別紙 3

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告書

生体インピーダンス法を応用した腹部内臓脂肪蓄積の評価法に関する研究

分担研究者　中尾　一和　京都大学医学研究科教授

研究要旨　生体インピーダンス法（Bioimpedance Analysis, BIA）の原理を応用して開発されたDual BIA法による内臓脂肪量測定装置の有用性につき検討した。対象は年齢22-80歳の180名（男性90名、女性90名）。CTとDual BIA法による臍位での内臓脂肪面積(CT-VFAとDB-VFA)、及び腹囲を同日の午前中絶食下に測定した。DB-VFAと腹囲のCT-VFAとの相関関係について比較検討したところ、DB-VFAとCT-VFAの相関はr=0.884 (n=180, p<0.001)と強い相関を示し、腹囲とCT-VFAはr=0.766 (n=180, p<0.01)であった。BMIで層別分類した検討で、DB-VFAとCT-VFAとの相関は各BMI層において腹囲とCT-VFAとの相関よりも高い相関係数を示した。腹囲とCT-VFAとの相関はBMI35以上の層で相関係数が低下したが、DB-VFAとCT-VFAとの相関はBMIが高い層でも相関係数の低下はみられなかった。年齢層別の検討では、各年齢層においてDB-VFAとCT-VFAとの相関は腹囲とCT-VFAよりも相関係数が高かった。腹囲とCT-VFAの相関係数は年齢により変動する傾向を認めたが、DB-VFAとCT-VFAとの相関係数は年齢による変動を示さず、安定していた。各年齢層におけるDB-VFAとCT-VFAとの相関は腹囲とCT-VFAとの相関に比べて高い相関係数を示した。Dual BIA法による内臓脂肪量測定装置は被曝がなく簡便であり、腹部内臓蓄積のスクリーニングにおいて腹囲よりも有用であることが明らかになった。

A．研究目的

我々が開発してきたDual Bioimpedance Analysis(Dual BIA)法による内臓脂肪量測定装置の有用性につき、広い範囲の腹囲の集団を対象として、CTでの内臓脂肪面積及び腹囲との比較により検討した。

B．研究方法

【対象】年齢 22-80 歳で、臍位での腹囲が 65cm以上120cm以下の男女（男性 90 名、女性 90 名）。

【方法】CTとDual BIA法による臍位内臓脂肪面積(CT-VFAとDB-VFA)、臍位での腹囲を同一日の午前中空腹時に測定した。DB-VFAと腹囲それぞれについてCT-VFAとの相関をPearson法による相関係数(r)により評価し、被験者のBMI及び年齢の相関への影響について検討した。

（倫理面への配慮）

書面で同意を得た被験者のみで測定を行ない、匿名化したうえで、解析した。

C．研究結果

被験者のBMI及び腹囲はそれぞれ最小 17.0　一最大 44.0(kg/m2)及び最小 65.8一最大 120.0(cm)であった。

全被験者についてのDB-VFAとCT-VFA の相関は r=0.884(n=180, p<0.001)、腹囲とCT-VFAの相関は r=0.766(n=180, p<0.001)であった。BMIの層別比較において、DB-VFAとCT-VFAの相関はいずれのBMIの層でも、腹囲とCT-VFAとの相関よりも高い相関係数を示した。腹囲ではBMI35 以上の層での相関係数がBMI35-40 群　r=-0.128、BMI40 以上群　r=0.008 と低下したが、DB-VFAではBMI35-40 群　r=0.830、BMI40 以上群　r=0.965 とBMI高値群でも相関係数は低下しなかった。

年齢の層別比較において、DB-VFAとCT-VFAの相関は、いずれの年齢層でも、腹囲とCT-VFAの相関よりも高い相関係数を示した。腹囲は年齢により r=0.778-0.896 と相関係数が変動したが、DB-VFAは r=0.869-0.935 と年齢による変動は小さく、安定していることが観察された。

D．考察

E．結論

【結語】DB-VFAは広い範囲のBMI及び年齢において、CT-VFAとの高い相関を示したが、腹囲とCT-VFAの相関は、BMIや年齢により影響を受けることが示された。Dual BIA法による内臓脂肪量測定装置は被曝なく簡便に内臓脂肪面積を測定することが可能であり、成人における腹部内臓蓄積のスクリーニングにおいて腹囲よりも有用であることが明らかになった。

G．研究発表

1．　論文発表

投稿準備中

2．　学会発表

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H．知的財産権の出願・登録状況

なし

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
分担研究報告

生活習慣病予防の立場からみた総・高分子量アディポネクチンの意義

分担研究者　伊藤千賀子　ｸﾞﾗﾝﾄﾞﾀﾜｰ　ﾒﾃﾞｨｶﾙｺｰﾄ　所長

研究要旨：総・高分子量アディポネクチンを測定した4,014例を正常群、耐糖能低下群、糖尿病群に分けて検討を行った。男女ともに正常群に比し耐糖能低下群でアディポネクチン濃度の有意な低下が認められた。多変量解析の結果、正常群と耐糖能低下群では空腹時血糖値の上昇とともにアディポネクチンが有意に低下することが示された。アディポネクチン低下群への積極的な介入は糖尿病対策として有意義と思われる。

A. 研究目的

生活習慣病、中でも糖尿病患者の増加は著しく、これら疾病に対する予防は極めて重要である。今回は糖尿病の予備軍へのアプローチに対して介入対象の選出に総・高分子アディポネクチン測定の重要性を分析した。

B. 研究方法

対象は2005年10月から2011年3月の間、当所で人間ドック健診を受けた4,014例（男性 2,231例、女性 1,783例）で、早朝空腹時の血清脂質、血糖値、IRI、総・高分子量アディポネクチン値、血圧値を測定した。WC径は臍周囲、WHO（肋骨下縁と腸骨上縁の中間点）で測定した。低線量CTで内臓脂肪面積と皮下脂肪面積を測定した。空腹時血糖値≧126mg/dlまたはHbA1c (JDS)値≧6.1%および糖尿病治療中のものを糖尿病とした。正常群は空腹時血糖値＜110mg/dlかつHbA1c (JDS)値＜5.2%のものとした。上記に含まれないもの（110≦空腹時血糖値＜126かつ/または5.2≦HbA1c (JDS)値＜6.1）を耐糖能低下群とした。本研究はGrand Tower Medical Court Life Care Clinic治験審査委員会で承認を受け、対象例は全て文書による同意を得ている。

C. 研究結果

1) 耐糖能別の臨床背景の比較

耐糖能別に臨床的データの比較を行った。男女とも年齢に有意な差を認めたため、年齢以外の検討は年齢を調整した共分散分析を用いた。男性ではBMI、ウエスト周囲径、収縮期血圧、中性脂肪、内臓脂肪面積、空腹時血糖値、HbA1c（JDS）値は正常群（n=1219, 4.9±0.2%）で最も低値であり、次に耐糖能低下群（n=760, 5.3±0.2%）、糖尿病群（n=252, 6.7±1.4%）の順に有意に高値を示していた。拡張期血圧、HDLコレステロール、LDLコレステロールは耐糖能低下と糖尿病で差を認めなかった。女性ではBMI、ウエスト周囲径、収縮期血圧、中性脂肪、HDLコレステロール、LDLコレステロール、内臓脂肪面積、空腹時血糖値、HbA1c (JDS)値は正常群（n=1214, 4.9±0.2%）で最も低値であり、耐糖能低下群（n=509, 5.3±0.2%）、糖尿病群（n=60, 6.9±1.3%）の順に有意に高値を示していた。拡張期血圧は耐糖能低下と糖尿病で差を認めなかった。

