厚生労働科学研究費補助金

臨床研究基盤整備推進研究事業

糖尿病における血管合併症の発症予防と進展抑制に関する研究

(Japan Diadetes Complications Study;JDCS)

平成17年度～平成18年度　総合研究報告書

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研究要旨

Evidence-based Medicine(EBM)の重要性が強調され、大規模臨床研究や医師主導による治験の重要性はますます高まっている。それに伴い臨床研究実施チームの果たす役割も増大している。本研究 Japan Diabetes Complications Study (JDCS)は、臨床研究実施チームの統括のもとで、日本人 2 型糖尿病患者を対象に、生活習慣指導などの介入による治療改善を通じた合併症抑制の可能性を検討するとともに、日本の糖尿病患者の特徴や診療の現況を明らかにして、治療のためのエビデンスを確立することを目的として行われた。ＪＤＣＳは平成 8 年に開始され、北海道から九州までの全国 59 施設において 2205 症例が登録され 10 年間継続されている。欧米人糖尿病患者を対象にした類似研究と比較すると、日本人患者は肥満が顕著でないことや、血糖コントロールの経時的増悪が認められないことなどを始め多くの違いが認められた。今回の研究により得られたコホートとデータベースは、今後長期間にわたり様々な面からの追加研究に用いることができる貴重なものであり、欧米以外で初めての２型糖尿病患者を対象にした介入研究として、将来のわが国の糖尿病治療・対策に役立つものと期待される。さらに今回の臨床研究チームを有効に活用することによって多くの医師主導治験に結びつけることができ、今後の臨床研究における臨床研究チームのあり方についてモデルを作成することができた。

A．研究目的

生活習慣病の蔓延が指摘されて久しい。戦後の生活習慣の急速な変化、とりわけ食事の欧米化と交通の整備に伴う身体活動量の減少は、肥満・高脂質血症、糖尿病などの増加と切っても切れない関係がある。特に急激な 2 型糖尿病患者数の増大はその代表的な者である。たとえば、平成 14 年度に厚生労働省から発表された糖尿病実態調査では、疑い例を含めて成人の 6.3 人に一人が 2 型糖尿病もしくはその疑いが極めて高いという深刻な事態に陥っている。

これからの本格的な高齢化社会を迎え、生活の質や高騰する医療費との関係においても、2型糖尿病はもっとも重視すべき疾患のひとつである。この危機感は、日本のみならず世界中で共有されており、国連においても、'Unite for diabetes' を合い言葉に、感染症以外では初めて単独疾患として糖尿病を取り上げて、世界で団結して取り組む姿勢をアピールしている。

これまで糖尿病分野については、いくつかの欧米の研究が多くの重要なエビデンスを生み出し、その診療に多大な貢献をしてきた。代表的なものとしては、米国人 1 型糖尿病を対象にした Diabetes Control and Complications Trial(DCCT)と、英国人 2 型糖尿病を対象にした英国の United Kingdom Prospective Diabetes Study (UKPDS)が挙げられる。

しかし DCCT は 1 型糖尿病のみを対象にしたものであり、また UKPDS では、介入群、非介入群ともに体重の増加、血糖コントロールの長期的悪化がみられ、介入手段としてインスリンや薬物を用いることの問題点も明らかになった。

さらにもっとも重要な問題として、遺伝的背景やライフスタイルが欧米人とは大きく異なる日本人糖尿病患者の診療方針や保健施策決定に当たって、このような欧米人対象の研究から得られたエビデンスを、そのまま適用できるか否かは明らかでないという点が挙げられる。日本人患者の診療に安心して使える臨床エビデンスを確立するために、日本人患者を対象にした大規模臨床研究によるエビデンスが求められる所以である。

本研究 JDCS では日本全国より多数の症例を登録し、患者教育による生活習慣改善を中心的な介入手段として、前向きに追跡調査を進めてきた。平成 7 年度の報告書に JDCS の調査実施計画の詳細が記載されているが、そのプロトコールに基づいて平成 8 年 4 月より現在まで介入と追跡が継続されてきた。

臨床研究チームはこのプロジェクトに極めて大きな役割を果たしてきた。具体的には、患者と主治医の橋渡し的な役割に加えて、症例票の記入補助、臨床データの確認、転記ミスの発見と修正などデータベースの整備、参加施設間の連絡の支援などの地道な作業である。

今回のプロジェクトで、日本の糖尿病患者と糖尿病専門医、臨床研究チームが協力して築き上げた貴重なコホートは、今後とも日本のみならず東アジア諸国を始めとする世界の糖尿病診療に大きく貢献していくことが期待されている。

B．研究方法

JDCS の事務局は、茨城県つくば市にある筑波大学大学院臨床医学系内分泌代謝糖尿病内科におかれ、さらに東京お茶の水にある糖尿病データセンターにおいても、

データの収集・解析・事務などの作業が実施されている。登録症例のすべてのデータは、散逸を防ぎ質を保証するために、この糖尿病データセンターにおいて一元管理がなされている。

本研究の対象患者は、主治医が積極的に生活習慣改善を中心とした強化治療を行う「介入群」と、通常の外来診療を継続する「非介入群」に割り付けられている。そして両群間で、血糖コントロールや血管合併症などについて差があるかどうかを検討している。介入群の患者には、体重、血糖、血圧、血清脂質、飲酒・喫煙などについて「治療到達目標」が設定されており、主治医も患者もこれを到達するように努力することが求められている。各学会の診療ガイドラインの厳格化にともない、JDCSにおいても、途中、「治療到達目標」が改訂強化された（表１）。

各合併症の診断基準は予めプロトコールで定められており、たとえば網膜症についてはその発症(1次予防)および単純性網膜症の進展(2次予防)、腎症については尿アルブミン 300 mg/24hr 以上の出現とし、それぞれ専門家の判定委員により判定されている。各種データはコンピューターに入力し、統計専門家による解析や効果判定を実施している。

(倫理面への配慮)
本研究は倫理委員会の許可のもとに進められており、すべての対象者においてインォームドコンセントがなされ、同意書が得られている。従来の欧米の大規模臨床介入試験のように、非介入群をコントロール不良のまま観察することは倫理的配慮から避け、両群において内服薬やインスリンなどの変更は妨げず、非介入群についても治療目標を達成するように、通常の外来管理を継続している。また介入自体も、薬剤やインスリンによる介入と比較して安価で、低血糖などの副作用がないという点でも安全性に優れている。実際に開始後現在までの８年間、特に倫理的な問題を生じた事はなく、順調に進行している。

