厚生労働科学研究費補助金

循環器疾患・糖尿病等生活習慣病対策総合研究事業

糖尿病・メタボリックシンドロームにおける内臓脂肪蓄積の評価に関する疫学研究

（ H20-糖尿病等-若手-003 ）

平成22年度　総括研究報告書

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厚生労働科学研究費補助金(循環器疾患・糖尿病等生活習慣病対策総合研究事業)

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研究要旨　日本のメタボリックシンドローム診断基準では、腹囲カットオフは男性85cm、女性90cmである。国際基準との整合性や疾病発症との関連性を含めいくつか課題も指摘されている。腹囲はメタボリックシンドロームの上流に位置づけられる内臓脂肪の簡易指標であることを考えると、まずは内臓脂肪蓄積と諸病態との関連を解明しておく必要があろう。本研究は、糖尿病・メタボリックシンドローム、及び関連する病態における内臓脂肪蓄積の意義を明らかにすることを目的とする。このことによりメタボリックシンドローム診断基準を改訂する際に参考となる腹囲に関する知見を提供する。

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A. 研究目的

腹部CTにて計測した内臓脂肪面積と、インスリン抵抗性、メタボリックシンドローム、高血圧、糖尿病、脳心血管イベント、さらにはバイオマーカーとの関連を疫学的に明らかにする。この結果に基づき疾病リスクが高まる内臓脂肪面積の閾値を男女別に判定し、該当する腹囲を求める。内臓脂肪蓄積を基盤に耐糖能異常、脂質代謝異常、血圧高値をきたし、その状態が継続することにより、高血圧、糖尿病、さらには脳心血管疾患のリスクが高まるメタボリックシンドロームが世界的に注目されている。日本の腹囲基準は、腹部 CT で測定した内臓脂肪面積 $100cm^2$ に相当する値であり、男性より女性の方が大きいという特徴がある。申請者らは感度・特異度分析により、女性の現腹囲基準（90cm 以上）を用いた場合の問題点を指摘したが（Matsushita Y, et al. Diabetes Care. 5:1123-1124, 2006)、メタボリックシンドロームの発症機序を考えると、その上流にある内臓脂肪を正確

に把握した上で、インスリン抵抗性をはじめとする諸病態との関連を解明する必要がある。また、内臓脂肪の簡易指標である腹囲を診断的に補うバイオマーカーの検索も必要であろう。職域人間ドックで CT を行う受診者について、内臓脂肪面積とインスリン抵抗性、高血圧、糖尿病、脳心血管イベントとの関連を断面的、及び経時的に検討する。また、内臓脂肪蓄積を反映するバイオマーカーを測定し、その予防医学的な有用性を評価する。これらの病態のリスクが急激に変化する内臓脂肪面積の閾値を男女別に判定し、該当する腹囲を推定する。

B. 研究方法

対象：

日立製作所日立健康管理センタで通年行われている人間ドック成績のうち、腹部ＣＴ検査が導入された平成16年度以降を分析対象とした。さらに、平成20年度以降の受診者には同意を得た上で研究用の追加採血を行った。本研究は同社の産業医との共同研究として進めることで合意しており、国立国際医療研究センター、日立製作所の両施設において倫理審査委員会の承認を得た。

同センタ人間ドックでは、中性脂肪、HDL コレステロール、血圧、空腹時血糖、腹囲といったメタボリックシンドローム診断に必要な項目に加え、インスリンや高感度 CRP が受診者全員について測定されている。腹部 CT による内臓脂肪面積の計測は希望者に行われているが、人間ドック受診者 17,000 人の約 3 分の 1 にあたる 6,000 人が毎年、腹部 CT を受診している。なお、人間ドック受診者における男女比は 6：1 である。

方法：

1. 研究のセットアップ
   日立健康管理センタ産業医との共同研究として進めることで合意し、国立国際医療研究センター、日立製作所の両施設において倫理審査委員会の承認を得た上で、研究を開始した。作業手順書を作成し、現場で円滑に研究が遂行できるようにした。
2. 既存の人間ドックデータ（平成 16 年～平成 20 年）のデータベース化
   コーディングマニュアルを作成した。元データを連結可能匿名化し、解析用データベースを完成した。糖尿病、高血圧、高脂血症、脳心血管疾患の既往歴、治療の有無は人間ドックの調査票および欠勤時の診断書より把握した。(ICD10 コードによる分類を行った。)
3. 採血およびアディポネクチンの測定
   (同意書の得られた人のみ)
   人間ドック受付時に研究用採血についての説明・依頼文書と同意書を渡し、書面で同意を得た。同意の得られた人から静脈血 5ml を採取し、同施設にてアディポネクチンを測定した（約 9,000 名の測定を終了した)。残検体は健診施設内の冷凍庫（－80℃）に一時保管し、1 ヶ月ごとに国立国際医療研究センターへ低温で輸送し、凍結保管（－80℃）した。

（倫理面への配慮）

本研究の実施計画は「疫学研究に関する倫理指針」に則って作成し、研究実施前に、研究代表者及び実施する会社の分担研究者は研究計画書をそれぞれが所属する機関の倫理委員会に諮り、承認を得た。通常に行われている健診データの使用にあたっては、個別にインフォームドコンセント

をとらず、社内の掲示にて研究の目的と意義を説明した。また研究用採血に関して、調査内容をわかりやすく示したパンフレットを用いて、自由意志に基づく参加であることや個人情報の保護対策を含め人間ドックスタッフが対象者に説明した後に、本人から署名入りの同意書を得た上で実施した。人間ドック検査成績と採取した血液は匿名化（連結可能）した上で、鍵のかかるロッカー、－80℃の冷凍庫にそれぞれ保管した。結果の公表に際しては個人が特定できない形式で行った。

C. 研究結果

1) 内臓脂肪面積をはじめとする各体格指数がメタボリックシンドロームのリスク重積に及ぼす影響

腹部 CT 受診者 6,292 名（男性 5,606 名、女性 686 名）を対象として、CT による内臓脂肪面積、皮下脂肪面積、腹囲、BMI とメタボリックシンドロームのリスク重積のオッズ比を、各体格指数ごとに 5 分位に分け、比較した。腹囲測定は CT 測定による内臓脂肪面積に比べ、メタボリックシンドロームのリスク重積を女性では 5 割、男性では 7 割しか検出することができず、内臓脂肪蓄積の簡易指標として腹囲を用いることに限界があることを明かにした（Matsushita Y, et al. Diabetes Care. 33: 2117-2119, 2010）。

2) 禁煙期間と内臓脂肪面積・メタボリックシンドロームの関係

禁煙後の体重増加はメタボリックシンドロームなどの代謝性疾患のリスク上昇に繋がる可能性がある。その際、これが禁煙後の期間との間にどのような関係があるのか、また、内臓脂肪や皮下脂肪の変化がそれにどのように影響するのかについて、現状では明確な見解は得られていない。そこで、腹部 CT 検査を行った 5,697 名の男性（年齢 52.7 歳, BMI 24.1 kg/m^2, 内臓脂肪面積 124.0 cm^2 ; いずれも平均値）を対象として、喫煙歴のない非喫煙者を基準にし、メタボリックシンドロームとその要因の有無の OR を過去喫煙者（禁煙後 4 年以内、5～9 年、10～14 年、15 年以上）および現在喫煙者の群で求めた。年齢、飲酒、定期的な運動の有無によって調整したロジスティック回帰分析を用いた（Matsushita Y et al. Obesity. 19: 647 -651, 2011）。