2) 耐糖能別の総ディポネクチン、高分子量アディポネクチン濃度

男性の総アディポネクチン濃度は正常群4.51、耐糖能群 4.09、糖尿病群 4.49μg/mlであった。耐糖能低下群に比して正常群および糖尿病群では有意に高値を示した（それぞれ p<0.0001、p=0.01）。高分子量アディポネクチン濃度も同様で正常群 1.61、耐糖能低下群 1.37、糖尿病群 1.68μg/mlであった。耐糖能低下群では正常群・糖尿病群に比して有意に低値であった(p=0.0001 および p=0.0023)。

女性の総アディポネクチン濃度は正常群7.61、耐糖能低下群 6.69、糖尿病群 7.47μg/mlであった。耐糖能低下群では正常群に比して有意に低下していた (p<0.0001)。高分子量アディポネクチン濃度も同様で、正常群3.81、耐糖能低下群 3.15、糖尿病群 3.60μg/mlであり、耐糖能低下群では正常群に比し

て有意な低下が認められた (p<0.0001)。

薬剤がアディポネクチン濃度を上昇させる可能性があるので、高血圧（286 例）、脂質異常症（184 例）、糖尿病（133 例）の内服治療中を除外して同様の解析を行った。

男性において総アディポネクチン濃度は正常群 4.51、耐糖能群 4.11、糖尿病群 4.11 μg/ml で、正常群に比して耐糖能低下群では有意に低く(p<0.0001)、糖尿病群でも有意に低下した(p=0.0326)。高分子量アディポネクチン濃度も同様で、正常群 1.61、耐糖能低下群 1.39、糖尿病群 1.47μg/ml であり、正常群に比して耐糖能低下群では有意に低下していた (p=0.0007)。

女性では総アディポネクチン濃度は正常群 7.59、耐糖能低下群 6.76、糖尿病群 7.14 μg/ml であり、正常群に比して耐糖能低下群で有意に低値を示した (p<0.0001)。糖尿病群では正常群に比して低い傾向がみられたが例数も少なく有意ではなかった。高分子量アディポネクチン濃度も同様で、正常群 3.80、耐糖能低下群 3.20、糖尿病群 3.48μg/ml で、耐糖能低下群で有意に低下した (p<0.0001)。

3）総・高分子量アディポネクチンと関連する要因の分析

正常群では BMI、内臓脂肪面積、中性脂肪、空腹時血糖値と有意な負の相関が認められた。また、年齢、HDL コレステロールとは有意な正の相関が認められた。耐糖能低下群でも正常群と同様の結果であり、空腹時血糖値と有意な負の相関が認められた。血糖値の上昇と共にアディポネクチンが低下することが示された。

一方、糖尿病群においても総・高分子量アディポネクチンは中性脂肪と有意な負の相関、HDL コレステロールとは有意な正の相関が認められた。また、空腹時血糖値に有意な関連は認められなかった。

D.考察

今回の検討では、男女ともに正常群に比し耐糖能低下群で総・高アディポネクチン濃度の低下が認められた。このように耐糖能低下とアディポネクチンの関連を明確に示したことは大変意義がある。

耐糖能低下群は正常群に比し内臓脂肪面積が大であり、そのためアディポネクチン濃度は低下し、インスリンの感受性の低下をきたして耐糖能低下に至ると考えられた。

一方、全ての症例について分析すると、糖尿病群では正常群、耐糖能低下群に比しアディポネクチンの低下は認められなかった。糖尿病群では正常群、耐糖能低下群に比し内臓脂肪面積が大であり、血圧、中性脂肪が高値で HDL コレステロールが低値を示していた。一般的にはこれらの内臓脂肪蓄積、高血圧、高中性脂肪血症、低 HDL コレステロール血症ではアディポネクチン濃度は低下するとされている。そこで、糖尿病の血糖降下薬、高脂血症薬や高血圧に対する薬物によるアディポネクチン上昇が考えられることから対象からこれらの薬剤で治療中の症例を除いて分析すると、糖尿病群における総アディポネクチン濃度および高分子量アディポネクチン濃度は見られなくなり、薬剤の影響が大きいと考えられた。

今回の検討では、男女ともに正常群に比し耐糖能低下群でアディポネクチン濃度の低下が認められた。このように耐糖能低下とアディポネクチンの関連を明確に示したことは大変意義がある。正常群と耐糖能低下群では空腹時血糖値の上昇とともに総、高分子量アディポネクチンが有意に低下することを示しており、糖尿病発症がアディポネクチン値の低下群に多いというこれまでの報告と一致していた。今年度は糖尿病予防の立場からアディポネクチン測定の重要性について述べたが、今後はアディポネクチン濃度の cut off 値を設定し、現状のメタボリックシンドロームに対する精度の比較と共に follow-up 成績についても検討を行いたい。

E. 結論

男女ともに正常群に比し耐糖能低下群でアディポネクチン濃度の低下が認められた。多変量解析の結果、正常群と耐糖能低下群では空腹時血糖値の上昇とともにアディポネクチンが有意に低下することが示された。アディポネクチン低下群への積極的な介入は糖尿病発症予防として有意義と思われる。

別紙４

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
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「保健指導への活用を前提としたメタボリックシンドロームの診断・管理のエビデンス創出のための縦断・横断研究」分担報告書

メタボリックシンドロームのリスクファクターとウエストとの関連

-協和地区における横断研究-

研究分担者　磯　博康　大阪大学大学院医学系研究科教授

研究要旨：

茨城県筑西市協和地区では、昭和56年より脳卒中を中心とした循環器疾患病予防対策事業が開始され、現在まで継続している。メタボリックシンドロームの基準として、我が国では原則としてウエスト周囲径は臍レベルを採用している。WHO や国際糖尿病連合(IDF)で採用されている測定位置は、中点レベル（肋骨下縁と前上腸骨棘の中点レベル）である。本研究では、ウエストを臍レベルと中点レベル両方を測定し、コホート研究のベースラインデータを構築している。本年度は協和地区 40～74 歳の男性 613 人と女性 900 人を対象に、臍レベルと中点レベルの 2 点においてウエストを測定した。その結果、男女とも臍レベルのウエスト平均値が中点レベルに比べ、男性で平均 0.3cm、女性で平均 2.6cm 高値を示した。また、ウエスト周囲径を除くメタボリックシンドロームのリスクファクター2 個以上の割合は、臍レベルでのウエスト周囲径の増加に伴い増加した。中点レベルでのウエスト周囲径にしても同じ傾向を示した。

A．研究目的

茨城県筑西市協和地区（旧・真壁郡協和町）では、1981 年より健診による高血圧の把握と高血圧管理、食事改善指導を中心とする循環器疾患の予防対策を、町、医師会、保健所、健診機関、住民組織および大阪大学、大阪府立成人病センター（現・大阪府立健康科学センター）、筑波大学等の研究機関の組織的な協力の下に進めてきた。

