4. 家庭血圧のメタボリックシンドローム基準としての有用性

本研究より、家庭血圧が“血圧以外のリスク因子集積”と有意に関連することが示された。メタボリックシンドロームを有する者は、有さないものに比べ脳心血管疾患発症リスクが有意に高値であることが現在まで報告されている。すなわち、随時血圧を含む基準を用いて診断したメタボリックシンドロームの臨床的な有用性が確立されつつあるといえる。家庭血圧は随時血圧より脳心血管疾患予後予測能が高いことが既に示されており、本研究では家庭血圧は随時血圧より強くメタボリックシンドローム構成因子と関連した。したがって、家庭血圧を診断基準に導入することで、メタボリックシンドロームは一層高い予後予測能を有すると考えられる。

男女別解析の結果、男性において女性に比し家庭血圧と“血圧以外のリスク因子集積”との関連が強かった。本研究対象者において男性は、随時血圧が正常で家庭血圧が高値である、いわゆる“仮面高血圧”の頻度が有意に女性より高かった（男性 25%、女性 12%、$p < 0.01$）。仮面高血圧は脳心血管疾患の高リスクであることが数多く報告されており、男性では仮面高血圧発見のためにも家庭血圧測定が有用であることが示唆される。一方、本研究対象者において女性は、随時血圧が高値で家庭血圧が正常である、いわゆる“白衣高血圧”の頻度が有意に男性より高かった（男性 11%、女性 19%、$p = 0.04$）。Ugajin らは大迫一般住民において、白衣高血圧者は将来持続性高血圧へ移行するリスクが高いことを報告している。これより女性においても、持続性高血圧発症予測の観点より家庭血圧測定は重要であると考えられる。しかしながら、男女別解析におけるオッズ比は 95%信頼区間が広く、性差については今後のより大規模な検討が必要と思われる。

本研究の結果から、家庭血圧を導入したメタボリックシンドローム診断基準は脳心血管疾患予防に有用であることが示唆された。メタボリックシンドロームの簡便なスクリーニングのためには随時血圧が有用と思われるが、治療的介入を実施する上では家庭血圧による精緻なリスク評価の必要性が高いであろう。現在日本ではおよそ 3000 万台の家庭血圧計が普及しており、ギリシャやイタリアでも高血圧患者の 3 分の 2 が家庭血圧測定を実施している。したがって、家庭血圧を用いたスクリーニングは比較的容易になりつつあるといえる。今後の研究の成果が待たれるが、本研究により家庭血圧のメタボリックシンドローム診断基準への導入の意義がある程度示されたと考えられる。

5. 日本と ATPIII のメタボリックシンドローム診断基準の差異

本解析では、日本の基準に加え比較対象として ATPIII の基準を用いたが、どちらを用いた場合でも“血圧以外のリスク因子集積”は家庭血圧値の上昇と有意に関連した。国際比較の観点からは、より広範に引用される ATPIII 基準をメタボリックシンドローム診断に用いることも一部必要と思われるが、ATPIII 基準の日本人への適用については、ウエスト周囲径のカットオフ値を始めとした更なる検討が必要と考えられる。

6. 降圧薬・高脂血症治療薬服用率と性差

降圧薬の中で、利尿薬は血糖値の上昇や糖尿病の発症と関連することが知られている。

本研究の降圧薬服用者において、利尿薬服用者の頻度は男性が女性より有意に高かった。表2における血糖値項目ならびにメタボリックシンドローム（日本基準）の頻度に影響した可能性が考えられる。

一方で、高脂血症治療薬服用者の頻度は女性が男性より有意に高かった。一般に日本人女性において、血清総コレステロール値は閉経前では男性より低値であるが、閉経期を境に上昇し男性より高値となる。平成14年度国民健康・栄養調査では、60歳以上の女性の高脂血症治療薬服用率は、同年代の男性より高いことが報告されている。本研究の女性対象者は平均年齢が約63歳であり、多数の対象者が閉経後であったと考えられ、国民健康・栄養調査の報告と一致している。

7. 研究限界

第1に、本研究対象者は東北地方の一地域の一般住民であり、他の地域・都市部の住民への適用についてはさらなる検討が必要である。また本対象者は非対象者より有意に高齢で、家庭血圧値ならびに男性の割合が低値であった。これは、退職後等で時間に余裕があり、健康意識の高い者が任意である糖負荷試験に参加したためと考えられる。また、平日に糖負荷試験を実施したことが、男性対象者の割合が低かったことに繋がった可能性も考えられる。以上のことから、本研究のロジスティック解析において、性・年齢をモデルに補正項目として加えた。しかしながら、本研究の結果の一般化については、上記の選択バイアスを十分に考慮する必要がある。

第2に、本研究の対象者は比較的少数である。ウエスト周囲径以外の、あるいは血圧以外のリスク因子をすべて満たす対象者がほとんどおらず、リスクの集積とウエスト周囲径・血圧情報との関連をより深く解析することができなかった。

最後に、本研究は横断研究であり、因果関係については言及できない。家庭血圧を診断基準に据えた場合のメタボリックシンドロームの病態が、対象者の予後をどの程度適切に予測するかについては、今後の縦断的研究の結果が待たれる。

E. 結論

本研究の結論として、日本の一般地域住民におけるメタボリックシンドローム診断基準の女性のウエスト周囲径カットオフ値は、80cmが最適であることが示唆された。また、BMIをメタボリックシンドローム診断基準に用いる場合、24～25 kg/m^2 が最適であることが示唆された。最後に、メタボリックシンドローム診断基準の血圧項目に、随時血圧の代わりに家庭血圧を用いることで、メタボリックシンドロームの有用性がより向上した。このことから、メタボリック診断基準として、随時血圧の代わりに家庭血圧を用いることで、メタボリックシンドローム有病者を一層的確に捉え得る可能性が示された。

F. 研究発表

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G. 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

3. その他

なし

論文題名　Kidney dysfunction as a risk factor for first symptomatic stroke events in a Japanese general population: The Ohasama study.

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項目	抽出する内容（アブストラクトおよび本文中から抽出する）
目次	病因・予防
目的	慢性腎疾患(CKD)は一般住民において、脳心血管疾患(CVD)発症および死亡の危険因子であることが示されている。しかし、CVDを心疾患と脳卒中に二分すると、その割合は欧米とアジアで異なっている。日本人においては、特に脳卒中患者の割合が高いにも拘らず、CKDが脳卒中発症の危険因子であるかは明らかになっていない。そこで本研究では、この問題を明確にすることを目的とした。
研究デザイン	前向きコホート研究。 1992-97年にベースライン調査。その後2001年まで追跡。
セッティング	岩手県大迫町(現花巻市大迫町)
対象者	35歳以上の大迫住民3076名のうち、1992年から1997年までの住民基本健診に参加したのは2192名。このうち、血清クレアチニン値、尿検査、交絡因子が欠損している215名を除く1977名を解析対象者とした(平均年齢62.9歳、男性731人・女性1246人)。
エンドポイント	1. 脳卒中とTIAの新規発症。2. 全死亡。3. CVD死亡
統計解析	Cox比例ハザードモデル(年齢・性別・収縮期血圧・BMI・喫煙歴・降圧薬服用・CVD既往歴・糖尿病既往歴・高コレステロール血症既往歴で補正。統計学的有意水準は0.05未満。)
主な結果	ベースライン時に、尿タンパク陽性が154例(7.8%)。 観察期間7.8年の間、脳卒中発症112例、全死亡187例(うちCVD死亡58例)を把握。 対象者をCcr(ml/min)の値で3群(～40、40～70、70～)に分類し、70以上の群をリファレンスとして、脳卒中発症の相対ハザード(RH)を算出した。その結果、40以下の群 (RH=3.1: 95%信頼区間 1.24-7.84)、40から70の群 (1.9: 1.06-3.75)で有意にRHが高値を示した。また、全死亡のRHも同様に40以下の群(5.3: 2.46-11.59)、40から70の群(2.3: 1.29-4.23)で有意に高値だった。
結論	日本の一般地域住民において、腎機能の低下は脳卒中の発症リスクを増加させた。日本には脳卒中患者が非常に多いことから、CKDが危険であることを共通認識として持つ必要がある。
CQ	1. CKDは脳卒中発症の危険因子か？
Answer	1. Yes. CKDは脳卒中の発症リスクを増加させる。
備考	特になし

