リスクファクターを保有する対象者は、血圧高値が 738 名（64%）、脂質異常が 258 名（22%）、血糖高値が 144 名（12%）であった。女性においてリスクファクターを2つ以上保有する対象者は、292 名（25%）であった。リスクファクターを2つ以上保有する割合と腹囲径の関連を検討したところ、カイ 2 乗=89.89、p<0.0001 で有意な関連を認めた。この関連を ROC 曲線を用いて検討したところ、曲線下面積（AUC）は 0.694 であり、ROC 曲線から、感度、特異度ともに最適な腹囲を求めたところ、73cm という結果が得られた。

ベースラインから平成19年12月31日まで対象者を追跡し、心血管イベントの発症を調査したところ、女性1,157名のうち150名にイベントが発症した。平均追跡機関は134か月であった。追跡期間中の心血管イベント発症の有無とベースラインの腹囲径の関連を検討したところ、カイ 2 乗=18.03、p<0.0001 で有意な関連を認めた。ROC 曲線を用いて検討したところ、AUC は 0.610 であり、感度、特異度ともに最適な腹囲を求めたところ、80cm という結果が得られた。

以上の結果より、端野・壮瞥町の女性の対象においては、リスクファクターの重積を反映している腹囲径は73cm、心血管イベントの発症を反映している腹囲径は 80cm となった。これは、現行の日本基準メタボリックシンドロームの「女性は腹囲 90cm 以上を腹部肥満の基準とする」という定義と異なっているが、今回の結果からは、少なくとも、90cm より小さい値がカットオフ値として適していると考えられた。

さらに、女性におけるメタボリックシンドロームの最適な基準を探るべく、腹囲 80cm をカットオフとして、日本基準に準じたメタボリックシンドローム、米国 NCEP-ATPⅢ基準に準じたメタボリックシンドロームのどちらが有効であるかを検討した。ベースラインにおいて、女性では日本基準に準じたメタボリックシンドローム基準を満たす対象者は 142 名（13%）であり、米国 NCEP-ATPⅢ基準に準じたメタボリックシンドローム基準を満たす対象者は 174 名（16%）であった。Kaplan-Meier 法により、これらのメタボリックシンドロームの有無と追跡期間中の心血管イベント発症との関連を検討したところ、どちらもメタボリックシンドロームを有する対象者が心血管イベントを多く発症していたが、ログランク検定を行ったところ、米国 NCEP-ATPⅢ基準に準じたメタボリックシンドローム基準のみ、カイ 2 乗=5.44、p=0.0197 で有意な差が認められた。この結果は、ベースラインの年齢、血清総コレステロール値、喫煙

の有無で補正しても同様であった。

D.　考察

今回の検討の結果から、端野・壮瞥町の女性の対象においては、リスクファクターの重積を反映している腹囲径は73cm、心血管イベントの発症を反映している腹囲径は 80cm となった。これは、現行の日本基準メタボリックシンドロームの「女性は腹囲 90cm 以上を腹部肥満の基準とする」という定義と異なっているが、今回の結果からは、少なくとも、90cm より小さい値がカットオフ値として適していると考えられた。

また、メタボリックシンドロームの診断において腹部肥満のカットオフを腹囲径 80cm とした場合、従来の 90cm とした場合よりも将来の心血管イベント発症を予測する上で有用であることが明らかとなった。特にその際のメタボリックシンドロームの基準は、腹部肥満を必須項目とする日本基準よりも、腹部肥満を5つの危険因子のうちの一つとして同列に扱う米国 NCEP-ATPⅢ基準の方が適しているという結果が得られた。

今後、我々が行っている端野・壮瞥町研究の追跡調査を継続して行い、さらに長期にわたって予後を検討することはもちろんのこと、他の分担研究者とも共同して、さらに多人数での横断研究、縦断後向き研究、縦断前向き研究を行うことにより、より実態に即した日本人のための腹部肥満の定義、腹部肥満への対策、そしてこれらをふまえた日本人のための最適なメタボリックシンドロームの基準を策定することが可能になると考えられる。

E.　研究発表

1.　論文発表：本年度の該当研究による発表はない。
2.　学会発表：本年度の該当研究による発表はない。

F.　知的財産権の出願・登録状況（予定を含む）

1.　特許取得：なし
2.　実用新案登録：なし
3.　その他：なし

G.　研究協力者

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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横断・縦断研究

分担研究報告書

一般住民におけるメタボリックシンドロームがタイプ別脳梗塞の発症に及ぼす影響

清原　裕(九州大学大学院医学研究院環境医学・教授)

研究要旨

メタボリックシンドローム(MetS)と脳梗塞の関係をみた追跡研究の報告が散見されるが、脳梗塞をタイプ別にわけてこの問題を検討した報告は極めて稀である。そこで、福岡県久山町における長期追跡調査において、MetSがタイプ別脳梗塞の発症に及ぼす影響を検討した。1988年に福岡県久山町の循環器健診を受診した40歳以上の住民のうち、虚血性心疾患・脳卒中の既往がなく、腹囲測定と空腹時採血が可能であった2,452名(男性1,050名、女性1,402名)を対象として14年間追跡し、その間に発症した145例の脳梗塞をタイプ別にわけて検討した。わが国の診断基準(腹囲基準を男性90cm以上，女性80cm以上に修正)で定義したMetSは、性、年齢、血清総コレステロール、蛋白尿、心電図異常、喫煙、飲酒、運動習慣を用いた多変量調整後、脳梗塞発症の独立した有意な危険因子となった［ハザード比 2.5、95%信頼区間(CI)1.7-3.6］。さらに脳梗塞をタイプ別に検討すると、MetSの多変量調整後のハザード比(95%CI)は、ラクナ梗塞で1.9(1.1-3.3)、アテローム血栓性脳梗塞で2.6(1.3-5.2)、心原性脳塞栓症で3.9(1.9-8.2)と、いずれも有意であった。一方、米国 National Cholesterol Education Program(腹囲基準を同様に修正)およびInternational Diabetes Federationの診断基準でMetSを定義した場合、MetSはアテローム血栓性脳梗塞および心原性脳塞栓症に対して有意な危険因子となるものの、ラクナ梗塞では有意な関連を認めなかった。以上より、腹囲基準を男性90cm以上、女性80cm以上に修正したわが国の診断基準で定義したMetSは、全てのタイプの脳梗塞に対する独立した有意な危険因子であった。

A. 研究目的

近年わが国では、生活習慣の欧米化に伴い肥満やメタボリックシンドローム(MetS)などの代謝性疾患が急増し、医学的のみならず社会的にも大きな問題となりつつある。これらの疾患は、動脈硬化症と関連するため、高齢人口が急増しているわが国では、適切なMetSの診断基準を早期に確立し、その予防対策を講じることは国民の健康を守るうえで最も重要な課題の一つといえる。一方、動脈硬化症の中で、特に脳梗塞は生活の質(QOL)や日常生活動作(ADL)の低下の大きな原因となり、生命予後にも重大な影響を与える。これまで、MetSと脳梗塞の関係を検討した追跡研究の報告が散見されるが、脳梗塞をタイプ別にわけて検討した報告は極めて稀である。そこで本報告では、福岡県久山町における長期追跡調査の結果をもとに、各診断基準のMetSが脳梗塞のタイプ別の発症に及ぼす影響を検討した。

B. 研究方法

1988年に福岡県久山町の循環器健診を受診した40歳以上の住民のうち、虚血性心疾患・脳卒中の既往がなく、腹囲測定と空腹時採血が可能であった2,452名(男性1,050名、女性1,402名)を対象とし、14年間追跡した。追跡期間中に発症した脳梗塞145例をラクナ梗塞72例、アテローム血栓性脳梗塞40例、心原性脳塞栓症33例にわけた。用いたMetSの診断基準は、米国National Cholesterol Education ProgramのAdult Treatment PanelⅢ Report(腹囲基準を男性90cm