C．D.研究結果と考察
将来の日本の糖尿病診療に役立つエビデンスを日本人データで造り上げる、という本研究の趣旨を、専門医の先生方と患者さんの双方がよくご理解の上、大変な努力をしていただいたにも関わらず、10 年という歳月の間には、主治医の交代、患者さんの異動などでどうしても消息が不明になってしまった患者さんがある程度おられたことは事実で、この種の研究の難しさが実感された。臨床研究チームはこのような点においても威力を発揮し、この貴重な経験とノウハウは、今後わが国で行われる類似研究に活かされるものと思われる。

全患者の平均 HbA_{1C} は約 7.6%であり、残念ながら介入群と非介入群との差は統計的有意に達せず、生活習慣介入の難しさを示す結果となった。しかしその背景には、本研究参加施設（すべてが糖尿病診療の専門施設）の通常診療（非介入群に施されている治療）のレベルがもともと高かったこともあるとみられる。また全登録者の平均肥満度(BMI)もまったく増加しておらず、このことはむしろ、欧米の前向き調査結果では見られない本邦の糖尿病患者の特徴と言える。

本研究では、このほかにも欧米とは異なる日本人糖尿病患者の興味深い特徴が数多く捉えられた。たとえば昨年度までの解析では、JDCS 登録患者と UKPDS 登録患者との肥満度とエネルギー摂取量を比較した結果、日本人２型糖尿病患者は、白人患者と比較して平均肥満度は少ないにも関わらず、単位体重あたりのエネルギー摂取

量は逆に多く、過食による肥満以外の要素もかなり大きく影響している可能性が示唆された。このような著明な差の背景として、白人と日本人とのインスリン分泌能やインスリン抵抗性の違いが関与しているものと推測される。

さらに日本人糖尿病患者と欧米人糖尿病患者とのアルコール摂取の影響の違いも興味深い。すなわち欧米人糖尿病患者を対象にした研究のメタアナリシスでは、適度（エタノール換算で一日 38ｇ以下）のアルコール摂取は、冠動脈疾患抑制効果を有することが示されている。しかし JDCS 登録患者ではそのような現象は認められなかった（表 2)。したがって日本人２型糖尿病患者に対しては、たとえ適量だとしても、飲酒はあまり勧められないことになる。

また、JDCS 登録患者と米国の糖尿病患者では、血圧や脂質の平均値がそれほど違わないにも関わらず、降圧薬・高脂血症薬の使用頻度が極端に違うことも示唆され（表 3)、日本人と欧米人とで、これらの薬物に対する感受性が異なる可能性も考えられる。このような日本人糖尿病の特徴を抽出していくことは、その病態背景を理解し、日本人糖尿病患者に適した対策を考える上で重要であろう。

前向き研究による日本人患者における細小血管合併症の発症率とリスクファクターのデータは多くないので、これらのデータはその意味でも貴重であり今後のさらなる解析が期待される。たとえば、網膜症とメタボリック症候群との関連が示唆され、最近の欧米の研究で指摘された糖尿病神経障害と心血管リスクファクターとの関連が指摘されていることとあわせて考えると興味深い結果である。

また腎症に関する解析結果では、収縮期血圧が 140 mmHg 以上の患者の腎症発症のリスクは、130 mmHg 未満の患者の 2.7 倍に上昇していた。また HbA_{1C} 9%以上以上の患者の腎症発症のリスクは、7%未満と比較して 3.3 倍であり、あらためて腎症における血圧と血糖の両方の管理の重要性が浮き彫りになった。

一方、大血管合併症については、わが国では冠動脈疾患より脳血管障害の頻度が多いことが以前から知られていた。しかし今回検討した糖尿病患者では、冠動脈疾患の発症率が脳血管障害の発症率を上回っており、言わば欧米型の動脈硬化疾病構造に変化しつつあることが注目される。これらの大血管イベント発症患者を、それぞれエンドポイントに達しなかったものと比較すると、日本人２型糖尿病患者においても、大血管合併症予防には、血糖コントロールと共に脂質や血圧のコントロールも重要であることが判明した。

また介入群に対する強化治療の効果については、以前からひき続いて、脳血管障害の発症が有意に少ないことが明らかになった。この点については、虚血性心疾患を含むその他の合併症や検査指標に両群間差がなかっただけに、その機序に興味が集まる。今後いろいろな側面から詳細に検討される予定である。

一方、今回組織された臨床研究チームはＪＤＣＳ以外にも様々な治験において活躍がみられ、特に医師主導治験においては極めて大きな貢献がみられた。現在進行中のものもあるため、そのすべてを公開することはできないが、全部で１９件に及んだ。その一部を表４にまとめた。

E. 結論

わが国におけるこれまでの糖尿病に関

する無作為割り付け前向き臨床試験の中では最も規模の大きい Japan Diabetes Complications Study (JDCS)を実施した。その中間成績は臨床現場に役立つエビデンスを生み出しつつあり、すでに多くの国際誌で報告され、国際的注目を集めている。今後も引き続き多くの成果が期待される。

JDCS はわが国の多くの糖尿病専門医・患者ならびに関係者の長年の努力の結晶である。今のところまだ中間データの段階であるが、今後のさらに詳細な解析が行われることにより、日本人（東アジア人）糖尿病のエビデンスを確立することを通じて、わが国の将来の糖尿病診療に大きく貢献することが期待される。

このような大規模臨床研究は、すでに日常の診療業務に忙殺される医師のみでは遂行不可能である。また内容的にも複雑化しているため、薬剤師、臨床検査技師、保健師、管理栄養士、生物統計学専門家などコメディカルスタッフとの協力関係抜きの実施は考えられない。今回の臨床研究チームは、この分野の充実に向けて、将来のモデルとなるものと期待される。