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Original Article

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Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population—the Ohasama study

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Abstract

Background. Chronic Kidney Disease (CKD) has been shown to be a risk factor for mortality as well as for morbidity such as cardiovascular disease (CVD) in the general population. However, in the context of CVD events, there is a difference in the incidence of cardiac and stroke events between Western and Asian populations. Although a high prevalence of stroke is a characteristic feature in Japanese populations, it is unclear whether CKD constitutes a risk for stroke events.

Methods. To clarify this issue, we estimated creatinine clearance and obtained dipstick tests from spot-urine samples in 1977 subjects (mean 62.9-years-old, men/women: 731/1246) from a general Japanese population. First symptomatic stroke events and all-cause mortality were analysed according to stratification of kidney function and by positive tests for macroalbuminuria using a Cox proportional hazards regression model adjusted for possible confounding factors.

Results. During the observation period (mean 7.76 years), we recorded 112 events of first symptomatic stroke and 187 deaths (58 cases due to CVD). After adjustment for all variables, we found that increases in relative hazard (RH) for the first symptomatic stroke events were associated with decreasing kidney function (RH, 3.1; 95% CI, 1.24–7.84 in Ccr < 40 ml/min, 1.9; 95% CI, 1.06–3.75 in Ccr 40–70 ml/min, ref in Ccr > 70 ml/min) and with the presence of macroalbuminuria (RH, 1.4; 95% CI, 0.80–2.41).

Conclusion. Decreased kidney function increased the risk of first symptomatic stroke events in a general Japanese population. The high prevalence of stroke in this population prompts the need for greater public awareness about risks for CKD.

Keywords: chronic kidney disease; Japanese general population; stroke

Introduction

Chronic Kidney Disease (CKD) [1] is an independent risk factor for all-cause mortality including cardiovascular disease (CVD) events among the general population in Western countries [2–5]. Recent reports from Japan have also confirmed CKD as a significant risk for CVD events and all-cause mortality [6–8], suggesting that CKD represents a major public health issue that is independent of ethnicity.

However, in the context of CVD events, there is a difference in the incidence of coronary heart disease and stroke events between Western and Asian populations [9]. A high prevalence of stroke has remained a major concern in Japan [10], where mortality resulting from stroke is 3-fold higher than that in the United States, while mortality from coronary heart disease is one-third of that in the United States [11,12]. In the atherosclerosis risk in a community (ARIC) study conducted in the United States [5], cardiac diseases represented a majority of CVD events, wherein 79.4% of CVD events were due to coronary heart disease. Thus, although the link between CKD and incidence of stroke events in the Asian population is of crucial interest, there is limited data in this area of research [6].

The present community-based longitudinal observational study aimed to explore this issue in the general Japanese population. We ascertained a significant role

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for kidney dysfunction in the development of first symptomatic stroke events as well as in all-cause and CVD-related mortality.

Subjects and methods

Design

The present report is based on a longitudinal observation of subjects who had been participating in a blood-pressure (BP) measurement project in Ohasama, Iwate Prefecture (Japan) since 1987. Ohasama, a rural community, had a total population of 7496 in 1992. The socio-economic and demographic characteristics of this region and details of this project have been previously described [13]. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government.

Study population

In Japan, annual health check-ups are available for farmers, the self-employed, pensioners and dependents aged ≥35 years. Among the residents of Ohasama, 3076 were eligible for annual health check-ups in 1992. Of the 2192 residents who participated in check-ups from 1992 to 1997, data on serum creatinine levels, dipstick tests for spot-urine and confounding factors were unavailable in 215 subjects. The present study population thus comprised 1977 individuals, representing 64% of the total eligible population.

Follow-up and outcomes

Residence in Ohasama as of 31 December 2001 was confirmed by residential registration cards. These cards are both accurate and reliable because they are used for pensions and social security benefits in Japan. Causes of death up to 31 December 2001 were investigated by referencing to the national mortality registry, in which underlying causes of death are classified by death certificates according to the recommendations of the 'International Classification of Disease, 10th revision' (ICD-10).

Incidences of stroke and transient ischaemic attack (TIA) up to 31 December 2001 were investigated by reference to the Stroke Registration System of Iwate Prefecture, the national mortality registry, National Health Insurance receipts and from interviews at the time of annual check-ups. Results were then confirmed by checking medical records at Ohasama Hospital, the only hospital in the community, where >90% of patients undergo regular check-ups. Death certificates were the sole source of information for only 2% of stroke cases. Most cases were diagnosed by computed tomography or magnetic resonance imaging of the brain. Diagnostic criteria for stroke and stroke subtypes were based on the Classification of Cerebrovascular Disease III by the National Institute of Neurological Disorders and Stroke [14].

Primary outcomes were defined as the first symptomatic event of stroke. We additionally analysed all cause mortality and mortality from CVD defined as death from diseases of the circulatory system (ICD-10:I00– I99).

Data collection

Serum creatinine was measured using the Jaffe assay. Kidney function was estimated by calculated creatinine clearance (Ccr) using the Cockcroft–Gault equation [15]. Diagnoses were made using a dipstick test for spot-urine (Urohemabonbix 5G08C; Bayer Medical, Japan). Positive macroalbuminuria was considered present for a dipstick result of + or more, corresponding to a urinary protein level >30 mg/dl [16]. BP was measured twice by nurses or technicians at local medical centres using an automatic USM-700F sphygmomanometer (UEDA Electronic Works, Tokyo, Japan) based on the Korotkoff sound technique (microphone method) [17] with subjects in a seated position after resting for ≥2 min. Casual BP was defined as the mean of two readings. Information on smoking status, use of antihypertensive medications at baseline, as well as history of CVD, diabetes mellitus or hypercholesterolaemia were obtained from interviews, from the results of blood examinations at the time of annual health check-ups, and from medical records at Ohasama Hospital. History of CVD was defined as disease of the circulatory system (ICD-10:I00 to I99), stroke and TIA. Subjects receiving administration of lipid-lowering drugs or displaying serum cholesterol levels ≥5.68 mmol/l (220 mg/dl) were considered to have hypercholesterolaemia. Subjects with fasting glucose levels ≥7.7 mmol/l (126 mg/dl) or non-fasting glucose levels ≥11.11 mmol/l (200 mg/dl), or who used insulin or oral anti-hyperglycaemic drugs were defined as having diabetes mellitus. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Data analysis

Associations between baseline kidney function, as defined by estimated Ccr, macroalbuminuria and incidence of primary outcomes, were examined using the Cox proportional hazards regression model, adjusted for age, gender, systolic BP, BMI and smoking status, for the use of antihypertensive medications at baseline and for history of CVD, diabetes mellitus or hypercholesterolaemia. Participants who died from other causes or who were lost to follow-up were designated as censored. The dependent variable in these analyses was the number of days from the date of observation to the date of death, stroke or TIA, or censoring, respectively.