以上、女性80cm以上に修正)(修正NCEP基準)、International Diabetes Federation(IDF基準)、わが国のMetS診断基準検討委員会(日本基準)および日本基準の腹囲基準を男性90cm以上、女性80cm以上に置き換えた修正日本基準の4つである。各診断基準で定義されるMetSが脳梗塞およびそのタイプ別の発症に及ぼす影響をCox比例ハザードモデルで求めた相対危険で比較・検討した。

倫理面の配慮

本研究は2省合同の「疫学研究に関する倫理指針」に準拠し、九州大学医学研究院等倫理委員会の承認の元で行われた。本研究は、健診受診者を対象とした疫学調査で、対象者が研究によって不利益を被ることはない。研究者は、対象者の個人情報の漏洩を防ぐうえで細心の注意を払い、その管理に責任を負っている。

C.研究結果

MetSの各診断基準と脳梗塞の関係

1)脳梗塞全体

MetSの各診断基準と脳梗塞の関係を図1に示す。性、年齢、血清総コレステロール、蛋白尿、心電図異常、喫煙、飲酒、運動習慣を多変量解析で調整した後も、各診断基準で定義されたMetSは脳梗塞発症の有意な危険因子であった。診断基準の間で相対危険を比べると、修正日本基準で定義されたMetSで最も高かった(日本基準:相対危険1.6;95%信頼区間 1.1-2.4;P=0.02、修正NCEP基準:相対危険 1.7;95%信頼区間 1.2-2.3;P=0.004、IDF基準:相対危険 2.0;95%信頼区間 1.4-2.9;P<0.001、修正日本基準:相対危険 2.5;95%信頼区間 1.7-3.6;P<0.001)。

同様の検討を脳梗塞のタイプ別に行った。

2)ラクナ梗塞

MetSと日本人の脳梗塞の中で最も頻度が高いラクナ梗塞との関係を各診断基準間で比較・検討した(図1)。上記と同様の多変量調整を行った結果、日本基準、修正NCEP基準、IDF基準で定義したMetSは、ラクナ梗塞発症の有意な危険因子ではなかった。一方、修正日本基準を用いた場合、MetSとラクナ梗塞との間に有意な関連を認めた(相対危険 1.9;95%信頼区間 1.1-3.3;P=0.02)。

3)アテローム血栓性脳梗塞

アテローム血栓性脳梗塞について同様の検討を行った(図1)。多変量調整後、IDF基準および修正日本基準によるMetSは、アテローム血栓性脳梗塞と有意な関係を認めた。両者の相対危険を比べると、修正日本基準でより大きかった(日本基準:相対危険 1.6;95%信頼区間 0.8-3.4;P=0.22、修正NCEP基準:相対危険 1.9;95%信頼区間 1.0-3.6;P=0.05、IDF基準:相対危険 2.2;95%信頼区間 1.1-4.3;P=0.03、修正日本基準:相対危険 2.6;95%信頼区間 1.3-5.2;P=0.01)。

4)心原性脳塞栓症

修正NCEP基準、IDF基準、修正日本基準によるMetSは、心原性脳塞栓症との間に有意な関係を認めた。相対危険は、修正日本基準によるMetSで最も大きかった(日本基準:相対危険 2.0;95%信頼区間 0.9-4.5;P=0.11、修正NCEP基準:相対危険 2.2;95%信頼区間 1.1-4.5;P=0.03、IDF基準:相対危険 2.7;95%信頼区間 1.3-5.7;P=0.01、修正日本基準:相対危険 3.9;95%信頼区間 1.9-8.2;P<0.001)。

D.考　察

これまでに提唱されたMetSの診断基準はいくつか存在し、わが国において未だどの基準が適切であるか明らかではない。これまでの久山町における追跡調査の成績によると、脳梗塞と虚血性心疾患を合わせた心血管病発症の検討では、本研究にも用いた修正日本基準の相対危険が最も大きく、有用な診断基準であると考えられた。本研究では、さらに脳梗塞をタイプにわけ詳細な検討を行った。その結果、脳梗塞全体、ラクナ梗塞、アテローム血栓性脳梗塞、心原性脳塞栓症のいずれにおいても、修正日本基準によって定義されたMetSは有意な関連を示し、その相対危険は他の診断基準によるものと比べ最も大きかった。さらに、本邦で有病率の高いラクナ梗塞でみると、修正日本基準によるMetSのみが有意な関連を示し、他の診断基準

のMetSでは関連を認めなかった。以上の結果を踏まえると、脳梗塞およびそのタイプにおける検討においても、わが国のMetSの診断基準には、修正日本基準が最も優れていることが示唆される。

MetSは、動脈硬化症の予防を念頭に考えられた概念である。修正日本基準で定義されたMetSの相対危険を脳梗塞のタイプ別に比べると、ラクナ梗塞よりもアテローム血栓性脳梗塞でより高かった。これはMetSが、細動脈の硝子化に伴って生じると考えられるラクナ梗塞に比べ、粥状動脈硬化を基盤として生じるアテローム血栓性脳梗塞でより強く関連する事を示めす整合性のある結果である。しかしMetSの相対危険が、脳梗塞のタイプの中で動脈硬化症との関連が比較的薄いとされる心原性脳塞栓症で最も高く観察されたことは、意外であり興味深い。近年の疫学研究によると、MetSは心原性脳塞栓症の主な原因である心房細動の発症の危険因子であることが報告されている。心原性脳塞栓症は、脳梗塞のタイプの中で最も重症化し、生命予後の悪化のみならずADLを強く障害し、寝たきりの原因にもなりやすい。本研究の結果に基づけば、MetSの有病率を低下させる事は、この心原性脳塞栓症の予防の有効な手段でもあると考えられる。

E. 結　論

腹部肥満の定義をアジア人基準(男性90cm以上、女性80cm以上)で置き換えた日本の診断基準で定義したMetSが脳梗塞発症と最も密接に関連した。この基準で定義されたMetSは、脳梗塞の全てのタイプの脳梗塞の有意な危険因子となった。

G. 研究発表

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H. 知的所有権の取得状況

1．特許取得　　なし
2．実用新案登録　なし

I. 研究協力者

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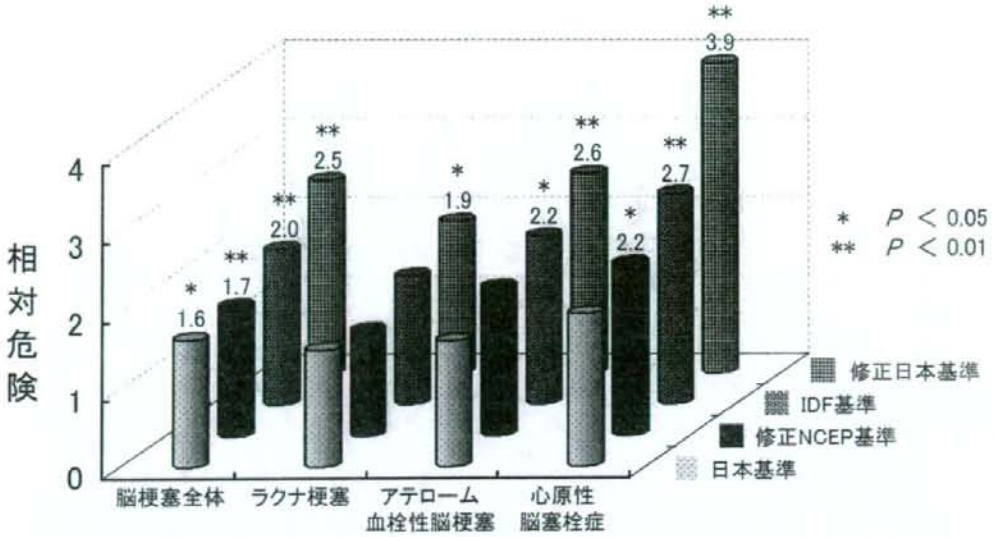