その結果、喫煙状況別にみると、現在喫煙者の内臓脂肪面積の平均値が 120.4 cm^{2}と最も低く、過去喫煙者（124.0～132.0 cm^2）は非喫煙者（123.1 cm^2）に比べ、内臓脂肪面積が多かった。過去喫煙者の内臓脂肪面積は禁煙後の期間が長くなるにしたがって減る傾向があり、15 年以上禁煙すると内臓脂肪面積は非喫煙者とほぼ同等になることが明らかになった。

メタボリックシンドロームの有無の非喫煙者に対するORは、現在喫煙者で1.02、禁煙後4年以内、5～9年、10～14年、15年以上の過去喫煙者ではそれぞれ1.33、1.36、1.40、1.09であった。これらを内臓脂肪面積でさらに調整すると、禁煙後15年未満の過去喫煙者のオッズ比は35～55.6%減少したが、皮下脂肪面積による調整ではそのような事象は認められなかった。禁煙後は、内臓脂肪面積が増加しないように身体活動を増やし、摂取エネルギー量を適正に保つことが必要である。現在喫煙者は、15年以上禁煙することにより、メタボリックシンドロームのリスク重積

が非喫煙者と同等まで減少するので、15年以上の地道な禁煙が必要である。

3) 腹囲測定部位とメタボリックシンドローム

メタボリックシンドロームの診断基準では、内臓脂肪蓄積の簡易指標として腹囲が使われているが、腹囲は測定方法によって誤差が出やすい問題があり、また、その測定部位は国際的にも統一されていない。そこで、腹囲について，1,140名（男性969名，女性171名）を対象に，世界で使用されている代表的な腹囲の4部位（①最も細い部位②肋骨弓下線端と前腸骨稜上線の中点③臍位④前腸骨稜上線）を測定し，メタボリックシンドロームのリスク重積を予測するうえで最適な部位をROC曲線を描き，検討した。(Matsushita Y et al. Obesity 18: 2374-2378, 2010)。

その結果，腹囲の最大値と最小値の差の平均は，男性では3.9cmであったが，女性では12.6cmであり，測定部位による大きな差が女性で認められた。また、各腹囲測定部位によるメタボリックシンドロームの予測能力に有意差は認められないことが明らかになった。さらに，アジアにおける腹囲のメタボリックシンドローム診断基準である男性 90cm，女性80cmをカットオフ値として，リスク重積の感度，特異度を各測定部位で比較したが，感度，特異度いずれも相当のばらつきが認められた。

今回の研究より、各メタボリックシンドロームの診断基準で定められた腹囲測定部位で正確に測定することが必要であることが示唆された。また，今後、メタボリックシンドロームの頻度などを国際的に比較検討していくためには，測定部位の国際的な統一が望ましい。

4) アディポネクチン・内臓脂肪面積がメタボリックシンドロームのリスク重積に及ぼす影響

男性6,221名、女性775名、合計6,996名を対象とし、アディポネクチン、内臓脂肪面積別にそれぞれ4分位、16群に群分けし、アディポネクチン最高値・内臓脂肪面積最低値群を基準（1.0）とした時のメタボリックシンドロームのリスク重積の調整オッズ比を求めた。アディポネクチン最低値・内臓脂肪面積最高値群が最も高いオッズ比（95%信頼区間）であった（男性：12.7（9.7-16.6）、女性：13.5（6.0-30.2））。

D. 考察

横断解析により、内臓脂肪蓄積が多いほど、メタボリックシンドロームのリスク重積が高まることが明らかになった。また、腹囲測定はCT測定による内臓脂肪面積に比べ、メタボリックシンドロームのリスク重積を女性では5割、男性では7割しか検出することができず、内臓脂肪蓄積の簡易指標として腹囲を用いることに限界があることが明かになった。さらに、年齢別にみると、内臓脂肪面積とBMI、腹囲の動きは必ずしも一致しないことがわかり、現在、メタボリックシンドロームの腹囲カットオフは年齢別には示されていないが、年齢も考慮する必要があると考えられる。

縦断解析では、内臓脂肪面積の3年間の増加を50 cm^2未満に抑制することにより、メタボリックシンドロームのリスク重積の解消につながる可能性が示唆され

た。

アディポネクチンは脂肪細胞が出すホルモンの一つで動脈硬化を防いだり、脂肪酸の燃焼を促したりする働きがあることが動物実験で分かっているが、今回、ヒトで同じ内臓脂肪の付き方でもアディポネクチン量によりメタボリックシンドロームのリスク重積が異なる事が明らかになった。

また、現在喫煙者が、15年禁煙することにより、メタボリックシンドロームのリスク重積が、非喫煙者と同等まで減少することが明らかになった。

E. 結論

得られたデータは、前向きコホート研究による発症率調査及び糖尿病・メタボリックシンドロームの曝露要因としての役割の検討の際、基礎データとして活用する。

今後は現在、申請者らが開発中である内臓脂肪の蓄積をより鋭敏に反映する効果的、経済的で簡便に測れる評価モデル式を身体計測値とバイオマーカー、生活習慣要因からさらに検討し、推定能力の高いものに改訂する。さらに、その式が循環器疾患リスクを予測できるかどうかについて10年間の追跡を行い、妥当性を検討する。エンドポイントは、高血圧、糖尿病、高脂血症、メタボリックシンドローム、心電図異常、心臓足首血管指数（CAVI）、さらに症例数が解析可能な数に達し時点で脳心血管イベントとする。

F. 健康危険情報

なし

G. 研究発表

論文発表

1. Matsushita Y, Tomita K, Yokoyama T, Mizoue T: Relations Between Waist Circumference at Four Sites and Metabolic Risk Factors. Obesity. 18：2374-2378, 2010.
2. Matsushita Y, Nakagawa T, Yamamoto S, Takahashi Y, Yokoyama T, Noda M, MizoueT: Associations of visceral and subcutaneous fat areas with the prevalence of metabolic risk factor clustering in 6292 Japanese individuals: the Hitachi Health Study. Diabetes Care. 33：2117-2119, 2010.
3. Matsushita Y, Nakagawa T, Yamamoto S, Takahashi Y, Yokoyama T, Noda M, Mizoue T: Associations of smoking cessation with visceral fat area and prevalence of metabolic syndrome in men: the Hitachi Health Study. Obesity. 19：647-651, 2011.

学会発表

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1）内臓脂肪蓄積及び軽微な慢性炎症と、大腸腫瘍の関連

山本修一郎、中川徹、松下由実、草野涼、溝上哲也

（第31回日本肥満学会　前橋　平成22年10月）

2）ウエスト測定部位ごとのメタボリックシンドロームのリスクファクター重積予測能力

松下由実、富田健太郎、横山徹爾、溝上哲也

（第21回日本疫学会学術総会　北海道　平成23年1月）

H. 知的財産権の出願・登録状況

1）特許取得

なし

2) 実用新案登録

なし

3) その他

なし

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
松下由実	コーヒーと卵巣がん コーヒーと肺がん	野田光彦	コーヒーの医学	日本評論社	東京	2010	152、 166
松下由実	Asian perspectives and evidence on health promotion and education	Takashi Muto, Toshitaka Nakahara, Eun Woo Nam	Asian perspectives and evidence on health promotion and education	Springer	New York	2011	343-357

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
野田光彦	禁煙とメタボリックシンドローム、高血糖	Diabetes Frontier	22	101	2011
中川徹	インターネットを利用した特定保健指導の実際	肥満と糖尿病	9	112-117	2010
中川徹	メタボリックシンドロームへの減量アプローチ　職場での取り組み	治療学	44	468-471	2010

Relations Between Waist Circumference at Four Sites and Metabolic Risk Factors

Yumi Matsushita[1], Kentaro Tomita[2], Tetsuji Yokoyama[3] and Tetsuya Mizoue[1]

