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Original Article

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Impact of Major Cardiovascular Risk Factors on the Incidence of Cardiovascular Disease among Overweight and Non-Overweight Individuals: The Circulatory Risk in Communities Study (CIRCS)

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Aim: We aimed to examine the impact of high-risk levels of cardiovascular risk factors on the incidence of cardiovascular disease (CVD) in overweight and non-overweight individuals without treatment for the risk factors.

Methods: A total of 8,051 individuals aged 40–74 years without a history of CVD and/or without treatment for hypertension, diabetes, hyperlipidemia, and kidney disease at baseline in 1995–2000 were followed up for a median of 14.1 years. We classified the participants into three risk categories (low-, intermediate-, and high-risk groups) on the basis of individual risk factors (blood pressure, serum glucose, low-density lipoprotein cholesterol [LDL-C], and urinary protein) according to the guidelines of Japanese clinical societies. The high-risk group (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg, fasting serum glucose ≥ 130 mg/dL or non-fasting serum glucose ≥ 180 mg/dL, LDL-C ≥ 180 mg/dL, proteinuria ≥ 2+) needed to refer to physicians or start treatment immediately. Overweight was defined as a body mass index of ≥ 25 kg/m^2.

Results: Compared with those in the non-overweight low-risk group, the hazard ratios (HRs) (95% confidence intervals, population-attributable fractions [PAFs]) of CVD in the high-risk categories of blood pressure were 2.0 (1.4–2.9, 7.0%) in the non-overweight high-risk group and 2.9 (1.9–4.3, 6.8%) in the overweight high-risk group. The corresponding HRs (95% confidence intervals, PAFs) of serum glucose were 2.0 (1.2–3.4, 2.5%) and 2.2 (1.1–4.3, 1.5%) in the non-overweight and overweight high-risk groups, respectively. Such associations were not observed for the high-risk group of LDL-C and proteinuria.

Conclusions: The present long-term observational study implies that targeting persons with non-treated severe hypertension and diabetes is prioritized to prevent CVD regardless of overweight status.

Key words: Risk factor, Cardiovascular disease, Population, Follow-up study, Epidemiology

Introduction

Hypertension, diabetes, dyslipidemia, and chronic kidney disease are known risk factors of cardiovascular disease (CVD)[1-5], and the prevention and management of these factors are important for prevention of incident CVD. In 2008, the Japanese government launched a nationwide intervention strategy for prevention of CVD among men and women aged 40–74 years[6]. This strategy focuses on persons with metabolic syndrome and helps them reduce their risk through health guidance about the

lifestyle modification. If the expected risk is high enough, they were referred to physicians for treatment for the prevention of CVD. However, it has been reported that more than half of Japanese patients who develop CVD had not consulted a physician before the onset[7]. Thus, it is necessary to prioritize the intervention for non-treated high-risk individuals with CVD. In this context, the Japan Trial in High-risk Individuals to Accelerate their Referral to Physicians (J-HARP) investigated whether health counseling of non-treated high-risk individuals with CVD accelerated their consultation to physicians[8]. It is important to estimate the preventive effect of interventions on non-treated high-risk individuals on the development of CVD. However, epidemiological evidence on the attributable risk of non-treated high-risk individuals with cardiovascular risk factors for the incidence of CVD in Japan has been scant.

Furthermore, previous studies showed that both non-overweight and overweight persons with CVD risk factors had high-risk for CVD and the population-attributable fractions (PAFs) of CVD in non-overweight persons were larger than those in overweight persons[9, 10]. However, these studies investigated the impact of accumulation of risk factors on CVD, stratified by overweight status, and that of each risk factor, especially among persons with non-treated CVD risk factors, has not been elucidated. Targeting only overweight persons among non-treated high-risk individuals is probably not enough for effective prevention strategies.

Aim

In this study, we aimed to calculate the hazard ratios (HRs) and PAFs of incident CVD associated with established risk factors for the high- and intermediate-risk groups, compared with the low-risk group among non-treated individuals, and investigate whether these associations were modified by overweight status.

Methods

Study Population

The study population included residents aged 40–74 years who participated in community health screening between 1995 and 2000 in four sites of the Circulatory Risk in Communities Study (CIRCS)[11]: Ikawa, Akita Prefecture; Minami Takayasu District of Yao City, Osaka Prefecture; Noichi, Kochi Prefecture; and Kyowa, Ibaraki Prefecture. The number of persons who participated in the baseline survey was 10,822 (4,099 men and 6,723 women).

Baseline Survey

Height was measured with socks on, and weight was measured with the participant wearing light clothing. The BMI at baseline was calculated as weight (kg) divided by the square of height (m^2). Overweight was defined as a BMI of ≥ 25 kg/m^2. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the right arm, using standard epidemiological methods with a standard mercury sphygmomanometer with a 14-cm-wide and 51-cm-long cuff, by a trained physician after the participant has rested for 5 min in the sitting position[12]. The measurements were repeated after the participant took five deep breaths if the SBP was ≥ 140 mmHg or the DBP was ≥ 90 mmHg. In the present study, the first reading was used for blood pressure levels. Dipstick urinalysis was performed with spontaneously voided fresh urine to assess proteinuria.