MetS(−)群に対するMetS(+)群の相対危険
調整因子： 性，年齢，血清総コレステロール，蛋白尿，心電図異常，喫煙，飲酒，運動習慣

図1 MetSの診断基準別にみたタイプ別脳梗塞発症の相対危険
久山町第3集団，40歳以上男女，2,452名，追跡14年（1988年～2002年），多変量調整

別紙4

書籍

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原著論文

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Arima Y et al.	High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama Study.	Arterioscler Thromb Vasc Biol	28	1385-1391	2008
Maebuchi D et al.	Arterial stiffness and QT interval prolongation in a general population: the Hisayama Study.	Hypertens Res	31	1339-1345	2008
Kubo M et al.	Secular trends in the incidence and risk factors of ischemic stroke and its subtypes in the Japanese population.	Circulation	118	2672-2678	2008
Ninomiya Y et al.	Impact of kidney disease and blood pressure on the development of cardiovascular disease: an overview from the Japan Arteriosclerosis Longitudinal Study.	Circulation	118	2694-2701	2008
Imamura T et al.	Low-density lipoprotein cholesterol and the development of stroke subtypes and coronary heart disease in a general Japanese population: the Hisayama Study.	Stroke	40	382-388	2009

Fasting Plasma Glucose Cutoff for Diagnosis of Diabetes in a Japanese Population

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Objective: We examined the relationship between fasting plasma glucose (FPG) and 2-h post-load glucose (PG) levels, and the optimal FPG cutoff level to correspond to a 2-h PG of 11.1 mmol/liter, the gold standard diagnostic criterion, in a general Japanese population.

Design: Cross-sectional study populations of 2421 subjects in 1988 and 2698 subjects in 2002, aged 40–79 yr and without antidiabetic medication, were tested with an oral glucose tolerance test. The relationship between FPG and 2-h PG was investigated by various regression models and a receiver operating characteristic curve.

Results: The best-fit model for the relationship between FPG and 2-h PG was a quadratic regression model. The FPG cutoff levels corresponding to the 2-h PG of 11.1 mmol/liter by this model were 6.2 mmol/liter in 1988 and 6.3 mmol/liter in 2002. In the combined populations, the FPG cutoff point was 6.3 mmol/liter; the sensitivity and specificity of this cutoff point for detecting a 2-h PG of 11.1 mmol/liter were 75.2 and 88.6%, respectively. The receiver operating characteristic curve analysis confirmed that the corresponding FPG point was 6.2 mmol/liter in both the 1988 and 2002 populations. In a stratified analysis, the FPG cutoff level increased with increasing body mass index levels; however, even in subjects with body mass index more than or equal to 30 kg/m^2, the FPG cutoff level was lower than 7.0 mmol/liter.

Conclusions: Our findings suggest that the FPG cutoff level corresponding to the 2-h PG of 11.1 mmol/liter in the general Japanese population is lower than the current diagnostic criterion. ***(J Clin Endocrinol Metab* 93: 3425–3429, 2008)**

A 2-h post-load glucose (PG) cutoff level of 11.1 mmol/liter is considered to be the gold standard diagnostic criterion for diabetes mellitus. This cutoff point was originally adopted for several reasons (1). First, 11.1 mmol/liter has been found to approximate the cutoff point separating the two components of the bimodal distribution of 2-h PG levels. Second, according to several epidemiological studies, including our own, the prevalence of microvascular disease sharply increases in patients having a 2-h PG above 11.1 mmol/liter (1–4). Third, a great number of clinical and epidemiological studies have used this criterion. By contrast, fasting plasma glucose (FPG) has not been adequately justified as a diagnostic criterion. The FPG cutoff point for diagnosing diabetes was revised by the Expert Committee of the American Diabetes Association (ADA) (1) in 1997; namely, the cutoff point defining diabetes was reduced from more than or equal to 7.8 mmol/liter to more than or equal to 7.0 mmol/liter, though the ADA itself has recognized that this new cutoff point is not the best equivalent of the 2-h value of 11.1 mmol/liter (1, 5). The World Health Organization adopted an FPG of 7.0 mmol/liter as a diagnostic criterion of diabetes in 1998 (6). This lowering was based on the following findings from several studies, primarily with cohorts of high body mass index (BMI) subjects: 1) the prevalence and incidence of diabetic retinopathy increased at an FPG of approximately 7.0 mmol/liter (1, 3, 4); 2) the discrepancy in the detection rate of diabetes between FPG and 2-h PG values was reduced when an FPG of 7.0 mmol/liter was

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Abbreviations: ADA, American Diabetes Association; BMI, body mass index; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; PG, post-load glucose; ROC, receiver operating characteristic.

used; and 3) the prevalence of diabetes by a 2-h PG cutoff point of 11.1 mmol/liter was identical to that of an FPG of approximately 7.0 mmol/liter in several populations. However, the Diabetes Prevention Program Research Group has recently shown that the retinopathy characteristic of diabetes was present in persons whose FPG was below the diabetic range and who had no known history of diabetes (7). Furthermore, an integrated study of three general populations suggested that although the prevalence of retinopathy increased with FPG concentration, there was no clear diagnostic cutoff (8). These findings imply that data of diabetic retinopathy alone are not adequate to determine an FPG cutoff point. Thus, another approach, such as a regression analysis, is needed to validate the FPG cutoff point.

On the other hand, it remains controversial whether the FPG of 7.0 mmol/liter is adequately diagnostic for diabetes in Asian populations, which tend to be leaner than Western populations. For instance, FPG cutoff levels corresponding to a 2-h PG of 11.1 mmol/liter were also lower than 7.0 mmol/liter in other Asian populations (9–11). There have been very few reports on this issue in the Japanese population, in which the prevalence of diabetes has been increasing rapidly in recent years. The purposes of this study were to determine the FPG cutoff value corresponding to a 2-h PG of 11.1 mmol/liter, and to check whether this cutoff value varied according to changes in the society over time by examining the relationship between FPG and 2-h PG values in a general Japanese population at two different time points separated by an interval of 14 yr.

Subjects and Methods

A population-based prospective study of cardiovascular disease has been underway since 1961 in the Town of Hisayama, a suburb in the Fukuoka metropolitan area on Kyushu Island, in Japan. Based on data from the national census, the age and occupational distributions for Hisayama have been almost identical to those of Japan as a whole from 1961 to the present. As a part of the study, two cross-sectional diabetes surveys of Hisayama residents were conducted in similar fashion in 1988 and 2002. A detailed description of the surveys has been published previously (12, 13); briefly, of the total of 3227 residents in 1988 aged 40–79 yr in the town registry, 2587 (participation rate, 80.2%) consented to take part in a comprehensive assessment, including a 75-g oral glucose tolerance test (OGTT) and an interview covering both medical histories (including items on diabetes, hypertension, and other chronic diseases) and current medical treatments with insulin and oral hypoglycemic agents. After excluding participants who had already had breakfast, those who were receiving insulin therapy for diabetes, and those who refused the OGTT due to complaints of nausea or general fatigue during the ingestion of glucose, we successfully completed the OGTT on 2480 subjects. An additional 59 subjects were excluded because they were taking oral hypoglycemic agents; thus, the final 1988 study group comprised 2421 subjects (1045 men and 1376 women) (Fig. 1). In 2002, we established another study population of 2698 (1162 men and 1536 women) using the same methods and criteria.