The estimated relative hazard (RH) and 95% confidence interval (95% CI) of variables were derived from the coefficient and standard error as determined by the Cox proportional hazards model. Data are shown as means±SD. Values of $P < 0.05$ were accepted as indicative of statistical significance. All statistical analyses were conducted using SAS version 9.1 software (SAS Institute, Cary, NC, USA).

Results

The mean age of the 1977 subjects was 62.9 ± 9.6 years, and the ratio of men to women was 37:63. There were 154 subjects (7.8%) who presented a positive test for urinary protein. Mean systolic/diastolic BP was 130/73 mmHg. Of all the subjects, 15.6% were classified as current or ex-smokers and 22.5% were

treated with antihypertensive medication, while 5.1, 8.8 and 37.7% subjects were classified as having a history of heart disease, diabetes mellitus or hyperlipidaemia, respectively. Mean BMI was 23.4 kg/m^2. A history of stroke was present in 83 subjects, indicating that 1914 subjects had never experienced a stroke.

The observational period averaged 7.8 ± 2.0 years. A total of 37 subjects (2%) moved away and were lost to follow-up. One hundred seventeen subjects developed first symptomatic strokes among 1914 cases who had never previously experienced a stroke. Of these, there was cerebral infarction in 78 cases, cerebral bleeding in 21 cases, subarachnoid haemorrhage in eight cases, TIA in four cases and other causes in one case. Of 187 deaths, 69 were due to neoplasma, 58 were due to CVD including stroke in 26 cases, 18 were due to respiratory disease and 42 were due to other causes (Table 1).

After the preliminary analysis, patients were stratified into three groups according to estimated Ccr levels: <40 ml/min, 40–70 ml/min and >70 ml/min. This classification was arbitrary but yielded the most powerful statistical difference with Cox analysis for all-cause mortality in terms of the magnitude of log likelihood ratio [18]. Basic characteristics of the respective groups are shown in Tables 1–3.

RH(s) for first symptomatic stroke events among subjects with negative stroke history, all-cause of mortality and CVD-related mortality adjusted for confounding factors were determined and compared with the reference group having Ccr > 70 ml/min (Figure 1).

RH for first symptomatic stroke event was 1.9 (95% CI:1.06–3.75) for Ccr 40–70 ml/min and 3.1 (95% CI:1.24–7.84) for Ccr < 40 ml/min. RH for all-cause mortality was 2.3 (95% CI:1.29–4.23), for Ccr 40–70 ml/min and 5.3 (95% CI: 2.46–11.59) for Ccr <40 ml/min. RH for CVD-related mortality was 1.6 (95% CI: 0.55–4.50), for Ccr 40–70 ml/min and 2.7 (95% CI: 0.67–10.63) for Ccr <40 ml/min.

Outcomes were also stratified by the presence or absence of macroalbuminuria after adjustment for the same factors employed in the analysis of kidney function. The RH for macroalbuminuria (as compared with negative) was 2.1 (95%CI:1.44–3.13) for all-cause mortality, was 2.8 (95% CI:1.49–5.21) for CVD-related mortality and was 1.4 (95% CI:0.80–2.41) for first symptomatic stroke (Figure 2).

When the analyses for macroalbuminuria or Ccr were adjusted beforehand by Ccr or macroalbuminuria, respectively, in addition to adjustment for basal confounding factors, nearly the same results were found.

Table 2. Subject characteristics (1)

Ccr (ml/min)	<40	40–70	70<
n	176	1246	555
Age (years old)	75.6 ± 7.2	64.5 ± 7.2	55.3 ± 9.0
Gender (male%)	34.7	35	42.2
Height (cm)	146.4 ± 8.6	151.1 ± 7.7	157.0 ± 8.1
Weight (kg)	44.4 ± 7.3	52.4 ± 7.5	62.3 ± 8.7
BMI	20.7 ± 2.7	23.0 ± 3.0	25.3 ± 3.1
SBP (mmHg)	133.0 ± 19.6	130.5 ± 17.5	130.3 ± 15.5
DBP (mmHg)	71.6 ± 11.4	72.6 ± 11.2	74.3 ± 10.4
Creatinine (mg/dl)	1.1 ± 0.3	0.9 ± 0.1	0.8 ± 0.1
TC (ml/dl)	187.0 ± 34.3	196.9 ± 34.2	196.9 ± 33.6
FBS (mg/dl)	89.0 ± 14.1	101.3 ± 18.2	110.3 ± 37.3
BS (mg/dl)	131.0 ± 67.3	118.0 ± 31.9	117.4 ± 42.7

(Mean ± SD).
SBP/DBP, systolic and diastolic blood pressure; TC, total colesterol; FBS/BS, fasting and non-fasting blood glucose.

Table 3. Subject characteristics (2)

Ccr (ml/min)	<40	40–70	70<
n	176	1246	555
Current or ex-smokers (%)	12.5	15.7	16.2
Antihypertensive medications (%)	31.8	24.2	15.7
History of cardiovascular disease (%)	10.8	5.2	2.9
Presence of hyperlipidemia (%)	21.0	28.9	29.7
Presence of diabetes mellitus (%)	21.6	17.6	19.8
Positive for macroalbumiuria (%)	30.1	1.7	5.4

Cardiovascular disease, defined as the circulatory systems (ICD-10:I00–I99) and stroke. Presence of hyperlipidemia, defined as subjects on lipid-lowering drugs or with serum choklesterol levels of ≥5.68 mmol/l (220 mg/dl). Presence of diabetes mellitus, defined as subjects on medical treatment such as insulin or antihyperglycemic drugs or subjects with a fasting glucose level of 77 mmol/l (126 mg/dl) or non-fasting glucose level of 11.11 mmol/l (200 mg/dl). Positive for proteinuria, defined as positive of dip-stick test for spot-urine.

Table 1. Outcomes

CCr (ml/min)	<40	40–70	70-	Total	*P*-value
n	176	1246	555		
All causes of death	58 (100%)	114 (100%)	15 (100%)	187 (100%)	
Cardiovascular	18 (31.0%)	32 (28.1%)	4 (26.7%)	54 (28.9%)	
Non-cardiovascular	40 (69.0%)	82 (71.9%)	11 (73.3%)	133 (71.1%)	NS
First symptomatic stroke event	20 (100%)	77 (100%)	15 (100%)	112 (100%)	
Cerebral bleeding	4 (20.0%)	12 (15.6%)	5 (33.3%)	21 (18.8%)	
Cerebral infarction	15 (75.0%)	54 (70.1%)	10 (66.7%)	79 (70.5%)	
Others	1 (5.0%)	11 (14.3%)	0 (0.0%)	12 (10.7%)	NS

(Chi-square analysis).