F. 健康危険情報

該当事項なし

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表１　強化治療群の新治療目標

下記のすべてを達成するように、主治医による強化治療を実施する。

① HbA_{1c}：　6.5%未満

② BMI：　22 kg/m^2未満

③ 血圧：　130 mmHg 未満／80 mmHg 未満［目標値に達しない場合は、ARB または ACE-I（またはその両方）を用いる］

④ 血清脂質：LDL コレステロール＜100 mg/dl（血清総コレステロール＜180 mg/dl）［目標値に達しない場合は、スーパースタチンの中でも　できるだけピタバスタチン（リバロ™）を用いる］（治療薬剤を統一する必要があるので）

⑤ 可能な限り抗血小板療法

表２　日本および欧米の糖尿病患者におけるアルコール摂取と心血管合併症の関係

	Howard, et al. (2004)	JDCS（/1000人年）（文献3より）	
	冠動脈疾患	冠動脈疾患	脳卒中
飲酒なし	100%	7.3	6.5
38gエタノール(=日本酒1.5合)までの飲酒	45-66%	9.1	7.6
それ以上の飲酒	143%	8.7	12.9*

表３　日本と米国における糖尿病患者の降圧薬・高脂血症薬の使用状況と血圧および血清脂質の状況（平均±標準偏差）（文献２より引用）

	JDCS （登録時）	MGH Revere Health Care Center
患者数［男性の比率%］	2205［55］	128［39］
年齢（歳）	59 ± 7	66 ± 12
HbA_{1C}（%）	7.7 ± 1.4	7.7 ± 1.5
収縮期血圧（mmHg）	132 ± 16	136 ± 18
拡張期血圧（mmHg）	77 ± 10	73 ± 10
総コレステロール（mg/dL）	201 ± 35	180 ± 37
降圧薬服用率（%）	28	80
高脂血症薬服用率(%)	26	57

表４　本臨床研究チームが携わったこれまでの治験の例（未報告のものもあるため、概要のみ表示）

（１）２型糖尿病患者におけるビグアナイド薬とインスリン抵抗性改善薬の効果比較に関する臨床試験

（２）２型糖尿病患者におけるカルシウム拮抗薬とアンジオテンシン受容体拮抗薬の効果比較に関する臨床試験

（３）２型糖尿病患者におけるスタチン系薬とフィブラート系薬の効果比較に関する臨床試験

（４）１型糖尿病患者に対するαグルコシダーゼ阻害薬の効果に関する臨床試験

（５）肥満２型糖尿病患者における超低カロリーフォーミュラ食品と通常食の比較試験

（６）２型糖尿病患者における各種インスリン混合製剤の効果に関する比較試験

（７）２型糖尿病患者における速効性インスリン分泌刺激薬とαグルコシダーゼ阻害薬の使い分けに関する比較試験

（８）MRFACT STUDY（糖尿病における動脈硬化対策のための多項目危険因子能動的及び積極的コントロール）

（９）厚生労働科学研究/難治性疾患克服研究事業　原発性高脂血症に関する調査研究におけるデータ収集と整理

（１０）長寿科学総合研究　高齢者糖尿病を対象とした前向き大規模介入研究におけるデータ収集と整理

別紙４

研究成果の刊行に関する一覧表

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
Sone H, Mizuno S, Fujii H, Yoshimura Y , Yamazaki Y, Ishibashi S, Katayama S, Saito Y, Hideki I, Ohashi Y, Akanuma Y, Yamada N. Japan Diabetes Complications Study (JDCS) Group.	Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in Asian diabetic patients? –Analysis from the Japan Diabetes Complications Study–.	*Diabetes Care*	28:	1463-1471,	2005.
Sone H, Yoshimura Y, Ito H, Ohashi Y, Yamada N, Japan Diabetes Complications Study Group.	Energy intake and obesity in Japanese patients with type 2 diabetes.	*Lancet*	363:	248-249,	2004
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Sone H, Mizuno S, Yamada N.,	Vascular risk factors snd diabetic neuropathy	*N Engl J Med.* author reply	352(18)	1925-7	2005
Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito H, Ohashi Y, Akanuma Y, Yamada Y,Japan Diabetes Complication Study Group.	The New Worldwide Definition of Metabolic Syndrome is Not aBetter Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions	*Diabetes Care*	29(1)	145-147,	2006

The New Worldwide Definition of Metabolic Syndrome Is Not a Better Diagnostic Predictor of Cardiovascular Disease in Japanese Diabetic Patients Than the Existing Definitions

Additional analysis from the Japan Diabetes Complications Study

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We previously reported (1) the limited clinical significance for Japanese diabetic patients of the widely used World Health Organization (WHO) (2) and National Cholesterol Education Program (NCEP) (3) definitions of metabolic syndrome and suggested that an international definition of metabolic syndrome that was applicable regardless of ethnicity was necessary (1).

Recently, the International Diabetes Federation published a long-awaited new worldwide definition of metabolic syndrome (4) that is intended to be applicable to various ethnic groups. The new definition is similar to the NCEP definition (3) but has several important differences. Notably, most components of the new definition now include subjects who are receiving specific treatments for the abnormalities that comprise metabolic syndrome. Also, central obesity (defined by waist circumference with ethnic modification in its thresholds) has become a mandatory component in the new definition. In this report, we evaluated the predictive power of the new international definition for cardiovascular disease (CVD), as compared with that of previous definitions, in Japanese diabetic patients.

RESEARCH DESIGN AND METHODS — The Japan Diabetes Complications Study (JDCS) has been described in detail elsewhere (1,5). The same dataset was used for evaluation so that the new definition of metabolic syndrome could be directly compared with the WHO and NCEP definitions (1–4). A total of 1,424 Japanese patients (771 men and 653 women, age 58.4 ± 7.4 years [means ± SD]) with previously diagnosed type 2 diabetes but without known CVD were followed for 8 years for coronary heart disease (CHD) and stroke events. Fatal and nonfatal CHD and stroke were defined as previously reported (1). The new International Diabetes Federation definition (4) was used with a recommended ethnic modification for Japanese subjects in relation to waist circumference (men ≥85 cm, women ≥90 cm). Since all of the subjects had diabetes, metabolic syndrome diagnosis was made in patients who met criteria for central obesity plus one or more of the following: increased triglycerides, increased blood pressure, or reduced HDL cholesterol (see Table 1 for detailed thresholds). Incidence rates in the two groups (with and without metabolic syndrome) were estimated under the Poisson assumption using person-year methods. Cox regression analysis was used to calculate the age-adjusted hazard ratio (HR) and 95% CI of metabolic syndrome risk factors with CHD, stroke, or both. The SAS software package (version 8.0; SAS Institute, Cary, NC) was used for all analyses. $P < 0.05$ was considered statistically significant.