In both the 1988 and 2002 surveys, clinical evaluation and laboratory measurements were performed in a similar manner. The study subjects underwent the OGTT between 0800 and 1030 h after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h post-load, and was separated into plasma and blood cells within 20 min. Plasma glucose levels were determined by the glucose-oxidase method. The between-assay and within-assay coefficients of variance of glucose measurement in our laboratory were 0.96 and 0.81% at 5.6 mmol/liter, and 0.81 and 0.56% at 16.7 mmol/liter, respectively. Total cholesterol and triglycerides were determined enzymatically. Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position; the average values were used in the analyses. Hypertension was defined as systolic blood pressure more than or equal to 140 mm Hg and/or diastolic blood pressure more than or equal to 90 mm Hg and/or current treatment with antihypertensive agents. The height and weight of each subject, wearing light clothes without shoes, were recorded, and the BMI (kg/m^2) was calculated. The interview investigated smoking habits and alcohol intake. Both were classified as either currently habitual or not. Subjects engaging in sports at least three times per week during their leisure time were classified into a regular exercise group.

SAS (SAS Institute Inc., Cary, NC) was used to perform all statistical analyses. Various regression models, including linear, quadratic, logarithmic, inverse, power, and exponential models, without covariates were examined to determine which best fit the relationship between FPG and 2-h PG levels. Furthermore, an FPG cutoff point corresponding to the 2-h PG of 11.1 mmol/liter was calculated from each regression equation. The sensitivity of the FPG cutoff point was defined as its ability to identify correctly individuals who had a 2-h PG of 11.1 mmol/liter or higher, and the specificity was its ability to identify correctly individuals who did not have a 2-h PG of 11.1 mmol/liter or higher. To compare the ability of FPG measurements to detect the presence or absence of a 2-h PG of 11.1 mmol/liter or higher across a range of values, we plotted receiver operating characteristic (ROC) curves. The diagnostic properties of specific cutoff levels of FPG were defined by maximizing the sensitivity and specificity to identify a 2-h PG of 11.1 mmol/liter or higher.

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from the participants.

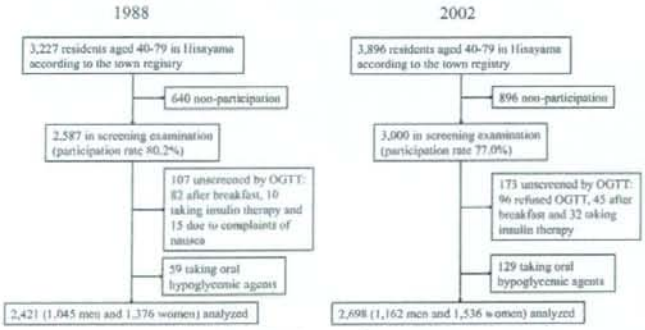

FIG. 1. Flow diagram of the study.

Results

The clinical characteristics of the subjects in 1988 and 2002 are summarized in Table 1. Mean values of age, FPG, 2-h PG, and BMI were higher in 2002 than 1988, whereas the frequency of men was not different between the populations.

To elucidate the relationship between FPG and 2-h PG, we analyzed their interrelationships using the various regression models listed in Table 2. FPG values corresponding to a 2-h PG of 11.1 mmol/liter and R^2 values were calculated for the combined populations

TABLE 1. Clinical characteristics of subjects: the Hisayama study in 1988 and 2002

	1988 (n = 2421)	2002 (n = 2698)	*P* value
Age (yr)	57 (10)	59 (11)	<0.001
Men (%)	43.2	43.1	0.94
FPG (mmol/liter)	5.7 (1.1)	6.0 (1.0)	<0.001
2-h PG (mmol/liter)	7.3 (3.2)	7.7 (3.1)	<0.001
BMI (kg/m^2)	23.0 (3.1)	23.3 (3.3)	<0.001

Values are means (SD).

of 1988 and 2002. The R^2 value was larger for the quadratic regression model, indicating that it is a better fit than the other models; the relevant FPG point in this model was 6.3 mmol/liter.

Figure 2 depicts the relationship between the FPG and 2-h PG in 1988 and 2002 considered separately. The quadratic model analyses were still the best fit among the various models for both the 1988 and 2002 populations (data not shown), with R^2 values of 64.0 in 1988 and 61.3 in 2002. The FPG point corresponding to a 2-h PG of 11.1 mmol/liter was 6.2 mmol/liter in 1988 and 6.3 mmol/liter in 2002.

To confirm the cutoff point of FPG corresponding to the 2-h PG of 11.1 mmol/liter, we plotted ROC curves and calculated the optimal cutoff points defined as the maximum combination of sensitivity and specificity, and their area under the ROC curves (Fig. 3). In the 1988 subjects, the corresponding FPG point was 6.2 mmol/liter. The sensitivity and specificity of this cutoff point were 81.2 and 88.7%, respectively; and the area under the curve was 91.0%. In the 2002 subjects, the cutoff point was 6.2 mmol/liter; the sensitivity, specificity, and area under the curve were 77.9, 81.3, and 86.7%, respectively.

Finally, we performed a stratified analysis by sex, age, and BMI levels in the combined population using both the quadratic regression model and ROC analysis (Table 3). The FPG level corresponding to the 2-h PG of 11.1 mmol/liter was slightly higher in men than women by both the quadratic regression model and ROC analysis. Higher FPG levels corresponding to a 2-h PG of 11.1 mmol/liter were observed in the younger age groups in the quadratic regression model analysis. However, in ROC analysis there was no association between age and FPG level. The FPG level corresponding to a 2-h PG of 11.1 mmol/liter increased with increasing BMI levels in both the quadratic regression model and ROC analysis. However, even in subjects with a BMI more than or equal to 30 kg/m^2, the FPG cutoff level was still lower than the diagnostic criterion of 7.0 mmol/liter.

Discussion

We examined the association between FPG and 2-h PG levels in a general Japanese population at two time points separated by a 14-yr interval, and using the quadratic model, which proved to be the best fit for the data, demonstrated that the FPG level corresponding to a 2-h PG of 11.1 mmol/liter, the gold standard for diagnosis of diabetes, was 6.2 mmol/liter for the 1988 data and 6.3 mmol/liter for the 2002 data. The FPG points derived from the ROC analyses corroborated these findings. It has been reported that the corresponding FPG cutoff level by the quadratic model was 5.7 mmol/liter in Chinese (9) and 6.3 mmol/liter in Taiwanese (10). Together with the findings of these other studies, our results suggest that, in relatively lean Asian populations, including the Japanese, the FPG cutoff level is clearly lower than the FPG value of 7.0 mmol/liter, which is currently used in various diagnostic criteria for diabetes (1, 6), and that this situation did not change over the course of 14 yr in the Japanese population.

Although a method using FPG values corresponding to the gold standard of 2-h PG levels for diagnosis of diabetes has not yet been established, regression analysis appears to be a useful method for detecting the FPG cutoff value. Two previous epidemiological studies determined FPG cutoff points by analyzing the relationship between FPG and 2-h PG using linear or exponential models (14, 15). However, in our study the quadratic model showed the highest positive correlation between FPG and 2-h PG, and, thus, was the best-fitted model. This is consistent with the findings of studies in Taiwanese (9) and Chinese (10) populations.