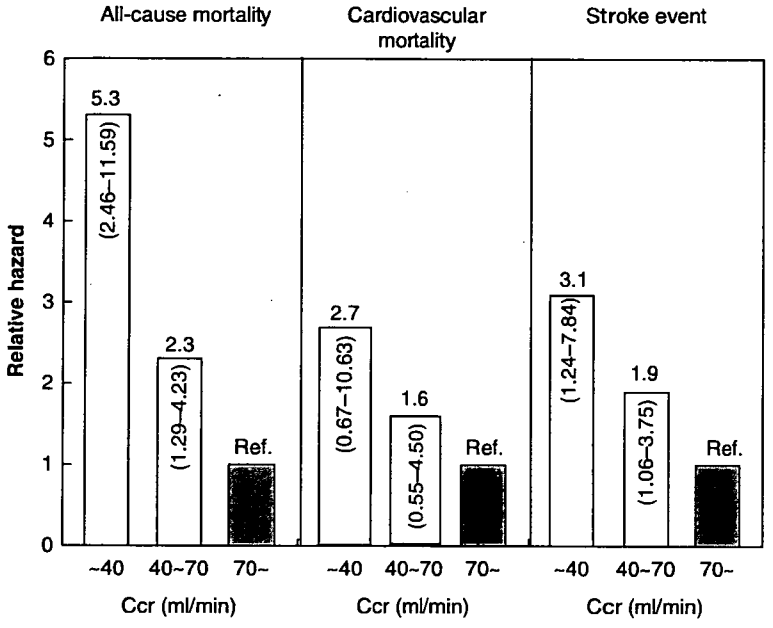

Fig. 1. Association of kidney function with the all-cause mortality, cardiovascular mortality and the first symptomatic stroke event. Relative hazard (RH) and 95% confidence intervals (CI) were adjusted for age, gender, systolic BP, BMI, smoking status, the use of antihypertensive medication, history of CVD, hypercholesterolaemia and diabetes for the three outcomes. Numbers inside the bars indicate 95% CI. The lowest group was treated as the reference category.

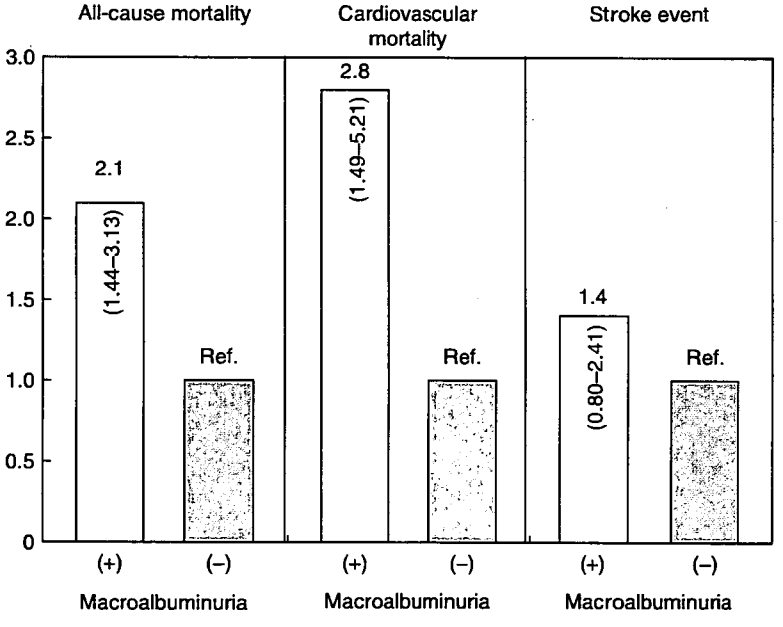

Fig. 2. Associations between macroalbuminuria and all-cause mortality, cardiovascular mortality and the first symptomatic stroke events. Relative hazard (RH) and 95% confidence intervals (CI) were adjusted for age, gender, systolic BP, BMI, smoking status, the use of antihypertensive medication, history of CVD, hypercholesterolaemia and diabetes for the three outcomes.

Analysis based on the combination of both Ccr and macroalbuminuria, adjusted for the primary confounding factors, demonstrated that combination of these two factors further increased the risks (Figure 3A–C).

Discussion

The present Ohasama study was based on longitudinal observations on a general population in a rural Japanese community. This survey was unique in that diagnosis of stroke was confirmed at the Ohasama Hospital, which is the only hospital in the community, and where >90% of residents undergo regular check-ups. Furthermore, 98% of the diagnoses for all stroke events were made during radiological examinations, and only 2% of cases diagnosed by death certificates. Therefore, most of the stroke events in this community were very accurately identified.

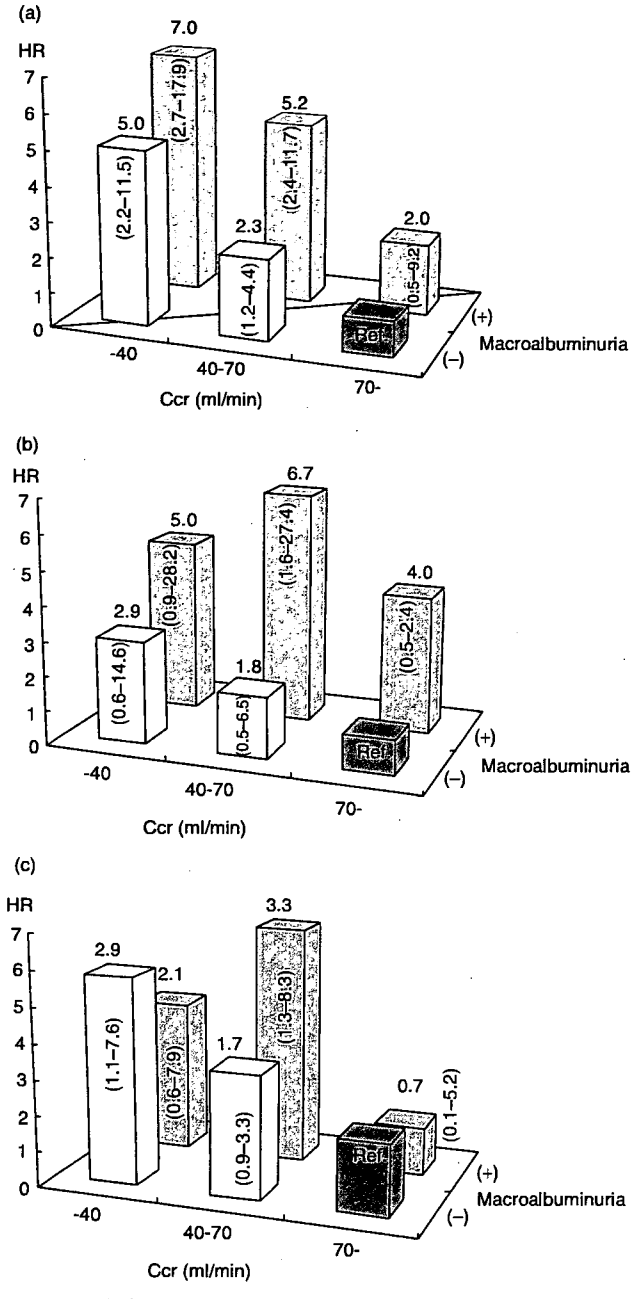

Fig. 3. Relative hazard (RH) all-cause mortality, cardiovascular mortality and the first symptomatic stroke event, according to kidney function and macroalbuminuria. RH and 95% confidence intervals (CI) were adjusted for presence of macroalbuminuria, age, gender, systolic BP, BMI, smoking status, the use of antihypertensive medication, history of CVD, hypercholesterolaemia and diabetes for the three outcomes.

During the mean follow-up period of 7.76 years, a total 112 events of first symptomatic stroke and 187 deaths (31% due to CVD) were recorded. These data revealed that decreased kidney function and the presence of macroalbuminuria were independent risk factors for all-cause and CVD-related mortality, confirming a previous large-scale report from Japan [6,7]. Thus, the cohort of the present study may well represent the general Japanese population. In the analysis of first symptomatic stroke events, decreasing kidney function was associated with increasing RH (RH, 3.1 in Ccr < 40 ml/min, 1.9 in Ccr 40–70 ml/min), and the presence of macroalbuminuria tended to increase RH, but this did not reach statistical significance (RH, 1.4).

