表 2. 曝露濃度カテゴリ毎の対象者と死亡数

	1988-90SPM 平均濃度 (μg/m3)				p-value for
	≦50	50-55	55-60	60>	trend
対象者	131	166	177	138	
年齢(標準偏差)	60.07 (13.67)	57.05 (12.99)	56.56 (13.29)	53.40 (13.31)	
死亡数(割合)					
全死亡	11 (8.4%)	24 (14.5%)	20 (11.3%)	14 (10.1%)	0.93
心血管系死亡	4 (3.1%)	8 (4.8%)	6 (3.4%)	4 (2.9%)	0.75
心疾患	1 (0.8%)	5 (3.0%)	2 (1.1%)	3 (2.2%)	0.73
虚血性心疾患	1 (0.8%)	1 (0.6%)	2 (1.1%)	2 (1.4%)	0.48
肺がん	1 (0.8%)	1 (0.6%)	0 (0%)	0 (0%)	0.17
肺炎	0 (0%)	2 (1.2%)	0 (0%)	3 (2.2%)	0.16

表 3. SPM10μg/m^3 の変化による調整ハザード比

	ハザード比(95%信頼区間)
全死亡	
年齢、性の調整	1.274(0.919-1.765)
年齢、性、喫煙、BMI の調整	1.358(0.975-1.892)
死因別死亡	
心血管系死亡 ‡	1.189(0.572-2.473)
心疾患 ‡	1.299(0.407-4.149)
虚血性心疾患 ‡	1.950(0.468-8.119)
肺炎¶	2.983(0.944-9.424)

‡年齢、性、喫煙、BMI、高血圧、糖尿病、血清コレステロールの調整

¶年齢、性、喫煙の調整

日本人の代表集団における腎機能低下と循環器疾患死亡の関連；NIPPON DATA90 における 10 年間の追跡による検討

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【 目的 】米国 The National Kidney Foundation は腎機能の指標である腎糸球体濾過量（Glomerular Filtration Rate; 以下、GFR）が 60 ml/min/1.73m2 未満である状態が 3 ヶ月以上続く場合を Chronic Kidney Disease（以下、慢性腎臓病）と定義し、将来の循環器疾患の発症や死亡に対してハイリスクな状態と位置づけている。そして、慢性腎臓病の者に対して循環器疾患の予防のための対策を積極的に講じていく必要性を訴えている。しかし、日本人集団におけるエビデンスは少ない。日本全国から無作為に選ばれた対象集団において、腎機能低下が将来の循環器疾患死亡に及ぼす影響を明らかにすることを試みた。

【 方法 】循環器疾患の既往のない日本人 7,316 名（平均年齢 52.4 歳、女性の割合 58%）を 10 年間（1990 年-2000 年）追跡した。GFR は血清クレアチニン値（Jaffe 法）を用いて The Cleveland Clinic laboratory for the Modification of Diet in Renal Disease study（以下、MDRD）の簡略式（今井らの補正を加える）と Cockcroft-Gault の式（体表面積は藤本らの算出式による）から計算した。Cox 比例ハザードモデルを用いて、GFR の循環器疾患死亡のハザード比を評価した。

【 結果 】慢性腎臓病（GFR<60）は全対象者 7,316 名中、MDRD の簡略式では 6.7%、Cockcroft-Gault の式では 4.1%に見られた。追跡期間に、183 名の対象者が循環器疾患によって死亡した。他の危険因子を調節しても、慢性腎臓病は循環器疾患死亡率の上昇と関係があり、GFR=60 を基準にした慢性腎臓病の循環器疾患、脳卒中、心臓病死亡のハザード比は、MDRD の簡略式ではそれぞれ 1.20 (0.82-1.76)、0.62 (0.31-1.22)、1.65 (1.01-2.72)、Cockcroft-Gault の式では 1.51 (1.04-2.20)、0.98 (0.54-1.76)、2.20 (1.32-3.69)であった。対象集団における慢性腎臓病の循環器疾患死亡に対する集団寄与危険割合は、MDRD の簡略式では 1.3%、Cockcroft-Gault の式では 4.2%であった。さらに正常腎機能（GFR=90）を基準にした GFR 低下の循環器疾患、脳卒中、心臓病死亡のハザード比

は、MDRD の簡略式では表１、Cockcroft-Gault の式では表２に示すとおりであり、GFR と循環器疾患死亡の間には負の相関が見られた。

【 結論 】地域在住の日本人集団において、腎機能低下は循環器疾患死亡の独立した危険因子である。

表1. MDRDの簡略式に基づくGFRと循環器疾患死亡の関連 (NIPPON DATA90)

	GFR (ml/min/1.73m^2)					
	GFR≥90 (n=2,423)	60≤GFR<90 (n=4,402)	45≤GFR<60 (n=424)	30≤GFR<45 (n=50)	15≤GFR<30 (n=9)	GFR<15 (n=8)
追跡人年	23,639	42,160	3,748	356	45	58
循環器疾患死亡						
ケース数	31	112	29	6	3	2
死亡率 (/1,000人年)	1.3	2.7	7.7	16.9	66.7	34.5
ハザード比 *	1.00	1.09 (0.72-1.64)	1.15 (0.67-1.99)	1.23 (0.49-3.09)	5.52 (1.62-18.75)	9.12 (2.12-39.29)
脳卒中死亡						
ケース数	10	53	8	1	1	1
死亡率 (/1,000人年)	0.4	1.3	2.1	2.8	22.2	17.2
ハザード比 *	1.00	1.60 (0.80-3.18)	0.83 (0.31-2.21)	0.51 (0.06-4.20)	4.49 (0.55-36.99)	3.32 (1.61-110.43
心臓病死亡						
ケース数	19	57	19	5	0	1
死亡率 (/1,000人年)	0.8	1.4	5.1	14.0	0.0	17.2
ハザード比 *	1.00	0.93 (0.55-1.60)	1.44 (0.72-2.89)	2.03 (0.70-5.91)	0.00 (-)	7.79 (1.00-60.64)

* 年齢, 性, BMI, 喫煙, 飲酒, 高血圧, 糖尿病, 高コレステロール血症, 心電図左胸部誘導高R波を調整

表2. Cockcroft-Gaultの式に基づくGFRと循環器疾患死亡の関連 (NIPPON DATA90)

	GFR (ml/min/1.73m^2)					
	GFR≥90 (n=3,848)	60≤GFR<90 (n=2,845)	45≤GFR<60 (n=484)	30≤GFR<45 (n=119)	15≤GFR<30 (n=12)	GFR<15 (n=8)
追跡人年	37,902	27,171	4,007	815	53	58
循環器疾患死亡						
ケース数	27	73	57	20	4	2
死亡率 (/1,000人年)	0.7	2.7	14.2	24.5	75.5	34.5
ハザード比 *	1.00	0.62 (0.37-1.03)	0.88 (0.46-1.68)	0.91 (0.41-2.04)	1.80 (0.52-6.28)	6.30 (1.39-28.50)
脳卒中死亡						
ケース数	10	35	24	2	2	1
死亡率 (/1,000人年)	0.3	1.3	6.0	2.5	37.7	17.2
ハザード比 *	1.00	0.66 (0.29-1.50)	0.72 (0.26-1.97)	0.16 (0.03-0.89)	1.62 (0.26-10.19)	6.24 (0.68-56.93)
心臓病死亡						
ケース数	17	34	32	17	0	1
死亡率 (/1,000人年)	0.4	1.3	8.0	20.9	0.0	17.2
ハザード比 *	1.00	0.54 (0.27-1.07)	1.04 (0.44-2.49)	1.79 (0.64-5.01)	0.00 (-)	6.20 (0.75-50.96)

* 年齢, 性, BMI, 喫煙, 飲酒, 高血圧, 糖尿病, 高コレステロール血症, 心電図左胸部誘導高R波を調整

【 研究成果の公表 】

Nakamura K, Okamura T, Hayakawa T, Kadowaki T, Kita Y, Ohnishi H, Saitoh S, Sakata K, Okayama A, Ueshima H. Chronic kidney disease is a risk factor for cardiovascular death in a community-based population in Japan: NIPPON DATA90. Circ J 2006; 70: 954-959.

Circ J 2006; **70:** 954–959

Chronic Kidney Disease is a Risk Factor for Cardiovascular Death in a Community-Based Population in Japan

— NIPPON DATA90 —

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Background Chronic kidney disease (CKD) has been identified as a risk factor for cardiovascular disease (CVD).

Methods and Results The risk of cardiovascular death was evaluated in a large cohort of participants selected randomly from the overall Japanese population. Participants (mean age, 52.4 years) free of previous CVD were followed up for 10 years. Glomerular filtration rate (GFR) was estimated using the abbreviated equation developed at the Cleveland Clinic laboratory for the Modification of Diet in Renal Disease study. Of the 7,316 participants, 6.7% had CKD with a GFR <60 at baseline. Even after adjustment for other risk factors, the presence of CKD conferred an increased risk of cardiovascular death with a hazard ratio of 1.20 (95% confidence interval, 0.82–1.76). Furthermore, a negative, graded correlation between GFR and risk of cardiovascular death was observed: 1.09 (0.72–1.64) for a 60≤GFR<90, 1.15 (0.67–1.99) for a 45≤GFR<60, 1.23 (0.49–3.09) for a 30≤GFR<45, 5.52 (1.62–18.75) for a 15≤GFR<30, 9.12 (2.12–39.29) for a GFR<15, as compared with normal kidney function (GFR ≥90). The proportion of excess cardiovascular death due to CKD was 1.3%.