The location of waist circumference (WC) measurement differs among diagnostic guidelines for the metabolic syndrome. The present study examined which of four WC measurements was associated most strongly with the clustering of metabolic risk factors in cross-sectional study. The subjects comprised 1,140 Japanese employees, aged 20–70 years, who underwent health examinations in 2007 and 2008. WC was measured at (i) the narrowest part of the waist, (ii) midway between the lowest rib and the iliac crest, (iii) the umbilical level, and (iv) immediately above the iliac crest. A receiver operator characteristic (ROC) curve was used to assess the ability of each WC measurement to predict the presence of two or more other components of the metabolic syndrome, as defined by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) in 2005. Multiple risk factors were seen in 43.0% of the men and 12.9% of the women. The minimum and maximum WC measurements differed by 3.9 cm among the men and 12.6 cm among the women. The areas under the curve examining the ability of the four WC measurements to predict the clustering of multiple risk factors were similar. If the same WC cutoff value was applied, the prevalence of the metabolic syndrome changed considerably according to the site of WC measurement. The four WC measurements had similar screening abilities. Given the differences in the WC values according to the site of measurement, WC must be measured at the site specified by each diagnostic guideline.

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INTRODUCTION

The metabolic syndrome is characterized by central obesity, impaired glucose tolerance, high blood pressure, and abnormal lipid metabolism (1), and is related to an increased risk of cardiovascular disease (2). The prevalence of the metabolic syndrome has been increasing worldwide, in parallel with the increasing prevalence of obesity (3), and an urgent need for preventive strategies exists.

BMI is used as a measure of overall obesity, but central obesity is increasingly recognized as a more important risk factor for hypertension, coronary heart disease, and type 2 diabetes (4). Visceral fat area, which is best measured using computed tomography, is reportedly more reliable for identifying components of the metabolic syndrome (5), but waist circumference (WC) is used as a measure of central obesity for practical reasons. So far, 14 different sites have been proposed for the measurement of WC; however, a universal standard for measuring WC does not yet exist (6). Among the diagnostic criteria for the metabolic syndrome, at least three different locations are used for WC measurements (1,7–9). Which WC measurement location best predicts the clustering of metabolic risk factors and related diseases remains uncertain.

In the present study, conducted in a population of Japanese workers, we measured WC at (i) the narrowest part of the waist, as recommended in the Anthropometric Standardization Reference Manual (10); (ii) midway between the lowest rib and the iliac crest, as defined by the WHO (World Health Organization) (7) and the IDF (International Diabetes Federation) (8); (iii) the umbilical level, as defined in the Japanese metabolic syndrome guidelines (1); and (iv) immediately above the iliac crest, as defined in the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) guidelines (9) in 2005. Then, we compared the abilities of these WC measurements to detect the clustering of metabolic risk factors to determine which WC measurement is most suitable for diagnosing the metabolic syndrome.

METHODS AND PROCEDURES

In 2007 and 2008, all 2,431 employees who underwent a routine health examination at the Koukankai Tsurumi Occupational Health Center, Kanagawa, Japan were invited to participate in the present study; 1,745 (71.8%) employees agreed and gave their consent. However, 605 employees who had not fasted for ≥6 h after their last meal were excluded. Thus, 1,140 subjects (969 men and 171 women) were included in the present analysis. The present study

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was approved by the Ethics Committee of the International Medical Center of Japan, and written informed consent was obtained from all the subjects.

A self-administered questionnaire that included questions regarding medical management, including both medications and lifestyle modification, for hyperlipidemia, hypertension, and diabetes was given to each participant at the time of the health examination. Body height and weight were measured using an automated scale (AD-6225A; A&D, Tokyo, Japan), and the BMI was calculated as the weight/height^2 (kg/m^2). Measurements were obtained with the subjects in a standing position, both arms free at their sides, breathing naturally. WCs were directly measured with fiberglass tape placed on the skin: the narrowest part of the waist (WC1), midway between the lowest rib and the iliac crest (WC2), the umbilical level (WC3), and immediately above the iliac crest (WC4) (7). Prior to the survey, a training session on WC measurements was held to reduce measurement biases. Each WC site was measured once by trained researchers and laboratory technicians. Blood drawing was conducted by a registered nurse at Koukankai Tsurumi Occupational Health Center, and measurements were conducted at Tsurumi Koukan Hospital. Blood pressure was measured using an automated sphygmomanometer (TM-2655P; A&D) after the subjects had rested for 15 min. The serum concentrations of fasting glucose, triglycerides, and high-density lipoprotein-cholesterol were measured using the HK enzyme method, the GK enzyme method, and a direct method, respectively. The coefficient of variations (%) of fasting glucose, triglycerides, and high-density lipoprotein-cholesterol were 0.56, 1.68, and 2.0%, respectively.

Definition of risk-factor clustering

According to the NCEP-ATP III diagnostic criteria for the metabolic syndrome in 2005 (9), we defined subjects with two or more of the following factors as having a cluster of metabolic risk factors: (i) triglycerides ≥150 mg/dl (1.69 mmol/l), (ii) high-density lipoprotein-cholesterol <40 mg/dl (1.03 mmol/l) in men and <50 mg/dl (1.29 mmol/l) in women, (iii) systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg, and (iv) fasting plasma glucose ≥100 mg/dl (5.51 mmol/l). Subjects receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of their health checkup data.

Statistical analyses

All the analyses were performed according to sex. We tested the difference between WC1 and other WCs using Dunnett's test after two-way analysis of variance, where the two factors were measurement sites and individuals. We calculated the Pearson's correlation coefficients for the five anthropometric measurements (four WCs and BMI). To establish equations for converting one WC to another, linear regression analyses were used to obtain the regression coefficients and intercepts (see **Supplementary Table S1**). We conducted a stratified analyses by BMI (<25, ≥25) and age (<55 years and ≥55 years). The stratified analyses were conducted only in men, due to the small sample size of women. However, the results of the analyses were similar; thus, we presented only the results for all subjects. We also drew the receiver operator characteristic (ROC) curves for each WC in association with the presence of two or more risk factors of the metabolic syndrome and calculated the corresponding area under the curve (AUC). Test for the equality of the AUC, using an algorithm suggested by DeLong, DeLong, and Clarke-Pearson, was conducted among four WCs, and four WCs plus BMI (11). The pairwise comparisons of BMI with four WCs were also done, where P values for multiple tests (four comparisons) were adjusted by Bonferroni–Holm's method. Furthermore, the cutoff value yielding an 80% sensitivity, together with the corresponding specificity, for the prediction of clusters of metabolic risk factors was calculated for each WC. A P value <0.05 was considered statistically significant. All analyses were performed using SPSS for Windows, version 15.0 (SPSS, Chicago, IL) and Stata 10 (StataCorp, College Station, TX).

RESULTS

The mean (s.d.) age of the study subjects was 52.9 (9.0) years for the men and 47.0 (9.8) years for the women. The characteristics of the subjects are shown in Table 1. The mean (s.d.) BMI was 24.1 (3.1) kg/m^2 for the men and 21.8 (3.0) kg/m^2 for the women. The BMI range was from 14.9 to 39.4 kg/m^2. Clusters of two or more risk factors were seen in 43.0% of the men and 12.9% of the women.

Table 2 shows the results of the WC measurements at the four sites. The WC values increased in the order of WC1, WC2, WC3, and WC4 for both sexes; the respective means were 83.3, 85.2, 86.8, and 87.2 cm in men and 69.6, 73.1, 78.8, and 82.5 cm in women. The mean difference between the minimum (WC1) and the maximum (WC4) values was much greater in women (12.6 cm) than in men (3.9 cm).