Decreased kidney function is, at least in part, related to traditional risk factors for CVD, such as age, history of CVD, smoking, atherosclerosis, diabetes and hypertension. It is known that hypertension plays a crucial role in the development of stroke events [19]. Even after adjustment for these factors, our study still revealed decreased kidney function as a significant risk factor for first symptomatic stroke events. Since cerebral infarction remained a leading disorder among stroke events in the subjects, these data indicate that decreased kidney function may constitute a risk for ischaemic stroke events. Interestingly, similar findings were reported in the UK [20], wherein high normal serum creatinine levels were a risk factor for stroke events among the general population. Furthermore, a recent study reported that mild degrees of renal dysfunction are associated with increased risk of incidental ischaemic stroke or TIA among patients with CVD [21]. Taken together, these findings indicate that a common pathological factor may be involved in the development of stroke and cardiac events in the course of CKD, and we speculate that non-classical risk factors may be involved in these mechanisms. These issues will require further clarification.

In this survey, the dipstick test was employed to test for the presence of macroalbuminuria, and proteinuria greater than + was defined as positive, which corresponds to a urinary protein level >30 mg/dl [16]. The significant links between macroalbuminuria and mortality in our subjects support findings from previous studies examining the effect of macroalbuminuria [22]. However, we unexpectedly found that macroalbuminuria was not a significant risk factor for first symptomatic stroke events in the current study. Interestingly, a recent report from Japan [6] revealed that macroalbuminuria was not a significant risk factor for death due to stroke, although it was a significant risk factor for all-cause and CVD mortality. We speculate that patients with macroalbuminuria are also likely to have systemic vasculopathy, and therefore the death events due to all-causes may be more apparent than those caused by first symptomatic stroke events. The potential importance of macroalbuminuria for stroke events warrants further study.

For the method of estimating kidney function, we could not employ the recently recommended IDMS-derived new MDRD formula to predict estimated GFR in the present study [23]. Instead, we used the Cockcroft–Gault equation even though it is not the best method. This was done because serum creatinines were measured by Jaffe assay, and the available racial coefficient in calculating the MDRD equation for the Japanese population is lacking. Thus, further studies to examine exact risk estimation based on the CKD staging are still needed.

In conclusion, decreased kidney function increased the risk for first symptomatic stroke events in a general Japanese population. The high prevalence of stroke in this population prompts the need for greater public awareness about risks for CKD.

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Conflict of interest statement. None declared.

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3. 滋賀国保コホート研究

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(1) 研究成果

1) 肥満および肥満以外の循環器疾患危険因子の集積と医療費の関連：滋賀国保コホートにおける10年間の追跡による検討

Okamura T, Nakamura K, Kanda H, Hayakawa T, Hozawa A, Murakami Y, Kadowaki T, Kita Y, Okayama A, Ueshima H; The Health Promotion Research Committee of the Shiga National Health Insurance Organizations. Effect of combined cardiovascular risk factors on individual and population medical expenditures. Circ J; 71: 807-13, 2007.

【目的】
本邦の診断基準を含めて幾つかのメタボリックシンドロームの基準は肥満を必須要件にしているが、肥満以外の危険因子が集積しても循環器疾患のリスクが高くなることが知られている。循環器疾患は医療費上昇の主たる要因であるが、危険因子の集積と医療費の関連が肥満の有無により異なるかどうかをコホート研究で検証する。
【方法】
滋賀県の7町1村の40～69歳の住民で、1989～1991年に基本健康診査(市町村の健診)を受診した国民健康保険加入者を2001年3月31日まで追跡した。該当者 4,535人のうちベースラインデータに欠損のある57人を除いた4,478人（男性 1,921人、女性 2,557人）を分析対象とした。追跡期間中の国民健康保険医科の入院外、入院、総医療費（加入期間で除した月平均医療費)、追跡期間中の国民健康保険からの異動理由（死亡または被用者保険等への転出）を把握した。ベースラインの高血圧（収縮期血圧 140 mmHg 以上、拡張期血圧 90 mmHg 以上、降圧剤服用のいずれ)、高コレステロール血症（220 mg/dl 以上)、糖尿病(既往歴または尿糖＋以上)を危険因子としてそれぞれカウントし、その合計数と医療費との関連を性別、年齢、喫煙、飲酒を調整して共分散分析で検討した。さらに肥満の有無（BMI 25 k g/㎡をカットオフ値）により再度同様の解析を行った。最後にリスク集積による集団全体の過剰医療費を算出した。
【結果】
平均追跡期間は 9.0 年であった。月平均の総医療費（調整幾何平均）は、危険因子数0個： 7,361円、危険因子1個： 9,382、危険因子2～3個：10,562円であった。外来医療費、入院医療費でも同様の傾向を示した。肥満の有無で層別化すると、非肥満

群と肥満群の月平均の総医療費(調整幾何平均)は、危険因子数0個で6,985円と9,168円、危険因子1個で9,091円と10,703円、危険因子2～3個で10,263円と12,048円であり、いずれも肥満群のほうが高かった。危険因子別に肥満の有無で層別化すると、非肥満群と肥満群の月平均の総医療費（調整幾何平均）は、高血圧で11,407円と12,991円、高コレステロール血症で9,210円と10,551円、糖尿病で15,139円と19,497円であり、やはり肥満群のほうが高かった。集団全体に占める過剰医療費の割合は、非肥満かつ危険因子1個で13.1%、非肥満かつ危険因子2個以上で3.4%、肥満のみで2.4%、肥満かつ危険因子1個で1.8%、肥満かつ危険因子2個以上で2.9%であった。

【結論】

高血圧、高コレステロール血症、糖尿病などの循環器疾患の危険因子の集積は、長期間にわたって医療費を上昇させる要因であり、肥満が加わると個人の医療費は更に上昇する。しかし肥満者の頻度が低く、集団全体に対する肥満の過剰医療費の割合は大きくなかった。

【補足】

なおこの論文に対して Circ J 20071 の 10 月号にて Letters to the Editor としてコメントが掲載され、同じ巻で著者の回答も掲載されている。その簡潔な要旨を下記に示した。

①Oda E. Metabolic syndrome and medical expenditures in Japan. Circ J 2007; 71: 1666. Letters to the Editor.

ほぼメタボリックシンドロームに相当する肥満かつ危険因子2個以上の過剰医療費は2.6%に過ぎず、医療費適正化策として肥満を必須とした現行のメタボリックシンドロームの基準は不適当であり、それは死亡や発症をエンドポイントとした研究でも明らかである。

②Okamura T. Cardiovascular risk clustering with obesity: A good target to reduce medical expenditures as a first step of high-risk approach in communities and worksites. Circ J 2007; 71: 1667. Author's Reply.

確かにこの研究では肥満かつ危険因子2個以上による過剰医療費は小さかった。しかしこの研究ではウエスト周囲径ではなくBMIを用いていること、HDLコレステロールなどの因子が測定されていないことを考慮すべきである。また肥満したリスク集積者への保健指導は比較的指導方法が確立しており、地域や職域の現場でも取り組みやすい。一方、非肥満のリスク集積は難易度が高い指導対象であり、今後の研究が必要である。とりあえずこられの対象者にはポピュレーションアプローチで対応するのが良い。肥満対策は少なくともハイリスクアプローチの導入としては適している。

Circ J 2007; **71:** 807–813

Effect of Combined Cardiovascular Risk Factors on Individual and Population Medical Expenditures

— A 10-Year Cohort Study of National Health Insurance in a Japanese Population —

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Background Although obesity is required for some criteria defining metabolic syndrome, clustering of other risk factors also indicates an increased risk of cardiovascular disease. Whether the relationship between cardiovascular risk factor clustering and medical expenditures differs with body mass index (BMI) requires investigation, especially in a population with a low prevalence of obesity such as that in Japan.