RESULTS — At baseline, the prevalence of metabolic syndrome, using the new definition (Table 1), was notably lower, especially in female patients, than the prevalence under the WHO (2) and NCEP (3) definitions, which was ~50% on average (1). Diabetes duration in patients with (9.9 ± 6.9 years) or without (10.7 ± 7.3 years) metabolic syndrome did not differ significantly ($P = 0.07$). The proportion of patients that met the central obesity criterion (an essential component of the new definition) was 36.7% for men and 9.7% for women, such that 87% of men and 95% of women with central obesity had metabolic syndrome.

The incidence (per 1,000 patient-years) of CHD (13.5 [with metabolic syn-

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*Members of the JDCS Study Group have been listed previously (1).

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; JDCS, Japan Diabetes Complications Study; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Patient prevalence at baseline, age-adjusted HRs with 95% CIs, and incidence of CHD, stroke, or both in 1,424 Japanese patients with type 2 diabetes (771 men and 653 women) according to individual cardiovascular risk factors comprising the metabolic syndrome as defined by the International Diabetes Federation* (b, c, and d include *specific treatment for each abnormality*)

	Prevalence at baseline (%)		HR for CHD		HR for stroke		HR for CHD and/or stroke	
	Men	Women	Men	Women	Men	Women	Men	Women
a) Waist circumference ≥85 cm (men), ≥90 cm (women)	36.7	9.7	1.68 (0.92–3.08)	1.13 (0.26–4.86)	0.91 (0.44–1.86)	1.11 (0.31–4.05)	1.32 (0.83–2.10)	1.13 (0.43–2.97)
b) Triglycerides ≥150 mg/dl	26.5	23.4	2.93 (1.55–5.53)	2.03 (0.81–5.04)	1.10 (0.51–2.36)	0.59 (0.20–1.78)	1.96 (1.21–3.19)	1.13 (0.56–2.26)
c) HDL cholesterol <40 mg/dl (men), <50 mg/dl (women)	19.3	36.3	1.82 (0.94–3.54)	1.48 (0.63–3.49)	0.99 (0.41–2.40)	1.34 (0.61–2.94)	1.53 (0.90–2.61)	1.34 (0.74–2.40)
d) SBP ≥130 mmHg or DBP ≥85 mmHg	64.1	68.8	1.04 (0.53–2.01)	1.05 (0.39–2.84)	2.08 (0.90–4.82)	1.63 (0.60–4.37)	1.29 (0.77–2.17)	1.29 (0.64–2.59)
a plus one or more of *b*, *c*, or *d*	32.0	9.2	1.72 (0.94–3.15)	1.15 (0.27–4.90)	1.14 (0.56–2.34)	1.13 (0.31–4.11)	1.47 (0.91–2.35)	1.14 (0.44–3.01)

DBP, diastolic blood pressure; SBP, systolic blood pressure.

drome] vs. 8.1 [without metabolic syndrome] in men; 5.8 vs. 5.5 in women) or stroke (8.1 vs. 7.5 in men; 8.8 vs. 7.0 in women) did not differ significantly between subjects with or without metabolic syndrome. Age-adjusted HRs were calculated to determine whether the new metabolic syndrome definition or its components could predict cardiovascular events (Table 1). Patients diagnosed as having metabolic syndrome, even when subgrouped by therapeutic contents (oral hypoglycemic agents or insulin use), did not show significantly raised HRs for CHD, stroke, or both compared with subjects without metabolic syndrome. However, male patients with raised triglyceride levels and/or having specific treatment for this condition had a significantly increased risk of CHD (HR 2.93, $P < 0.001$) and combined CHD and stroke (1.96, $P = 0.006$), regardless of whether they had metabolic syndrome (Table 1).

CONCLUSIONS— Our previous analysis (1) showed that HRs for CVD in patients with WHO-defined metabolic syndrome were significantly elevated compared with HRs in subjects without metabolic syndrome (although the HR for CHD in male patients was not elevated). Diagnosis of metabolic syndrome by the NCEP definition was less predictive but still associated with a significantly elevated HR for CHD in male patients. However, metabolic syndrome diagnosis by the new definition was not predictive for CVD in either male or female patients in the same prospective setting. Therefore, the new definition did not improve the prediction of adverse cardiovascular events, and its clinical usefulness in Japanese diabetic patients is rather less than that of the existing definitions or of hypertriglyceridemia alone in male patients.

The indispensability of central obesity to the new definition was a major cause of the decrease in the prevalence of metabolic syndrome observed using the new definition. The fact that most patients with central obesity were classified as having metabolic syndrome revealed that metabolic syndrome diagnosis by the new definition was highly dependent on waist circumference when applied to Japanese diabetic subjects. It also denoted that most patients with central obesity had at least one other cardiovascular risk factor, suggesting a close relationship between central obesity and other cardiovascular risk factors. However, this combination was not necessarily associated with an increased risk of CVD in our patients. This latter observation led us to further evaluate the significance of waist circumference in our patients by modifying the threshold within the 65- and 105-cm range and recalculating the HRs. Interestingly, we could not find any thresholds associated with significantly elevated HRs for cardiovascular events in either male or female subjects (data not shown). Therefore, the new definition's lower prediction power for CVD seemed to be derived from the indispensability of the waist circumference component.

To date, prospective trials examining the significance of metabolic syndrome as a predictor of CVD in diabetic patients (1,6–9) have been inadequate (10,11). Many important issues remain to be resolved. *1*) Is the new definition of metabolic syndrome a good predictor of CVD in diabetic patients of differing ethnicities (12)? *2*) Are there any other combinations of components (or different thresholds) that are better predictors of CVD in Asian diabetic patients (13–15)? *3*) Is the concept of metabolic syndrome truly applicable or relevant to diabetic patients in general? Investigations of these issues would aid the screening of diabetic patients at especially high risk of CVD, as well as inform and direct ethnic group–specific management of diabetes (16–19).

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Is the Diagnosis of Metabolic Syndrome Useful for Predicting Cardiovascular Disease in Asian Diabetic Patients?

