapid eye movement; AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; TST = total sleep time; PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol = total cholesterol; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol = high density lipoprotein cholesterol; BNP = brain natriuretic peptide.

r means correlation coefficient. <90(TST)% means the percentage of the total sleep time with SpO_2 < 90%.

Table E6. Correlation coefficients among variables significantly associated with VFA and SFA in the male OSA group (A) and in the male control group (B)

A. Male OSA Group

	BMI	WC	AHI	arousal	minimumSpO_2	meanSpO_2	4%ODI	<90(TST)%	PaO_2	$AaDO_2$	Glucose	HbA1c	insulin	HOMA-R
BMI	-	0.79	0.38	0.21	-0.34	-0.44	0.42	0.43	-0.31	0.30	0.23	0.22	0.36	0.37
WC	-		0.22	0.010	-0.31	-0.28	0.25	0.27	-0.23	0.25	0.17	0.17	0.28	0.29
AHI	-	-	-	0.70	-0.40	-0.73	0.96	0.92	-0.28	0.26	0.15	0.26	0.16	0.16
arousal	-	-	-	-	-0.29	-0.53	0.69	0.68	-0.19	0.17	0.12	0.16	0.14	0.14
minimumSpO_2	-	-	-	-	-	0.47	-0.45	-0.44	0.21	-0.19	-0.10	-0.13	-0.11	-0.12
meanSpO_2	-	-	-	-	-	-	-0.79	-0.81	0.39	-0.34	-0.15	-0.23	-0.21	-0.22
4%ODI	-	-	-		-	-	-	0.95	-0.32	0.28	0.14	0.26	0.19	0.19
<90(TST)%	-	-	-		-	-	-	-	-0.32	0.29	0.08	0.23	0.17	0.17
PaO_2	-	-	-		-	-	-	-	-	-0.91	-0.18	-0.22	-0.27	-0.29
A-aDO_2	-	-	-		-	-	-	-	-	-	0.19	0.21	0.27	0.30
Glucose	-	-	-		-	-	-	-	-	-	-	0.75	0.08	0.27
HbA1c	-	-	-		-	-	-	-	-	-	-	-	0.05	0.18
Insulin	-	-	-		-	-	-	-	-	-	-	-	-	0.96
HOMA-R	-	-	-		-	-	-	-	-	-	-	-	-	-

B. Male Control Group

	BMI	WC	minimum SpO_2	meanSpO_2	insulin	HOMA-R	TG	HDL-Chol
BMI	-	0.90	-0.47	-0.21	0.62	0.53	0.42	-0.38
WC	-	-	-0.49	-0.34	0.55	0.50	0.46	-0.43
minimum SpO_2	-	-	-	0.36	-0.32	-0.27	-0.06	0.17
meanSpO_2	-	-	-	-	-0.17	-0.17	-0.24	0.32
Insulin	-	-	-	-	-	0.96	0.25	-0.11
HOMA-R	-	-	-	-	-	-	0.23	-0.06
TG	-	-	-	-	-	-	-	-0.45
HDL-Chol	-	-	-	-	-	-	-	-

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; OSA = obstructive sleep apnea; BMI = body mass index; WC = waist circumference; AHI =

apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; TST = total sleep time; PaO_2 = arterial oxygen pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; HDL-Chol = high density lipoprotein cholesterol. Arousal means arousal index, and <90 (TST)% means the percentage of the total sleep time with SpO_2 < 90%.

Table E7. Correlation coefficients among variables significantly associated with VFA and SFA in the female OSA group (A) and in the female control group (B)

A. Female OSA Group

	Age	BMI	Waist circumference	Pack years	AHI	meanSpO$_2$	4%ODI	Glucose	HbA1c	insulin	HOMA-R
Age	-	-0.37	-0.34	-0.11	0.01	0.16	-0.09	-0.31	-0.26	-0.31	-0.32
BMI	-	-	0.91	0.45	0.26	-0.30	0.32	0.39	0.56	0.38	0.29
Waist circumference		-	-	0.46	0.23	-0.35	0.29	0.43	0.57	0.34	0.28
Pack years		-	-	-	0.38	-0.59	0.45	0.40	0.63	0.06	0.11
AHI		-	-	-	-	-0.68	0.96	0.28	0.49	0.17	0.20
meanSpO$_2$		-	-	-	-	-	-0.77	-0.29	-0.59	-0.15	-0.18
4%ODI		-	-	-	-	-	-	0.34	0.59	0.22	0.24
Glucose		-	-	-	-	-	-	-	0.77	0.61	0.79
HbA1c		-	-	-	-	-	-	-	-	0.36	0.44
Insulin		-	-	-	-	-	-	-	-	-	0.93
HOMA-R		-	-	-	-	-	-	-	-	-	-