Methods and Results A 10-year cohort study of 4,478 Japanese National Health Insurance beneficiaries aged 40–69 years in a community between 1990 and 2001 was carried out in the present study. The clustering of cardiovascular risk factors showed a positive and graded relationship to personal medical expenditures in participants who are overweight (BMI ≥25.0) and normal weight (BMI <25.0). The individual medical expenditures per month were 1.7-fold higher for participants with 2 or 3 risk factors and overweight than for those without these factors (26,782 vs 15,377 Japanese yen). Differences in the geometric means were similarly significant after adjustment for other confounding factors. However, the excess medical expenditures by risk clustering of normal weight categories within the total medical expenditures were higher than those of overweight categories because more participants were of normal weight.

Conclusions Cardiovascular risk factor clustering and being overweight can be a useful predictor of medical expenditures in a Japanese population. (*Circ J* 2007; **71:** 807–813)

Key Words: Medical expenditures; Metabolic components; Overweight; Risk factors

Hypertension, dyslipidemia, diabetes and obesity are cardiovascular risk factors that are difficult to control, but which are widespread in many developed countries! These factors are often clustered[2–6] which has resulted in a high incidence of cardiovascular disease accounted for by metabolic syndrome, recognized as visceral fat accumulation[2–7] The individual components of metabolic syndrome impose a major economic burden on the health-care system[8–12] However, few studies have examined the combined effects of multiple cardiovascular risk factors on medical expenditures![13,14]

Furthermore, the National Cholesterol Education Program considers each risk factor to have a similar effect on atherosclerosis![15] On the contrary, the International Diabetes Federation defines waist circumference as a requirement for a diagnosis of metabolic syndrome![16] However, other studies have shown that high-risk individuals with metabolic risk factors often go undetected if obesity is a required criterion![17,18] Thus, whether the relationship between cardiovascular risk factor clustering and medical expenditures differs with body mass index (BMI) should be determined, especially in a population with a low prevalence of obesity such as the Japanese.

The present study examines the influence of cardiovascular risk factor clustering on medical expenditures in individuals who are overweight and of normal weight defined by BMI. Our a priori hypothesis is that clustering of cardiovascular risk factors has a positive, graded association with medical expenditures. Furthermore, we investigated whether overweight participants with risk factor clustering actually have high medical expenditures and if so, the proportion of the excess medical expenditures in the total medical expenditures consumed by these participants.

Methods

Medical Expenditures in Japan

Medical expenditures in Japan are based on a public medical insurance institution[19,20] that comprises 2 systems. Everyone living in Japan is required to enrol in either of the 2 insurance systems, and this is called 'health-insurance for

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all'. One is for employees and their dependants and the other is for self-employed individuals, such as farmers and fishermen, retirees and their dependants. The 2 systems respectively cover 65.3% and 34.7% of the overall population. All prices are strictly controlled by a fee schedule that is set by the National Government, and calculated on the basis of 'fee-for-service'. The fee schedule is constant, regardless of insurance system. Furthermore, the same fee schedule applies to all clinics and hospitals that are approved to provide medical services under the public medical insurance system.

Study Population

Our study cohort comprised 4,535 Japanese beneficiaries of the National Health Insurance (NHI). Details of the cohort study have been reported elsewhere[9,21,22] Briefly, the 40–69-year-old participants lived in 7 rural towns and a village in Shiga Prefecture, West Japan, and had undergone a baseline survey between 1989 and 1991. In 1990, the study area had 82,155 residents, including 31,564 individuals aged 40–69 years, of whom 11,900 were NHI beneficiaries. Therefore, the participants in the present study represented approximately 38% of all NHI beneficiaries in this age group within this community. Monthly NHI claim files for over 10 years within the Shiga NHI Organizations were linked with the baseline survey data. Deleting the names of the participants from the linked data protected their privacy. We excluded 57 participants as a result of information missing from the baseline survey. Accordingly, 4,478 participants (1,921 men and 2,557 women) were included in the analysis. The Institutional Review Board of Shiga University of Medical Science for ethical issues approved the present study (No.16-15).

Baseline Survey and Follow-up

The baseline survey was performed by standardized methods in accordance with the Manual for Health Check-ups under the Medical Service Law for the Aged, issued by the Japan Public Health Association in 1987[23] Public health nurses measured blood pressure with a standard mercury sphygmomanometer in individuals who had rested for at least 5 min. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking anti-hypertensive medication. Diabetes was defined as a history of diabetes or glucosuria detected by a spot urine test with a dipstick containing a color pad. Serum high-density lipoprotein (HDL)-cholesterol and triglycerides as a marker of dyslipidemia were not measured at the baseline examination. Accordingly, dyslipidemia was defined as hypercholesterolemia with a total cholesterol level ≥5.69 mmol/L (220 mg/dl).

All participants were classified into the following categories on the basis of clustering of cardiovascular risk factors (hypertension, diabetes and hypercholesterolemia): none, 1, and 2–3. Because visceral fat accumulation was not measured at the baseline survey and the prevalence of obesity (BMI >30 kg/m^2) was very low (1.3%), we used a BMI of 25 kg/m^2 or greater as an indicator of being overweight in the present study[24] Smoking and alcohol consumption habits were determined from interviews administered by the public health nurses.

Information on medical expenditures for each participant was obtained from the monthly NHI claim files, starting from April in the year following their initial health check-up until March 2001. Medical expenditures are expressed in Japanese yen and US dollars (ie, 100 Japanese yen= $US 0.848, at the exchange rates published on November 7th, 2006). Data regarding medical expenditures for each individual differed depending on the period of subscription to the NHI. The medical expenditures for each participant were therefore divided by the period of subscription, and are expressed as expenditures per month of follow-up. If a beneficiary withdrew from the NHI or died, follow-up was stopped at that point. Follow-up was restarted for beneficiaries who withdrew and then re-enrolled in the NHI.

Data Analysis

We evaluated medical expenditures per person per month in each of 3 categories according to the number of cardiovascular risk factors. Because the distribution of real medical expenditures was positively skewed, the data were logarithmically transformed to normalize the distribution and the results are expressed as geometric means. For participants with expenditures of 0 yen per month, logarithmic transformations were achieved by replacing 0 yen with 1 yen. Fifteen participants had total medical expenditures of 0 yen and 16 had outpatient medical expenditures of 0 yen. To compare total and outpatient medical expenditures per person in each category we performed an analysis of covariance after adjusting for age, sex, BMI, smoking (non-smoker or current smoker) and alcohol consumption (none, occasional or daily consumption) with the Bonferroni correction for multiple post-hoc comparisons. A similar analysis was also performed after stratifying by BMI at 25 kg/m^2. The significance of multiplicative interaction between risk factor clustering and being overweight for medical expenditures was examined by cross-product terms in the model. Because 2,604 participants had inpatient medical expenditures of 0 yen, logarithmic transformations were not performed, and we applied the Kruskal–Wallis test to compare inpatient medical expenditures among the 3 categories.

Furthermore, we compared the medical expenditures per person between overweight and normal weight participants with individual cardiovascular risk factors.

Finally, we calculated excess medical expenditures attributable to the number of metabolic risk factors. The excess medical expenditures were estimated as follows: Σ [(the arithmetic mean of total medical expenditures in each of the 5 groups except for normal weight and no risk factor group, ie, (1) normal weight with 1 risk factor, (2) normal weight with 2 or 3 risk factors, (3) overweight alone, (4) overweight with 1 other risk factor, and (5) overweight with 2 or 3 other risk factors−the arithmetic mean of total medical expenditures in normal weight and no risk factor group)×(the number of individuals in each of the 5 categories.)]. We also examined the ratio of excess medical expenditure to the entire total medical expenditures of the population.