メタボリックシンドロームが循環器疾患のリスクであることが先行研究で報告されている。我が国ではメタボリック症候群の診断基準として、腹部肥満を必須基準項目にし、2005 年の日本 8 学会合同基準が策定された。また、平成 20 年度より特定健康診査・特定保険指導制度を導入し、メタボリックシンドローム予防の観点から、内臓肥満の指標としてウエスト周囲径の測定を実施することとなった。我が国でのウエスト測定は、臍レベルを基本的な測定位置として採用されているが、WHO や国際糖尿病連合(IDF)で採用されている国際的な測定位置は、中点レベル（肋骨下縁と前上腸骨棘の中点レベル）である。我が国では、臍が下方に偏位している場合は中点レベルで測定することが附記されている。しかしながら、我が国の研究においては、ベースライン調査において臍レベルのウエスト周囲径を計測している研究は多いが、中点レベル周囲径とメタボリックシンドロームのリスクファクターに関するエビデンスはこれまで十分でなかった。そこで、本研究では、

ウエストを臍レベルと中点レベル両方を測定し、データベースを作成し、将来的にコホート研究につながることを目的とする。

B．研究対象と方法

対象は茨城農村の筑西市K地区（人口1.7万人）の住民で、2009年の循環器検診でウエストを臍レベルと中点レベル両方を測定した40～74歳男性613人と女性900人である。

日本8学会のメタボリックシンドローム診断基準によるウエスト以外のメタボリックシンドロームリスクファクターの2個以上の割合とウエスト周囲径との関連をロジスティック回帰分析した。

C．研究結果

男女とも臍レベルのウエスト平均値は中点レベルよりも男性で平均0.3cm、女性で平均2.6cmの高値を示した（表１）。ウエスト周囲径を除く、メタボリックシンドロームのリスクファクター2個以上の割合やメタボリックシンドロームのリスクファクター数の割合は男女ともウエスト周囲径の増加に伴い増加傾向を示した（表2）。また、メタボリックシンドロームのリスクファクター2個以上の年齢調整オッズ比は男女ともウエスト周囲径の増加に伴い、増加傾向を示した。この関連は中点レベルのウエスト周囲径にしても同じ傾向であった。

D．考察

本研究により、ウエスト周囲径の増加に伴い、メタボリックシンドロームのリスクファクター2 以上の割合は男女ともに増加する傾向は、臍レベルあるいは中点レベルでのウエスト周囲径の測定値でも同じ傾向を示した。しかしながら、女性においてウエスト周囲径が臍レベルでの測定は中点レベルより大きいな差を示していることから、女性において臍レベルでのウエスト周囲径の測定は中点レベルの測定に比べ、過大に評価される。したがって、大規模なコホート研究によるウエスト周囲径の臍レベルと中点レベル間での比較分析が今後必要である。

表１．性別にみたウエスト周囲径（臍レベル、中点レベル）の平均値±標準偏差

	人数	年齢±標準偏差、歳	ウエスト±標準偏差（臍レベル）、cm	ウエスト±標準偏差（中点レベル）、cm
男性	613	61.7 ±8.7	86.5±7.9	86.2±8.3
女性	900	60.6 ±8.1	83.7±8.8	81.1±8.8

表 2 ウエストとメタボリックシンドロームのリスクファクター数 2 個以上の集積との関連

	男性				女性			
ウエスト(cm)	人数	リスクファクター2個以上の人数	割合	オッズ比	人数	リスクファクター2個以上の人数	割合	オッズ比
臍レベル								
<80	105	8	7.6	1.00	306	13	4.3	1.00
80-84	153	27	17.7	2.6 (1.1-6.0)	209	18	8.6	2.0 (1.0-4.2)
85-89	159	42	26.4	4.3 (1.9-9.6)	178	37	20.8	5.5 (2.8-11)
90-94	103	41	39.8	7.9 (3.5-18)	101	24	23.8	6.5 (3.1-13)
95-99	66	38	57.6	16 (6.8-39)	68	12	17.7	4.4 (1.9-10)
≧100	27	11	40.7	8.4 (2.9-24)	38	12	31.6	9.3 (3.8-23)
中点レベル								
<80	118	9	7.6	1.00	401	19	4.7	1.00
80-84	147	28	19.1	2.8 (1.3-6.2)	212	32	15.1	3.4 (1.9-6.1)
85-89	160	41	25.6	4.1 (1.9-8.9)	141	28	19.9	4.6 (2.5-8.6)
90-94	91	38	41.8	8.6 (3.9-19)	75	20	26.7	6.6 (3.3-13)
95-99	65	36	55.4	15 (6.4-34)	55	12	21.8	5.2 (2.4-12)
≧100	32	15	46.7	11 (4.0-28)	16	5	31.3	8.4 (2.6-27)

* MS リスクは①高血圧値：血圧値≧130/85mmHg または降圧剤服薬者；②高血糖値：血糖値≧110mg/dL（空腹）、<140mg/dL（非空腹）または服薬者；③脂質異常：中性脂肪≧150mg/dL または HDL≧40mg/dL である。

E．結論

臍レベルのウエスト周囲径は中点レベルのウエスト周囲径により高値を示したが、メタボリックシンドロームのリスクファクターとの関連は、臍レベル、中点レベルで同じ傾向を示した。

F．データ管理・更新（倫理面への配慮）

対象地区からの転出は市町村と協力して調査を進めている。氏名や住所など個人を特定できる情報を削除し、解析を行う。このコホート研究全体については、2008 年に大阪大学の倫理審査委員会で倫理審査を受け、承認を得ている。

G. 論文発表

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Noda H, Iso H, Yamashita S, Ueno H, Yokode M, Yamada N, Ouchi Y.	Risk Stratification Based on Metabolic Syndrome as well as Non-Metabolic Risk Factors in the Assessment of Carotid Atherosclerosis	J Atheroscler Thromb	18	In press	2011
Nishina M, Nishina K, Ohira T, Makino K, Iso H	Associations of Psychological Distress with Metabolic Syndrome Among Japanese Urban Residents.	J Atheroscler Thromb	18	In press	2011
磯博康、崔仁哲、野田博之、大平哲也	我が国におけるメタボリックシンドロームの疫学 —有病率・予後・性差など—	日本臨床	69増1	40-46	2011

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

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Original Article

Risk Stratification Based on Metabolic Syndrome as well as Non-Metabolic Risk Factors in the Assessment of Carotid Atherosclerosis

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Aim: We aimed to develop a new approach to risk stratification using metabolic syndrome as well as traditional non-metabolic risk factors, and to examine its validity in carotid atherosclerosis.
Methods: A total of 1,189 men and women aged 21-93 years old were stratified according to the absence or presence of metabolic syndrome defined by Japanese criteria, non-metabolic risk factors, and a past history of coronary heart disease. The risk stratification was as follows: (S-1) persons without a past history, non-metabolic risk factors and metabolic syndrome, (S-2a) those with metabolic syndrome only, (S-2b) those with non-metabolic risk factors only, (S-3) those with non-metabolic risk factors and metabolic syndrome but no past history, and (S-4) those with a past history. Carotid atherosclerosis was defined as maximum intima-media thickness ≥1.1 mm of the far wall of the common carotid artery.
Results: Compared with individuals without these three risk components (S-1), the odds ratio was 7.2 (2.8-18.6) for a past history (S-4), 4.3 (1.7-10.9) for non-metabolic risk factors plus metabolic syndrome but no past history (S-3), 2.6 (1.1-6.4) for non-metabolic risk factors only (S-2b) and 0.5 (0.0-5.7) for metabolic syndrome only (S-2a). Net reclassification improvement from metabolic syndrome only (presence versus absence) to our risk stratification (≥S-3 versus <S-3) was 16.4% ($p<0.0001$), suggesting that our risk stratification improved the classification of atherosclerosis in comparison to metabolic syndrome only.
Conclusion: Risk stratification based on traditional non-metabolic risk factors plus metabolic syndrome rather than metabolic syndrome only appears to be more useful for the clinical assessment of atherosclerosis, and probably in the prevention and control of atherosclerotic disease.