Conclusion CKD was an independent risk factor for cardiovascular death in a community-dwelling Japanese population. (*Circ J* 2006; **70:** 954–959)

Key Words: Cardiovascular disease; Chronic kidney disease; Glomerular filtration rate; Mortality

Chronic kidney disease (CKD) with a glomerular filtration rate (GFR) less than 60 ml/min per 1.73 m^2 is an independent risk factor for all-cause death or cardiovascular disease (CVD) in the general population[1–5] as well as in high-risk populations[6–8] The National Kidney Foundation (NKF)[9,10] recommends evaluating the estimated GFR using simplified prediction equations with serum creatinine in order to identify individuals with CKD and intervene to reduce their risk of CVD[11,12]

However, to our knowledge, only 2 studies have quantified GFR in a general Japanese population in order to clarify the risk of CVD from CKD[4,5] which, in Japan, is still controversial. We attempted to determine this risk in a large cohort of participants selected randomly from the overall Japanese population.

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Methods

Study Design and Participants

Cohort studies of the National Survey on Circulatory Disorders in 1980 or 1990 in Japan were called the NIPPON DATA80 or 90 (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged). The details of the present cohort have been previously reported[13–16] In the present study, we analyzed data from NIPPON DATA90 to evaluate the relationship between CKD and CVD over a period of 10 years.

A total of 8,384 community residents (3,504 men, 4,880 women; ≥30 years old) from 300 randomly selected districts participated in the baseline survey in 1990 and were followed until November 15, 2000. The overall population aged 30 and greater in all districts was 10,956, and the participation rate in this survey was 76.5%. Accordingly, these participants were thought to be representative of the Japanese population. Of the 8,384 participants, 1,068 were excluded for the following reasons: previous coronary heart disease or stroke (n=261), information missing in the baseline survey (n=532), and failure to obtain access due to incomplete residential information in baseline survey (n=182). The remaining 7,316 participants (3,047 men, 4,269 women) were included in the analysis.

Follow-up Survey

The underlying causes of death for the National Vital

Table 1 Baseline Risk Characteristics of 7,316 Participants in 1990 by Sex and Kidney Function Estimated by the Abbreviated MDRD Equation: NIPPON DATA90

	Men			Women		
	GFR (ml/min per 1.73 m²)			GFR (ml/min per 1.73 m²)		
	GFR ≥60 (n=2,901)	GFR <60 (n=146)	p value	GFR ≥60 (n=3,924)	GFR <60 (n=345)	p value
Age (years)*	52.2±13.2	67.3±11.3	<0.01	50.6±13.1	68.9±11.1	<0.01
GFR (ml/min per 1.73 m²)*	85.5±15.4	51.4±9.7	<0.01	87.3±16.8	52.5±8.9	<0.01
Serum creatinine (mg/dl)*	0.90±0.12	1.48±1.30	<0.01	0.69±0.10	1.08±0.84	<0.01
Body mass index (kg/m²)*	23.1±3.0	21.5±1.7	0.11	22.8±3.3	23.5±3.2	<0.01
Smoking habit†			<0.01			0.87
Never smoked (%)	21.1	15.1		88.5	88.7	
Ex-smoker (%)	22.5	37.0		2.4	4.1	
Current smoker (%)	56.4	47.9		9.1	7.2	
Drinking habit†			<0.01			<0.01
Never drank (%)	34.5	45.2		92.2	97.4	
Ex-drinker (%)	5.7	12.3		1.0	0.0	
Daily drinker (%)	59.7	42.5		6.8	2.6	
Hypertension (%)†	48.2	71.9	<0.01	39.3	72.8	<0.01
Diabetes mellitus (%)†	7.0	15.1	<0.01	3.7	8.1	<0.01
Hypercholesteloremia (%)†	16.4	24.7	0.01	21.3	38.0	<0.01
Left high voltage on ECG (%)†	17.0	18.5	0.65	5.9	8.1	0.10

Values are mean±SD or the % of participants in that category.
**One-way analysis of variance.*
†Chi-square test.
GFR, glomerular filtration rate; ECG, electrocardiogram.

Statistics were coded according to the 9th International Classification of Disease for deaths occurring to the end of 1994 and the 10th International Classification of Disease for deaths occurring from the beginning of 1995. The details of death classification in the present study are described elsewhere![13–16]

We were permitted to use the National Vital Statistics by the Management and Coordination Agency, Government of Japan. The present study was approved by the Institutional Review Board of Shiga University of Medical Science for ethical issues (No. 12-18, 2000).

Baseline Examination

Non-fasting blood samples were obtained and the serum was separated and centrifuged soon after blood coagulation. Plasma samples were also obtained in a siliconized tube containing sodium fluoride. These samples were shipped to 1 laboratory (SRL, Tokyo, Japan) for blood measurements. Serum creatinine (mg/dl) was measured using the alkaline picric acid method (Jaffe). We estimated the GFR using the following 2 simplified prediction equations. First, GFR (ml/min per 1.73 m²) was calculated using the abbreviated equation developed at the Cleveland Clinic laboratory for the Modification of Diet in Renal Disease (MDRD) study: $186\times[\text{serum creatinine (mg/dl)}]^{-1.154}\times[\text{age (years)}]^{-0.203}\times[0.742 \text{ if female}]\times[1.212 \text{ if black}]$[17,18] Imai et al recommend multiplying the value calculated using the abbreviated MDRD equation by 0.881 for Japanese![9] Second, creatinine clearance (ml/min) was regarded as the GFR and calculated using the Cockcroft-Gault equation: $\{[140-\text{age (years)}]\times\text{weight (kg)}\times[0.85 \text{ if female}]\}/[72\times\text{serum creatinine (mg/dl)}]$[20] GFR was expressed in ml/min per 1.73 m² by multiplying each estimated GFR by 1.73/body surface area (m²). Body surface area (m²) was calculated using the following equation;[21] which is suitable for Japanese adults: $[\text{weight (kg)}]^{0.444}\times[\text{height (cm)}]^{0.663}\times 88.83\times 10^{-4}$. Referring to the NKF classification of CKD;[9,10] the participants were classified into the 2 groups: GFR ≥60 and GFR <60. The latter group was defined as CKD.[9,10] In addition, the participants were classified into 6 groups based on GFR: GFR ≥90, 60≤GFR <90, 45≤GFR <60, 30≤GFR <45, 15≤GFR <30 and GFR <15. The group with a GFR ≥90 was defined as normal kidney function.[9,10] These classifications were done for each calculated value of GFR.

Serum total cholesterol (mg/dl) was measured using an enzymatic method. Lipid measurements were standardized by the CDC-NHLBI (Centers for Disease Control/National Heart, Lung, and Blood Institute) Lipids Standardization program.[22] Hypercholesterolemia was defined as serum total cholesterol ≥240 mg/dl, medication for hypercholesterolemia or both. Plasma glucose (mg/dl) was also measured using an enzymatic method. Diabetes mellitus was defined as plasma glucose ≥200 mg/dl, medication for diabetes mellitus or both.

A standard 12-lead electrocardiogram (ECG) was recorded in the supine position. Each record was coded independently by 2 researchers according to the Minnesota Code.[23] Codes in agreement were accepted, whereas codes in disagreement were adjudicated by a panel of study epidemiologists and cardiologists. Left high R-wave was defined as R-wave in V_5 or V_6 >2.6 mV, or R-wave in I, II, III or aV_F >2.0 mV, or R-wave in aV_L >1.2 mV (the Minnesota Code, 3-1), and/or R-wave in I >1.5 mV but ≥2.0 mV, or S-wave in V_1 plus R-wave in V_5 or V_6 >3.5 mV (the Minnesota Code, 3-3).

Baseline blood pressure was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a sufficient period of rest. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, medication for hypertension, or any combination of these.

Body mass index (BMI) was calculated using the following equation: [weight (kg)]/[height (m)]². Public health nurses obtained information on smoking, drinking, and medical histories.

Table 2 Risk of Death From Kidney Dysfunction Over 10 Years of Follow-up From 1990 to 2000 in 7,316 Participants When GFR is Estimated by the Abbreviated MDRD Equation: NIPPON DATA90

	GFR (ml/min per 1.73 m²)					
	GFR ≥90 (n=2,423)	60≤ GFR <90 (n=4,402)	45≤ GFR <60 (n=424)	30≤ GFR <45 (n=50)	15≤ GFR <30 (n=9)	GFR <15 (n=8)
Person-years of follow-up	23,639	42,160	3,748	356	45	58
Death due to all-cause						
Cases	122	397	98	28	7	3
Mortality (per 1,000 person-years)	5.2	9.4	26.1	78.7	155.6	51.7
*Age-and sex-adjusted hazard ratio**	1.00	1.02 (0.83–1.26)	1.11 (0.84–1.47)	1.79 (1.16–2.77)	3.96 (1.82–8.61)	4.48 (1.42–14.14)
Multivariate-adjusted hazard ratio†	1.00	1.08 (0.88–1.33)	1.22 (0.91–1.62)	1.99 (1.28–3.08)	4.60 (2.11–10.04)	3.74 (1.18–11.87)
Death due to cardiovascular disease						
Cases	31	112	29	6	3	2
Mortality (per 1,000 person-years)	1.3	2.7	7.7	16.9	66.7	34.5
*Age-and sex-adjusted hazard ratio**	1.00	1.07 (0.71–1.60)	1.10 (0.64–1.87)	1.18 (0.48–2.95)	5.16 (1.53–17.46)	10.67 (2.52–45.25)
Multivariate-adjusted hazard ratio†	1.00	1.09 (0.72–1.64)	1.15 (0.67–1.99)	1.23 (0.49–3.09)	5.52 (1.62–18.75)	9.12 (2.12–39.29)
Death due to stroke						
Cases	10	53	8	1	1	1
Mortality (per 1,000 person-years)	0.4	1.3	2.1	2.8	22.2	17.2
*Age-and sex-adjusted hazard ratio**	1.00	1.54 (0.78–3.06)	0.80 (0.31–2.10)	0.51 (0.06–4.11)	4.03 (0.49–32.87)	14.85 (1.85–119.41)
Multivariate-adjusted hazard ratio†	1.00	1.60 (0.80–3.18)	0.83 (0.31–2.21)	0.51 (0.06–4.20)	4.49 (0.55–36.99)	13.32 (1.61–110.43)
Death due to heart disease						
Cases	19	57	19	5	0	1
Mortality (per 1,000 person-years)	0.8	1.4	5.1	14	0.0	17.2
*Age-and sex-adjusted hazard ratio**	1.00	0.91 (0.54–1.54)	1.35 (0.68–2.65)	1.93 (0.68–5.49)	0.00 (–)	9.53 (1.26–72.31)
Multivariate-adjusted hazard ratio†	1.00	0.93 (0.55–1.60)	1.44 (0.72–2.89)	2.03 (0.70–5.91)	0.00 (–)	7.79 (1.00–60.64)