The statistical package SPSS 14.0J for Windows performed these analyses. All probability values were 2-tailed and the significance level was established at $p<0.05$.

Results

The prevalence of being overweight was 21.0% (men, 18.1%; women, 23.3%) of the entire study population. Table 1 summarizes the baseline risk characteristics of the 4,478 participants grouped according to risk factor clustering. Among them, 12.9% (men, 10.7%; women, 14.5%) had 2 or 3 risk factors, and 39.5% (men, 40.8%; women,

Table 1 Baseline Risk Characteristics in 1989–1991 of 4,478 National Health Insurance Beneficiaries in Shiga, Japan, Grouped by Sex and Risk Status

Risk characteristics	Risk status category			p value
	None	1 risk factor	2 or 3 risk factors	
Men				
No. of participants (%)	931 (48.5)	782 (40.7)	208 (10.8)	
*Age (years)**	52.4±8.3	55.2±8.0	55.6±8.0	<0.01
*Body mass index (kg/m²)**	22.1±2.5	22.9±2.7	24.0±2.9	<0.01
Smoking habit†				
Current smoker (%)	61.0	58.7	59.1	0.61
Drinking habit†				
Non-drinker (%)	21.3	19.4	22.1	
Occasional drinker (%)	22.4	19.3	24.0	0.18
Daily drinker (%)	56.3	61.3	53.8	
Hypertension (%)	0.0	67.4	94.7	<0.01
Hypercholesterolemia (%)	0.0	23.0	76.9	<0.01
Diabetes (%)	0.0	9.6	35.1	<0.01
Women				
No. of participants (%)	1,204 (46.1)	984 (38.5)	369 (14.4)	
*Age (years)**	52.0±8.1	56.0±7.5	58.2±6.5	<0.01
*Body mass index (kg/m²)**	22.3±2.7	23.4±3.1	24.4±2.9	<0.01
Smoking habit†				
Current smoker (%)	3.6	3.3	2.7	0.71
Drinking habit†				
Non-drinker (%)	79.9	79.6	80.8	
Occasional drinker (%)	16.5	16.2	15.4	0.92
Daily drinker (%)	3.6	4.3	3.8	
Hypertension (%)	0.0	54.2	97.6	<0.01
Hypercholesterolemia (%)	0.0	43.6	93.8	<0.01
Diabetes (%)	0.0	2.2	12.5	<0.01

**One way analysis of variance.*
†Chi-square test.
Values located after the mark, ±, indicate standard deviation.

Table 2 Medical Expenditures (Total, Outpatient and Inpatient) per Person Grouped by Number of Cardiovascular Risk Factors, After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Medical costs per person per month				
		Total		Outpatient		Inpatient
		Arithmetic mean	Adjusted geometric mean	Arithmetic mean	Adjusted geometric mean	Arithmetic mean
None	2,135	16,400 yen (139 dollars)	7,361 yen (62 dollars)	8,545 yen (72 dollars)	5,420 yen (46 dollars)	7,872 yen (67 dollars)
1 risk factor	1,766	23,002 yen (195 dollars)	9,382 yen† (80 dollars)	12,470 yen (106 dollars)	7,034 yen† (60 dollars)	10,538 yen (89 dollars)
2 or 3 risk factors	577	25,090 yen (213 dollars)	10,562 yen† (90 dollars) p<0.01*	15,494 yen (131 dollars)	7,929 yen† (67 dollars) p<0.01*	9,597 yen (81 dollars) p<0.01‡

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Analysis of covariance adjusted for age, sex, body mass index, smoking habit and drinking habit.*
†Significance, vs none, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.
‡Kruskal Wallis test.

38.6%) had 1 risk factor. In both groups with 1 or more risk factors, the prevalence of hypertension was highest followed by hypercholesterolemia. Smoking and alcohol consumption did not significantly differ between the 3 groups in both men and women. The mean BMI values were higher in participants with more risk factors.

Total person-years were 40,815 and the mean follow-up was 9.0 years. Sex-specific analyses of the medical expenditures among the 3 categories showed similar results for men and women. Therefore, we reported our findings for men and women combined. Table 2 shows that during follow-up, the total medical expenditures per person per month with 2–3 risk factors (25,090 yen or $US 213) and with 1 risk factor (23,002 yen or $US 195) were higher than those in the group with no risk factors (16,400 yen or $US 139). The geometric means of total medical expenditures after adjusting for other confounding factors showed significant differences in personal medical expenditures between the 3 categories.

Table 3 shows the medical expenditures per person in normal weight and overweight groups stratified by a BMI of 25.0 kg/m². The total medical expenditures were highest in overweight individuals with 2–3 risk factors (26,782 yen or $US 227). On the contrary, the total medical expenditures were lowest in the normal weight group with no risk factors (15,377 yen or $US 130). The relationship between

Table 3 Total Medical Expenditures per Person Grouped by Number of Cardiovascular Risk Factors, Stratified by Having Overweight (BMI ≥25.0) or Not After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Total medical costs per person per month	
		Arithmetic mean	Adjusted geometric mean
None			
BMI<25.0	1,849	15,377 yen (130 dollars)	6,985 yen (59 dollars)
BMI≥25.0	286	23,011 yen (195 dollars)	9,168 yen† (78 dollars)
1 risk factor			
BMI<25.0	1,336	24,245 yen (206 dollars)	9,091 yen† (77 dollars)
BMI≥25.0	430	19,143 yen (162 dollars)	10,703 yen† (91 dollars)
2 or 3 risk factors			
BMI<25.0	351	24,002 yen (203 dollars)	10,263 yen† (90 dollars)
BMI≥25.0	226	26,782 yen (227 dollars)	12,048 yen† (102 dollars) p<0.01*

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Analysis of covariance adjusted for age, sex, smoking habit and drinking habit.*
†Significance, vs none without overweight, for multiple post-hoc comparisons with Bonferroni correction, p<0.05.
BMI, body mass index.

Table 4 Total Medical Expenditures per Person Grouped by Type of Cardiovascular Risk Factors, Stratified by Having Overweight (BMI ≥25.0) or Not After 10-Year Follow-up From 1990 to 2001, in National Health Insurance in Shiga, Japan

Risk status category	No. of participants	Total medical costs per person per month	
		Adjusted geometric mean (Model 1)*	Adjusted geometric mean (Model 2)**
Hypertension			
BMI<25.0	1,098	9,045 yen (77 dollars)	11,407 yen (97 dollars)
BMI≥25.0	519	11,026 yen† (94 dollars)	12,991 yen (110 dollars)
Hypercholesterolemia			
BMI<25.0	803	9,252 yen (78 dollars)	9,210 yen (78 dollars)
BMI≥25.0	312	10,420 yen† (88 dollars)	10,551 yen (89 dollars)
Diabetes			
BMI<25.0	153	15,308 yen (130 dollars)	15,139 yen (128 dollars)
BMI≥25.0	63	18,974 yen (161 dollars)	19,497 yen (165 dollars)

100 Japanese yen=0.848 US dollars, at the foreign exchange rate on November 7th, 2006.
**Model 1, analysis of covariance adjusted for age, sex, smoking habit and drinking habit.*
***Model 2, analysis of covariance adjusted for age, sex, smoking habit, drinking habit and other risk factors except for categorized risk factor; for example, in hypertension, hypercholesterolemia and diabetes were adjusted.*
†Significance, between normal weight and overweight, p<0.05.
Abbreviation see in Table 3.

the number of risk factors and adjusted geometric means of medical expenditures in both the normal weight and overweight groups was positively graded. The increase in the rate of medical expenditures according to the number of risk factors was not parallel; however, the interaction term between the number of cardiovascular risk factors and overweight criteria did not reach statistical significance (p=0.351). Individual medical expenditures per month were higher in overweight individuals, than in the normal weight group when the number of other cardiovascular risk factors was consistent.