B. Female Control Group

	BMI	Waist circumference	meanSpO$_2$	HbA1c	LDL-Chol	HDL-Chol
BMI	-	0.91	-0.43	0.29	0.30	-0.37
Waist circumference	-		-0.53	0.30	0.30	-0.44
meanSpO$_2$	-	-	-	-0.36	0.07	0.31
HbA1c	-	-	-	-	-0.04	-0.13
LDL	-	-	-	-		0.05
HDL	-	-	-	-	-	-

Definition of abbreviations: VFA = visceral fat area; SFA = subcutaneous fat area; OSA = obstructive sleep apnea; BMI = body mass index; AHI = apnea-hypopnea index; SpO_2 = arterial oxygen saturation; ODI = oxygen desaturation index; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol = high density lipoprotein cholesterol.

Table E8. Univariate analyses of relationships between variables and AHI in men and in women

Variables	Men (n = 271)		Women (n = 100)	
	r	***P* Value**	**r**	***P* Value**
Age, yr	0.06	0.30	0.20	0.049
BMI, kg/m^2	0.33	< 0.001	0.34	< 0.001
Waist circumference, cm	0.23	< 0.001	0.29	0.004
pack years	0.08	0.19	0.29	0.003
VFA, cm^2	0.28	< 0.001	0.34	< 0.001
SFA, cm^2	0.19	0.002	0.21	0.036
PaO_2, mmHg	-0.24	< 0.001	-0.29	0.004
$PaCO_2$, mmHg	0.02	0.71	0.28	0.006
A-aDO_2, mmHg	0.23	< 0.001	0.17	0.088
%VC, %	-0.04	0.54	-0.28	0.005
%FVC, %	-0.06	0.38	-029	0.005
$FEV_{1.0}$%, %	0.06	0.33	0.06	0.54
Glucose, mg/dl	0.17	0.005	0.25	0.015
HbA1c, %	0.23	< 0.001	0.43	< 0.001
Insulin, μU/ml	0.15	0.018	0.11	0.31
HOMA-R	0.16	0.008	0.19	0.071
TG, mg/dl	0.19	0.002	-0.03	0.75
T-Chol, mg/dl	0.14	0.021	-0.06	0.58
LDL-Chol, mg/dl	0.06	0.35	0.04	0.74
HDL-Chol, mg/dl	-0.09	0.14	-0.03	0.77
BNP, pg/ ml	0.02	0.76	-0.11	0.29

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; VFA = visceral fat area; SFA: = subcutaneous fat area; PaO_2 = arterial oxygen pressure; $PaCO_2$ =

arterial carbon dioxide pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; VC = vital capacity; FVC = forced vital capacity; $FEV_{1.0}$ = forced expiratory volume in 1 second; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol = total cholesterol; LDL-Chol = low density lipoprotein cholesterol; HDL-Chol = high density lipoprotein cholesterol; BNP = brain natriuretic peptide. r means correlation coefficient.

Table E9. Correlation coefficients among variables significantly associated with AHI in men (A) and in women (B)

A. Men

	BMI	WC	VFA	SFA	PaO_2	$AaDO_2$	Glucose	HbA1c	insulin	HOMA-R	TG	T-Chol
BMI	-	0.81	0.54	0.82	-0.29	0.29	0.22	0.22	0.42	0.4	0.23	0.08
WC	-	-	0.60	0.71	-0.24	0.27	0.18	0.20	0.34	0.34	0.17	0.08
VFA	-	-	-	0.42	-0.33	0.41	0.19	0.23	0.22	0.24	0.24	0.07
SFA	-	-	-	-	-0.17	0.18	0.12	0.14	0.45	0.41	0.14	0.005
PaO_2	-	-	-	-	-	-0.91	-0.18	-0.25	-0.24	-0.26	-0.19	-0.09
$A\text{-}aDO_2$	-	-	-	-	-	-	0.20	0.25	0.24	0.28	0.19	0.02
Glucose	-	-	-	-	-	-	-	0.72	0.09	0.28	0.30	0.11
HbA1c	-	-	-	-	-	-	-	-	0.06	0.19	0.34	0.07
Insulin	-	-	-	-	-	-	-	-	-	0.96	0.10	0.04
HOMA-R	-	-	-	-	-	-	-	-	-	-	0.14	0.06
TG	-	-	-	-	-	-	-	-	-	-	-	0.43
T-Chol	-	-	-	-	-	-	-	-	-	-	-	-