Table 3 shows the correlations among the four WC measurements and BMI. The WC measurements were strongly correlated (r >0.9) in both men and women. Each WC was also strongly correlated with the BMI in both men and women (r >0.8).

An ROC analysis was performed to determine which WC best predicted clusters of multiple risk factors. The ROC curves

Table 1 Characteristics of study subjects

	Men (n = 969)	Women (n = 171)
Age (years)[a]	52.9 (9.0)	47.0 (9.8)
Body height (cm)[a]	169.0 (6.1)	156.3 (5.9)
Body weight (kg)[a]	68.9 (10.3)	53.3 (8.2)
BMI (kg/m^2)[a]	24.1 (3.1)	21.8 (3.0)
High serum triglycerides (%)	33.8	8.8
Low serum HDL-cholesterol (%)	12.8	7.0
High blood pressure (%)	52.0	25.7
Impaired fasting glucose (%)	40.2	12.9
Multiple risk factors (%)	43.0	12.9
Current smoking (%)	36.1	7.1

High serum triglyceridβs: , 150 mg/dl (1.69 mmol/l). Low serum HDL-cholesterol: <40 mg/dl (1.03 mmol/l) for men and <50 mg/dl for women (1.29 mmol/l). High blood pressure: systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg. Impaired fasting glucose: ≥100 mg/dl (5.51 mmol/l). Multiple risk factors: having two or more risk factors of metabolic syndrome defined by NCEP-ATP III (2005).
HDL, high-density lipoprotein; NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III.
[a]Values are mean (s.d.).

Table 2 Comparisons among waist circumference measurements at different sites

Measurement site	Men (n = 969)	Women (n = 179)
WC1	83.3 (7.8)	69.9 (7.8)
WC2	85.2 (8.3)*	73.1 (8.5)
WC3	86.8 (8.0)*	78.8 (8.9)
WC4	87.2 (7.8)*	82.5 (8.6)

Values are mean (s.d.) (cm).
WC1, narrowest part of waist; WC2, midway between the lowest rib and the iliac crest; WC3, umbilical level; WC4, immediately above the iliac crest.
*P value <0.05 (compared with WC1).

Table 3 Correlation between waist circumference measurements at each site and BMI

	Men				Women			
	WC2	WC3	WC4	BMI	WC2	WC3	WC4	BMI
WC1	0.980	0.960	0.937	0.903	0.958	0.922	0.912	0.923
WC2		0.977	0.954	0.896		0.943	0.930	0.899
WC3			0.979	0.887			0.936	0.894
WC4				0.871				0.873

Values are the Pearson's correlation coefficients.
WC1, narrowest part of waist; WC2, midway between the lowest rib and the iliac crest; WC3, umbilical level; WC4, immediately above the iliac crest.

Table 4 Areas under the curve of receiver operator characteristic for diagnosing two or more metabolic syndrome risk factors for each waist measurement site and BMI

	Area under the curve				Asian WC cutoff	
Measurement site	Mean	s.e.	WC or BMI corresponding to 80% sensitivity	Specificity corresponding to 80% sensitivity (%)	Sensitivity of multiple risk factors (%)	Specificity of multiple risk factors (%)
Men						
WC1	0.668*	0.017	79.7 cm	43.8	27.1	86.8
WC2	0.671*	0.017	81.3 cm	44.4	35.7	81.7
WC3	0.660	0.017	83.0 cm	42.0	41.0	77.0
WC4	0.657	0.018	83.6 cm	41.5	43.9	76.3
BMI	0.639	0.018	22.6 kg/m^2	42.6	—	—
Women						
WC1	0.780	0.058	69.7 cm	61.1	50.0	95.3
WC2	0.780	0.056	71.9 cm	57.0	59.1	83.9
WC3	0.772	0.057	78.1 cm	55.0	72.7	65.1
WC4	0.748	0.065	81.1 cm	51.7	86.4	46.3
BMI	0.779	0.060	21.6 kg/m^2	61.7	—	—

Asian WC cutoff: 90 cm for men and 80 cm for women. Multiple risk factors: having two or more risk factors of metabolic syndrome defined by NCEP-ATP III (2005). NCEP-ATP III, National Cholesterol Education Program's Adult Treatment Panel III; WC1, narrowest part of waist; WC2, midway between the lowest rib and the iliac crest; WC3, umbilical level; WC4, immediately above the iliac crest.
*P value <0.05 (BMI vs. each WC).

for the four WC measurements were similar (data not shown). Table 4 shows the AUC values for the four WC measurements and the BMI. In general, the AUC values were greater in women than in men. The WC measurement with the largest AUC value was WC2 for men, and WC1 and WC2 for women. However, the AUC values for the four WC measurements were not significantly different among either men or women. The respective cutoff levels yielding an 80% sensitivity for the prediction of clusters of multiple risk factors for WC1, WC2, WC3, and WC4 were 79.7, 81.3, 83.0, and 83.6 cm in men and 69.7, 71.9, 78.1, and 81.1 cm in women.

DISCUSSION

In a population of Japanese workers, we measured WC at four sites and assessed the relations of these measurements to metabolic risk factors. We identified a significant difference in WC according to the site of measurement, especially in women, although the four WC measurements were each strongly correlated with metabolic risk factors in both men and women. In an ROC analysis for the prediction of clusters of metabolic risk factors, the AUC values did not differ significantly among the four WC measurements.

Some previous studies have also examined differences in WC measurements according to the site of measurement. Wang *et al.* (12) reported that, in a population consisting of several ethnicities, the mean difference between the narrowest part of the waist (WC1) and midway between the lowest rib and the iliac crest (WC2) was 1.6 cm in men (n = 49) and 2.7 cm in women (n = 62). In a Danish study of 416 middle-aged subjects (13), the mean difference between WC1 and measurements at the umbilical level (WC3) was 0.7 cm for men and 5.0 cm for women. Willis *et al.* (14) reported that in 266 overweight and obese white men and women, the mean difference between WC1 and WC3 was 4.6 cm for men and 10.0 cm for women. Mason and Katzmarzyk (15,16) reported that in about 500 men and women, the mean difference between WC1 and WC3 was 2.5–2.6 cm for men and 8.6 cm for women. In the present study of Japanese workers, the difference between WC1 and WC2 was 1.6 cm in men and 2.2 cm in women and that between WC1 and WC3 was 3.3 cm in men and 8.4 cm in women.

Findings from our study and previous ones suggest WC differs according to the location of the measurement that the magnitude of the difference varies according to sex and ethnicity. In order to compare the prevalence of the metabolic syndrome worldwide, a particular WC site should be defined as the standard. Currently, the NCEP-ATP III, IDF, and WHO each have different WC sites in their guidelines. In the future, these guidelines should be unified and standardized. Furthermore, based on research findings such as those presented herein, ethnicity-specific cutoff values should also be defined.

Such differences in WC measurements inevitably influence the prevalence of the metabolic syndrome. When the NCEP-ATP III criteria in 2005 (90 cm for men and 80 cm for women, values used for Asian populations (17)) for the metabolic syndrome were used with the WC values measured at WC1, WC2, and WC3 rather than at WC4 (the position defined by the NCEP-ATP III criteria), 18, 10, and 3% fewer men and 26, 21, and 11% fewer women, respectively, met the criteria for the metabolic syndrome. Thus, caution should always be exercised when interpreting the prevalence of the metabolic syndrome in studies where the WC was not measured at the site specified by the guidelines that were being used. We proposed to use the regression equation to convert each WC to another to adjust for the difference among WCs measured at different locations because there is a high correlation between each WC measurement site.