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Key words; Metabolic syndrome, Risk factor, Carotid atherosclerosis, Risk stratification

Introduction

Metabolic syndrome, which has become a major worldwide disease management target[1-8], is a constellation of cardiovascular risk factors associated with an increased risk of cardiovascular disease[9-15], and the Japanese government started a nationwide screening and intervention strategy for metabolic syndrome since April 2008[16]. However, recent epidemiological studies have shown that the emphasis on metabolic syndrome may dismiss some high-risk individuals, especially in the non-obese population[14, 15, 17]. Therefore, we need further classification of the population

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with and without metabolic syndrome to reduce misclassified high-risk patients in general clinical practice.

The Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), Final Report[3] concludes that individuals with a past history of cardiovascular disease have a substantially higher risk of coronary heart disease than those without, and that current smoking, older age, and a family history of cardiovascular disease are independent risk factors for coronary heart disease. Because these risk factors are easy to identify in general clinical practice, reclassification using this information as well as metabolic syndrome may be more useful for the clinical assessment of atherosclerosis.

For identification in clinical practice of groups at high risk of atherosclerotic disease, we attempted to develop a new method of risk stratification based on the combination of metabolic syndrome and traditional non-metabolic risk factors. We also examined the validity of this new stratification method in terms of intima-media thickness (IMT) of carotid arteries.

Materials and Methods

Study Population

We, the Defining Vascular Disease (DVD) group, conducted a cross-sectional study of 41 collaborating clinical centers in 2004. Healthy individuals and patients with cardiovascular disease, who had clinical records of risk factors and a history of cardiovascular disease, were recruited as study subjects from the institutes. They consisted of 3,415 individuals (2,034 men and 1,381 women) aged 16 to 97 years. We recruited the participants at health check-ups and from clinical outpatients at each clinical institute. The average number of participants was 88 with 631 maximum, and the percentage of individuals with a past history of coronary heart disease was 0% to 17% among the 41 institutes. Informed consent was obtained to conduct an epidemiological study based on guidelines of the Council for International Organizations of Medical Science[18]. The study protocol was approved by each institute's human ethics review committee.

We excluded 1,422 individuals who did not undergo carotid ultrasound examination and 804 without data of a past and/or family history and/or waist circumference. We did not exclude patients with familial hypercholesterolemia, because we did not collect that information; however, none of the subjects had serum total cholesterol levels ≥500 mg/dL. Therefore, 1,189 individuals (581 men and 608 women), 21 to 93 years old, from 18 clinical centers were enrolled in this study.

Cardiovascular Risk Factors

The cardiovascular risk factor data included age, height and weight, waist, circumference systolic and diastolic blood pressure, serum total cholesterol, HDL-cholesterol, triglycerides and glucose at fasting, hs-CRP, use of medication for hypertension, hyperlipidemia and diabetes mellitus, smoking status (never smoker, ex-smoker, and current smoker), alcohol intake category (never drinker, ex-drinker, and current drinker), past history of coronary heart disease, past history of other vascular diseases (transient ischemic attack, stroke, arteriosclerosis thrombangiitis obliterans, and/or aortic aneurysm), and a family history of coronary heart disease. We calculated body mass index (BMI) as weight (kg) divided by the square of height in meters (m^2), LDL-cholesterol with the Friedewald formula[19] as LDL-cholesterol (mg/dL) = total cholesterol (mg/dL) − HDL-cholesterol (mg/dL) − 0.2*triglycerides (mg/dL), and the LDL/HDL ratio as LDL-cholesterol (mg/dL)/HDL-cholesterol (mg/dL). Only two individuals had severely high levels of triglycerides (≥800 mg/dL), and we treated then as missing LDL-cholesterol, because the estimated LDL-cholesterol may have been biased.

Identification of Carotid Atherosclerosis

Carotid arteries were evaluated with high-resolution B-mode ultrasonography. We adopted the same ultrasonography protocol used in one of the largest population-based studies of carotid atherosclerosis conducted among elderly Americans, i.e., the Cardiovascular Health Study[20]. The imaging protocol involved obtaining a single longitudinal lateral view of the distal 10 mm of the right and left common carotid arteries (CCAs). To quantify the degree of thickening of the carotid artery walls, we assessed the maximum IMT of CCA, which was defined as the thickest section of either the far right or left wall of the CCA. Carotid atherosclerosis was measured at each clinical center. The carotid atherosclerosis measurement was not standardized, but we assumed that the maximum IMT of CCA is frequently measured in clinical practice and may be reliable. Carotid atherosclerosis was defined as maximum IMT of CCA ≥1.1 mm.

Risk Stratification Algorithm

For risk stratification, we used the presence or absence of 1) a past history of coronary heart disease, 2) non-metabolic risk factors and 3) metabolic syndrome, data which are easily obtained in medical prac-

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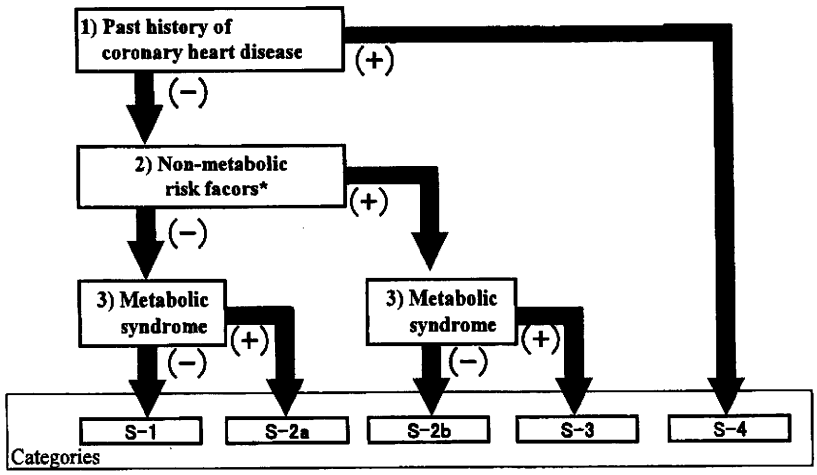

Fig. 1. Algorithm of risk stratification according to a past history of coronary heart disease, non-metabolic risk factors, and metabolic syndrome.

*Non-metabolic risk factors include older age, current smoking, family history of coronary heart disease, and a past history of other vascular diseases.

tice.