Table 4 shows the medical expenditures between overweight and normal weight participants with hypertension, hypercholesterolemia and diabetes. The medical expenditures per person in all 3 groups were higher in the overweight group than in the normal weight group. The difference in medical expenditures between overweight and normal weight were largest in diabetics.

The calculated excess medical expenditures attributable to normal weight individuals with 1 risk factor, those who were of normal weight with 2–3 risk factors, only overweight, overweight with 1 other risk factor and overweight with 2–3 other risk factors were 11,847,648 yen, 3,027,375 yen, 2,183,324 yen, 1,619,380 yen and 2,577,530 yen, respectively. Fig 1 shows the share of each excessive medical cost of the total medical expenditures of the entire population. The excess medical expenditures of the 2 normal weight categories combined (16.5%) were higher than

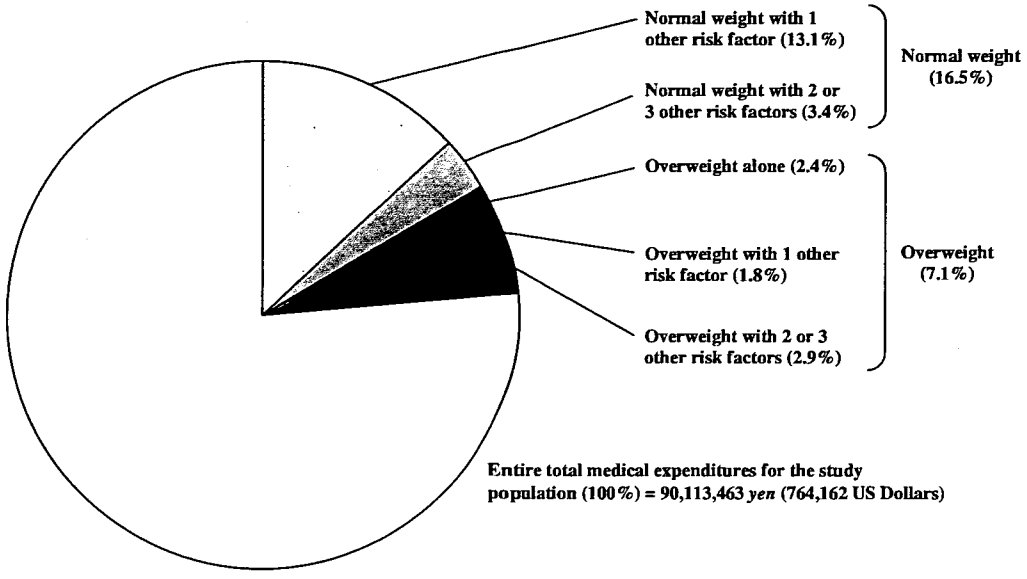

Fig 1. Ratio (%) of excess medical expenditures related to number of cardiovascular risk factors stratified by body mass index (25 kg/m^2) in whole population after 10-year follow-up, from 1990 to 2001, in National Health Insurance in Shiga, Japan (men and women combined). White area represents predicted medical expenditures if all participants were of normal weight without risk factors.

those of 3 overweight categories combined (7.1%).

Discussion

We performed a follow-up study of a Japanese community between 1990 and 2001 and found a positive graded relationship between clustering of cardiovascular risk factors and personal medical expenditures irrespective of being overweight. The mean personal medical cost was higher in overweight, than in normal weight individuals when the number of other risk factors was consistent. Furthermore, the total medical expenditures were the highest in overweight individuals with 2–3 risk factors. Nevertheless, the excess medical expenditures in these participants in entire population were only a few percent and the excess expenditures observed in normal weight categories were rather higher than those in overweight categories.

Findings from the Framingham study have already shown that the risk of atherosclerotic disease increases with combinations of risk factors, such as hypertension, glucose intolerance and hypercholesterolemia[25] Japanese epidemiological studies have also found similar results in community[6] and occupational[26] settings. However, few studies to our knowledge have investigated the association between cardiovascular risk clustering or metabolic syndrome and medical expenditures[13,14] Most other studies have focused on the effect of hypertension combined with diabetes on medical economics[22,27,28]

The continuous increase in medical expenditures is an important concern in most developed countries[29] Furthermore, the effect of cardiovascular diseases on medical economics is a major concern. For example, the medical expenditures for cardiovascular disease including hypertension was 20.4% of the total national medical expenditures in the Japanese population aged 45–69 years, which was larger than any other disease groups during 2001[30] The effective way to control medical expenditures incurred by cardiovascular diseases is to detect those at high risk and provide intensive health and lifestyle guidance or opportunities for early clinical visits for primary care. The present findings showed that overweight people with cardiovascular risk clustering should be detected as priority targets for a high-risk strategy[31] and that overweight people with cardiovascular risk factors such as hypertension, hypercholesterolemia and diabetes can also be potential targets for high-risk strategies that could significantly affect individual medical expenditures. If an individual has accumulated visceral fat or impaired glucose tolerance, which is now classified as a metabolic syndrome, then their medical expenditures should be reduced by implementing appropriate dietary measures and by increasing physical activity.

By contrast, irrespective of high individual medical expenditures, the proportion of excess medical expenditures in the normal weight categories with 1 or more other risk factors was higher than those of all overweight categories combined. The low proportion of excess medical expenditures incurred by overweight individuals is a result of relatively small number of overweight participants identified in the present study. The 1989 to 1991 baseline survey defined only 21% of participants as being overweight (25 kg/m^2 or more). Accordingly, from the viewpoint of an entire population and a population strategy[31] regardless of being overweight, the presence of other cardiovascular risk factors such as hypertension, diabetes and hypercholesterolemia significantly effects medical expenditures. Normal weight people with other risk factors, especially in non-Western populations with a low prevalence of obesity, should be carefully considered.

The present study has several limitations. First, the public medical insurance system in Japan differs from that in other countries. Therefore, absolute values of medical expenditures for the participants in the present study might not be directly relevant to other populations. Second, we clustered risk factors from a single measurement at the baseline survey, which generated a regression dilution bias. Third, we did not have values for fasting blood glucose,

triglycerides or HDL-cholesterol, which are important components of metabolic syndrome![15] We used BMI as an indicator of being overweight. One report indicates that waist circumference predicts visceral fat accumulation (which plays a major role on atherosclerosis) better than BMI?[32] Accordingly, we might have underestimated or misclassified obesity or being overweight by the BMI method. Finally, details of medical diagnoses, medical treatment status (eg, prescriptions), clinical condition and cause of mortality were not available. Thus, further studies are required to clarify the effects of these variables.

In conclusion, cardiovascular risk clustering and being overweight can be a useful predictor of medical expenditures. On the contrary, the sum of excess medical expenditures because of risk factor clustering in normal weight individuals is larger than that in overweight individuals because of the relatively small ratio of overweight individuals in Japan. However, the obesity epidemic is not restricted to Western countries. Furthermore, mean BMI is rapidly increasing in Asian countries such as Japan. Accordingly, being overweight might increase population medical expenditures in the future.

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Appendix 1

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