Analysis from the Japan Diabetes Complications Study

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OBJECTIVE — The metabolic syndrome (MetS) is believed to be associated with an increased risk of cardiovascular disease (CVD). Although its prevalence is extremely high among diabetic patients, its prevalence in those with no history of CVD has not been determined. Moreover, prospective studies published on the association between MetS and cardiovascular events in diabetic populations have used only the World Health Organization (WHO) definition of MetS and included only white European subjects. The aim of this study was to determine the prevalence of MetS, as defined by both the WHO and the National Cholesterol Education Program (NCEP), and its predictive value for CVD in Asian diabetic patients in a long-term, prospective setting.

RESEARCH DESIGN AND METHODS — The baseline characteristics and incidence/hazard ratio of cardiovascular events (coronary heart disease and stroke) were determined in 1,424 Japanese type 2 diabetic patients with and without MetS, as defined by WHO (WHO-MetS) or the NCEP.

RESULTS — A high prevalence (38–53%, depending on sex and definition) of MetS was found among diabetic patients, even those with no history of CVD. During the 8-year study period, only WHO-MetS was a predictor for CVD in female patients. In male patients, although both definitions of MetS were significant predictors for CVD, individual components of MetS, such as hyperlipidemia or hypertension, were equivalent or better predictors.

CONCLUSIONS — We found that MetS is relatively common in diabetic patients with no history of CVD. We suggest that the commonly used definitions of MetS, at least in their present forms, have limited clinical usefulness for Asian diabetic patients and may need some ethnic group–specific modifications for global use.

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The metabolic syndrome (MetS) is an important cluster of metabolic abnormalities linked with insulin resistance and cardiovascular disease (CVD) (1). The diagnostic criteria of MetS proposed by the World Health Organization (WHO-MetS) (2) and the National Cholesterol Education Program (NCEP-MetS) (3) are currently the most widely used. Although the prevalence of MetS in the general population reportedly differs widely among ethnic groups (4–8) and according to the definition of MetS used (7,9–11), the prevalence among patients with known diabetes is consistently high (70–90%) regardless of ethnicity or definition (12–20). Considering the high prevalence of CVD in the diabetic population (21) and the fact that subjects with a history of CVD often have multiple cardiovascular risk factors, it has been speculated that the extremely high prevalence of MetS among diabetic patients (12–20) may be due to the large number of patients who already have a history of CVD. However, the prevalence of MetS in diabetic patients without CVD has not been widely investigated to date. It is rational to examine this because diabetic patients with MetS have a higher incidence of CVD than those without MetS (15,16) and MetS is a stronger risk factor for CVD in patients with type 2 diabetes than in nondiabetic subjects (12).

Most prospective studies have shown that subjects with MetS are at increased risk of incident CVD (22,23) and mortality due to CVD (9,24–27). However,

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*A complete list of members of the Japan Diabetes Complications Study Group can be found in the APPENDIX.

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; HOMA-IR, homeostasis model assessment of insulin resistance; JDCS, Japan Diabetes Complications Study; MetS, metabolic syndrome; NCEP, National Cholesterol Education Program; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

many of these studies excluded diabetic patients from their study populations (9,22–24). Diabetic patients are known to be at greater risk for CVD than nondiabetic subjects (21), and it has been suggested that MetS is responsible for the increased prevalence of coronary heart disease (CHD) seen in diabetic patients (20). Therefore, it is important to evaluate the predictive value of MetS on incident CVD in diabetic patients in long-term, prospective studies. To the best of our knowledge, there have been four cohort studies specifically targeting diabetic patients to determine the relative risk of MetS on the incidence of CVD (12,15,16) and mortality due to CVD (17). Although these studies involved only white European subjects and used only the WHO definition of MetS, most of them (12,15,16) demonstrated, as expected, that the presence of MetS is associated with at least a severalfold increase in the risk of CVD. The above findings notwithstanding, it remains unclear *1*) whether such predictive values of MetS are also applicable to diabetic patients of other ethnicities, 2) which features of MetS are the best predictors of CVD and should become the critical therapeutic targets for the optimal management of CVD risk in diabetic patients (28), and 3) whether the commonly used NCEP definition of MetS (3) possesses the same predictive value for CVD as the WHO definition in diabetic patients.

The incidence of CVD in Asian subjects is known to be much less than in white subjects in general (29) and in diabetic populations in particular (30). In addition, the degree of obesity is very different between white and Asian diabetic patients (31,32), and the impact of obesity on CHD risk is known to be entirely different between whites and Asians (33,34). These differences could affect the apparent clinical significance of MetS (35,36), so that it is questionable whether the overall concept of MetS itself and the diagnosis of MetS under the present definitions based on data from mostly European and American patients are applicable to the evaluation of CVD risk in Asian diabetic patients. Therefore, in this long-term, prospective study of Japanese diabetic patients with no history of CVD, we determined the prevalence of MetS and analyzed its individual features and predictive value for incident CVD using the two most widely used definitions of MetS (2,3). Such comparisons are helpful in possibly establishing a global definition of MetS (10,37) and are also warranted to determine if there is heterogeneity in the power of individual MetS components to predict CVD (28).

RESEARCH DESIGN AND METHODS

— The Japan Diabetes Complications Study (JDCS) is a nationwide, multicenter, prospective study of type 2 diabetic patients (38). In 1996, 2,205 patients aged 40–70 years with previously diagnosed type 2 diabetes and HbA_{1c} levels >6.5% were recruited and registered. The eligibility criteria for participating patients has been previously described (38). The duration of the study was 8 years. Of the 2,205 patients, the present study focused on 1,424 patients (771 men and 653 women) who had a complete set of data, including those parameters necessary to satisfy the WHO (2) and NCEP (3) criteria for the definition of MetS at baseline. The JDCS protocol, which is in accordance with the Declaration of Helsinki, received ethical approval from the institutional review boards of all of the participating institutes and was undertaken in accordance with the Ethical Guidelines for Clinical Studies of the Japanese Ministry of Health, Labor, and Welfare. All of the study participants gave written informed consent.