The definition by the Japanese Committee to Evaluate Diagnostic Standards for Metabolic Syndrome[6,7] was used for the diagnosis of metabolic syndrome. This definition is based on abdominal obesity (waist ≥85 cm for men and ≥90 cm for women) plus two or more components of metabolic risk factors, namely, 1) high blood pressure: ≥130/85 mmHg; 2) high glucose: fasting glucose ≥6.1 mmol/L (110 mg/dL); 3) dyslipidemia: HDL cholesterol <1.03 mmol/L (40 mg/dL) and/or triglycerides ≥1.69 mmol/L (150 mg/dL).

We stratified the participants into five categories (S-1, S-2a, S-2b, S-3, and S-4) based on the absence or presence of 1) a past history of coronary heart disease, 2) non-metabolic risk factors, and 3) metabolic syndrome (**Fig. 1**). Non-metabolic risk factors were: 2-1) older age: ≥45 years for men and ≥55 years for women, 2-2) current smoker, 2-3) family history of coronary heart disease, and 2-4) past history of other vascular diseases (transitory ischemic attack, stroke, arteriosclerosis obliterans, and/or aortic aneurysm). Although LDL-cholesterol levels or novel risk factors such as hs-CRP were not used for our risk stratification, they were used as adjustment variables.

Statistical Analysis

Student's *t* test and the chi square test were used to compare the characteristics of subjects with and without carotid atherosclerosis. A logistic regression model including the random effect of clinical-center levels was used to calculate crude and multivariable odds ratios (ORs) and 95% confidence intervals (95%CIs) for carotid atherosclerosis according to risk stratification. Tertiles of hs-CRP and the LDL/HDL ratio were used for multivariable adjustment as potential confounding factors, because the distribution of hs-CRP and the LDL/HDL ratio were skewed.

To assess the improvement of misclassification using our risk stratification, we calculated net reclassification improvement[21], which focuses on reclassification tables constructed separately for participants with and without incidences and quantifies the correct movement in categories.

All statistical tests were two-sided and $p<0.05$ was regarded as significant. SAS, version 9.13 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Risk Factors between Subjects with and without Carotid Atherosclerosis

Compared with subjects without carotid atherosclerosis, those with carotid atherosclerosis were older, more likely to smoke, to use medication for hypertension and hyperlipidemia, and to have a past history of coronary heart disease and other vascular diseases, and were less likely to drink (**Table 1**). They also had higher mean values of weight, body mass index, waist

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Table 1. Characteristics of cardiovascular risk factors stratified by the absence and presence of carotid atherosclerosis

Mean±SD/Percentage	Total			Men			Women		
	Carotid atherosclerosis			Carotid atherosclerosis			Carotid atherosclerosis		
	(−)	(+)	*p*-value	(−)	(+)	*p*-value	(−)	(+)	*p*-value
	(*n*=784)	(*n*=405)		(*n*=353)	(*n*=228)		(*n*=431)	(*n*=177)	
Men, %	45.0	56.3	0.0002						
Age, year	59.1±11.0	66.3±9.9	<0.0001	57.8±11.7	64.9±10.3	<0.0001	60.3±10.3	68.0±9.2	<0.0001
Current smoker, %	35.7	47.7	<0.0001	65.4	73.7	0.04	11.4	14.1	0.34
Current drinker, %	45.0	29.7	<0.0001	63.7	43.2	<0.0001	30.1	12.3	<0.0001
Past history of coronary heart disease, %	7.9	32.1	<0.0001	10.5	38.2	<0.0001	5.8	24.3	<0.0001
Past history of other vascular disease, %	4.5	9.1	0.002	4.5	9.6	0.02	4.4	8.5	0.05
Family history of coronary heart disease, %	15.7	18.5	0.22	13.0	20.2	0.03	17.9	16.4	0.72
Body mass index, kg/m^2	23.3±3.6	24.1±3.8	0.0007	24.0±3.3	24.4±3.4	0.24	22.8±3.8	23.8±4.2	0.004
Waist, cm	83.1±10.0	85.4±9.7	0.0001	85.7±8.5	86.5±8.6	0.24	80.9±10.6	83.9±10.7	0.002
Systolic blood pressure, mmHg	126.6±18.0	135.9±19.0	<0.0001	127.4±16.7	135.4±18.1	<0.0001	125.9±19.1	136.4±20.1	<0.0001
Diastolic blood pressure, mmHg	73.0±10.4	74.5±11.4	0.02	74.6±10.4	76.1±11.1	0.09	71.6±10.3	72.4±11.4	0.39
Fasting blood glucose, mg/dL	103.7±23.1	114.3±35.6	<0.0001*	107.7±25.7	114.6±34.1	<0.0001*	100.4±20.2	114.0±37.6	0.01*
Total cholesterol, mg/dL	212±37	209±42	0.37	204±36	203±41	0.72	218±37	218±43	0.98
LDL-cholesterol, mg/dL	130±33	132±39	0.26	125±31	128±36	0.30	134±34	138±41	0.21
HDL-cholesterol, mg/dL	59±16	52±15	<0.0001	53±15	48±14	<0.0001	64±16	57±14	<0.0001
LDL/HDL ratio	2.35±0.89	2.70±0.98	<0.0001	2.50±0.91	2.84±1.04	<0.0001	2.23±0.86	2.53±0.86	0.0001
Triglycerides, mg/dL	118±86	125±65	0.002*	137±105	135±69	0.01*	103±61	112±57	0.30*
Hs-CRP, mg/L	1.1±2.1	1.2±2.1	0.23*	1.2±2.3	1.4±2.4	0.45*	1.0±2.0	1.0±1.7	0.21*
Medication use for hypertension, %	67.9	85.4	<0.0001	69.5	87.5	0.001	66.4	82.7	0.01
Medication use for diabetes, %	68.6	78.9	0.07	61.4	76.2	0.05	79.2	82.4	0.81
Medication use for hyperlipidemia, %	40.6	57.6	<0.0001	34.1	54.3	0.001	45.0	61.2	0.01
Metabolic syndrome and its components									
Metabolic syndrome, %	26.1	48.6	<0.0001	35.7	55.7	<0.0001	18.3	39.5	<0.0001
Abdominal obesity, %	36.6	47.4	0.0004	55.0	59.6	0.30	21.6	31.6	0.01
High blood pressure, %	53.8	77.0	<0.0001	56.4	76.8	<0.0001	51.7	77.4	<0.0001
High glucose, %	26.8	48.4	<0.0001	34.6	50.0	0.0003	20.4	46.3	<0.0001
Dyslipidemia, %	51.0	72.3	<0.0001	51.8	71.9	<0.0001	50.3	72.9	<0.0001

*: Student's *t*-test using log-transformed values because of skewed distributions.

circumference, systolic and diastolic blood pressure, fasting blood glucose, LDL/HDL ratio, and triglycerides, and lower mean values of HDL-cholesterol, and to have metabolic syndrome. These results did not change substantially after stratification for men and women; therefore, further analyses were conducted for men and women combined, adjusted for sex.