B. Women

	Age	BMI	WC	Pack years	VFA	SFA	PaO_2	$PaCO_2$	$A\text{-}aDO_2$	%VC	%FVC	Glucose	HbA1c	HOMA-R
Age	-	-0.39	-0.31	0.01	-0.18	-0.46	-0.10	-0.05	0.14	-0.11	-0.14	-0.13	-0.08	-0.25
BMI	-		0.91	0.35	0.79	0.88	-0.21	0.14	0.16	-0.18	-0.18	0.34	0.47	0.30
WC	-	-	-	0.39	0.75	0.85	-0.15	0.17	0.08	-0.24	-0.25	0.37	0.48	0.31
Pack years	-	-	-	-	0.34	0.22	-0.25	0.30	0.13	-0.17	-0.18	0.33	0.50	0.12
VFA	-	-	-	-	-	0.66	-0.15	0.003	0.16	-0.30	-0.30	0.38	0.50	0.25
SFA	-	-	-	-	-	-	-0.12	0.06	0.10	-0.07	-0.07	0.22	0.35	0.26
PaO_2	-	-	-	-	-	-	-	-0.41	-0.89	0.19	0.20	-0.23	-0.24	-0.10
$PaCO_2$	-	-	-	-	-	-	-	-	-0.06	-0.08	-0.03	0.16	0.34	0.02
$A\text{-}aDO_2$	-	-	-	-	-	-	-	-	-	-.0.16	-0.21	0.17	0.20	0.10
%VC	-	-	-	-	-	-	-	-	-	-	0.96	-0.23	-0.40	-0.03
%FVC	-	-	-	-	-	-	-	-	-	-	-	-0.25	-0.40	-0.03
Glucose	-	-	-	-	-	-	-	-	-	-	-	-	0.80	0.72
HbA1c	-	-	-	-	-	-	-	-	-	-	-	-	-	0.46
HOMA-R	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; WC = waist circumference; VFA = visceral fat area; SFA: = subcutaneous fat area; PaO_2 = arterial oxygen pressure; $PaCO_2$ = arterial carbon dioxide pressure; A-aDO_2 = alveolar-arterial oxygen pressure difference; VC = vital capacity; FVC = forced vital capacity; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride; T-Chol = total cholesterol.

Table E10. Multiple regression analyses to reveal independently associated factors with A-aDO_2 in men

	Model 1				Model 2			
	β	***P* Value**	**r**	**R^2 (%)**	**β**	***P* Value**	**r**	**R^2 (%)**
Age, yr	0.11	0.12	-	-	0.08	0.24	-	-
Pack years	-0.09	0.14	-	-	-0.09	0.14	-	-
BMI, kg/m^2	0.08	0.33	-	-	NA	NA	NA	NA
SFA, cm^2	NA	NA	NA	NA	-0.005	0.95	-	-
VFA, cm^2	0.20	0.008	0.41	8.5	0.24	0.001	0.41	9.9
4%ODI, %	0.13	0.074	-	-	0.14	0.049	0.26	3.6
minimum SpO_2, %	0.006	0.93	-	-	-0.001	0.99	-	-
$PaCO_2$, mmHg	-0.20	< 0.001	-0.30	6.2	-0.20	< 0.001	-0.30	6.2
%FVC, %	-0.03	0.67	-	-	-0.03	0.76	-	-
$FEV_{1.0}$%, %	-0.15	0.015	-0.19	2.9	-0.16	0.015	-0.19	2.9
HbA1c, %	0.13	0.035	0.26	3.3	0.13	0.032	0.26	3.3
HOMA-R	0.14	0.023	0.28	3.9	0.16	0.012	0.28	4.4
TG, mg/dl	0.06	0.35	-	-	0.06	0.36	-	-
Cumulative R^2				24.6				30.3

Definition of abbreviations: A-aDO_2 = alveolar-arterial oxygen pressure difference; BMI = body mass index; SFA = subcutaneous fat area; VFA = visceral fat area; ODI = oxygen desaturation index; SpO_2 = arterial oxygen saturation; $PaCO_2$ = arterial carbon dioxide pressure; FVC = forced vital capacity; $FEV_{1.0}$ = forced expiratory volume in 1 second; HbA1c = hemoglobin A1c; HOMA-R = homeostasis model assessment of insulin resistance; TG = triglyceride.

β means standard regression coefficient, r means correlation coefficient, and R^2 means contribution rate.