The ADA recommends the use of the FPG instead of 2-h PG for diagnosing diabetes because it is difficult to perform an OGTT in routine clinical practice (1). Thus, it is very important to determine the appropriate FPG cutoff value for the diagnosis of diabetes in different populations. The FPG of 7.0 mmol/liter for diagnosing diabetes is based on several population studies examining the relationship between the glycemic threshold and diabetic retinopathy (1, 3, 4); however, optimal cutoff levels of plasma glucose for defining diabetes depend on ethnicity. In a Pima Indian study, the ROC curve analysis in a diabetic retinopathy study identified the optimal FPG cutoff level as 6.8 mmol/liter (3). The National Health and Nutrition Examination Survey III study of the U.S. population also reported that the prevalence of retinopathy increased dramatically at FPG levels of 6.7 mmol/liter (1). These findings were apparently confirmed by a similar study in Egypt (4), in which the optimal FPG cutoff level

TABLE 2. Relationship between FPG (Y) and 2-h PG (X) in various regression models for the combined population of 1988 and 2002

Model	Equation	FPG corresponding to 2-h PG of 11.1 mmol/liter (mmol/liter)	R^2 (%)
Quadratic	$Y = 0.0149X^2 - 0.102X + 5.621$	6.3	62.3
Linear	$Y = 0.243X + 4.024$	6.7	51.8
Exponential	$Y = 2.718^{(0.0323X + 1.511)}$	6.5	48.6
Power	$Y = 3.512X^{0.255}$	6.5	36.6
Logarithmic	$Y = 1.831 \log X + 2.277$	6.7	35.6
	$\text{Log}(Y) = 0.255 \log X + 1.256$	6.5	36.6
	$\text{Log}(Y) = 0.243 (\log X)^2 - 0.748 \log X + 2.260$	6.5	50.2
Inverse	$Y = 7.265 - 9.416/X$	6.4	20.1

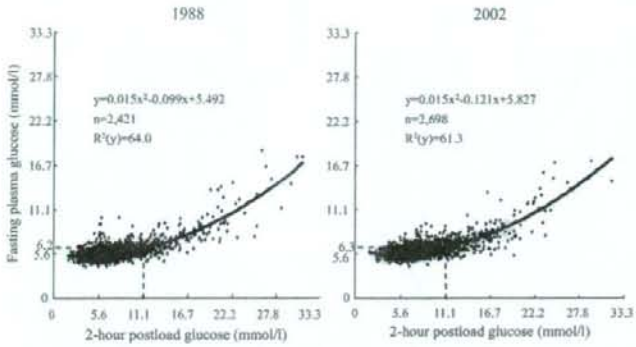

FIG. 2. The relationship between FPG and 2-h PG by a 75-g OGTT in Hisayama residents aged 40–79 yr in 1988 (*left panel*) and 2002 (*right panel*). *Solid line* represents the regression line by the quadratic regression model.

for detecting diabetic retinopathy was 6.9–7.2 mmol/liter. However, these three populations have higher BMI levels compared with Asian populations. We previously reported that although the glycemic threshold of 2-h PG for retinopathy in Japanese was 11.1 mmol/liter, that of FPG was only 6.4 mmol/liter (2). Other Asian population studies have reported optimal FPG cutoff levels for retinopathy ranging between 5.6 and 6.0 mmol/liter (16, 17). These findings suggest that FPG cutoff levels are lower in Asian populations than in other populations.

In our subjects the FPG cutoff levels corresponding to a 2-h PG of 11.1 mmol/liter increased with increasing BMI levels. However, even in subjects with a BMI more than or equal to 30 kg/m^2, the FPG cutoff level using the quadratic model was 6.4 mmol/liter, much lower than the diagnostic criterion of 7.0 mmol/liter. It is not clearly understood why FPG cutoff levels differ among ethnic groups. One possible explanation is that the capacity for acute insulin response to glucose load may influence the FPG cutoff level. The acute insulin response is known to be lower in Asian populations than other populations (18). In some clinical studies, the loss of acute insulin response by somatostatin was associated with a marked impairment in the initial suppression of hepatic glucose production, which led to higher 2-h PG concentrations (19, 20). Thus, impairment of acute insulin response may lead to a wide gap between FPG and 2-h PG; in other words, much lower FPG cutoff levels correspond to the 2-h PG diagnostic standard level. These findings might explain why the FPG cutoff level for the diagnosis of diabetes is lower in Asian populations, including ours, even in those with high BMI.

In the present study, the R^2 value in the quadratic model and the sensitivity, specificity, and area under the curve in the ROC analysis were all lower in 2002 than 1988. Although this phenomenon was not clearly understood, one possible reason may be that individuals in 2002 had more diverse lifestyles compared with those in 1988. Nevertheless, it is noteworthy that the FPG cutoff value corresponding to a 2-h PG of 11.1 mmol/liter was similar in the two populations.

Two limitations of our study should be discussed. First, in our study we determined the FPG cutoff level that corresponded to a 2-h PG of 11.1 mmol/liter, the gold standard for the diagnosis of diabetes, rather than that corresponding directly to diabetic complications. However, our previous study showed that the glycemic threshold of FPG for retinopathy is 6.4 mmol/liter (2), a result very similar to that of the present study. These findings suggest that the quadratic model precisely predicts the relationship between FPG and 2-h PG levels, making the FPG cutoff level nearly as accurate as the 2-h PG level, as well as more useful in clinical settings. Second, it is known that 2-h PG values in a 75-g OGTT have lower reproducibility than FPG (21, 22). It might be reasonable to propose FPG as the "gold standard." However, in the National Health and Nutrition Examination Survey III, 2-h PG was more specific for diabetic retinopathy than FPG (1). In several epidemiological studies, 2-h PG was also a stronger predictor of cardiovascular disease and total death compared with FPG (23–27). In addition, a 2-h PG of 11.1 mmol/liter was established in some revised processes for the diagnosis of diabetes. Based on these studies, then, a 2-h PG of 11.1 mmol/liter remains the "gold standard." Nevertheless, the present study found that two cross-sectional populations in 1988 and 2002 had nearly the same cutoff FPG values. This suggests that the high variability in 2-h PG values did not invalidate the present findings.

In conclusion, we have shown that the quadratic regression model is best fitted for the relationship between FPG and 2-h PG in a general Japanese population. The FPG cutoff level corresponding to a 2-h PG of 11.1 mmol/liter was 6.3 mmol/liter, and this result did not change over the course of 14 yr. Furthermore, the FPG cutoff levels were higher in subjects with higher BMI levels. The findings of the present study together with those of previous studies examining diabetic retinopathy sug-

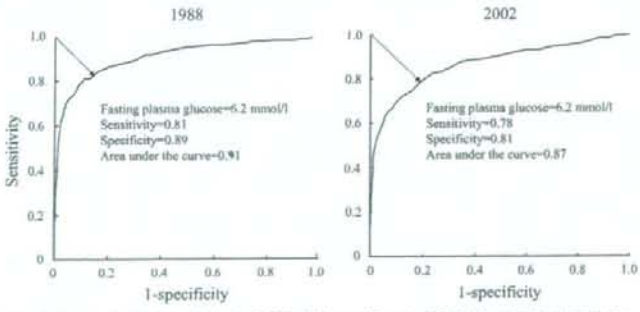

FIG. 3. ROC curves for FPG for predicting the 2-h PG of 11.1 mmol/liter using 1988 (*left*) and 2002 (*right*) data sets. The *arrow* shows the optimal cutoff point for detecting the 2-h PG of 11.1 mmol/liter defined as the maximum combination of sensitivity and specificity.

TABLE 3. FPG cutoff points corresponding to the 2-h PG of 11.1 mmol/liter by quadratic regression model and receiver operating curve analysis in the combined population of 1988 and 2002

Factors	No.	Cutoff point defined by quadratic regression analysis (mmol/liter)	Cutoff point defined by ROC analysis (mmol/liter)
Sex			
Men	2207	6.4	6.3
Women	2912	6.3	6.1
Age (yr)			
40–49	1341	6.4	6.0
50–59	1569	6.4	6.2
60–69	1363	6.3	6.2
70–79	846	6.2	6.1
BMI (kg/m^2)			
<20	818	6.1	5.9
20–24.9	2978	6.3	6.1
25–29.9	1192	6.3	6.2
≥30	131	6.4	6.7

gest that in Asian populations, the FPG cutoff level corresponding to a 2-h PG of 11.1 mmol/liter is lower than 7.0 mmol/liter, the current diagnostic criterion for diabetes. Considering the growing importance of the FPG test in screening for diabetes, further investigations are required to clarify the optimal FPG cutoff level in Asian and other ethnic populations.