Odds Ratios of carotid Atherosclerosis According to Risk Factors

A significantly higher prevalence of carotid atherosclerosis was observed in association with each of the components except current smoking, a past history of other vascular diseases and a family history of coronary heart disease (**Table 2**). The multivariable odds ratios (95% confidence intervals) for carotid atherosclerosis were 2.5 (1.6-3.9; $p=0.0004$) for the presence versus absence of a past history, 3.8 (1.7-8.8; $p=0.003$) for the presence versus absence of non-metabolic risk factors, and 1.4 (1.0-2.0; $p=0.04$) for the presence versus absence of metabolic syndrome. These results were similar for men and women (not shown in the table). Among the components of metabolic syndrome, high blood pressure and then high glucose were strongly associated with the prevalence of carotid atherosclerosis.

Risk Stratification Algorism and Odds Ratio of Carotid Atherosclerosis

After risk stratification (**Table 3** and **Fig. 2**), we

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Table 2. Crude and multivariable odds ratios (OR) and 95% confidence intervals (95%CI) of carotid atherosclerosis according to cardiovascular risk factors for men and women combined

	No. at risk	No. of cases	Crude OR (95%CI)	Multivariable* OR (95%CI)
Past history of coronary heart disease	192	130	3.0 (2.0-4.5)	2.5 (1.6-3.9)
Non-metabolic risk factors	1,096	396	4.1 (1.8-9.3)	3.8 (1.7-8.8)
Older age	1,015	384	3.9 (2.2-6.7)	3.8 (2.2-6.8)
Current smoking	473	193	1.5 (1.1-2.0)	1.3 (0.9-1.9)
Family history of coronary heart disease	198	75	1.0 (0.7-1.5)	1.0 (0.7-1.5)
Past history of other vascular diseases	72	37	1.5 (0.8-2.7)	1.4 (0.8-2.6)
Metabolic syndrome	324	148	1.7 (1.3-2.4)	1.4 (1.0-2.0)
Abdominal obesity	479	192	1.6 (1.2-2.2)	1.4 (1.0-1.9)
High blood pressure	734	312	2.4 (1.7-3.3)	2.2 (1.6-3.1)
High glucose	406	196	2.1 (1.5-3.0)	1.9 (1.4-2.7)
Dyslipidemia	693	293	1.7 (1.3-2.4)	1.4 (1.0-2.0)

*: Adjusted for sex, drinking status, hs-CRP (tertile), and LDL/HDL ratio (tertile).

observed the higher prevalence of carotid atherosclerosis in high-risk categories (S-2b, S-3, and S-4), compared with the reference category (S-1). Adjustment for potential confounding factors, i.e., sex, drinking status, hs-CRP, and the LDL/HDL ratio, did not result in a substantial change in these associations. The multivariable odds ratios (95%CI) for the study population compared to subjects without a past history, non-metabolic risk factors and metabolic syndrome (S-1) were 7.2 (2.8-18.6) for subjects with a past history (S-4), 4.3 (1.7-10.9) for those with non-metabolic risk factors and metabolic syndrome but no past history (S-3), 2.6 (1.1-6.4) for those with non-metabolic risk factors but no metabolic syndrome and no past history (S-2b), and 0.5 (0.0-5.7) for those with metabolic syndrome but no other two risk components (S-2a). Net reclassification improvement from metabolic syndrome only (presence versus absence) to our risk stratification (≥S-3 versus <S-3) was 16.4% ($p<0.0001$), suggesting that our risk stratification improved the classification of atherosclerosis in comparison to metabolic syndrome only.

The odds ratios of potential confounding factors was 1.2 (0.8-1.6) for sex (men versus women), 0.8 (0.6-1.1) for drinking status (current versus never drinkers), 1.2 (0.8-1.6) for hs-CRP (the highest versus lowest categories), and 1.9 (1.3-2.8) for LDL/HDL ratio (the highest versus lowest categories).

When subjects in S-1 were further divided into those without any metabolic risk factors (S-1a) and those with metabolic risk factors (S-1b), these was only one case of carotid atherosclerosis in S-1a and seven in S-1b (not shown in Table). The respective multivariable odds ratio of carotid atherosclerosis with reference to S-1a was 2.8 (0.3-30.3) for S-1b, 1.1 (0.1-25.6) for S-2a, 5.8 (0.7-51.6) for S-2b, 9.5 (1.1-85.8) for S-3, and 15.9 (1.7-146.5) for S-4.

Odds Ratio According to Risk Factors Stratified by Abdominal Obesity

Of 996 subjects with metabolic risk factors, 552 (55%) had no abdominal obesity but had a similarly high prevalence of a past history for coronary heart disease (17.9% versus 19.1%) and of non-metabolic risk factors (93.1% versus 96.6%), as did those with abdominal obesity (not shown in Table). As shown in **Table 4**, we observed a higher prevalence of carotid atherosclerosis in subjects with the higher number of metabolic risk factors, irrespective of abdominal obesity. Subjects with abdominal obesity but no other metabolic risk factors had higher age- and sex-adjusted triglyceride levels (67.1 mg/dL versus 89.6 mg/dL; $p=0.001$) and lower HDL-cholesterol levels (64.8 mg/dL versus 57.7 mg/dL; $p=0.009$) than those without abdominal obesity or other metabolic risk factors (not shown in Table). There were no differences in the mean blood pressure, glucose and LDL-cholesterol levels between them. The excess prevalence of carotid atherosclerosis was similarly observed for subjects with each metabolic risk factor, i.e. high blood pressure, high glucose and dyslipidemia, irrespective of abdominal obesity (**Table 4**).

Discussion

In this large cross-sectional study of Japanese men and women, we developed a new risk stratification for prevention and control of atherosclerotic dis-

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Table 3. Crude and multivariable odds ratio (95% confidence interval) for subjects with ≥1.1 mm of IMT(intima-media thickness)-Cmax-far wall according to risk stratification using a past history of coronary heart disease, non-metabolic risk factors and metabolic syndrome for men and women combined.

Past history of coronary heart disease	[---------- Absence ----------]								Presence
Non-metabolic risk factors	[------ Absence ------]		1	2	3-4	1	2	3-4	
Metabolic syndrome	Absence	Presence	[---------- Absence ----------]			[---------- Presence ----------]			Absence/ Presence
Names of categories	S-1	S-2a	[---------- S-2b ----------]			[---------- S-3 ----------]			S-4
No. at risk	82	10	374	244	43	113	110	21	192
No. of cases	8	1	84	71	11	42	45	13	130
Crude OR (95%CI)	1.0	0.8 (0.1-8.7)	2.7 (1.1-6.7)	3.4 (1.4-8.4)	2.7 (0.9-8.6)	4.7 (1.8-12.5)	6.0 (2.3-15.6)	12.1 (3.2-45.3)	9.1 (3.5-23.8)
Crude OR (95%CI)	1.0	0.8 (0.1-8.5)	[----------	3.0 (1.2-7.1)	----------]	[----------	5.8 (2.3-14.4)	----------]	9.1 (3.5-23.7)
Multivariable OR (95%CI)*	1.0	0.6 (0.1-6.6)	2.6 (1.1-6.5)	3.1 (1.2-8.0)	2.5 (0.8-8.2)	4.0 (1.5-11.2)	4.9 (1.8-13.4)	10.0 (2.6-38.7)	7.9 (3.0-21.1)
Multivariable OR (95%CI)*	1.0	0.5 (0.0-5.7)	[----------	2.6 (1.1-6.4)	----------]	[----------	4.3 (1.7-10.9)	----------]	7.2 (2.8-18.6)

*: Adjusted for sex, drinking status, hs-CRP (tertile), and LDL/HDL ratio (tertile).