Values in parentheses indicate the 95% confidence interval of the hazard ratios.
**Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age and sex.*
†Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age, sex, body mass index, smoking habit, drinking habit, hypertension, diabetes mellitus, hypercholesterolemia and left high voltage on ECG.
Abbreviations see in Table 1.

Statistical Analysis

One-way analysis of variance or a chi-square test was used to compare risk characteristics at baseline of participants grouped according to kidney function. A Cox proportional hazards model was used to calculate the hazard ratios for death due to all-causes, CVD, stroke and heart disease, for participants with CKD (GFR<60) as compared to participants without CKD (GFR≥60). This model incorporated the following variables as covariates: age, sex, BMI, smoking habit (non-, ex- or current smoker, using 2 dummy variables with the non-smoker as a reference), drinking habit (non-, ex- or daily drinker, using 2 dummy variables with the non-drinker as a reference), hypertension, diabetes mellitus, hypercholesterolemia and left high voltage on the ECG. Similarly, the hazard ratios were calculated for 5 of the groups with an abnormal GFR (60≤GFR<90, 45≤GFR<60, 30≤GFR<45, 15≤GFR<30 and GFR<15), as compared to the group with normal kidney function (GFR ≥90). We estimated the proportion of excess cardiovascular death due to CKD (GFR<60) among all participants taking into account its prevalence and hazard ratio using the following equation: {prevalence×[adjusted hazard ratio−1]}/{1+the prevalence×[adjusted hazard ratio−1]}.

The statistical analysis package, SPSS 14.0J for Windows, was used for all statistical processing (Chicago, IL, USA). All probability values were 2-tailed, and the significance level was set at $p<0.05$.

Results

There were 70,006 person-years of follow-up for the 7,316 participants (mean age, 52.4 years) in the study. Among all the participants, 655 died, including 74 who died from strokes and 101 who died from heart disease. The mean value of GFR calculated using the abbreviated MDRD equation and the Cockcroft-Gault equation in all the participants was 84.2 and 92.1 ml/min per 1.73 m², respectively.

The baseline risk characteristics of participants classified into 2 groups based on GFR calculated using the abbreviated MDRD equation are summarized in Table 1. Of all the participants, 6.7% had CKD with GFR <60 at baseline. The mean value of age and the prevalence of hypertension, diabetes mellitus and hypercholesterolemia for both sexes were higher in the participants with CKD, whereas the mean value of BMI for women was higher in the participants with CKD. In addition, the prevalence of current smokers, daily drinkers, diabetes mellitus and left high voltage on the ECG was higher in men than women in all categories of kidney function.

Of all the participants, 8.5% had CKD at baseline, evaluated using the Cockcroft-Gault equation. The baseline risk characteristics of participants classified into 2 groups based on GFR calculated using the Cockcroft-Gault equation were similar to the results presented in Table 1 (data not shown).

When we performed sex-specific analyses of the relationships between death and CKD based on GFR calculated

Table 3 Risk of Death From Kidney Dysfunction Over 10 Years of Follow-up From 1990 to 2000 in 7,316 Participants When GFR is Estimated by the Cockcroft-Gault Equation: NIPPON DATA90

	GFR (ml/min per 1.73 m²)					
	GFR ≥90 (n=3,848)	60≤ GFR <90 (n=2,845)	45≤ GFR <60 (n=484)	30≤ GFR <45 (n=119)	15≤ GFR <30 (n=12)	GFR <15 (n=8)
Person-years of follow-up	37,902	27,171	4,007	815	53	58
Death due to all-cause						
Cases	101	286	183	71	11	3
Mortality (per 1,000 person-years)	2.7	10.5	45.7	87.1	207.5	51.7
*Age-and sex-adjusted hazard ratio**	1.00	0.87 (0.68–1.13)	1.24 (0.89–1.73)	1.55 (1.03–2.33)	2.44 (1.20–4.97)	4.45 (1.39–14.22)
Multivariate-adjusted hazard ratio†	1.00	0.81 (0.62–1.06)	1.12 (0.79–1.58)	1.40 (0.92–2.15)	2.53 (1.24–5.18)	3.29 (1.02–10.60)
Death due to cardiovascular disease						
Cases	27	73	57	20	4	2
Mortality (per 1,000 person-years)	0.7	2.7	14.2	24.5	75.5	34.5
*Age-and sex-adjusted hazard ratio**	1.00	0.67 (0.41–1.12)	1.02 (0.54–1.90)	1.05 (0.48–2.27)	1.99 (0.58–6.85)	8.49 (1.93–37.47)
Multivariate-adjusted hazard ratio†	1.00	0.62 (0.37–1.03)	0.88 (0.46–1.68)	0.91 (0.41–2.04)	1.80 (0.52–6.28)	6.30 (1.39–28.50)
Death due to stroke						
Cases	10	35	24	2	2	1
Mortality (per 1,000 person-years)	0.3	1.3	6.0	2.5	37.7	17.2
*Age-and sex-adjusted hazard ratio**	1.00	0.70 (0.31–1.56)	0.79 (0.30–2.09)	0.17 (0.03–0.94)	1.56 (0.26–0.94)	1.56 (0.26–9.50)
Multivariate-adjusted hazard ratio†	1.00	0.66 (0.29–1.50)	0.72 (0.26–1.97)	0.16 (0.03–0.89)	1.62 (0.26–10.19)	6.24 (0.68–56.93)
Death due to heart disease						
Cases	17	34	32	17	0	1
Mortality (per 1,000 person-years)	0.4	1.3	8.0	20.9	0.0	17.2
*Age-and sex-adjusted hazard ratio**	1.00	0.59 (0.30–1.17)	1.23 (0.53–2.85)	2.13 (0.80–5.67)	0.00 (–)	8.87 (1.12–70.11)
Multivariate-adjusted hazard ratio†	1.00	0.54 (0.27–1.07)	1.04 (0.44–2.49)	1.79 (0.64–5.01)	0.00 (–)	6.20 (0.75–50.96)

Values in parentheses indicate the 95% confidence interval of the hazard ratios.
**Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age and sex.*
†Hazard ratios were calculated by a Cox proportional hazards regression model adjusted for age, sex, body mass index, smoking habit, drinking habit, hypertension, diabetes mellitus, hypercholesterolemia and left high voltage on ECG.
Abbreviations see in Table1.

using the abbreviated MDRD equation and the Cockcroft-Gault equation, the results were similar for men and women. Therefore, we analyzed and reported the relationships for both sexes combined.

The participants with CKD based on GFR calculated using the abbreviated MDRD equation had a multivariate-adjusted hazard ratio of 1.31 (95% confidence interval (CI), 1.06 to 1.60) for all-cause death, 1.20 (95% CI, 0.82 to 1.76) for cardiovascular death, 0.62 (95% CI, 0.31 to 1.22) for stroke death, 1.65 (95% CI, 1.01 to 2.72) for heart disease death, compared with the participants without CKD. The participants with more severe kidney dysfunction tended to have a higher multivariate-adjusted hazard ratio for all-cause and cardiovascular death (Table 2). The proportion of excess cardiovascular death due to CKD was 1.3%, when using a prevalence of 6.7% and a hazard ratio of 1.20.

The participants with CKD based on GFR calculated using the Cockcroft-Gault equation had a multivariate-adjusted hazard ratio of 1.47 (95% CI, 1.21 to 1.80) for all-cause death, 1.51 (95% CI, 1.04 to 2.20) for cardiovascular death, 0.98 (95% CI, 0.54 to 1.76) for stroke death, 2.20 (95% CI, 1.32 to 3.69) for heart disease death, compared with the participants without CKD. The participants with more severe kidney dysfunction tended to have a higher multivariate-adjusted hazard ratio for all-cause and cardiovascular death (Table 3). The proportion of excess cardiovascular death due to CKD was 4.2%, when using a prevalence of 8.5% and a hazard ratio of 1.51.

Discussion

In the present prospective, community-based study, CKD defined as a GFR less than 60 ml/min per 1.73 m² was an independent risk factor for cardiovascular death. Depending on the equation used to calculate GFR, the prevalence of CKD was 6.7–8.5% in the present study population. CKD contributed to excess cardiovascular death by 1.3–4.2%.