Both the WHO (2) and the NCEP (3) definitions were used to diagnose MetS in this study. However, because the original cut-off for abdominal obesity in the NCEP definition (waist circumference ≥102 cm for men and ≥89 cm for women) has previously been shown to be inappropriate for Asian populations (35,37) and the number of subjects who met these criteria was extremely low, the cut-off limit was adjusted according to the criteria proposed by the Japan Society for the Study of Obesity (≥85 cm for men or ≥90 cm for women), which were based on the risk of obesity-related disorders in a Japanese population (39). The WHO criteria for obesity were adopted because the waist-to-hip ratio (WHR) was used rather than waist circumference. The criteria used for analysis in this study are shown in Table 3. Because all of the study subjects were diabetic, those who fulfilled two or more of criteria 1a, 2a, 5, or 6 were classified as having WHO-MetS and those who fulfilled two or more of criteria 1b, 2b, 3, or 4 were diagnosed as having NCEP-MetS, using a modified NCEP definition (Table 3). For comparisons with other traditional risk factors for CVD, we also evaluated high LDL cholesterol levels, cigarette smoking, and excessive alcohol intake (40). Medication use, including agents for hypertension and hyperlipidemia, were not considered when diagnosing MetS in this study.

Waist and hip circumferences were measured at the umbilicus and trochanter level, respectively. A baseline dietary survey, comprised of food records and a food frequency questionnaire that included alcohol consumption, was undertaken. Information regarding cigarette smoking was collected using a standardized questionnaire. All laboratory tests were undertaken using the standard methods of each of the participating institutes, apart from the HbA_{1c} assays, which used a common standard, with 5.8% as the upper normal limit. Plasma LDL cholesterol was calculated using Friedewald's equation, except for triglyceride levels >400 mg/dl, in which case the LDL cholesterol data were treated as "missing." To estimate insulin resistance, the homeostasis model assessment of insulin resistance (HOMA-IR) was used (41). Plasma insulin levels and the HOMA-IR were not evaluated in patients treated with insulin.

Patients were assessed for CHD and stroke at baseline and yearly thereafter. In all subjects, a 12-lead electrocardiogram (ECG) was recorded at each assessment. Fatal and nonfatal CHD and stroke events identified during follow-up were certified by at least two members of the experts' committee who were masked as to risk factor status and the other member's diagnosis. With regard to CHD, myocardial infarction was defined according to the WHO Monitoring of Trends and Determinants in Cardiovascular Disease criteria (42) and angina pectoris was defined as typical effort-dependent chest pain or oppression relieved at rest or by using nitroglycerine, as validated by exercise-positive ECG and/or angiography. Stroke events were defined as a constellation of focal or global neurological deficits of sudden or rapid onset and for which there was no apparent cause other than a vascular accident, as determined by a detailed history, a neurological examination, and ancillary diagnostic procedures such as computed tomography, magnetic resonance imaging, cerebral angiography, and lumbar puncture. Stroke events were

classified as cerebral infarction (including embolus), intracranial hemorrhage (including subarachnoid hemorrhage), transient ischemic attack, or stroke of undetermined type in accordance with WHO criteria (43). No cases of asymptomatic lesions detected by brain imaging (i.e., silent infarction) were included. Only "first-ever" CHD or stroke events during the study period were counted for the analysis; if a patient had both CHD and stroke events, each event was counted separately.

Data are presented as means ± SD or as a proportion, unless otherwise specified. To compare the distributions of baseline characteristics between groups, Wilcoxon's rank-sum test or Fisher's exact test was used. Incidence rates in the two groups were assessed by a score test under the Poisson assumption. Cox regression analysis was used to calculate the adjusted hazard ratio (HR) and 95% confidence interval (CI) of MetS risk factors with CHD, stroke, or both. Statistical analyses were performed separately by sex. The SAS software package (Version 8.0, Cary, NC) was used for all analyses. $P < 0.05$ was considered to be significant.

RESULTS

Baseline characteristics and prevalence of the metabolic syndrome

The baseline characteristics of the study subjects are shown in Table 1. In all, 51% of male and 53% of female subjects met WHO criteria for MetS, whereas 45% of male and 38% of female subjects met NCEP criteria for MetS. Plasma insulin levels and HOMA-IR were significantly higher in patients with MetS (both definitions) than in those without MetS; however, there were no significant differences in HbA_{1c} or the frequency of oral hypoglycemic agent use. Insulin usage was significantly lower in women with MetS by either definition and in men with NCEP-MetS. Blood pressure and serum triglycerides were significantly higher and HDL cholesterol was significantly lower in MetS patients, despite the fact that the use of medications for both hypertension and hyperlipidemia was much more common than in patients without MetS. Daily energy intake did not differ between patients with and without MetS (data not shown).

Incidence of cardiovascular disease during follow-up

During the 8-year study period, the total number of CVD events was 117, comprised of 62 CHD and 59 stroke events. The combined incidence (per 1,000 patient-years) of CHD and/or stroke was significantly greater in patients with MetS (except in female patients with NCEP-MetS) than in those without MetS (Table 2).

Hazard ratios of the metabolic syndrome and its individual components for coronary heart disease and stroke

HRs were calculated to determine which definition of MetS was the better predictor of CVD and which of the individual MetS components (or other classic risk factors) could most efficiently predict CVD events in our subjects (Table 3). In male patients, WHO-MetS was not significantly associated with an increased risk for either CHD or stroke separately, but was associated with the combination of both (HR = 1.6). Triglyceride, LDL cholesterol (both for CHD), and blood pressure (≥140/90 mmHg) levels (for stroke) showed higher HRs. NCEP-MetS was a significant predictor of CHD in male patients, although its HR (1.9) was lower than that for triglycerides (2.9) or LDL cholesterol (2.1). Thus, neither definition of MetS was a substantially better predictor of CVD than the component parts in male patients. In contrast, in the female patients, WHO-MetS was a significant and strong predictor of CHD (HR = 2.8), stroke (HR = 3.7), and both CHD and stroke (HR = 3.2). In female patients, none of the individual elements nor the other classic risk factors showed significant increases in HRs, with the exception of hypertension (≥140/90 mmHg) for stroke, although its HR (2.4) was still lower than that for WHO-MetS. NCEP-MetS was not a significant risk factor for CHD or stroke in female patients (Table 3).