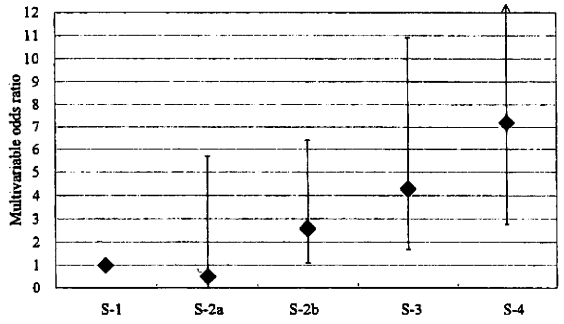

Fig. 2. Multivariable odds ratio (95% confidence interval) for subjects with ≥1.1 mm IMT (intima-media thickness) according to risk stratification using a past history of coronary heart disease, non-metabolic risk factors and metabolic syndrome.

ease based on non-metabolic risk factors (past history of coronary heart disease, older age, current smoker, family history of coronary heart disease, past history of other vascular diseases) and metabolic syndrome, which we can easily obtain in general clinical practice. We also examined the validity of this risk stratification in relation to intima-media thickness (IMT) of common carotid arteries as an indicator of carotid atherosclerosis. Our risk stratification may improve the detection of carotid atherosclerosis, compared with that using metabolic syndrome alone, since the net reclassification improvement from metabolic syndrome only to our risk stratification was large (16.4%, $p<0.0001$).

The advantage of our risk stratification is its ease of application because we used general information from medical interviews and metabolic risk factors. Previous frames for risk stratifications required the measurement of serum total cholesterol[22, 23], creatinine, aspartate transaminase, alanine transaminase and urinary protein[22], total cholesterol[23] and LDL-cholesterol[24], but some risk factors (e.g. total cholesterol) and creatinine are no longer measured in the Japanese nationwide screening and intervention program for metabolic syndrome[16].

Subjects with both non-metabolic risk factors plus metabolic syndrome (S-3) had a 4.3 times higher risk of atherosclerotic disease than the reference group (S-1), while the risk for subjects with non-metabolic risk factors only (S-2b) was still 2.6 times higher. This result suggests the importance of non-metabolic risk factors in the risk stratification of high-risk individuals, as described in a previous study[24].

On the other hand, the presence of metabolic syndrome was associated with a higher risk of atherosclerotic disease among subjects with non-metabolic risk factors. Subjects with non-metabolic risk factors plus metabolic syndrome (S-3) had a 1.7 higher prevalence of carotid atherosclerosis than those with non-metabolic risk factors only (S-2b); therefore, our results suggest the importance of both metabolic syndrome and non-metabolic risk factors for the detection of atherosclerotic disease.

It also should be mentioned that subjects without metabolic syndrome included high-risk individuals, such as those with high blood pressure, high glucose, or dyslipidemia but not abdominal obesity, when we used the Japanese criteria for metabolic syndrome

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Table 4. Multivariable odds ratios (OR) and 95% confidence intervals (95%CI) of carotid atherosclerosis according to metabolic risk factors stratified by abdominal obesity for men and women combined

Abdominal obesity	[---------- Absence ----------]			[---------- Presence ----------]		
Number of metabolic risk factors	0	1	2-3	0	1	2-3
No. at risk	158	239	313	35	120	324
No. of cases	8	56	149	7	37	148
Multivariable OR (95%CI)*	1.0	4.3 (1.8-10.3)	8.5 (3.7-20.0)	3.9 (1.1-13.3)	5.9 (2.3-14.7)	8.0 (3.4-18.6)
High blood pressure	(−)	(+)		(−)	(+)	
No. at risk	332	378		123	356	
No. of cases with carotid atherosclerosis	61	152		32	160	
Multivariable OR (95%CI)*	1.0	2.3 (1.5-3.5)		1.3 (0.7-2.3)	2.5 (1.7-3.9)	
High glucose	(−)	(+)		(−)	(+)	
No. at risk	516	194		267	212	
No. of cases	108	105		101	91	
Multivariable OR (95%CI)*	1.0	3.3 (2.0-5.2)		2.0 (1.3-3.0)	2.2 (1.4-3.5)	
Dyslipidemia	(−)	(+)		(−)	(+)	
No. at risk	339	371		157	322	
No. of cases	67	146		45	147	
Multivariable OR (95%CI)*	1.0	1.6 (1.1-2.5)		1.7 (1.0-2.8)	2.0 (1.3-3.2)	

*: Adjusted for sex, drinking status, hs-CRP (tertile), and LDL/HDL ratio (tertile).

where abdominal obesity as an essential component. In fact, 55% of subjects with metabolic risk factors had no abdominal obesity but had a similar high prevalence of a past history of coronary heart disease and non-metabolic risk factors, as did those with abdominal obesity. Subjects with and without abdominal obesity also had a similar high prevalence of carotid atherosclerosis. Our finding correlates with the results from recent cohort studies that non-overweight individuals with metabolic risk factors had a similar excess risk of cardiovascular disease to overweight individuals with metabolic risk factors[14, 15, 17].

There are a few limitations to our study. First, the epidemiological data were obtained from a cross-sectional study. A causal inference could thus not be assessed. However, evidence from previous cohort studies and clinical trials supports the causality of metabolic syndrome and non-metabolic risk factors in the development of atherosclerosis. Second, our study participants were recruited from medical centers, which may have caused a selection bias. In fact, the prevalence of metabolic syndrome (28.1% for men and 25.7% for women) was higher than in the national survey (23.0% for men and 8.9% for women), especially for women[25]. Risk prediction in our study may thus have been underestimated. Third, carotid atherosclerosis was measured at each clinical center, and was not centralized; however, previous studies showed that the assessment of maximum IMT of CCA ≥1.1 mm had high reliability and was of use for the prediction of coronary heart disease events[20, 26, 27]. Fourth, we did not measure some potential cardiovascular risk factors (e.g. socioeconomic status and psychosocial factors), which may have led to residual confounding. Fifth, in our primary analysis, we did not divide S-1 into those without any metabolic risk factors (S-1a) and those with metabolic risk factors (S-1b) due to the relatively small sample size of cases in S-1; however, as discussed above, subjects with high blood pressure, high glucose or dyslipidemia, but not abdominal obesity were also likely to be at high risk. Thus, we need to pay attention to these patients in the prevention and control of atherosclerotic disease. Finally, we recruited participants with a wide range of health status (i.e. health check-ups and clinical outpatients), and excluded 2,226 subjects from our analyses due to missing data. These selections may have led to potential bias; therefore, further studies are necessary to confirm the generalizability of our risk stratification.

In summary, the study presented here provides epidemiological evidence that risk stratification based on metabolic syndrome as well as non-metabolic risk

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factors is useful for the clinical assessment of atherosclerosis and probably in the prevention and control of atherosclerotic disease. We also need to pay attention to high-risk individuals without abdominal obesity, but with high blood pressure, high glucose or dyslipidemia.

Conflict of Interest Statement

None declared.