Data Supplement

Differences in Associations between Visceral Fat Accumulation and Obstructive Sleep Apnea by Sex

Yuka Harada[1], Toru Oga[2], Yuichi Chihara[1], Masanori Azuma[1], Kimihiko Murase[1], Yoshiro Toyama[1], Kensaku Aihara[1], Kiminobu Tanizawa[2], Chikara Yoshimura[2], Takefumi Hitomi[2], Tomohiro Handa[1], Tomomasa Tsuboi[3], Michiaki Mishima[1], and Kazuo Chin[2]

Figure legends

Figure E1. Study flowchart

Definition of abbreviations: CT = computed tomography;

OSA = obstructive sleep apnea

Figure E2. Relationships between AHI and VFA in men (A), in women (B), and in the whole (both men and women) (C).

Definition of abbreviations: AHI = apnea-hypopnea index;

VFA = visceral fat area.

r means correlation coefficient.

Figure E1.

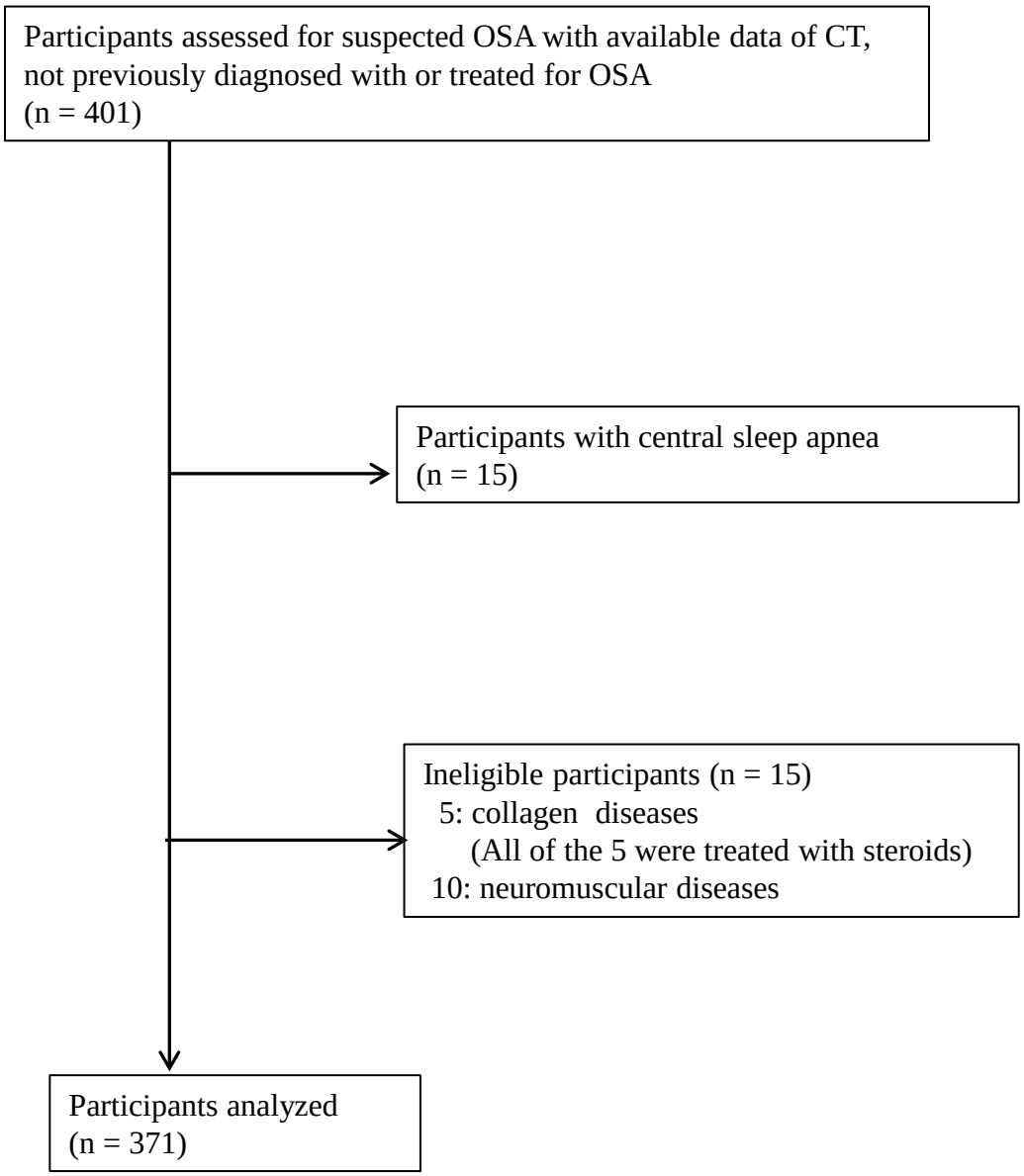
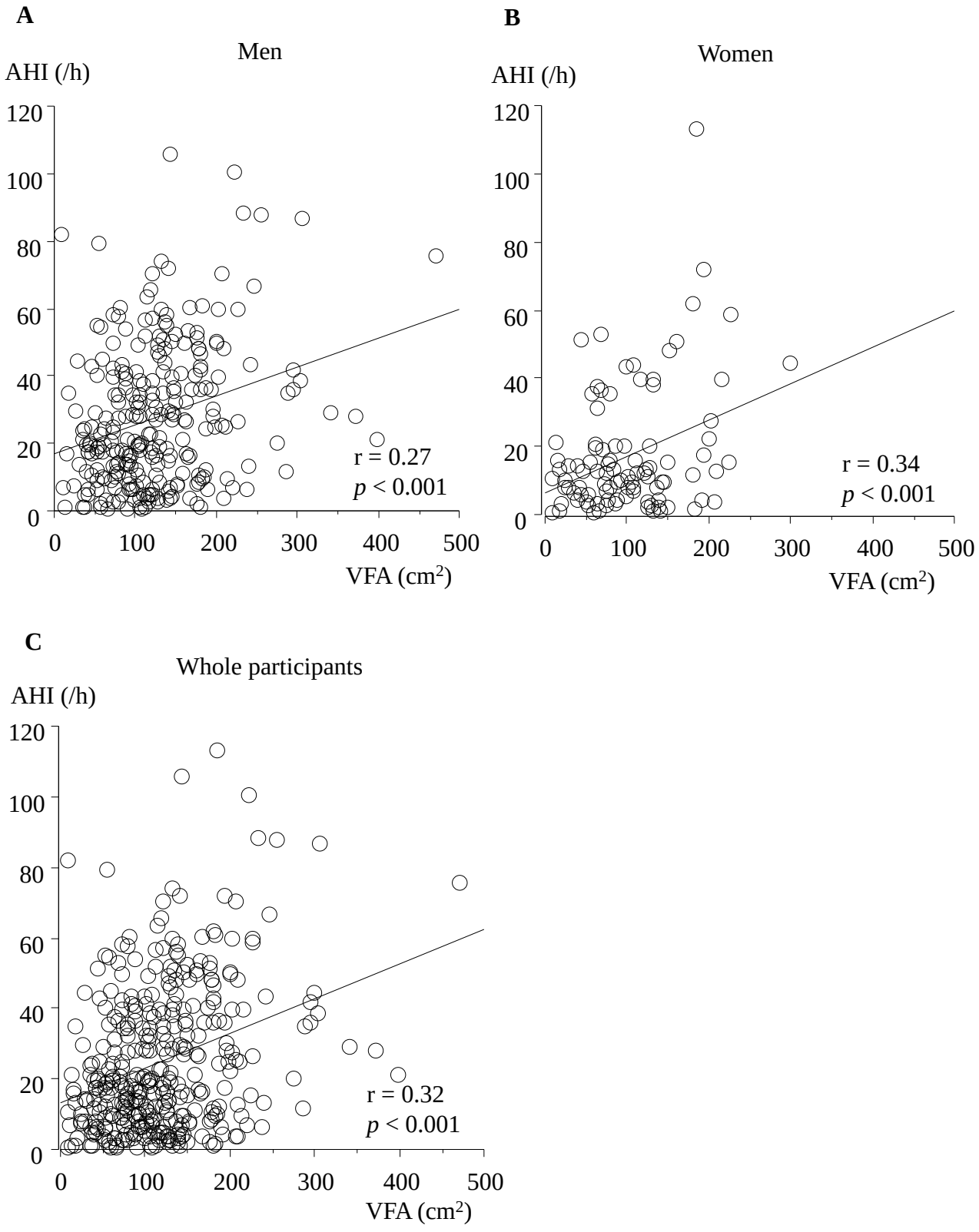

Participants assessed for suspected OSA with available data of CT, not previously diagnosed with or treated for OSA
(n = 401)
Participants with central sleep apnea
(n = 15)
Ineligible participants (n = 15)
5: collagen diseases
(All of the 5 were treated with steroids)
10: neuromuscular diseases
Participants analyzed
(n = 371)

Figure E2.


A
Men
AHI (/h)
120
100
80
60
40
20
0
0
100
200
300
400
500
VFA (cm²)
r = 0.27
p < 0.001
B
Women
AHI (/h)
120
100
80
60
40
20
0
0
100
200
300
400
500
VFA (cm²)
r = 0.34
p < 0.001
C
Whole participants
AHI (/h)
120
100
80
60
40
20
0
0
100
200
300
400
500
VFA (cm²)
r = 0.32
p < 0.001