CKD represents a reduction of the normal GFR level in young individuals by more than half. This condition was found by the prevalence of 6.7–8.5% in the present study population. Two previous studies in a community-based population in Japan also reported a prevalence of CKD of approximately 10% or less[4,5] Therefore, the prevalence of CKD may be approximately 10% in the community-dwelling population in Japan in general.

CKD is associated with increased prevalence and severity of traditional cardiovascular risk factors such as hypertension[1–4] Increased levels of traditional cardiovascular risk factors may have an effect on CVD. Furthermore, traditional cardiovascular risk factors are associated with a decline in renal function[2,4] Thus, CKD may be a marker for CVD, which includes the effects of traditional cardiovascular risk factors. However, the risk of CKD for CVD is independent of traditional cardiovascular risk factors[1–5] which was confirmed in the present study. Increased non-traditional cardiovascular risk factors related to CKD, such as hyper-

homocysteinemia[25,26] may also be associated with CVD. However, we could not adjust our statistical analysis for such risk factors because they were not measured. In addition to the effects of cardiovascular risk factors on renal function, CKD itself may decrease cardiac function?[27]

Furthermore, we demonstrated a negative, graded correlation between GFR and the risk of cardiovascular death. However, the relationship between GFR and risk depended on the equation used to calculate GFR. Using the abbreviated MDRD equation to calculate GFR, the risk of cardiovascular death tended to increase at a GFR<60, compared with normal kidney function (GFR≥90). In contrast, when GFR was calculated using the Cockcroft-Gault equation, the risk tended to increase at a GFR<30. We should be careful in interpreting these results because of the limited number of participants who died from CVD in the groups with a lower GFR. Irie et al reported that the risk of cardiovascular death due to kidney dysfunction, when calculated using the abbreviated MDRD equation (but without correcting the GFR for Japanese), tended to increase at a GFR <70 in men and a GFR<60 in women, compared with normal kidney function (GFR≥100).[5] However, that study did not evaluate the risk of cardiovascular death due to more severe kidney dysfunction. If we take the correction of GFR into account in the present study, our results are consistent with those of Irie et al. When we calculate GFR using the abbreviated MDRD equation, it may be appropriate to regard a GFR of 60 ml/min per 1.73 m^2 as the cutoff value for increasing the risk of cardiovascular death in Japanese. On the other hand, we would predict more excess cardiovascular death due to CKD, when GFR is calculated using the Cockcroft-Gault equation. However, there are some controversies as to whether the MDRD and Cockcroft-Gault equations are applicable to Japanese. Therefore, further investigations of the influence of CKD on the risk of CVD in the Japanese population are needed.

Study Limitations

First, GFR was estimated using 2 simplified prediction equations. Furthermore, when we used the abbreviated MDRD equation to calculate GFR, which includes a term based on race (black and white),[17,18] we regarded Japanese as white. Second, the classification of our participants was based only on the baseline GFR. Changes in GFR during the 10-year follow-up period were not taken into account. Finally, the details of medication status were not available in the present study. For example, the use of angiotensin-converting enzyme inhibitors[11,28] may need to be taken into account when evaluating the risk of cardiovascular death due to CKD.

In conclusion, kidney dysfunction may be an important risk factor for cardiovascular death in Japanese. Appropriate strategies are needed for identifying and intervening in high-risk individuals with kidney dysfunction?[29,30]

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Appendix 1

NIPPON DATA90 Research Group

NIPPON DATA90: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged.

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NIPPON DATA80 の 14 年追跡による循環器疾患の性差とその要因

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【背景】近年、我が国の循環器疾患死亡は減少し、疾患別では、脳卒中は 1965 年以降、心疾患は 1970 年以降減少しているが、性別にみると循環器疾患死亡は女性より男性に多く、これまで諸外国で循環器疾患死亡の男女差にリスク要因の性差がどの程度関与しているかが報告されてきた。しかし、アジア諸国ではいまだ十分検討されていない。一方、日本や中国、シンガポールといった他のアジア諸国での喫煙率の男女差は西欧諸国より大きく、我が国の 2004 年の喫煙率は 男性で 43.3%、女性で 12.0% と報告されている。

【目的】そこで、NIPPON DATA80 の 14 年追跡データを用いて循環器疾患のリスク要因、特に喫煙が、循環器疾患死亡の男女差にどの程度関与しているかを検討した。

【対象と方法】本解析では、1994 年に生死の確認および死因が同定できた 9,638 人中、ベースライン時に 30 ～89 歳で循環器疾患の既往をもたない男性 3,976 人、女性 4,962 人を解析対象とした。循環器疾患のリスク要因における性差が 男性における循環器疾患死亡の超過リスクにどの程度関与しているかを、以下に示す Jousilahti らが用いた方法で検討した。男性の女性に対する循環器疾患死亡の年齢調整ハザード比と年齢及びリスク要因で調整したハザード比の差を、(年齢調整ハザード比－１)で除した値を算出し検討した [$(HR_0–HR_1) / (HR_0–1)$, HR_0 は、男性の女性に対する年齢調整ハザード比、 HR_1 は、年齢及びリスク要因で調整したハザード比]。

【結果】女性に対する男性の年齢調整死亡率比は、 循環器疾患で 1.60 (95% 信頼区間 1.32–1.94)と男性の死亡リスクが有意に高かった。循環器疾患死亡に関するコックス比例ハザードモデルに、性、年齢を投入すると男性の女性に対する年齢調整ハザード比は 1.61 であった。次に、性、年齢、およびリスク要因（高血圧、肥満、高コレステロール、糖尿病、喫煙習慣有り、飲酒習慣有りのいずれか）を投入したところ、リスク要因で調整した女性に対する男性のハザード比が最も小さかったのは喫煙習慣有りを変数として投入したモデルで、男性の女性に対する年齢調整ハザード比は 1.33、超過リスクのうち喫煙の性差で説明できた割合[$(HR_0–HR_1) / (HR_0–1)$]は 46%であった。飲酒習慣の性差で説明できた割合は -24%と男性の超過リスクに負に関連していた。循環器疾患における男性の超過リスクのうち、全リスク要因の性差で説明できた割合は 36%であった。

【考察】今回の検討で循環器疾患死亡における男性の超過リスクの 4 割強が喫煙習慣の性差によって説明された。しかし喫煙習慣を含めたリスク要因の性差全体で説明されたのは約 3 分の 1 であった。これは、冠動脈疾患に対する飲酒習慣の予防的効果によると思われる。循環器疾患に関するハザード比は、飲酒習慣を除き男女で違いがみとめられなかった。日本人の代表性のあるコホート集団で喫煙率の男女差が循環器疾患死亡の男性の超過リスクのおよそ半分に寄与していた解析結果は、禁煙が循環器疾患死亡における男性の超過リスクを減少し得ることを示唆していると言える。

Circ J 2006; **70:** 370–375

Effect of Conventional Risk Factors for Excess Cardiovascular Death in Men

— NIPPON DATA80 —

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Background The present study examined how sex differences in conventional risk factors for cardiovascular disease (CVD), especially smoking, account for excess male mortality from CVD in Japan.

Methods and Results In a 14-year follow-up study, causes of death were ascertained among 10,546 Japanese aged 30 years or older at the baseline. The proportion of the excess male risk of CVD explained by the differences in risk factors was estimated as $(HR_0-HR_1)/(HR_0-1)$, where HR_0 is the age-adjusted hazard ratio (men vs women) and HR_1 is the age and risk factor-adjusted hazard ratio. The age-adjusted male:female ratios were 1.60 (95% confidence interval (CI), 1.32–1.94) for CVD, 1.75 (95% CI, 1.33–2.30) for stroke, and 1.55 (95% CI, 0.97–2.49) for coronary heart disease. The proportion of excess male risk of CVD explained by smoking was 46% and excess risk explained by all risk factors including smoking was 36%. In men, drinking habits decreased the excess risk of CVD. Except for the association between drinking habits and CVD, the impact of the hazard ratios of conventional risk factors had no sex difference.

Conclusions Smoking contributes substantially to excess male mortality from CVD when the smoking rates vary substantially by sex. (*Circ J* 2006; **70:** 370–375)

Key Words: Cardiovascular disease; Cohort study; Japan; Risk factor; Sex difference; Smoking

The decrease in mortality from cardiovascular disease (CVD) over the past 35 years in Japan has significantly contributed to the longevity of its people[1] The mortality rate from stroke has decreased since 1965, and mortality from coronary heart disease (CHD) has not risen since 1970[2] Declining CVD mortality might be attributed to declines in blood pressure[2,3] Myocardial infarction and coronary death were lower compared with those from Western reports[4] However, CVD continues to be a major cause of death in Japan[1]

International studies have reported an excess in male mortality for CVD[5,6] In addition, explanations for how sex differences in conventional risk factors for CVD account for that excess have been investigated[7–9] However, it is not yet understood how conventional risk factors contribute to sex differences in CVD in Asian countries[10] Likewise, as benefits of smoking cessation for patients with acute myocardial infraction[11] sex differences in smoking should be investigated. Smoking rates substantially vary by sex in Japan and in other Asian countries, such as China, Singapore, and the Republic of Korea[12,13] and are much greater than in Western countries[13] In 2002, the smoking rate was 43.3% for Japanese men and 10.2% for Japanese women[12]

In the current study, we investigated how sex differences in conventional risk factors for CVDs, especially differences in smoking, explain the excess in male deaths from CVD in Japan. We used a 14-year follow-up study consisting of a representative sample of Japanese subjects.