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Appendix 1

The following individuals were Defining Vascular Disease (DVD) Research Group Members: A Kitamura, H Daida, T Shoji, T Mannami, T Murohara, K Kukiyama, M Masutani, K Kitagawa, T Hiro, A Kawaguchi, M Kuroki, M Kinoshita, S Ishibashi, M Eto, H Kotake, T Hayashi, K Shimada, Y Kumon, T Miura, H Bujo, E Nomura, T Gotohda, N Yoshioka, Y Ishigaki, S Koba, K Hirata, M Akishita, H Ogawa, S Sugiyama, K Ishiwata, K Kozaki, Y Sato, K Shirai, M Yoshida, T Hirano, K Mizuno, K Node.

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Original Article

Associations of Psychological Distress with Metabolic Syndrome Among Japanese Urban Residents

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Aims: To examine and evaluate the association between psychological distress and metabolic syndrome (MetS).

Methods: Between 2005 and 2006, 1,613 men and women aged 30-79 participated in annual health examinations at Takarazuka City Health Promotion Center in Takarazuka, Japan. Psychological stress was assessed with the General Health Questionnaire (GHQ) and MetS was evaluated using three criteria based on those of the Japanese Society of Internal Medicine as the Japanese counterpart of the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (NCEP/ATPⅢ) and the International Diabetes Federation (IDF).

Results: The mean depression score after adjustment for age, smoking, alcohol intake and serum total cholesterol levels was higher for men with than without MetS as defined by Japanese criteria as well as for men with than without fasting glucose ≥110 mg/dL. Multivariable-adjusted, odds ratio associated with increments of one standard deviation in the depression score was 1.48 (1.19-1.84) for MetS, and anxiety and depression scores were 1.32 (1.08-1.61) and 1.24 (1.03-1.50) for fasting glucose ≥110 mg/dL, respectively. Similar trends were observed for the depression score and MetS as defined by NCEP/ATPⅢ and IDF. For women, somatic symptoms, anxiety, and depression were not associated with MetS and its components.

Conclusions: Depressive symptoms are considered to be associated with MetS and, more specifically, glucose abnormality among urban Japanese men.

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Key words; Cross-sectional studies, Depression, Metabolic syndrome, Psychological distress

Introduction

Metabolic syndrome (MetS) consists of a cluster of abnormalities of metabolic origin, defined as a combination of abdominal obesity, dyslipidemia, high blood pressure and glucose abnormality[1, 2], which increases the risk of type 2 diabetes mellitus (DM) and cardiovascular disease not only in Western populations[3], but also in their Japanese counterparts[4-7].

Psychological distress is considered to be a risk factor for MetS. A cross-sectional study of 87 monozygotic and 86 dizygotic male twin pairs in the US showed that depressive symptoms were associated with metabolic risk factors such as body mass index, waist-to-hip ratio, mean arterial pressure, triglycerides and glucose[8]. A 7-year prospective study of 425 middle-aged women in the US showed that depressive symptoms were predictive of a risk of MetS[9]. A 14-year large-scale prospective study of 10,308 middle-aged men and women in England showed that chronic work stress was associated with a risk of MetS[10]. Finally, a recent 15-year prospective study of 523 middle-aged pre-menopausal women in the US also indi-

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cated that depressive symptoms and stressful life events were associated with a risk of MetS[11].

However, few studies have addressed the association between psychological distress and MetS in Asian populations. A cross-sectional study of 1,215 male Japanese workers showed a positive relationship between depression and MetS[12], but no women were included in this study.

The aim of this study was to determine whether psychological distress is associated with MetS and its components in Japanese men and women.

Methods

Participants

We conducted a cross-sectional study of 1,694 persons (868 men and 826 women) aged 30-79 years who participated in annual health examinations for citizens at Takarazuka City Health Promotion Center in Takarazuka, Japan, between April 1, 2005 and March 31, 2006. The study protocol was approved by Takarazuka City Health Promotion Center and informed consent was obtained from each participant. We excluded participants with insufficient answers to the psychological stress questionnaire and analyzed the data of the remaining 1,613 participants (825 men and 788 women).

Metabolic Risk Factors

All of the participants underwent risk factor examinations at Takarazuka City Health Promotion Center after an overnight fast. Blood pressure was measured twice with a standard mercury sphygmomanometer on the right arm of seated participants after a 5-minute rest, and the second measurement was used in analysis. Hypertension was defined as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg. Blood was drawn from the seated participants into a plain, siliconized glass tube after which the serum was separated. Serum total cholesterol, triglycerides and glucose were measured with enzymatic assays, and high-density lipoprotein (HDL) cholesterol was measured with a direct homogenous assay using an Olympus AU-5431 spectrophotometer (Olympus Japan Co., Ltd., Tokyo, Japan) at Hyogo Prefecture Health Promotion Association.

The participants completed a self-administered questionnaire about the frequency of alcohol intake per week and the usual amount consumed daily in units of "*go*" (a Japanese traditional unit of volume measurement, corresponding to 23 g ethanol). Weekly alcohol intake was calculated and then converted to daily alcohol consumption. The questionnaire also asked about smoking status (never, former, or current smoker), and former or current smokers were asked about the number of cigarettes smoked per day and the number of smoking years.

We used the modified definition of MetS according to the guideline of the Japanese Society of Internal Medicine, known as the modified Japanese criteria[13]. Body mass index (BMI) ≥25 kg/m^2 was used as representing obesity for the analysis, because waist circumference was not measured in this study. This BMI level reportedly corresponds well to the Asian criterion for a large waist circumference of ≥90 cm for men and ≥80 cm for women[14]. MetS was defined as being overweight (BMI ≥25 kg/m^2) plus two or more of the following components: 1) serum triglycerides ≥150 mg/dL and/or HDL cholesterol <40 mg/dL, 2) fasting glucose ≥110 mg/dL, and 3) blood pressure ≥130/85 mmHg (**Table 1**).

We also used the modified criteria of the third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (NCEP/ATPIII)[1, 15] and of the International Diabetes Federation (IDF)[16]. MetS was defined by the modified NCEP/ATPIII as the presence of three or more of the following components: 1) serum triglycerides ≥150 mg/dL, 2) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, 3) fasting glucose ≥100 mg/dL, 4) blood pressure ≥130/85 mmHg, and 5) BMI ≥25 kg/m^2. MetS was defined by the modified IDF as being overweight (BMI ≥25 kg/m^2) plus two or more of the following components: 1) serum triglycerides ≥150 mg/dL, 2) HDL cholesterol <40 mg/dL for men and <50 mg/dL for women, 3) fasting glucose ≥100 mg/dL, and 4) blood pressure ≥130/85 mmHg (**Table 1**).

Psychological Distress Questionnaire

For the self-administered questionnaire on psychological distress we used the 28-item version of the General Health Questionnaire (28-item GHQ)[17], which was derived from the 60 items in the original version of the GHQ developed by Goldberg *et al.*[18]. All 28 questions were scored according to the Likert method (1, 2, 3, 4 : 1='not at all', 2='no more than usual', 3='rather more than usual' , and 4='much more than usual')[19]. The 28-item GHQ is composed of 4 subscales: 1) somatic symptoms, 2) anxiety, 3) social dysfunction, and 4) depression, and each subscale has 7 questions. The total score ranges from 7 to 28. The validity and reliability of the 28-item GHQ has been confirmed[19]. In the present study, the score showed a normal distributive pattern as in a previous study[19].