In our study, the shapes of the ROCs and their AUCs did not significantly differ among the four WC measurements for either men or women, indicating that measurements at any of the sites have a similar ability to screen for multiple components of the metabolic syndrome. Willis *et al.* measured WC at two locations (WC1 and WC3) among overweight subjects (14) and found that WC1 was more strongly associated with cardiovascular disease risk factors and the metabolic syndrome than WC3. In our study, according to ROC stratified by BMI (<25 and ≥25) to predict multiple risk factors, the AUC did not differ significantly among four WC sites. Such inconsistency may be partly attributable to ethnic differences.

The prevalence of metabolic syndrome is much higher in men than in women according to an epidemiological study of Japanese subjects (18,19) as well as the National Nutrition Survey of Japan (20). Our results were similar to those of previous studies. The AUC for all WC sites measured were much greater in women (0.75–0.78) than in men (0.66–0.67). Although the AUC, derived from sensitivity and specificity, was greater in women than in men, the proportion of people who had two or more risk factors among the screened people (i.e., positive predictive value) was lower in women than in men (e.g., 50.8–52.0% for men and 19.1–22.7% for women, respectively, when sensitivity = 80%) because positive predictive value depended on prevalence of risk factors in the target population. The low positive predictive value could result in the low efficiency of screening, and therefore, we should carefully consider not only sensitivity and specificity but also positive predictive value to compare the performances of WC measurements between men and women in this population.

This finding may be ascribed to lifestyle differences between the sexes. For example, men are much more likely to smoke than women (21), and smoking is known to influence body weight (22). Thus, smoking may attenuate the association between WC measurements and clusters of metabolic risk factors in men.

The major strengths of our study included the large sample size (>1,000 subjects) and the provision of a training session on WC measurements prior to the survey. This study has two limitations. First, given the cross-sectional design, a longitudinal study examining the risk of metabolic syndrome incidence is needed to verify our results. Second, there were relatively few female subjects in this study (n = 171). Additional larger studies are required to confirm our findings in women. These limitations should be addressed in future research.

In conclusion, a moderate-to-large difference in WC measurements was observed, depending on the site of measurement, in Japanese adults. The four WC measurements assessed in the present study appear to have similar screening abilities for multiple components of the metabolic syndrome. To ensure accurate comparisons among studies, however, we strongly recommend that the WC be measured at the site specified by the guidelines adopted by each study.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/oby

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DISCLOSURE

The authors declared no conflict of interest.

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Associations of Visceral and Subcutaneous Fat Areas With the Prevalence of Metabolic Risk Factor Clustering in 6,292 Japanese Individuals

The Hitachi Health Study

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OBJECTIVE — We examined the relationships of visceral fat area (VFA), subcutaneous fat area, and waist circumference, determined using computed tomography (CT), and BMI with metabolic risk factors in a large Japanese population.

RESEARCH DESIGN AND METHODS — Study subjects comprised 6,292 men and women who participated in the Hitachi Health Study and received CT examinations in 2007 and 2008.

RESULTS — Regarding the clustering of metabolic risk factors, the odds ratios (ORs) 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). For the highest quintiles, the OR for VFA was 1.5 to 2 times higher than those of the other anthropometric indexes in both sexes.

CONCLUSIONS — We demonstrated a superior performance of VFA to predict the clustering of metabolic risk factors compared with other anthropometric indexes.

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Metabolic syndrome (MS) has been growing globally with the clusters of obesity, high blood pressure, impaired lipid metabolism, and hyperglycemia. Individuals with MS have a higher risk of cardiovascular disease and a subsequent increase in disease mortality or morbidity (1–3). For the diagnosis of MS, waist circumference (WC) is almost always used as one of the criteria, and this measure is typically used as a simplified measure of the visceral fat area (VFA) (4–7). Visceral fat is regarded as an endocrine organ that secretes adipocytokines and other vasoactive substances that can influence the risk of developing traits of MS (8). A few studies have shown the impact of visceral fat on MS and its components in large-scale epidemiological research efforts (9). The present study analyzed the epidemiological impact of VFA compared with that of subcutaneous fat area (SFA), WC, and BMI against the clustering of metabolic risk factors and its components.

RESEARCH DESIGN AND METHODS

— Of 17,606 employees and their spouses who, after more than 12 h of fasting, underwent a health examination in Hitachi, Ibaraki Prefecture, between 2007 and 2008, we analyzed data for 6,292 subjects (5,606 men and 686 women), aged 26 to 75 years, who underwent a computed tomography (CT) examination, answered a questionnaire on lifestyle and health, and did not have a history of serious illness (cancer, cerebrovascular disease, or myocardial infarction). VFA, SFA, and WC were measured using a CT scanner according to a protocol described elsewhere (10). The present study was approved by the ethics committee of the National Center for Global Health and Medicine. Written informed consent was obtained from all subjects.

In this study, subjects with two or more of the four risk factors (high blood pressure, high triglyceride, low HDL cholesterol, and hyperglycemia) defined in 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.

We divided the subjects into quintiles (Q1 to Q5) according to each anthropometric value and calculated the odds ratio (OR) of the clustering of metabolic risk factors and its components adjusted for age, smoking habits, alcohol consumption, and regular physical activity using a logistic regression analysis, with Q1 as the reference. All analyses were performed using SPSS for Windows, Version 15.0 (SPSS, Chicago, IL).

RESULTS

— The mean VFA was 123.7 ± 51.2 cm^2 in men and 85.1 ± 45.2 cm^2 in women. The mean SFA was 134.8 ± 56.6 cm^2 in men and 182.5 ± 72.9 cm^2 in women. The ratio of VFA to SFA was ~1:1 for men and 1:2 for women. The mean WC was 86.4 ± 8.3 cm in men and 83.2 ± 9.2 cm in women.

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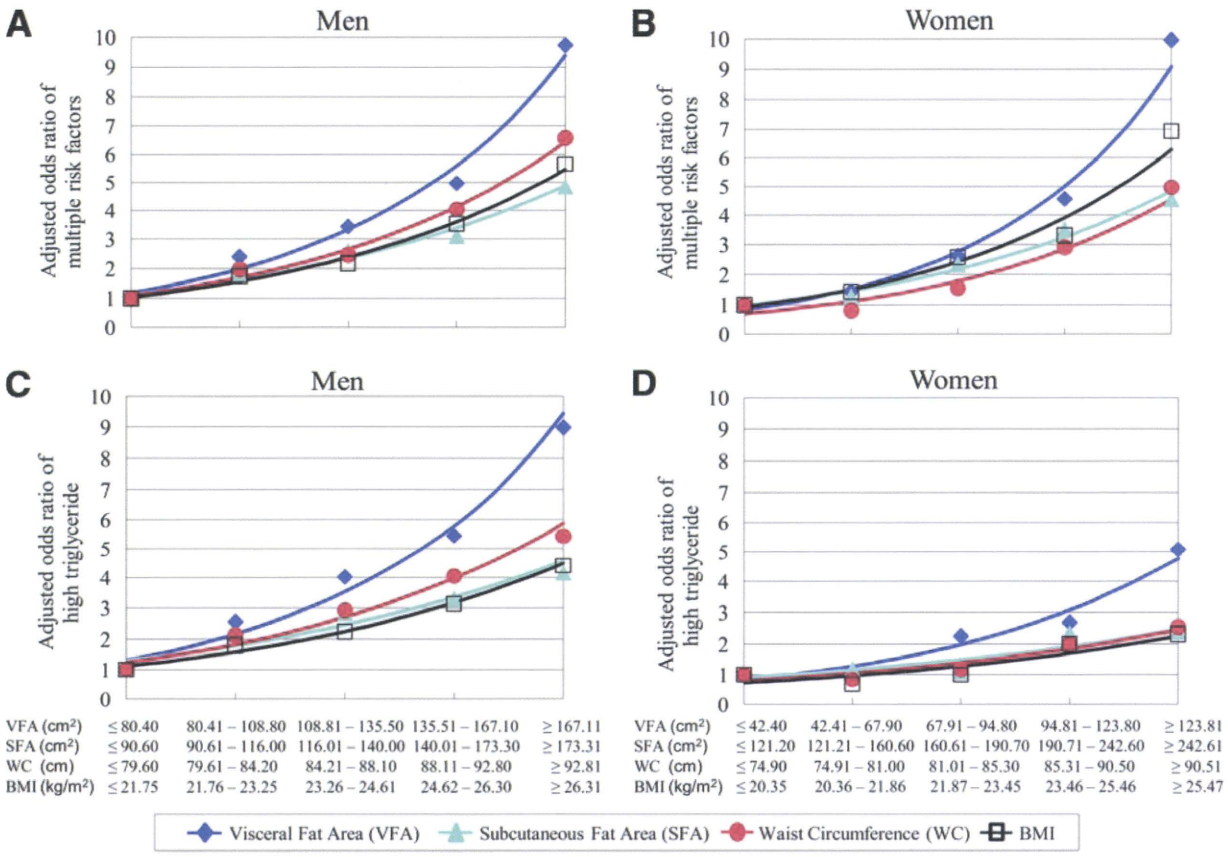