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Methods

Setting and Follow-up Study

NIPPON DATA80 (National Integrated Projects for Prospective Observation of Non-communicable Disease And its Trends in the Aged) is a 14-year follow-up study, whose baseline survey was conducted in 1980 as the National Cardiovascular Survey[14] Sampling procedures have been reported in detail elsewhere[15–17] In the National Cardiovascular Survey, people in 300 districts across Japan were selected by random sampling of all residents aged 30 years or older and were then invited to participate in the survey. The survey was conducted during November 1980, with 10,897 subjects (response rate=79.1%). Of the total subjects, 10,546 with complete information on age, sex, and blood pressure at the baseline were defined as the cohort.

In 1994, the NIPPON DATA80 research group conducted a follow-up study. The vital status of subjects was determined by reviewing registration records linked to their present address from local public health centers in 1994.

Table 1 Distribution of Mean and Prevalence (%) of Risk Factors at Baseline Survey in 1980 for Men and Women Aged 30–89 Years, NIPPON DATA80 (N=8,938)

	Men (n=3,976)		*Women (n=4,962)*	
*Age (years)**				
30–39 (%)	*26.6*		*26.8*	
40–49	*27.4*		*26.2*	
50–59	*22.6*		*23.2*	
60–69	*14.4*		*15.2*	
70–79	*7.7*		*7.2*	
80–89	*1.2*		*1.5*	
<50 years old	*Mean*	*SD*	*Mean*	*SD*
*Systolic blood pressure†,** (mmHg)*	*131.5*	*(16.9)*	*125.0*	*(16.6)*
*Diastolic blood pressure†,** (mmHg)*	*81.8*	*(11.9)*	*76.7*	*(11.2)*
≥50 years old				
*Systolic blood pressure†,** (mmHg)*	*145.8*	*(21.9)*	*142.8*	*(22.9)*
*Diastolic blood pressure†,** (mmHg)*	*85.3*	*(12.4)*	*82.5*	*(11.9)*
All ages				
*Body mass index (kg/m²)†,***	*22.5*	*(2.9)*	*22.8*	*(3.4)*
*Serum cholesterol (mg/dl)†,***	*186.2*	*(32.7)*	*190.2*	*(33.9)*
*Serum glucose (mg/dl)†,***	*130.7*	*(38.3)*	*129.1*	*(34.0)*
Hypertension,‡,** %*	*49.3*		*39.9*	
Obesity,§,** %*	*19.3*		*22.3*	
High cholesterol,‖,** %*	*15.0*		*18.4*	
Diabetes mellitus,¶,** %*	*6.8*		*4.0*	
Cigarette smoking history,** %*				
Current	*63.6*		*8.7*	
Former	*18.1*		*2.1*	
Never	*18.2*		*89.1*	
Drinking habit,** %*				
Daily	*48.4*		*2.9*	
Occasionally	*26.5*		*17.0*	
Former	*5.1*		*1.3*	
Never	*19.9*		*78.6*	

*SD, standard deviation; SI conversion factors, to convert milligrams per deciliter to millimoles per liter, multiply by 0.0259. *Chi-square test was used to compare between both genders. †Comparisons of mean values between both genders were performed by using a t-test. ‡Hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg, or on antihypertensive drug. §Obesity was defined by a body mass index ≥25.0 kg/m². ‖High cholesterol was defined as total cholesterol ≥220 mg/dl (5.7 mmol/L). ¶Diabetes mellitus was defined as a casual blood glucose ≥200 mg/dl, or with a present history of diabetes mellitus. **p<0.05.*

When a subject's change of residence was detected in registration records, we requested registration records in the cities or towns where they were currently living. The details, including date of death, of subjects who had died were taken from registration records. The underlying causes of death were derived from the National Vital Statistics. By matching the area code of the place of death, sex, date of birth, and date of death using data from mortality statistics in Japan, the underlying cause of death was determined. Thus, we could identify the cause of death for 99.5% of 1,327 deceased subjects. Using NIPPON DATA80, this follow-up study ascertained the vital status of 9,638 (91.4% of the original 10,546 subjects).

Study Population

Of the 10,546 subjects initially examined in 1980, those excluded from the present study were aged over 90 years and had a history of CVD in the baseline data. After exclusion criteria were applied, 4,347 men and 5,440 women aged between 30 and 89 years without CVD at baseline were identified. Among these subjects, 3,976 (91.5%) of men and 4,962 (91.2%) of women were followed up; these 8,938 subjects were used for the analyses in the current study.

Study Variables and Mortality

The method of risk factor measurement used in the baseline survey of 1980 has been described elsewhere[13,15,16] Briefly, standardized measures were made of blood pressure, height, weight, and serum total cholesterol. Data on drinking and smoking habits and history of diseases were obtained from a self-administered questionnaire. Drinking status was classified as never, formerly, occasionally, or daily. Data on smoking habits were obtained by asking subjects to note whether they were a 'non-', 'current-', or 'ex-' smoker, and, in the case of smokers, recorded the number of cigarettes smoked per day.

Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or greater and/or a diastolic blood pressure (DBP) of 90 mmHg or greater, or the regular use of an antihypertensive drug. Hypercholesterolemia was defined as total cholesterol of 220 mg/dl (5.7 mmol/L) or greater. The criteria for diabetes mellitus in these analyses were defined as a casual blood glucose level of 200 mg/dl or greater, or with a current history of diabetes mellitus. Obesity was defined by a body mass index equal to or greater than 25.0 kg/m².

Causes of death were classified according to the International Classification of Diseases, Ninth Revision (ICD-9). CVD deaths were those assigned ICD codes 390 to 459, which include CHD (codes 410–414) and stroke (codes 430–438). Permission to use the National Cardiovascular Survey in 1980 and vital statistics for determining causes of death were obtained from the Management and Coordination Agency, Government of Japan.

Table 2 Age-Adjusted Death Rate, and Hazard Ratio of Men and Women for Cardiovascular Diseases NIPPON DATA80, 1980–1994 (N=8,938)

	Cardiovascular disease		Stroke		Coronary heart disease	
	Men	Women	Men	Women	Men	Women
Number of deaths	217	196	111	91	36	33
Crude death rate*	419	295	214	137	69	50
Age-adjusted death rate†	344	218	176	102	56	36
Age-adjusted men/women ratio‡	1.60		1.75		1.55	
95%confidence interval	(1.32–1.94)		(1.33–2.30)		(0.97–2.49)	

*Crude death rate per 100,000 person-years of observation.
†Age-adjusted death rate per 100,000 person-years of observation, adjusted by direct methods to the population of Japan who were 30–89 years old in 1985 for the 5-year age groups.
‡Age-adjusted hazard ratio for men vs women.

Table 3 Hazard Ratio and Proportion of Excess Risk in Men Associated With the Difference of Risk Factors in Each Model, NIPPON DATA80, 1980–1994

Risk factors included in the model	Cardiovascular disease			Stroke			Coronary heart disease		
	HR*	(95%CI)	Excess risk† %	HR*	(95%CI)	Excess risk† %	HR*	(95%CI)	Excess risk† %
Age, sex	1.61	(1.32–1.95)		1.77	(1.34–2.33)		1.56	(0.97–2.50)	
Age, sex, HT‡	1.59	(1.31–1.93)	3.6	1.74	(1.31–2.29)	4.0	1.56	(0.97–2.50)	–0.4
Age, sex, obesity§	1.63	(1.34–1.98)	–3.3	1.79	(1.35–2.36)	–2.9	1.60	(0.99–2.58)	–7.6
Age, sex, high cholesterol‖	1.60	(1.31–1.94)	1.7	1.76	(1.33–2.33)	1.5	1.63	(1.01–2.62)	–13.0
Age, sex, DM¶	1.55	(1.28–1.88)	9.2	1.74	(1.32–2.30)	3.7	1.50	(0.93–2.41)	10.3
Age, sex, current smoker	1.33	(1.06–1.66)	46.2	1.49	(1.08–2.06)	36.0	1.23	(0.70–2.15)	59.3
Age, sex, current drinker**	1.75	(1.41–2.19)	–24.4	1.69	(1.23–2.33)	10.3	1.72	(0.996–2.98)	–29.5
Age, sex, HT, obesity, high cholesterol DM, current smoker, current drinker	1.39	(1.08–1.79)	36.4	1.41	(0.98–2.02)	46.8	1.34	(0.71–2.51)	39.3

*Hazard ratio of men vs women. Hazard ratio and 95%confidence interval determined by Cox proportional hazard regression. †Proportion of excess risk in men defined as (HR0–HR1)/(HR0–1); HR0=age-adjusted hazard ratio of men vs women; HR1=age-, and risk factor-adjusted hazard ratio of men vs women. HR0=1.61, 1.77, and 1.56, for CVD, stroke, and coronary heart disease, respectively. ‡Hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg, or on antihypertensive drug. §Obesity was defined by a body mass index ≥25.0 kg/m². ‖High cholesterol was defined as total cholesterol ≥220 mg/dl (5.7 mmol/L). ¶Diabetes mellitus was defined as a casual blood glucose ≥200 mg/dl, or with a present history of diabetes mellitus. **Current drinker was defined as subjects who drink occasionally or daily.
HR, hazard ratio; CI, confidence interval; HT, hypertension; DM, diabetes mellitus; CVD, cardiovascular disease.

Statistical Analysis

Chi-square tests were used to compare the risk-factor distribution, and the t-test was used to compare the mean of continuous variables between women and men. The age-adjusted death rate was calculated by direct methods with the 1985 model population of Japan as the standard population. Cox proportional hazard models were used to calculate age and multivariate-adjusted hazard ratios and corresponding 95% confidence intervals (CI) of CVD deaths for each risk factor. The assumption that the hazard ratio of the primary exposure remained constant over time for each risk factor was confirmed by Cox regression with time-dependent covariates.