To examine the clustering effects of the individual components of MetS, the association between CVD risk and the number of MetS components fulfilled (other than diabetes) was analyzed (Table 3). Increasing the cut-off component number for the diagnosis of NCEP-MetS from ≥2 to ≥3 in male subjects did not dramatically improve the HR but did greatly reduce the number of patients diagnosed as having MetS, from 45 to 14.5% (Table 3). In female patients, changing the diagnostic cut-off component numbers was not particularly beneficial in improving the prognostic value of WHO-MetS (Table 3).

CONCLUSIONS — The prevalence of MetS in our diabetic patients who were free from CVD was not as high as that reported in previous studies that included patients with previous CVD (12–20) but was nevertheless relatively high (38–53%). Although we did not have age-matched nondiabetic control subjects, the prevalence of MetS was much higher than that reported in Japanese general population workers, namely 19.5% in men and 7.9% in women (33). Hypertension and dyslipidemia are much more common in diabetic patients than in nondiabetic subjects (21), and it has been speculated that the features of MetS more easily aggregate, even in the absence of current or previous CVD, leading to the observed increase in the prevalence of MetS. On the other hand, the prevalence of NCEP-MetS in the U.S. general population age 50 years and older is 44% (20), which is relatively close to that in our Japanese diabetic patients. However, even in the U.S. (excluding Asian Americans), the prevalence of MetS in those who have a BMI range equivalent to that of Japanese subjects is not >10% (44). This implies that in the U.S., obesity has a potent impact on the prevalence of MetS, as has also been shown in a recent study (45). This is in contrast to findings in Japan, where diabetes rather than obesity may have the greater influence on the prevalence of MetS, as Japanese diabetic patients are not obese by comparison with white diabetic patients or nondiabetic Japanese subjects (31,32).

The clinical importance of MetS is related to its putative impact on CVD morbidity and mortality. Among Italian patients with type 2 diabetes, the risk for CVD was 4.9 (CI 1.2–20.7) times higher in patients with WHO-MetS than in those without it (16), which was a higher rate than that seen in our male (1.6 [CI 1.0–2.6] times) and female (3.2 [CI 1.6–6.5] times) patients. These results suggest that the clinical impact of MetS on diabetic patients varies by ethnic group. Comparing cardiovascular risk factors in our Japanese patients to those in patients in the U.K. Prospective Diabetes Study (UKPDS) (46,47), hypertension is a common

Table 1—*Baseline characteristics of study subjects, grouped by metabolic syndrome status*

	Total	WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
		Without	With	*P*	Without	With	*P*
n							
Men	771	376 (48.8)	395 (51.2)	—	424 (55.0)	347 (45.0)	—
Women	653	310 (47.4)	343 (52.6)	—	405 (62.0)	248 (38.0)	—
Age (years)							
Men	58.2 ± 7.4	57.4 ± 7.6	58.9 ± 7.2	0.01	58.0 ± 7.6	58.4 ± 7.2	0.50
Women	58.7 ± 7.4	57.9 ± 7.7	59.5 ± 7.0	0.01	58.4 ± 7.4	59.4 ± 7.2	0.11
Diabetes duration (years)							
Men	10.9 ± 7.6	11.0 ± 7.6	10.9 ± 7.6	0.66	11.5 ± 7.8	10.2 ± 7.4	0.01
Women	10.1 ± 6.7	10.7 ± 7.3	9.5 ± 6.0	0.10	10.6 ± 7.0	9.4 ± 6.0	0.07
BMI (kg/m^2)							
Men	22.9 ± 2.6	22.0 ± 2.4	23.7 ± 2.6	<0.01	21.8 ± 2.3	24.2 ± 2.4	<0.01
Women	23.4 ± 3.3	22.3 ± 3.0	24.3 ± 3.3	<0.01	22.6 ± 3.1	24.6 ± 3.3	<0.01
Waist circumference (cm)							
Men	82.3 ± 7.7	79.0 ± 7.1	85.3 ± 7.0	<0.01	78.4 ± 6.4	87.0 ± 6.5	<0.01
Women	76.5 ± 9.8	72.4 ± 8.3	80.1 ± 9.7	<0.01	74.1 ± 8.6	80.4 ± 10.4	<0.01
Waist-to-hip ratio							
Men	0.89 ± 0.07	0.86 ± 0.05	0.92 ± 0.06	<0.01	0.87 ± 0.06	0.92 ± 0.06	<0.01
Women	0.83 ± 0.08	0.80 ± 0.06	0.86 ± 0.07	<0.01	0.82 ± 0.07	0.86 ± 0.08	<0.01
Blood pressure (mmHg)							
Men	132 ± 16/78 ± 10	124 ± 13/74 ± 9	139 ± 15/81 ± 10	<0.01	127 ± 16/75 ± 9	137 ± 15/81 ± 9	<0.01
Women	132 ± 17/76 ± 10	124 ± 13/73 ± 9	139 ± 16/79 ± 11	<0.01	128 ± 17/74 ± 10	138 ± 14/80 ± 10	<0.01
HbA_{1c} (%)							
Men	7.61 ± 1.36	7.53 ± 1.42	7.67 ± 1.30	0.05	7.54 ± 1.36	7.68 ± 1.36	0.18
Women	8.05 ± 1.45	8.07 ± 1.51	8.04 ± 1.40	0.79	8.09 ± 1.47	7.99 ± 1.42	0.41
Fasting plasma glucose (mmol/l)*							
Men	8.3 (7.2–10.0)	8.2 (7.0–9.7)	8.6 (7.4–10.4)	<0.01	8.2 (7.1–9.8)	8.6 (7.4–10.3)	0.02
Women	8.6 (7.3–10.2)	8.6 (7.2–10.2)	8.6 (7.3–10.2)	0.74	8.6 (7.2–10.3)	8.5 (7.4–9.9)	0.77
Fasting plasma insulin (pmol/l)†‡							
Men	6.2 (0.5–1.9)	5.4 (0.5–1.9)	7.2 (0.5–1.9)	<0.01	5.2 (0.5–1.9)	7.7 (0.5–1.9)	<0.01
Women	7.1 (0.5–1.9)	5.9 (0.5–1.9)	8.3 (0.6–1.8)	<0.01	6.2 (0.5–1.9)	8.7 (0.5–1.9)	<0.01
HOMA-IR‡							
Men	3.1 ± 3.1	2.6 ± 2.6	3.6 ± 3.4	<0.01	2.4 ± 2.1	3.9 ± 3.8	<0.01
Women	3.3 ± 2.6	2.8 ± 2.2	3.8 ± 2.8	<0.01	2.9 ± 2.1	4.1 ± 3.1	<0.01
Serum total cholesterol (mmol/l)							
Men	5.01 ± 0.90	4.93 ± 0.84	5.09 ± 0.94	0.01	4.97 ± 0.82	5.07 ± 0.98	0.16
Women	5.44 ± 0.85	5.38 ± 0.84	5.50 ± 0.86	0.05	5.41 ± 0.83	5.50 ± 0.89	0.28
Serum HDL cholesterol (mmol/l)							
Men	1.34 ± 0.39	1.42 ± 0.39	1.27 ± 0.38	<0.01	1.48 ± 0.38	1.18 ± 0.34	<0.01
Women	1.47 ± 0.44	1.57 ± 0.45	1.37 ± 0.41	<0.01	1.65 ± 0.43	1.17 ± 0.26	<0.01
Serum triglycerides (mmol/l)†							
Men	1.2 (0.6–1.6)	1.0 (0.7–1.5)	1.5 (0.6–1.6)	<0.01	1.0 (0.7–1.5)	1.6 (0.6–1.6)	<0.01
Women	1.1 (0.6–1.7)	0.9 (0.6–1.6)	1.4 (0.6–1.6)	<0.01	9 (0.7–1.5)	1.6 (0.6–1.6)	<0.01