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High-Sensitivity C-Reactive Protein and Coronary Heart Disease in a General Population of Japanese

The Hisayama Study

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Objective—The purpose of this study was to investigate the effects of high-sensitivity C-reactive protein (hs-CRP) on the risks of coronary heart disease (CHD) in a general population of Japanese.

Methods and Results—The Hisayama study is a population-based prospective cohort study. A total of 2589 participants aged 40 years or older were followed up for 14 years. Outcomes are incident CHD (myocardial infarction, coronary revascularization, and sudden cardiac death). The median hs-CRP level was 0.43 mg/L at baseline. During the follow-up period, 129 coronary events were observed. Age- and sex-adjusted annual incidence rates of CHD rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years for quartile groups defined by hs-CRP levels of <0.21, 0.21 to 0.43, 0.44 to 1.02, and >1.02 mg/L, respectively ($P<0.0001$ for trend). The risk of CHD in the highest quartile group was 2.98-fold (95% CI, 1.53 to 5.82) higher than that in the lowest group even after controlling for other cardiovascular risk factors.

Conclusions—hs-CRP levels were clearly associated with future CHD events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. (***Arterioscler Thromb Vasc Biol.* 2008;28:1385-1391**)

Key Words: inflammation ■ C-reactive protein ■ coronary heart disease ■ prospective cohort study ■ general population

Coronary heart disease (CHD) is estimated to be one of the leading causes of death in Japan as well as other countries around the world, placing a burden on the community.[1] Although the burden of CHD has been reduced in several developed countries in the past few decades,[2] its incidence rates have not declined in Japan.[3] Effective prevention will require a strategy based on knowledge of the importance of novel and traditional risk factors for CHD in Japan.

See accompanying article on page 1222

Recently, inflammation has emerged as an important factor in atherosclerosis,[4] and high-sensitivity C-reactive protein (hs-CRP) has attracted clinical attention as a novel risk factor for CHD. However, current knowledge of the importance of hs-CRP as a risk factor for CHD is derived mainly from studies done in Western populations,[5–12] and it is unclear to what extent these findings apply to Japanese populations. The Hisayama Study is a prospective cohort study of a general Japanese population. A previous report from the Hisayama Study showed a positive association between hs-CRP levels and the risks of ischemic stroke among Japanese men.[13] The objective of the present analysis is to examine the relationship between serum hs-CRP levels and future development of coronary heat disease in a general population of Japanese.

Methods

Study Design and Participants

Since 1961, we have been conducting a long-term prospective cohort study of cardiovascular disease in the town of Hisayama, a suburb of Fukuoka City in Southern Japan.[3,14] In 1988, a screening survey for the present study was performed in the town. A total of 2736 residents aged 40 years or older (80.9% of the total population of this age group) consented to participate in the examination.[13,15] After the exclusion of 102 subjects with a history of stroke or CHD and 45 subjects whose frozen blood samples were of insufficient quantity for the measurement of serum hs-CRP, the remaining 2589 individuals were enrolled in this study.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Follow-Up Survey

The subjects were followed up prospectively from December 1988 to November 2002 by repeated health examinations. A detailed description of the study methods has been published previously.[3,13,15] In

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brief, the health status of any subject who had not undergone a regular examination or who had moved out of town was checked yearly by mail or telephone. We also established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Departments of Pathology of Kyushu University. During the follow-up period, 545 subjects died, of whom 412 (75.6%) underwent autopsy. Only one participant was lost to follow-up.

Outcomes

The primary outcome of the present analysis was CHD. The criteria for a diagnosis of CHD included first-ever acute myocardial infarction (MI), silent MI, sudden cardiac death within 1 hour after the onset of acute illness, or coronary artery disease followed by coronary artery bypass surgery or angioplasty.[3,14] Acute MI was diagnosed when a subject met at least 2 of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain; (2) abnormal cardiac enzymes more than twice the upper limit of the normal range; (3) evolving diagnostic electrocardiographic (ECG) changes; (4) morphological changes including local asynergy of cardiac wall motion on echocardiography, a persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. The secondary outcomes of the present investigation were deaths attributable to any cardiovascular disease (ICD-10[16] codes I00-I99), deaths attributable to noncardiovascular disease, and total deaths.

Risk Factors

Plasma glucose levels were determined by the glucose-oxidase method, and diabetes was defined by a 75-g oral glucose tolerance test and by fasting (≥7.0 mmol/L) or postprandial (≥11.1 mmol/L) blood glucose levels or by the use of hypoglycemic agents. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were determined enzymatically. Low-density lipoprotein (LDL) cholesterol level was estimated using the Friedewald formula.[17] Hypercholesterolemia was defined as a serum cholesterol level of 5.69 mmol/L or higher. Serum specimens collected at the time of CRP measurement were stored at −20°C until they were used in 2002. Serum hs-CRP levels were analyzed using a modification of the Behring latex-enhanced CRP assay on a BN-100 nephelometer (Dade Behring) with a 2% interassay coefficient of variation. Sitting blood pressure (BP) was measured 3 times at the right upper arm using a sphygmomanometer after 5 minutes of rest; an average of 3 measurements was used for the analysis. Hypertension was defined as BP levels of ≥140/90 mm Hg or current treatment with antihypertensive agents. The waist circumference was measured at the umbilical level in a standing position. Height and weight were measured in light clothes without shoes, and body mass index (BMI, kg/m^2) was calculated. Obesity was defined as a BMI of ≥25kg/m^2. ECG abnormalities were defined as Minnesota code 3-1 or 4-1,2,3. Information on smoking habits, alcohol intake, and physical activity during leisure time was obtained using a standard questionnaire. Smoking habits and alcohol intake were classified as either current or not. Subjects engaging in sports or other forms of exertion ≥3 times a week during their leisure time made up a regular exercise group. Metabolic syndrome was defined using criteria recommended in the National Cholesterol Education Program Adult Treatment Panel III guideline[18] with a modification of abdominal obesity, which was defined as a waist circumference ≥90 cm in men and ≥80 cm in women according to the International Obesity Task Force central obesity criteria for Asia.[19]

Statistical Analysis

We used quartiles of hs-CRP levels for the analysis of the effects of hs-CRP on the risks of CHD. The contributions of relevant factors to an elevated hs-CRP level, which was defined as the highest quartile, were examined using a logistic regression model, with an estimated odds ratio (OR) and 95% confidence interval (95% CI). The cumulative incidence of CHD was estimated using Cox's proportional hazards model. The incidence rates were calculated by the person-year method and standardized for age and sex distribution of the world standard population by the direct method using 10-year age groupings. The age- and sex-adjusted or multivariate-adjusted hazard ratio (HR) and 95% CI were estimated using Cox's proportional hazard model. Comparison of the effects hs-CRP between participants with and without other cardiovascular risk factors was done, and the probability value for homogeneity was estimated by adding an interaction term to the statistical model. All analyses were performed using the SAS software package (SAS Institute).

Results

Among the 2589 participants, the median hs-CRP level was 0.43 mg/L. The baseline characteristics of the subjects by hs-CRP quartile groups are shown in Table 1. Subjects with higher hs-CRP levels were older and less frequently women. The age- and sex-adjusted logistic regression analysis revealed that hypertension (OR, 1.40; 95% CI, 1.16 to 1.69), diabetes (OR, 1.67; 95% CI, 1.29 to 2.16), obesity (OR, 1.80; 95% CI, 1.47 to 2.22), hypercholesterolemia (OR, 1.32; 95% CI, 1.09 to 1.60), metabolic syndrome (OR, 2.04; 95% CI, 1.67 to 2.50), and smoking habits (OR, 1.96; 95% CI 1.56 to 2.47) were significantly associated with elevated hs-CRP levels, which were defined as the highest quartile (>1.02 mg/L).