To examine how the sex differences in the risk factors explain the excess CVD risk in men, a model with sex as an independent variable was built with data including both males and females, to which the other risk factors were added to the model as used by Jousilahti et al[9] The proportion of the excess CVD risk in men that was explained by the sex differences in the risk factors was estimated as follows. The differences in CVD hazard ratios of men vs women before and after adjustment for risk factors was divided by the denominator that subtracted background risk from hazard ratio (men vs women) as [(HR0–HR1)/(HR0–1), where HR0 is age-adjusted hazard ratio (men vs women), HR1 is age, and risk factor-adjusted hazard ratio][9]

We tested for differences in the hazard ratio of CVD between both males and females by including interaction terms between sex and risk factor in the proportional hazard model. The percentage change in modifiable risk with each change or each 10-unit change was calculated by Cox proportional hazard models. Analyses were calculated using the software SPSS 10.0J for Windows (SPSS10.0J for Windows, Standard Version, SPSS, 2000).

The Ethics Committee of Shiga University of Medical Science, Japan, approved the research protocol of the study.

Results

Baseline Characteristics

The distribution of mean and prevalence of risk factors at the baseline of 8,938 subjects is shown in Table 1. Average age at baseline was 50.0±12.9 (mean±standard deviation (SD)) years for men and 50.2±13.1 years for women. The means of SBP and DBP, body mass index, and serum cholesterol were lower in men than in women, and higher for serum glucose ($p<0.05$).

Statistically significant differences by sex were found in proportions of current smokers (men, 63.6%; women, 8.7%) and current drinkers (men, 74.9%; women, 19.9%). The prevalence of hypertension and diabetes mellitus was higher in men, and the prevalence of obesity and hypercholesterolemia was higher in women. Average blood pressures of those who took antihypertensive drug were SBP 159±20.1 mmHg (mean±SD), DBP 92.5±11.9 mmHg in

men, and SBP 158.0±21.6 mmHg (mean±SD), DBP 89.9±12.8 mmHg in women.

CVD Mortality

The mean (±SD) follow-up periods were 13.0±2.7 years for men and 13.7±2.2 years for women. There were 51,851 person-years of follow-up in the men, and 66,336 person-years in the women. The mean (±SD) of ages at CVD death were 75.5±11.4 years old in men and 78.2±10.4 years old for women. The mean age at CVD death in women was older than that among men ($p<0.05$). The mean (±SD) of ages at stroke death were 76.4±10.7 years old for men and 77.3±11.2 years old for women, those at CHD death were 71.9±13.3 years old for men and 77.3±10.0 years old for women. The mean age at CHD death in women was older than that in men ($p<0.05$).

Table 2 shows age-adjusted death rates and the hazard ratio of men compared with women for CVD. When adjusted for age, men were 1.60 (95% CI, 1.32–1.94) times more likely to die from CVD than women, and 1.75 (95% CI, 1.33–2.30) times more likely to die from stroke.

Excess Male CVD Risk Explained by the Differences in Risk Factors

Table 3 shows risk in men relative to women, and the proportion of excess risk in men which was explained by the sex difference in risk factor for each model. The age-adjusted hazard ratios for men vs women were 1.61 (95% CI, 1.32–1.95) for CVD, 1.77 (95% CI, 1.34–2.33) for stroke, and 1.56 (95% CI, 0.97–2.50) for CHD. The sex difference in smoking explained the largest proportion of risk factor-associated CVD and stroke deaths. As for CVD death, the sex difference in current drinking was negatively associated with excess deaths of men. Overall, 36% of the excess deaths of men from CVD were associated with the gender difference in all risk factors added to the model, and 46% for stroke.

As a result of testing for sex differences in the hazard ratio of risk factors by including interaction terms between sex and risk factor in the proportional hazard model, interactions between risk factors and sex were not statistically significant in the model of developing CVD, stroke, and CHD, with the exception of the interaction between current drinking and sex in the model of developing CVD (data not shown).

Total Mortality and Excess Male Risk Explained by the Differences in Risk Factors

Numbers of total deaths were 606 for men and 506 for women. When adjusted for age, men were 1.70 (95% CI, 1.51–1.92) times more likely to die for total death. The sex difference in smoking explained 25.5% of the excess total deaths of men. Overall, 25% of the excess total deaths of men were associated with the sex difference in all risk factors; hypertension, obesity, high cholesterol, diabetes mellitus, current smoker, and current drinker (data not shown).

Effect of Risk Factors for CVD in Men and Women

The associations between risk factors and deaths from CVD in men and women are shown in Table 4. In multivariate analysis, hazard ratios of CVD for current smokers were 1.49 in men, and 1.56 in women. Hypertension and diabetes mellitus were also statistically significant risk factors for CVD in both men and women. Hazard ratios of

Table 4 Hazard Ratio of Cardiovascular Disease, Stroke, and Coronary Heart Disease for Men and Women, NIPPON DATA80, 1980–1994 (N=8,938)

Risk factors		Cardiovascular disease				Stroke		Coronary heart disease	
		Death no.	Crude death rate*	Men	Women	Hazard ratio (95%confidence interval)†			
						Men	Women	Men	Women
Hypertension‡	*No*	*51*	*189*						
	Yes	*166*	*666*	*1.64 (1.18–2.28)*	*1.54 (1.08–2.19)*	*1.86 (1.15–3.01)*	*2.63 (1.46–4.74)*	*1.20 (0.57–2.54)*	*0.83 (0.39–1.77)*
Obesity§	*No*	*180*	*433*						
	Yes	*37*	*361*	*1.15 (0.79–1.66)*	*1.01 (0.73–1.41)*	*1.21 (0.73–2.01)*	*0.95 (0.59–1.53)*	*1.44 (0.63–3.25)*	*1.04 (0.46–2.36)*
High cholesterol‖	*No*	*186*	*424*						
	Yes	*31*	*389*	*0.97 (0.66–1.43)*	*0.88 (0.63–1.23)*	*0.84 (0.48–1.48)*	*0.92 (0.57–1.49)*	*2.21 (1.04–4.67)*	*0.9 (0.42–2.07)*
Diabetes mellitus¶	*No*	*179*	*369*						
	Yes	*37*	*1,118*	*1.56 (1.09–2.24)*	*1.98 (1.28–3.07)*	*1.17 (0.68–2.03)*	*1.78 (0.92–3.44)*	*1.58 (0.64–3.88)*	*2.65 (1.02–6.88)*
Current smoker	*No*	*78*	*417*						
	Yes	*139*	*420*	*1.49 (1.12–1.98)*	*1.56 (1.04–2.35)*	*1.40 (0.94–2.08)*	*1.52 (0.84–2.77)*	*1.97 (0.93–4.18)*	*1.29 (0.44–3.75)*
*Current drinker***	*No*	*96*	*772*						
	Yes	*120*	*305*	*0.63 (0.46–0.85)*	*1.2 (0.81–1.76)*	*0.88 (0.57–1.36)*	*1.31 (0.75–2.27)*	*0.51 (0.25–1.06)*	*1.25 (0.51–3.08)*

**Per 100,000 person-years. †Risk without each risk factor is defined as 1 for reference, hazard ratio and 95%confidence interval determined by Cox proportional hazards regression where the model included all 6 risk factors, age, and ex-drinker or not. ‡Hypertension was defined as a systolic blood pressure ≥160 mmHg and/or a diastolic blood pressure ≥95 mmHg, or on antihypertensive drug. §Obesity was defined by a body mass index ≥25.0kg/m². ‖High cholesterol was defined as total cholesterol ≥220 mg/dl (5.7 mmol/L). ¶Diabetes mellitus was defined as a casual blood glucose ≥200 mg/dl, or with a present history of diabetes mellitus. **Current drinker was defined as subjects who drink occasionally or daily.*

CVD of current male drinkers were 0.63 (with statistical significance), but had no statistical significance for women. For stroke, only high blood pressure was a statistically significant risk factor for both men and women. For coronary heart disease, high cholesterol was a statistically significant risk factor for men, and diabetes mellitus was a statistically significant risk factor for women.

Omitted from Table 4, the observed percentage changes in risk for CVD death with each change in risk factors, a 10 mmHg increase in SBP, 10 mg/dl increase in casual glucose, and smoking, are expected to increase risk by 15.7%, 4.5%, and 50.9% in men, and 8.6%, 5.0%, and 58.9% in women, with statistical significance, respectively. Current drinking is expected to decrease the risk of CVD by 39.1%, a statistical significant value in men, but not in women.

Discussion

In this nationally representative study in Japan, we found that the major determinant of the sex difference in CVD death was the difference in smoking, which explained nearly half of the excess CVD deaths of men. However, the sex difference in the conventional risk factors, including smoking, explained only one-third of the excess CVD deaths of men. The smaller proportion of excess risk explained by all risk factors other than smoking could be attributed to the preventive effect of alcohol intake for CHD[18] Except for drinking, the hazard ratio for CVD did not differ significantly between men and women.

Our study as well as previous studies[10,19,20] found no sex difference in the hazard ratio for CVD of smoking[10,19,20] A previous analysis of 40 cohort studies[20] found no sex difference in the hazard ratio for stroke from smoking, although a meta-analysis found a slightly increased risk in women[21] A review noted no sex difference in the hazard ratio for CHD from smoking[8] In contrast, an analysis of 40 cohort studies found that women tend to have a higher hazard ratio for CHD from smoking[20] These analyses suggest that the hazard ratio of smoking for CVD is not affected or is increased slightly in women. Thus, the excess of CVD deaths in males explained by sex differences in smoking could be attributed mainly to sex differences in the prevalence of smoking.