Figure 1—*ORs for high triglyceride and the clustering of metabolic risk factors according to the quintiles (Q1–Q5) of VFA, SFA, WC, and BMI adjusted for age, smoking habits (never, current, past), alcohol consumption (nondrinker, drinker consuming two go or less per day [a go is a conventional unit of alcohol intake in Japan and contains ~23 g of ethanol], or consuming more than two go per day), and regular fitness habit (yes/no). The symbols are the estimated ORs using Q1 as the reference category. The curves are fitted by the logistic regression models. The slope for VFA is significantly steeper than those for SFA, WC, and BMI on high triglyceride and on clustering of metabolic risk factors* ($P < 0.05$) *except for that on the clustering of metabolic risk factors in women. (A high-quality digital representation of this figure is available in the online issue.)*

The mean BMI was 24.1 ± 3.0 kg/m^2 in men and 23.0 ± 3.3 kg/m^2 in women. The prevalence of the clustering of metabolic risk factors was 46.0% in men and 30.0% in women.

In Fig. 1, the ORs for the clustering of metabolic risk factors are shown according to each anthropometric index. The OR was 1.5 to 2 times higher for the Q5 VFA category than for the other Q5 categories for both men and women. The OR (95% CI) of the VFA quintiles were, respectively, 1.0, 2.4 (2.0–2.9), 3.4 (2.8–4.2), 5.0 (4.1–6.0), and 9.7 (8.0–11.9) for men and 1.0, 1.5 (0.7–3.2), 2.6 (1.3–5.3), 4.6 (2.3–9.1), and 10.0 (5.0–19.9) for women ($P < 0.001$ for trends in both sexes). According to the SFA quintiles, ORs were, respectively, 1.0, 1.8 (1.5–2.2), 2.6 (2.2–3.1), 3.1 (2.6–3.7), and 4.8 (4.0–5.8) for men and 1.0, 1.3 (0.7–2.5), 2.3 (1.3–4.3), 3.5 (1.9–6.4), and 4.5 (2.5–8.4) for women ($P < 0.001$ for trends in both sexes).

The OR for a high triglyceride level, a low HDL level, high blood pressure, and hyperglycemia increased with increasing quintile categories of each anthropometric index. The OR (95% CI) of the Q5 VFA category for a high triglyceride level was 9.0 (7.3–11.1) in men and for a low HDL level was 7.1 (4.8–10.5) in men and 11.0 (4.0–30.1) in women, exhibiting extremely high ORs.

The slope for VFA is significantly steeper than those for SFA, WC, and BMI on high triglyceride and on clustering of metabolic risk factors ($P < 0.05$) except for the slope on the clustering of metabolic risk factors in women.

CONCLUSIONS — In the present study, a stronger association between an increasing VFA and the clustering of metabolic risk factors and its components than for an increasing SFA, WC, or BMI was observed. Among metabolic risk factors, a high triglyceride level in men and a low HDL cholesterol level in both men and women showed particularly strong associations with VFA.

BMI and WC are used clinically to measure obesity, but do not exactly reflect visceral adiposity. A previous report showed that some individuals with a normal BMI and WC actually had an excessive amount of visceral fat and metabolic risk factors (11). In our study, the ORs for the clustering of metabolic risk factors were similar for BMI and WC in men, but the OR for WC was lower than that for BMI (which was similar to that for SFA) in women. The OR of VFA and SFA differed according to sex. Furthermore, a stronger correlation was observed between WC and SFA than between WC and VFA. Fox et al. (9) reported similar results. These findings suggest that WC measurements in women may have the same meaning as SFA measurements, explaining the similarity of the OR for the clustering of metabolic risk factors in WC and SFA.

The present study adds evidence to support an important role for VFA in the

pathogenesis of metabolic risk factor clustering in Japanese adults. Further studies are needed to confirm this association prospectively and to examine the impact of VFA on the risk of cardiovascular disease.

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Y.M. derived the hypothesis, collated data from the Hitachi Health Study trials, planned and performed the analyses, and wrote the manuscript. T.N. and S.Y. collected data. T.Y. advised on analyses and commented on drafts of the manuscript. T.N., Y.T., T.Y., M.N., and T.M. contributed to the interpretation and discussion of the results. This report was critically reviewed and subsequently approved by all authors.

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Associations of Smoking Cessation With Visceral Fat Area and Prevalence of Metabolic Syndrome in Men: The Hitachi Health Study

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Weight gain after smoking cessation may deteriorate metabolic risk profiles, including that for metabolic syndrome. How risk profiles change according to the duration of smoking cessation and whether the visceral fat area (VFA) or the subcutaneous fat area (SFA) contributes to these changes remains uncertain. The subjects comprised 5,697 Japanese men who underwent an abdominal computed-tomography examination during a health check-up. Using never smokers as a reference group, the odds ratios of having metabolic syndrome and its components, defined using the National Cholesterol Education Program Adult Treatment Panel IIIcriteria, were calculated for each smoking category with adjustments for age, alcohol drinking, and physical activity (model 1) using a logistic regression analysis. Additional adjustments were also made for either VFA (model 2) or SFA (model 3). Current smokers had the lowest VFA (120.4 cm^2) whereas ex-smokers (124.0–132.0 cm^2) had a higher VFA than nonsmokers (123.1 cm^2). Among the ex-smokers, VFA tended to decrease with increasing years of smoking cessation. In model 1, the odds ratios of having metabolic syndrome for current smokers and ex-smokers with smoking cessation for ≤4, 5–9, 10–14, and ≥15 years were 1.02, 1.33, 1.36, 1.40, and 1.09, respectively. The elevated odds ratios among ex-smokers (≤14 years) were reduced by 35–55.6% after further adjustment for VFA but not for SFA. Smoking cessation is associated with a deterioration of the metabolic risk profile, which can be ascribed, at least in part, to an increase in VFA not SFA.

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INTRODUCTION

Metabolic syndrome is associated with an increased risk of cardiovascular mortality or morbidity (1,2). BMI is a measure of overall obesity, but the importance of central obesity, which can be easily measured as waist circumference, is known to have a stronger relation to the prevalence of each component of metabolic syndrome (hyperglycemia, diabetes, and hypertension) than BMI (3).