During the 14 years of follow up, 129 coronary events were observed. The Figure shows the age- and sex-adjusted cumulative incidence of CHD according to hs-CRP quartiles. The cumulative incidence of CHD clearly increased with rising hs-CRP levels. The age- and sex-adjusted incidence rates of CHD according to hs-CRP quartiles are shown in Table 2. The incidence rates rose progressively with higher hs-CRP levels: 1.6, 3.3, 4.5, and 7.4 per 1000 person-years from the first to the fourth quartile groups, respectively ($P<0.0001$ for trend). Table 2 also shows age- and sex-adjusted and multivariate-adjusted HRs and 95% CIs for the development of CHD according to the hs-CRP quartiles. The risks of CHD significantly increased with rising hs-CRP levels even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise ($P=0.0002$ for trend). The risk of CHD in the highest quartile group was significantly higher than that in the lowest group (multivariate-adjusted HR, 2.98; 95% CI, 1.53 to 5.82).

During the follow-up period, 545 participants died (158 died of cardiovascular disease and 387 died of noncardiovascular disease). The age- and sex-adjusted total and cause-specific mortality rates are shown in Table 3. The age-and sex-adjusted all-cause mortality rates rose progressively with higher hs-CRP levels ($P<0.0001$ for trend). The age- and sex-adjusted and multivariate-adjusted HRs also increased with rising hs-CRP levels even after controlling for other risk factors (Table 3; $P<0.0001$ for trend). When causes of death were divided into cardiovascular and noncardiovascular diseases, the relationship of hs-CRP to cardiovascular deaths was stronger than that to noncardiovascular deaths.

Age- and sex-adjusted hazard ratios of hs-CRP (highest versus lowest quartiles) for the development of CHD among

Table 1. Baseline Characteristics by Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	*P* Trend
Age, y	55 (11)	58 (12)	59 (11)	62 (12)	<0.0001
Women, %	64	63	55	51	<0.0001
Systolic blood pressure, mm Hg	128 (20)	132 (22)	136 (21)	138 (21)	<0.0001
Diastolic blood pressure, mm Hg	76 (11)	78 (11)	79 (11)	79 (12)	<0.0001
Hypertension,* %	29	39	45	52	<0.0001
ECG abnormalities,† %	15	15	16	18	0.1
Diabetes,‡ %	6	9	16	17	<0.0001
Waist, cm	77.4 (8.8)	80.6 (9.0)	83.8 (8.8)	83.8 (9.5)	<0.0001
Body mass index, kg/m^2	22 (3)	23 (3)	24 (3)	24 (3)	<0.0001
Total cholesterol, mmol/L	5.21 (1.02)	5.38 (1.09)	5.44 (1.11)	5.40 (1.13)	0.002
Triglycerides, mmol/L	1.15 (0.99)	1.37 (1.22)	1.56 (1.71)	1.48 (1.02)	<0.0001
HDL cholesterol, mmol/L	1.38 (0.30)	1.34 (0.31)	1.27 (0.29)	1.22 (0.30)	<0.0001
LDL cholesterol,§ mmol/L	3.30 (1.01)	3.41 (1.12)	3.46 (1.14)	3.50 (1.09)	0.0009
Metabolic syndrome, %	14	24	33	39	<0.0001
Current smoker, %	19	20	26	35	<0.0001
Current alcohol use, %	27	27	35	33	0.006
Regular exercise, %	10	9	9	12	0.2

Values are means (SD) or frequencies.

hs-CRP indicates high-sensitivity C-reactive protein; ECG, electrocardiographic; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.

†Minnesota codes 3-1 or 4-1,2,3.

‡Fasting glucose ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.

§LDL cholesterol level was estimated using the Friedewald formula.

major clinical subgroups defined by the absence or presence of other cardiovascular risk factors are shown in Table 4. There were comparable effects of hs-CRP on the risk of CHD for participants who were and those who were not hypertensive (*P* homogeneity=0.7). Likewise, there were no clear differences in the effects of hs-CRP for participants with and without other cardiovascular risk factors such as diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits (all *P* homogeneity >0.4).

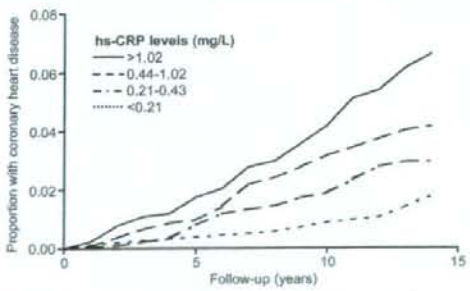

Figure. Age- and sex-adjusted cumulative incidence of coronary heart disease according to quartiles of high-sensitivity C-reactive protein. hs-CRP indicates high-sensitivity C-reactive protein.

Discussion

The present analysis demonstrated that serum hs-CRP levels were clearly associated with future coronary events in a general population of Japanese. The association between hs-CRP and CHD was strong and continuous down to very low hs-CRP levels of less than 0.21 mg/L. These associations remained strong even after controlling for age, sex, systolic BP, ECG abnormalities, diabetes, BMI, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise. Furthermore, the effects of hs-CRP were comparable for subjects with and without other cardiovascular risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, and smoking habits.

Large-scale nested case-control studies have reported that participants with incident CHD had higher levels of hs-CRP.[5,6,8–11] Likewise, large-scale cohort studies have clearly demonstrated that hs-CRP levels predicted future coronary events.[7,12] However, these studies were mainly conducted in Western populations, and it is unclear to what extent these associations apply to Japanese populations. The Honolulu Heart Program has reported a clear association between hs-CRP levels and the future development of CHD in a population of Japanese Americans.[20] The present analysis from the Hisayama Study confirmed the results from these previous observational studies in a general population of Japanese, finding that the relative risks of increasing hs-CRP levels for the development of CHD were similar to those

Table 2. Incidence Rates and Adjusted Hazard Ratios for Development of Coronary Heart Disease According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	P Trend
No. of events/person-years	11/8589	22/8297	36/8073	60/7485	
Crude incidence rate (per 1000 person-years)	1.3	2.7	4.5	8.0	
Age- and sex-adjusted incidence rate (per 1000 person-years)	1.6	3.3	4.5	7.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.75 (0.85 to 3.61)	2.55 (1.30 to 5.02)	3.96 (2.07 to 7.57)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.60 (0.77 to 3.31)	1.97 (0.98 to 3.95)	2.98 (1.53 to 5.82)	0.0002

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

obtained from other observational studies conducted in Western populations[5–12] or in a population of Japanese Americans.[20] These findings suggest that hs-CRP is an important risk factor for CHD among Japanese as well as among Westerners.