Sex differences in all of the conventional risk factors explained about one-third of male excess deaths for CVD in our study. A prospective cohort study also showed that differences in conventional risk factors for CVD explained half of the excess CHD deaths in men in Finland, although drinking habits were not included[9] These data indicate that excess mortality in men can be modified by lifestyle changes.

Study Limitations

One limitation of our study is that we could not follow cardiovascular events during follow-up from the baseline study in 1980, as this study was conducted as a retrospective cohort study in 1994. Another limitation of our study is the potential misclassification of subjects because we examined CVD risk status only at baseline. Using a single measurement to estimate the effect of risk factors can cause regression-dilution bias[22] and our data might have underestimated the risk factors. Another possible limitation is the potential sex difference when tracking CVD risk factors over time, although a previous 16-year follow-up study found no major sex differences[23] Other limitations of our study are the inclusion of frequency of drinking to estimate alcohol consumption, the inability to measure a dose effect of smoking, and the inclusion of casual blood glucose concentration, which might have underestimated the prevalence of diabetes or impaired glucose tolerance because these require measurement of fasting glucose concentration or a glucose challenge test. Additionally, we have not investigated the sex differences in the effect of smoking stratified by cigarettes per day for CVD, although men who smoked more than 20 cigarettes per day would have a higher risk for stroke and CHD death than those who smoked 1 to 20 cigarettes per day[10] That is because our primary purpose was to investigate the effect of sex differences in smoking rates for CVD, and a goal of the intervention relating to smoking would be smoking cessation rather than reducing the numbers of cigarettes per day.

In our sample, the sex difference in smoking represented the largest proportion of risk factor-associated CVD deaths. Sex differences in smoking rates might also explain the large sex differences in CVD deaths in other Asian countries, such as China, Singapore, and the Republic of Korea, where smoking rates vary widely by sex and age-standardized death rates for CVD are higher than in Japan[13,24] However, the female smoking rate has been increasing in these countries, and further studies are needed to evaluate whether the recent increase in smoking rates in women reduces the sex differences in CVD mortality using follow-up data classified according to the ICD-10.

We found sex differences in mortality and risk factors for CVD. Focusing on the risk factors for CVD rather than individual diseases such as stroke or CHD might clarify the total effect of risk factors for CVD, including heart failure and other causes. In particular, heart failure as a cause of death was officially recorded more frequently during the follow-up period in Japan, where the ICD-9 was used until 1994.

Conclusion

In conclusion, our findings from a nationally representative cohort study in Japan indicate that differences in smoking among men and women explain half of the sex differences in CVD deaths. All conventional risk factors for CVD including smoking explained about one-third of the sex difference in CVD deaths. Hence, excess deaths among men from CVD are not inevitable and can be avoided through interventions. In particular, smoking contributes substantially to excess male CVD deaths in areas where the smoking rate is much higher in men than in women.

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Appendix 1

List of the NIPPON DATA80 Research group

NIPPON DATA80: "National Integrated Projects for Prospective Observation of Non-communicable Diseases And its Trends in the Aged"

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はじめに

高脂血症、高血圧、高血糖、肥満などのリスクファクターは一症例に集積することが多く、最近メタボリック症候群として注目されている。インスリン抵抗性と関連するメタボリック症候群の診断基準、診断項目の境界値に関して欧米から数種の提案がある。しかしこれら全ては経験的なもので、エビデンスに基づいていない。まして日本人には適応できない。たとえばWHOの基準では肥満をBMI ≧30 kg/m^{2}としている。平均BMIが28 kg/m^{2}程度の欧米人の基準を平均BMIが23 kg/m^{2}程度の日本人に当てはめるのは不合理である。したがって日本在住日本人で、しかも縦断研究による予後を反映した検討が必要である。そこでわれわれは疫学研究：NIPPON DATA80のデータベースを用いてハイリスク患者診断に必要な項目およびその境界値の設定し、ハイリスク群と0リスク群の心筋梗塞、脳卒中死亡率のリスク比率を検討した。

方法

1980年に全国保健所の中から300カ所を無作為抽出し、30才以上の男女を対象に検診と血液生化学検査を行い、その後14年間追跡し死亡例の死因を特定した。住民の受診率は77%、追跡率91%であった。 追跡開始時に客体は男女合計約10,000人あった。検査項目の主なものは、随時採血の血糖(BS)、総コレステロール(TCH)、身長、体重、血圧などがあり、腹囲、中性脂肪、HDL等は無かった。したがってBS, TCH, BMI（体重kg/身長m^2）, SBP/DBPを診断項目に選定した。またそれぞれの境界値についてCox解析を用いて心筋梗塞、脳卒中死亡ハザード比を基に探索的に求めた。例えばBS=130mg/dl、TCH=200mg/dl、SBP/DBP=130/85mmHgのように3項目の境界値を仮に固定して、第4番目の項目BMIを25, 26 - - - 30 kg/m2と段階的に変えてCox解析(年齢、飲酒、喫煙を調整）をくり返し、リスク0群と比べたリスク3-4（ハイリスク）群の死亡ハザード比が有意に増加した値をその項目の境界値と定めた。このようにして最終的に4項目の境界値を決定した。表1には男性での例を示す。BMIでは27 kg/m^{2}になったとき心筋梗塞、脳卒中死亡ともハザード比が有意に増加した。

結果

Cox 解析を用いて探索的に得た男性での境界値はBS=130 mg/dl、TCH=200 mg/dl、SBP/DBP=130/85 mmHg、BMI=27 kg/m^{2}であった。女性ではもともと心筋梗塞、脳卒中死亡が低いため境界値を定めることが出来なかったので男性での境界値を代用した。リスクを3-4有したハイリスク群は男性では全体の13.0%、女性では16.8%あった。男性のハイリスク群は0リスク群に比べると、心筋梗塞死亡ハザード比が8倍、脳卒中死亡ハザード比が5倍になった（表2）。女性では有意な死亡ハザード比の増加を認めなかった。

考案

本研究が得た診断基準を用いたハイリスク群はわが国の少なくとも男性に於いて心筋梗塞、脳卒中死亡が有意に増加し、予後に対して意義が重要であることが判明した。今回の診断基準の意義を今後他のデータベースで再検証する必要があるし、またHDLコレステロール、空腹時血糖、中性脂肪、腹囲、腹囲/ヒップ比等の因子を用いた縦断的研究も必要である。

表１　境界値の探索的設定

	ハイリスク群（%）	心筋梗塞HR（P）	脳卒中HR（P）
BMI（kg/m²）			
26	15	6.94（0.064）	4.77（0.010）
27	**13**	**8.04（0.046）**	**5.06（0.008）**
28	11.5	9.17（0.035）	5.26（0.007）
血糖（mg/dl）			
120	17.5	6.12（0.081）	4.43（0.042）
130	**13**	**8.04（0.046）**	**5.06（0.008）**
140	10	7.11（0.068）	4.33（0.007）
総コレステロール（mg/dl）			
180	20	2.39（0.144）	4.80（0.131）
200	**13**	**8.04（0.046）**	**5.06（0008）**
220	7.8	10.29（0.028）	5.24（0.008）
SBP/DBP（mmHg）			
120/80	14.9	＞50（0.986）	4.56（0.137）
130/85	**13**	**8.04（0.046）**	**5.06（0.008）**
140/90	10.3	3.20（0.053）	4.51（0.002）

各項目の境界値を Cox 解析を用いて心筋梗塞、脳卒中死亡ハザード比(HR)を基に探索的に求めた。例えばBS=130mg/dl、TCH=200mg/dl、SBP/DBP=130/85mmHg のように３項目の境界値を仮に固定して(太文字)、第４番目の項目 BMI を 25，26 － － － 30 kg/m² と段階的に変えて Cox 解析(年齢、飲酒、喫煙を調整）をくり返し、リスク０群と比べたリスク 3-4（ハイリスク）群の死亡ハザード比が有意に増加した値をその項目の境界値と定めた。BMI では 27 kg/m² になったとき心筋梗塞、脳卒中死亡ともハザード比が有意に増加した。SBP=収縮期血圧、DBP=拡張期血

表２　ハイリスク群の心筋梗塞、脳卒中死亡ハザード比(男性)

	リスク０群	リスク 1-2 群	リスク 3-4 群	傾向 P
群内人数	655	2950	539	
心筋梗塞，人数	1	33	8	
/1000 人年	0.1	0.9	1.2	
HR*	1	3.51（0.47-26.1）	8.04（1.03-62.6）	0.0002
脳卒中，人数	3	85	30	
/1000 人年	0.3	2.2	4.4	
HR*	1	2.64（0.83-8.39）	5.06（1.53-16.7）	<0.0001

各群内の人数、心筋梗塞-、脳卒中死亡数、その 1000 人年当たりの死亡率、リスク０群に比べた各群のハザード比（95%信頼区間）、および傾向 P 値を示す。男性のハイリスク群は０リスク群に比べると、心筋梗塞死亡ハザード比が８倍、脳卒中死亡ハザード比が５倍になった。HR*＝年齢、飲酒、喫煙で調整したハザード比

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Combined Cardiovascular Risk Factors and Outcome
—— NIPPON DATA80, 1980–1994 ——