Numerous studies have investigated the relationship between smoking and body weight or BMI. Cigarette smokers tend to have a lower BMI than nonsmokers (4–6), and smoking cessation leads to weight gain to various extents (4,7,8). This difference or change in body weight can be ascribed to an increased metabolic rate and decreased caloric absorption by smoking (9).

Because weight gain deteriorates metabolic profiles (10), whether weight gain following smoking cessation leads to an increased risk of metabolic syndrome is a concern. However, epidemiologic data on the prevalence of metabolic syndrome according to the duration of smoking cessation are limited. Moreover, which type of fat deposition, the visceral fat area (VFA) or the subcutaneous fat area (SFA), contributes to these changes after smoking cessation is uncertain. Here, we assessed the prevalence of metabolic syndrome and its risk components in relation to the duration of smoking cessation and examined the contribution of VFA and SFA to an increased prevalence, if any, of metabolic syndrome after smoking cessation.

METHODS AND PROCEDURES

Overall, a total of 15,196 male employees and their spouses underwent a annual health check-up after having fasted overnight. All the examinations were performed in 2007 in Hitachi, Ibaraki prefecture. Of these participants, 6,405 subjects received an abdominal computed-tomography (CT) scan. We next excluded 708 subjects who did not provide lifestyle information regarding smoking, physical activity, or alcohol drinking. Finally, 5,697 men aged between 26 and 75 years were included in the analysis.

Body height and weight were measured using an automated scale (BF-220; TANITA; Itabashi-Ku, Tokyo, Japan), and the BMI was defined as weight/height^2 (kg/m^2). VFA, SFA, and waist circumference

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were measured using a CT scanner, the details of which are described elsewhere (11). In brief, single slice imaging was performed at the umbilical level in a spine position using a CT machine (Redix Turbo; Hitachi Medico, Chiyoda-Ku, Tokyo). The imaging conditions were 120 kV, 50 mA, and a slice thickness of 5 mm. VFA, SFA, and waist circumference were calculated using the software fatPointer (Hitachi Medico).

The triglyceride and high-density lipoprotein (HDL) cholesterol levels were measured using the oxygen method (Hitachi 7600; Sekisui Medical; Chuo-Ku, Tokyo, Japan). The blood glucose level was measured using the glucose electrode technique (ADAMS glucose GA-1170; Arkrey; Chukyo-Ku, Kyoto, Japan). Blood pressure was measured using an oscillometric method (Kentaro ADVANCE BP-203RV III A/B; Colin; Bunkyo-Ku, Tokyo, Japan). Written informed consent was obtained from each participant. The present study was approved by the ethics review committee of the National Center for Global Health and Medicine.

The subjects were divided into six groups: nonsmokers, current smokers, and ex-smokers with ≤4, 5–9, 10–14, and ≥15 years of smoking cessation. We tested the difference between current smokers and other smoking status groups using pair-wise test after analysis of covariance adjusted for age, regular physical activity (yes/no), and alcohol drinking (nondrinker, drinker consuming 2 *go* or less per day (one *go* contains ~23 g of ethanol), or drinker consuming ≥2 *go* per day). The multiple comparisons were adjusted by Bonferroni's method (five comparisons).

Using nonsmokers as the reference, we calculated the odds ratios of (i) waist circumference (≥90 cm), (ii) high triglyceride level (≥150 mg/dl), (iii) low HDL cholesterol level (<40 mg/dl), (iv) high blood pressure (systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg), (v) hyperglycemia (fasting glucose level ≥110 mg/dl), and (vi) metabolic syndrome as defined using the National Cholesterol Education Program Adult Treatment Panel III criteria (having three or more of components (i) to (v) listed above), adjusted for age, regular physical activity (yes/no), and alcohol drinking (nondrinker, drinker consuming 2 *go* or less per day, or drinker consuming ≥2 *go* per day) (model 1). Additional analyses were adjusted for VFA (model 2) or SFA (model 3). All analyses were performed using logistic regression analysis. Subjects currently receiving treatment for hyperlipidemia, hypertension, or diabetes were deemed as having the respective risk factors, regardless of their biochemical values ((ii) to (vi)). All analyses were performed using SPSS for Windows, version 15.0 (SPSS, Chicago, IL).

RESULTS

The subject characteristics are shown in Table 1. The mean (s.d.) age of the subjects was 52.7 (10.0) years, the mean (s.d.) BMI was 24.1 (3.0) kg/m^2, and the mean (s.d.) VFA was 124.0 (51.2) cm^2. The prevalence of metabolic syndrome was 19.2%.

Table 1 Characteristics of the subjects

	Mean (s.d.)
n	5,697
Age, years	52.7 (10.0)
BMI, kg/m^2	24.1 (3.0)
Waist circumference, cm	86.4 (8.3)
Visceral fat area, cm^2	124.0 (51.2)
Subcutaneous fat area, cm^2	134.8 (56.5)
High blood pressure, %	38.1
High triglyceride, %	35.3
Low HDL cholesterol, %	10.0
Hyperglycemia, %	26.9
Metabolic syndrome, %	19.2

The means of the anthropometric indexes according to smoking status are shown in Table 2. Current smokers had the lowest VFA (120.4 cm^2), whereas ex-smokers (124.0 to 132.0 cm^2) had a higher VFA than nonsmokers (123.1 cm^2). Among ex-smokers, the VFA tended to decrease with increasing years of smoking cessation, and those with ≥15 years of smoking cessation had almost the same VFA as nonsmokers. Similar results were observed for SFA and waist circumference. Current smokers had a lower mean BMI and waist circumference than nonsmokers and ex-smokers. Ex-smokers with <15 years of smoking cessation had a higher mean waist circumference than nonsmokers, whereas ex-smokers with ≥15 years of smoking cessation had a mean BMI and waist circumference similar to those of nonsmokers.

The odds ratios of having metabolic syndrome and its components according to smoking status are shown in Table 3. For metabolic syndrome, the odds ratios for current smokers and ex-smokers with smoking cessation for ≤4, 5–9, 10–14, and ≥15 years were 1.02, 1.33, 1.36, 1.40, and 1.09, respectively. The odds ratio for ex-smokers with ≥15 years of smoking cessation was almost the same as nonsmokers. The odds ratios of metabolic syndrome for ex-smokers with ≤4 years of smoking cessation in model 1 (1.33, 95% CI: 1.04–1.70) was reduced after adjustment for VFA (1.16, 95% CI: 0.88–1.53) but remained basically unchanged after adjustment for SFA (1.46, 95% CI: 1.12–1.90). Similar results were obtained in other groups with different periods of smoking cessation. The odds ratios of having metabolic syndrome for ex-smokers with ≤4, 5–9, and 10–14 years of smoking cessation after adjustment for VFA (model 2) were 1.16, 1.16, and 1.26, respectively; these values were 51.5%, 55.6%, and 35% lower than the values without adjustment for VFA, respectively.

Regarding high blood pressure, current smokers had a significantly lower odds ratio than nonsmokers (0.71; 95% CI: 0.61–0.82). Ex-smokers, irrespective of the length of period of smoking cessation, had almost the same odds ratio as nonsmokers. Regarding high triglyceride levels, current smokers had a significantly higher odds ratio (1.30; 95% CI: 1.13–1.50). Also, ex-smokers with ≤4 and 10–14 years of smoking cessation had significantly increased odds ratios of 1.26 (95% CI: 1.03–1.55) and 1.36 (95% CI: 1.04–1.79), respectively. Regarding low HDL cholesterol levels, current smokers had a significantly higher odds ratio of 1.65 (95% CI: 1.32–2.06). The odds ratios of ex-smokers were not significantly different from that of nonsmokers. Regarding hyperglycemia, the odds ratio (95% CI) of current smokers was 1.08 (0.93–1.27). On the other hand, the odds ratios (95% CI) of ex-smokers with ≤4, 5–9, and 10–14 years of smoking cessation were 1.44 (1.16–1.80), 1.50 (1.19–1.88), and 1.44 (1.07–1.92), respectively.