Current smoker (%; men/women)	43.9/8.7	46.6/8.1	41.3/9.2	0.08/0.38	44.7/7.1	42.9/11.3	0.33/0.049
Excessive alcohol intake (%; men/women)§	12.4/0.2	8.2/0.0	16.4/0.3	<0.01/0.51	7.7/0.3	18.4/0.0	<0.01/0.62
OHA use (without insulin) (%; men/women)	72/77	72/76	73/78	0.38/0.33	72/75	72/79	0.50/0.20
Insulin use (with or without OHA) (%; men/women)	16/20	18/24	15/16	0.16/0.01	20/22	11/15	<0.01/0.02
Medication for hypertension (%; men/women)	22/29	12/17	32/40	<0.01/<0.01	16/23	30/40	<0.01/<0.01
Medication for hyperlipidemia (%; men/women)	15/35	11/30	19/39	<0.01/<0.01	10/32	21/40	<0.01/0.02

Data are *n* (%), means ± SD, *median (interquartile range), or †geometric means (1 SD). ‡Patients with insulin therapy were excluded. §Excessive alcohol intake was defined as more than three drinks (38 g ethanol) per day. OHA, oral hypoglycemic agent.

and potent risk factor for stroke (Table 3) (46). By contrast, HDL cholesterol levels, hypertension, and smoking, all of which were identified as significant risk factors for CHD in UKPDS patients (47), were not associated with a significant elevation of HRs in our Japanese patients (Table 3). Instead, triglyceride levels, which were not significant in UKPDS patients (47), were a strong predictor for CHD in male Japanese patients. These findings imply that the critical therapeutic targets among the components of MetS for preventing cardiovascular complications (28) may need to be modified according to a patient's ethnic group.

Most of the previous studies evaluating the predictive power of MetS for CVD calculated the HRs by including sex as one of the independent variables for statistical adjustment, and very few studies have analyzed CVD risk separately by sex (24). Sex is reportedly an independent predictor for CVD, with an odds ratio of 2.6, which is larger than that of age, HbA_{1c}, and even of MetS itself in type 2 diabetic patients (16). Our results revealed drastic differences in the HRs between sexes. In our female patients, WHO-MetS presented an increased risk for CVD events to a greater degree than could be predicted by the sum of the individual components (Table 3), whereas, in contrast, in our male patients, WHO-MetS was not even a significant risk factor for CVD. At baseline, obvious sex differences were observable in the proportion of subjects who smoked or consumed excessive alcohol, both of which were much higher in male patients. Of particular interest, the proportion of male subjects with excessive alcohol intake was at least twice as high in male patients with MetS than in those without MetS, whereas the proportion of current smokers did not differ in patients with and without MetS (Table 1). It can be speculated that excessive alcohol intake could be closely associated with MetS in male Japanese diabetic patients. Moreover, moderate alcohol intake, which has been shown to be beneficial for preventing CHD in U.S. and European diabetic patients, is not beneficial for Japanese patients (40).

Few studies have applied both the WHO and NCEP definitions of MetS to the same subjects to compare the prevalence of MetS or its predictive value for CVD. It has been reported that the prevalence of WHO-MetS is generally higher than that of NCEP-MetS in both sexes (7,12). This was confirmed in our Japanese diabetic subjects, although the difference in prevalence was not great. Regarding the predictive value of MetS, in subjects without diabetes or other cardiovascular risks, Hunt et al. (27) reported that the NCEP-MetS tended to be more predictive for cardiovascular mortality than the WHO-MetS, whereas Lakka et al. (9) reported a contrary result. In our diabetic patients, the NCEP guidelines, even modified for optimal use by Japanese subjects, were not more predictive than the WHO guidelines in female patients nor did they show excellent clinical usefulness in male patients. One possible explanation for this difference in our patients could be the hypertension cut-off used, with 140/90 mmHg in the WHO defini-

Table 2—*Incidence of coronary heart disease and/or stroke (per 1,000 patient-years) among study subjects grouped by metabolic syndrome status*

		WHO-defined metabolic syndrome			NCEP-defined metabolic syndrome		
	Total (%)	Without (%)	With (%)	*P*	Without (%)	With (%)	*P*
Incidence among Men							
CHD	9.8	8.4	11.3	0.34	7.0	13.5	0.04
Stroke	7.7	5.1	10.3	0.05	6.6	9.1	0.35
CHD and/or stroke	17.1	12.7	21.6	0.03	13.0	22.6	0.02
Incidence among Women							
CHD	5.5	2.9	8.0	0.04	4.4	7.3	0.27
Stroke	7.2	2.8	11.2	<0.01	6.2	8.8	0.38
CHD and/or stroke	12.6	5.7	19.0	<0.01	10.7	15.6	0.22