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Background To examine the prognostic significance of the high-risk group with combined cardiovascular risk factors in the Japanese, we analyzed the relationship between the high-risk group with combined risks and coronary heart disease (CHD) and stroke mortality using the NIPPON DATA80 database.
Methods and Results At baseline in 1980, those of age ≥30 years were randomly selected and 4,144 men and 5,318 women without CHD and/or stroke at baseline were followed for 14 years. The cutoff values for risk components obtained heuristically by Cox analysis were hypertension (systolic ≥130, or diastolic ≥85 mmHg, or on antihypertensive drugs), hypercholesterolemia (total cholesterol ≥200 mg/dl), hyperglycemia (≥130 mg/dl, or self-reported diabetes) and obesity (body mass index ≥27 kg/m^2). Subjects were divided into 3 groups (0, 1–2 and 3–4 risks). Compared with those men in the risk 0 group, the hazard ratios in men in the risk 3–4 for CHD mortality was 8.04 (95% confidence interval: 1.03–62.6), and the stroke mortality was 5.06 (1.53–16.7). In women, no statistically significant difference was found due to a lesser number of events.
Conclusion The high-risk group with combined risk factors is important risk for Japanese men. (*Circ J* 2006; **70:** 960–964)

Key Words: Cohort study; Coronary heart disease; Risk factors; Stroke

Cardiovascular risk factors, such as dyslipidemia, hypertension, hyperglycemia and obesity, are consistent and common but largely undertreated and undercontrolled in many countries[1] although it is known that these risk factors often cluster together[2,3] This clustering is now considered to be the "metabolic syndrome", which is closely related to insulin resistance[3,4] Cutoff values for cardiovascular risk factors have beene derived either empirically or from the results of cross-sectional studies[3,5–7] but ideally, such cutoff values should be derived from the data of longitudinal cohort studies, so that risk factors have prognostic implications. Furthermore, the cutoff values for these risk factors and the prognostic significance of combined risk factors have not yet been reported in Asian populations, where coronary heart disease (CHD) mortality and obesity are relatively rare, but susceptibility to diabetes mellitus has been reported to be higher[8–10] The individual cutoff values should be determined for different populations, so to examine the prognostic significance of the high-risk group with combined risk factors we analyzed the relationship between combined cardiovascular risk factors and CHD and stroke mortality using the database of the National Integrated Project for Prospective Observation of Noncommunicable Diseases and Its Trends in the Aged, 1980 (NIPPON DATA80), which includes more than 10,000 subjects in Japan who were followed for 14 years[11–13]

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Methods

Subjects

The subjects in this cohort were participants in the 1980 National Survey on Circulatory Disorders;[14] the detailed methods of the NIPPON DATA80 have been described previously[13] but are summarized here. A total of 10,546 community-based subjects aged ≥30 years in 300 randomly selected health districts throughout Japan participated in the survey, which consisted of a medical history, physical examinations, blood tests and a self-administered questionnaire on lifestyle. The cohort was followed until 1994[11–13] To clarify the causes of death, we used the National Vital Statistics.

Of the 10,546 subjects, a total of 1,084 were excluded for the following reasons: past history of CHD or stroke (n=166), missing information on the baseline survey (n=48), lost to follow-up (n=870). We analyzed the remaining 9,462 subjects (4,144 men, 5,318 women). Ethical approval for this study was obtained from the Institutional Review Board of Shiga University of Medical Science (No. 12-18, 2000).

Biochemical and Baseline Examinations

The baseline surveys were conducted by public health centers. Systolic and diastolic blood pressures (SBP, DBP)

Table 1 Results of Principal Component Analysis Among 3,820 Men and 4,857 Women Not Taking Medication (NIPPON DATA80: 1980–1994)

	Men		Women
	Factor 1	Factor 2	Factor 1
Variables			
BMI	0.44	0.65	0.50
SBP	0.84	−0.37	0.86
DBP	0.88	−0.18	0.85
Total cholesterol	0.33	0.72	0.44
Glucose	0.24	−0.25	0.31
Total variance	0.37	0.23	0.40
Cumulative variance	0.37	0.60	0.40

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

were measured by trained operators using a standard mercury sphygmomanometer on the subjects' right arm while the subjects were seated and after they had rested for more than 5 min. Height in stockinged feet and weight in light clothing were measured. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m).

A lifestyle survey was carried out using a self-administered questionnaire. Non-fasting blood samples were drawn and centrifuged within 60 min of collection, and then stored at −70°C until analysis. Total cholesterol was analyzed in a sequential auto-analyzer (SMA12/60; Technicon, Tarrytown, NY, USA) at a single laboratory (Osaka Medical Center for Health Science and Promotion), which is a member of the Cholesterol Reference Method Laboratory Network[15] The serum concentration of glucose was measured using the cupric-neocuproline method[16]

Combined Cardiovascular Risk Factors

The previous cutoff values used for the definition of metabolic syndrome[6,7] were not applied in the present study for the following reasons. Waist girth was not measured during the baseline examinations in 1980. The modified WHO definition uses BMI ≥30 kg/m^2 as a criteria for abdominal obesity, but because the average BMI for Japanese adult men and women is around 23 kg/m^2, there are very few subjects whose BMI is more than 30 kg/m^2.[17–20] Non-fasting blood samples were used in the present study, and direct measurement of high density lipoprotein (HDL) cholesterol was not performed. Therefore, we selected 4 components of the combined risk factors, namely, obesity, hyperglycemia, hypercholesterolemia and hypertension. The cutoff value for each component was determined heuristically using the mortality data described below. We considered those who were on antihypertensive medication as having hypertension, and those who with self-reported diabetes mellitus as having hyperglycemia. We then divided the study subjects into 3 groups: risk 0 for subjects who had none of the above components, risk 1–2 for subjects who had 1 or 2 of the components, and risk 3–4 for subjects who had 3 or 4 of the above components.

Statistical Analyses

SAS version 8.02 for WINDOWS (SAS Institute Inc, Cary, NC, USA) was used throughout the analyses. Men and women were analyzed separately. The chi-square test was used to compare dichotomous variables. To compare the means among the 3 groups, one-way analysis of variance was used.

Table 2 Results of Heuristic Analysis in Men to Obtain the Cutoff Values for Risk Components Among 4,144 Men (NIPPON DATA80: 1980–1994)

	Risk 3–4 (%)	CHD HR (p)	Stroke HR (p)
BMI (kg/m^2)			
26	*15*	*6.94 (0.064)*	*4.77 (0.010)*
27	*13*	*8.04 (0.046)*	*5.06 (0.008)*
28	*11.5*	*9.17 (0.035)*	*5.26 (0.007)*
BG (mg/dl)			
120	*17.5*	*6.12 (0.081)*	*4.43 (0.042)*
130	*13*	*8.04 (0.046)*	*5.06 (0.008)*
140	*10*	*7.11 (0.068)*	*4.33 (0.007)*
TC (mg/dl)			
180	*20*	*2.39 (0.144)*	*4.80 (0.131)*
200	*13*	*8.04 (0.046)*	*5.06 (0.008)*
220	*7.8*	*10.29 (0.028)*	*5.24 (0.008)*
SBP/DBP (mmHg)			
120/80	*14.9*	*>50 (0.986)*	*4.56 (0.137)*
130/85	*13*	*8.04 (0.046)*	*5.06 (0.008)*
140/90	*10.3*	*3.20 (0.053)*	*4.51 (0.002)*

Fixing the values of 3 components, value of the 4th component was varied categorically and the Cox analyses were performed. Hazard ratios (HR) with p values for CHD and stroke mortality were compared. The risk 0 group was used as the reference group. The Cox analyses were repeated until the lowest cutoff value for each component that had a prognostic significance for CHD and/or stroke mortality was obtained. The obtained cutoff values were BMI=27 kg/m^2, BG=130 mg/dl, TC=200 mg/dl, SBP/DBP=130/85 mmHg for men. Risk 3–4= subjects who had 3 or 4 of the risk (risks are: hypertension: SBP ≥130 mmHg, or DBP ≥85 mmHg, or on anti-hypertensive drugs; hypercholesterolemia: TC ≥200 mg/dl; hyperglycemia: BG ≥130 mg/dl or self-reported diabetes mellitus; obesity: BMI ≥27 kg/m^2).
CHD, coronary heart disease; BG, blood glucose; TC, total cholesterol. Other abbreviations see in Table 1.

Principal component analysis was conducted using the FACTOR procedure of SAS in order to examine clustering. Subjects who were taking antihypertensive, antidiabetic or cholesterol-lowering medications were excluded from this principal component analysis. The number of components to be retained was based on eigenvalue criteria (≥1.0). The resulting factor pattern was interpreted using factor loadings of ≥0.40.

The multivariate-adjusted hazard ratios for CHD, and stroke mortality were calculated using the Cox proportional hazard model, including age, cigarette smoking (currently smoking or not), and alcohol intake (drinkers or non-drinkers) as covariates. The risk 0 group was used as the reference group. The cutoff values for each of the 4 components were determined heuristically using the Cox analyses on CHD and stroke mortality. Namely, fixing the values of 3 components, the value of the 4th component was categorically varied and the Cox analyses were performed. The Cox analyses were repeated until we found the lowest cutoff value for each component that had prognostic significance for CHD and/or stroke mortality. The entered values for each component were BMI: from 25 to 30 kg/m^2 with 1 kg/m^2 increments; blood glucose: from 100 to 160 mg/dl with 10 mg/dl increments; total cholesterol: from 180 to 260 mg/dl with 20 mg/dl increments; SBP/DBP: 120/80, 130/85 and 140/90 mmHg. Because most of the analyses in women did not yield cutoff values that had prognostic significance, the cutoff values for men were applied in the analyses of women.

Hazard ratios for the association of CHD and stroke mortality with the component conditions were analyzed by the Cox proportional hazard model as above. Tests of linear