In the present analysis, hs-CRP levels in Japanese (median 0.43 mg/L) were much lower than those in Western populations (median approximately 1.5 to 2.0 mg/L).[21,22] This is consistent with the findings of other cross-sectional studies in which Asian subjects had lower hs-CRP levels compared to Western subjects.[21–24] The reason for this ethnic difference is not clearly resolved, but genetic diversity has been reported to influence hs-CRP levels.[25] The relatively low BMI in Japanese and differences in diet and lifestyle may also have modulated hs-CRP levels.[26] The Honolulu Heart Program reported a median hs-CRP level of 0.54 mg/L among Japa-

Table 3. Mortality Rates and Adjusted Hazard Ratios for Total and Cause-Specific Deaths According to Quartiles of High-Sensitivity C-Reactive Protein

	hs-CRP Levels, mg/L				
	<0.21 (n=648)	0.21 to 0.43 (n=647)	0.44 to 1.02 (n=645)	>1.02 (n=649)	P Trend
Total deaths					
No. of events/person-years	79/8624	106/8365	143/8181	217/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	12.7	15.2	18.9	23.5	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.08 (0.81 to 1.45)	1.30 (0.99 to 1.72)	1.80 (1.39 to 2.34)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.13 (0.84 to 1.51)	1.41 (1.06 to 1.87)	1.85 (1.41 to 2.43)	<0.0001
Cardiovascular deaths					
No. of events/person-years	16/8624	28/8365	47/8181	67/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	2.2	3.7	6.0	7.2	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.75 to 2.55)	2.15 (1.22 to 3.80)	2.77 (1.60 to 4.80)	<0.0001
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.40 (0.75 to 2.60)	2.28 (1.27 to 4.09)	3.00 (1.70 to 5.28)	<0.0001
Noncardiovascular deaths					
No. of events/person-years	63/8624	78/8365	96/8181	150/7626	
Age- and sex-adjusted mortality rate (per 1000 person-years)	10.5	11.5	12.9	16.4	
Age- and sex-adjusted hazard ratio (95% CI)	1 (reference)	1.00 (0.72 to 1.40)	1.09 (0.79 to 1.50)	1.55 (1.15 to 2.08)	0.0004
Multivariate-adjusted hazard ratio* (95% CI)	1 (reference)	1.06 (0.76 to 1.48)	1.18 (0.85 to 1.64)	1.56 (1.14 to 2.13)	0.001

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.

*Hazard ratios controlling for age, sex, systolic blood pressure, ECG abnormalities, diabetes, body mass index, total and HDL cholesterol, smoking habits, alcohol intake, and regular exercise.

Table 4. Age- and Sex-Adjusted Hazard Ratios of High-Sensitivity C-Reactive Protein (Highest vs Lowest Quartiles) for Development of Coronary Heart Disease Among Major Clinical Subgroups Defined by the Absence or Presence of Other Cardiovascular Risk Factors

	No. of Events/Person-Years			
	Highest Quartile (hs-CRP>1.02 mg/L)	Lowest Quartile (hs-CRP<0.21 mg/L)	Hazard Ratio* (95% CI)	*P* Homogeneity
Hypertension†				
Absent	18/3843	6/6224	3.18 (1.25 to 8.08)	0.7
Present	42/3643	5/2365	4.27 (1.68 to 10.82)	
Diabetes‡				
Absent	45/6276	9/8122	3.73 (1.81 to 7.68)	0.7
Present	15/1210	2/467	2.84 (0.65 to 12.43)	
Obesity§				
Absent	45/5113	10/7412	3.63 (1.81 to 7.28)	0.7
Present	15/2373	1/1177	5.42 (0.71 to 41.35)	
Hypercholesterolemia‖				
Absent	32/4448	5/5975	4.74 (1.83 to 12.26)	0.4
Present	28/3037	6/2614	2.83 (1.16 to 6.88)	
Metabolic syndrome¶				
Absent	27/4340	7/7068	3.34 (1.44 to 7.75)	1.0
Present	29/2631	3/1122	3.31 (1.00 to 10.92)	
Current smoking				
Absent	34/4910	9/7030	3.39 (1.61 to 7.15)	0.5
Present	26/2576	2/1559	5.94 (1.40 to 25.12)	

hs-CRP indicates high-sensitivity C-reactive protein; 95% CI, 95% confidence interval.
*Hazard ratios for the highest vs the lowest quartile of high-sensitivity C-reactive protein.
†Blood pressure ≥140/90 mm Hg or current use of antihypertensive agents.
‡Fasting glucose ≥7.0 mmol/L, postprandial blood glucose ≥11.1 mmol/L, or current use of hypoglycemic agents.
§Body mass index ≥25kg/m^2.
‖Total cholesterol ≥5.69 mmol/L.
¶Defined by the modified National Cholesterol Education Program Adult Treatment Panel III criteria.

nese Americans without CHD,[20] which was lower than that of Western populations but higher than that obtained from the present analysis. These findings suggest that lower hs-CRP levels among Asian populations are derived from differences in genetic factors as well as differences in BMI, diet, and lifestyle.

Another important finding obtained from the present analysis is that the association between hs-CRP levels and CHD was continuous from very low hs-CRP levels and that a slightly elevated hs-CRP level of more than 1 mg/L was clearly associated with increased risk of future coronary events in Japanese. Similar findings were obtained from the Honolulu Heart Program, whose subjects were Japanese American.[20] A low cut-off point of hs-CRP (<1 mg/L) has also been suggested as the target of lipid lowering therapy with statin for maximum reduction of recurrent coronary events or deaths among Western patients with acute coronary syndrome.[27–29] These findings imply that the association between hs-CRP and CHD are likely to be continuous down to very low hs-CRP levels among Asian as well as Western subjects. The American Heart Association and the Centers for Disease Control have recommended categorizing subjects using hs-CRP cut-off points of <1, 1 to 3, and >3 mg/L into low-, average-, and high-risk categories, respectively, based mainly on the findings obtained from studies done in Western populations.[30] Among Asian subjects whose hs-CRP levels are much lower than those of Western subjects, however, an hs-CRP level of >1 mg/L is likely to be the cut-off point for the high-risk category.

In the present analysis, the effects of hs-CRP on the risks of future coronary events were independent of other cardiovascular risk factors and did not differ between participants with and those without traditional risk factors such as hypertension, diabetes, obesity, hypercholesterolemia, metabolic syndrome, or smoking habits. These results suggest that measurement of hs-CRP is likely to provide additional information for the detection of high-risk individuals among subjects without traditional risk factors as well as for the detection of extremely high-risk individuals among those with traditional risk factors. This finding is consistent with other observational studies suggesting that inclusion of hs-CRP into risk prediction models improves the accuracy of cardiovascular risk classification.[31,32]

Several limitations of our study should be discussed. The primary limitation is that we estimated the cut-off point of hs-CRP for detection of high-risk subjects based on analysis using quartile groupings despite continuous relationships between hs-CRP and the risks of CHD. The cut-off point

could change depending on the way of grouping the subjects or on the way of selecting the reference group. Given that this limitation might have overestimated the cut-off point, the true cut-off point for detection of high-risk subjects may be lower than 1 mg/L. A second limitation is that our findings are based on a 1-time measurement of serum hs-CRP, which may not accurately reflect the status of a study participant. However, this source of variability could not account for the relationship observed in the present study, because a random misclassification of such nature would tend to underestimate study findings and bias the results toward the null hypothesis. Thus, the true association may be stronger than that observed in our study. A third limitation is that the serum samples were measured after being stored at −20°C for a long period. However, the Reykjavik Study confirmed the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years.[10] The last limitation is that our study lacked information on drug use at baseline and during the follow-up period. It is known that several medications, including statin, angiotensin-converting enzyme inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone can alter CRP levels.[33] However, these medications were rarely used in Japan in 1988, when the serum samples for our study were collected. This suggests that such a bias did not invalidate the present findings. It is also known that some medications have been shown to be beneficial for prevention of CHD, and high-risk individuals with higher hs-CRP levels were likely to receive these medications. Given that this limitation might have underestimated the association between hs-CRP and CHD, the true association may be stronger than that obtained from the present analysis.

In conclusion, the present analysis has clearly demonstrated that hs-CRP levels were associated with future coronary events in a general population of Japanese. In Japanese populations, the hs-CRP cut-off point for high-risk of future development of CHD is likely to be >1.0 mg/L, which is much lower than that for Western populations. High-risk approaches for the prevention of CHD using hs-CRP measurement are likely to provide additional protection against the burden of CHD in Japan.

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Disclosures

None.

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