DISCUSSION

In this study, we examined the association of smoking cessation and metabolic syndrome and its components while considering the potential influence of VFA and SFA. We found that VFA, SFA, and the prevalence of metabolic syndrome were higher among ex-smokers (<15 years of smoking cessation) than

Table 2 Mean values of anthropometric indexes of subjects according to smoking status

		Ex-smokers (years of smoking cessation)				
	Nonsmokers	≥15	10–14	5–9	≤4	Current smokers
n	1,578	734	256	461	530	2,138
BMI, kg/m^2	24.3 (0.1)**	24.3 (0.1)*	24.4 (0.2)	24.5 (0.1)***	24.1 (0.1)	23.9 (0.1)
Waist circumference, cm	86.4 (0.2)	86.4 (0.3)	87.2 (0.5)	87.7 (0.4)***	87.0 (0.4)*	85.9 (0.2)
Visceral fat area, cm^2	123.1 (1.3)	124.0 (1.9)	131.7 (3.2)**	132.0 (2.4)***	130.6 (2.2)***	120.4 (1.1)
Subcutaneous fat area, cm^2	137.7 (1.4)***	136.0 (2.1)*	139.9 (3.4)*	142.9 (2.6)***	136.1 (2.4)	129.6 (1.2)
Visceral fat/subcutaneous fat area	0.95 (0.01)*	0.96 (0.01)	1.00 (0.02)	0.97 (0.02)	1.01 (0.02)	0.98 (0.01)

Note: Values are mean (s.e.) adjusted for age, regular physical activity, and alcohol drinking.
*P value <0.05, **P value <0.01, ***P value <0.001 (compared with current smokers).

Table 3 Association of period of smoking cessation with metabolic syndrome and its components

		Nonsmokers (Reference)	Ex-smokers (years of quitting)				Current smokers
			≥15	10–14	5–9	≤4	
n		1,578	734	256	461	530	2,138
Waist circumference	Model 1	1	1.01 (0.83–1.23)	1.11 (0.83–1.48)	1.33 (1.07–1.66)*	1.13 (0.91–1.40)	0.94 (0.81–1.09)
High blood pressure	Model 1	1	1.01 (0.84–1.22)	1.17 (0.89–1.55)	1.04 (0.83–1.29)	0.98 (0.80–1.21)	0.71 (0.61–0.82)*
	Model 2	1	1.00 (0.83–1.22)	1.08 (0.81–1.43)	0.95 (0.76–1.19)	0.91 (0.73–1.13)	0.72 (0.62–0.83)*
	Model 3	1	1.03 (0.85–1.24)	1.16 (0.87–1.53)	1.00 (0.80–1.25)	1.00 (0.80–1.23)	0.75 (0.64–0.86)*
High Triglyceride	Model 1	1	1.11 (0.92–1.35)	1.36 (1.04–1.79)*	1.13 (0.91–1.41)	1.26 (1.03–1.55)*	1.30 (1.13–1.50)*
	Model 2	1	1.11 (0.91–1.36)	1.26 (0.94–1.67)	1.01 (0.80–1.28)	1.16 (0.94–1.45)	1.38 (1.19–1.60)*
	Model 3	1	1.13 (0.93–1.38)	1.36 (1.03–1.79)*	1.10 (0.88–1.37)	1.29 (1.04–1.59)*	1.39 (1.21–1.60)*
Low HDL cholesterol	Model 1	1	0.83 (0.60–1.16)	1.02 (0.64–1.65)	1.19 (0.83–1.70)	1.05 (0.74–1.50)	1.65 (1.32–2.06)*
	Model 2	1	0.82 (0.59–1.15)	0.96 (0.59–1.56)	1.08 (0.75–1.55)	0.98 (0.68–1.40)	1.70 (1.36–2.13)*
	Model 3	1	0.85 (0.61–1.18)	1.01 (0.62–1.63)	1.15 (0.81–1.65)	1.07 (0.75–1.53)	1.76 (1.40–2.20)*
Hyperglycemia	Model 1	1	1.08 (0.88–1.32)	1.44 (1.07–1.92)*	1.50 (1.19–1.88)*	1.44 (1.16–1.80)*	1.08 (0.93–1.27)
	Model 2	1	1.08 (0.88–1.33)	1.36 (1.01–1.83)*	1.41 (1.12–1.79)*	1.37 (1.10–1.72)*	1.11 (0.94–1.30)
	Model 3	1	1.10 (0.90–1.34)	1.43 (1.07–1.91)*	1.47 (1.17–1.85)*	1.47 (1.17–1.83)*	1.13 (0.97–1.33)
Metabolic syndrome	Model 1	1	1.09 (0.87–1.36)	1.40 (1.02–1.92)*	1.36 (1.05–1.75)*	1.33 (1.04–1.70)*	1.02 (0.86–1.22)
	Model 2	1	1.08 (0.84–1.39)	1.26 (0.89–1.80)	1.16 (0.87–1.54)	1.16 (0.88–1.53)	1.06 (0.87–1.29)
	Model 3	1	1.16 (0.91–1.48)	1.42 (1.01–2.00)*	1.32 (1.01–1.73)*	1.46 (1.12–1.90)*	1.18 (0.97–1.42)

Note: Values are odds ratios adjusted for age, physical activity, and alcohol drinking.
Waist circumference ≥ 85 cm. High blood pressure: systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg. Triglyceride ≥150 mg/dl. HDL cholesterol <40 mg/dl. Impaired fasting glucose: fasting glucose ≥110 mg/dl. Model 1: Values are odds ratios adjusted for age, regular physical activity, and alcohol drinking. Model 2: Values are odds ratios adjusted for age, regular physical activity, and alcohol drinking, and visceral fat area. Model 3: Values are odds ratios adjusted for age, regular physical activity, and alcohol drinking, and subcutaneous fat area.
*P < 0.05 compared with nonsmokers.

among nonsmokers and current smokers. However, the odds ratio of metabolic syndrome among ex-smokers was decreased after adjustment for VFA but not for SFA. Furthermore, the odds ratios of metabolic syndrome and its component for ex-smokers with ≥15 years of smoking cessation were almost the same as those for nonsmokers, though ex-smokers with ≤14 years of smoking cessation generally had higher odds ratios than nonsmokers.

Several previous studies have reported the risk of metabolic syndrome after smoking cessation. Ishizaka *et al.* assessed the prevalence of metabolic syndrome according to the duration of smoking cessation; using subjects who had never smoked as the reference group, the odds ratios (95% CI) for ex-smokers with <1, 1–4, and ≥5 years of smoking cessation were 2.17 (1.36–3.46), 1.97 (1.33–2.92), and 1.61 (1.26–2.08), respectively (12). Similarly, Wada *et al.* showed that the odds ratios (95% CI) for ex-smokers (who smoked 20–39 cigarettes per day) with ≤5, 6–10, 11–20, and >20 years of smoking cessation were 1.48 (1.21–1.81), 1.52 (1.16–2.00), 1.25 (1.01–1.54), and 1.09 (0.86–1.39), respectively (13). Both studies found that the odds ratios of metabolic syndrome among ex-smokers tended to decrease with an increasing duration of smoking cessation, similar to the results of the present study. Further, we found that the prevalence of metabolic syndrome and its components among ex-smokers who had quit ≥15 years ago was similar to those among nonsmokers. Hence, the risk of metabolic