Blood was drawn from seated participants, and serum was immediately separated. Serum glucose was measured using the glucokinase method; total cholesterol (TC) was measured using an enzymatic assay; high-density lipoprotein cholesterol (HDL-C) was measured with a dextran sulfate-phosphotungstate-$MgCl_2$ precipitation method; and triglyceride (TG) was measured using an enzymatic assay for free glycerol with a Hitachi 7250 autoanalyzer (Hitachi Medical, Tokyo, Japan) at the laboratory of the Osaka Center for Cancer and Cardiovascular Disease Prevention, which is an international member of the US National Cholesterol Reference Method Laboratory Network[13-15]. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula, as follows: LDL-C (mg/dL) = TC (mg/dL) – HDL-C (mg/dL) – (TG [mg/dL] / 5)[16]. In this study, 67% of the participants were non-fasting. As a previous study reported that LDL-C calculated using the Friedewald formula and values measured using direct methods as the gold standard were comparable only when TG is <781 mg/dL at both fasting and non-fasting conditions[4], we excluded participants with TG ≥ 781 mg/dL.

Smoking status, number of cigarettes smoked per

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Table 1. Classification of participants into three risk categories for each risk factor at the baseline survey

	Low-risk group	Intermediate-risk group	High-risk group
Blood pressure	SBP <140 mmHg and DBP <90 mmHg	The persons with neither low risk group nor high-risk group	SBP ≥ 160 mmHg or DBP ≥ 100 mmHg
Serum glucose	Fasting serum glucose <110 mg/dL or Non-fasting serum glucose <140 mg/dL	110≤ Fasting serum glucose <130 mg/dL or 140≤ Non-fasting serum glucose <180 mg/dL	Fasting serum glucose ≥ 130 mg/dL or Non-fasting serum glucose ≥ 180 mg/dL
LDL-C	LDL-C <140 mg/dL	140 ≤ LDL-C <180 mg/dL	LDL-C ≥ 180 mg/dL
Proteinuria	– or ±	1+	≥ 2+

SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.

day, usual alcohol intake per day, family history of CVD, and use of medication for hypertension, diabetes, hyperlipidemia, and kidney disease were ascertained through interviews.

Definition of Risk Categories

As shown in **Table 1**, we classified the participants into three risk categories for each risk factor (blood pressure, serum glucose, LDL-C, and urinary protein) according to the J-HARP criteria[8], which defined high-risk individuals (basically levels of immediate need to consult a physician) on the basis of the guidelines of clinical societies in Japan[17-20]. Participants who were receiving treatment for hypertension, diabetes, hyperlipidemia, or kidney disease were excluded.

Follow-Up Survey of the Incidence of CVD

The incidence of CVD was surveyed from the time of the baseline survey until the end of 2013 for Ikawa, 2012 for Minami Takayasu, 2011 for Kyowa, and 2007 for Noichi. CVD included stroke and coronary heart disease (CHD). CHD included myocardial infarction (MI), definite angina pectoris, and sudden cardiac death. To systematically catch cases of incident stroke and CHD in the CIRCS communities, the municipal governments of these communities, collaborating with the CIRCS investigators, launched a systematic community stroke and CHD registration system. Details of the system were described elsewhere[11]. Briefly, the possible incident CVD case was extracted on the basis of at least one of the following sources: death certificate; national health insurance claim; reports from local physicians, public health nurses, and community health volunteers (neighbors); cardiovascular risk surveys; and/or household visit surveys. To make the diagnosis of CVD, participants or their families were contacted by telephone, visited, or invited to obtain the history of incidence. We also reviewed the medical records of local clinics and hospitals. Stroke was diagnosed when a sudden onset occurred and when neurological symptoms have persisted for at least 24 h after onset or until death. We reviewed computed tomography (CT) and/or magnetic resonance imaging (MRI) scans to confirm the diagnosis of stroke subtype. CT and MRI data were available for approximately 92% of the stroke cases. The diagnostic criteria of CHD were based on modified World Health Organization criteria[21]. MI was diagnosed according to the following two conditions: (1) typical severe chest pain persisting for ≥ 30 min and (2) appearance of abnormal Q or QS wave on the electrocardiogram, or a consistent change in the myocardial enzyme level. If symptom (1) was observed but finding (2) was not, we diagnosed possible MI. Definite angina pectoris was diagnosed in the presence of repeated episodes of chest pain during effort, especially when walking, usually rapidly disappearing after the cessation of effort or with the use of sublingual nitroglycerin. If the person died within 24 h from onset except with MI and angina pectoris as causes, it was considered sudden cardiac death. Finally, several physicians blinded to the baseline data determined the incidence of stroke or CHD by reviewing available information.

Statistical Analysis

We excluded participants with history of CVD (n=510); those with treatment for hypertension, diabetes, hyperlipidemia, and kidney disease (n=2,068); those with TG ≥ 781 mg/dL (n=14); and/or those with missing information at the baseline survey (n=179). Finally, the data of 8,051 persons (2,959 men and 5,092 women) were used for the analyses. The person-years value for each individual

Table 2. Baseline characteristics for study population without clinical treatment, stratified by developing cardiovascular disease (CVD) or remaining free of CVD

	CVD	Free of CVD	*P* value
No. at risk	327	7724	
Age, years	62.3 (8.5)	56.1 (9.2)	<0.001
Women, %	42.5	64.1	<0.001
BMI, kg/m^2	23.5 (3.2)	23.2 (3.1)	0.09
SBP, mmHg	142.0 (21.0)	132.6 (19.5)	<0.001
DBP, mmHg	85.0 (12.1)	80.3 (11.6)	<0.001
Fasting serum glucose, mg/dL (n=2,678)	101.4 (24.1)	96.7 (16.9)	0.006
Non-fasting serum glucose, mg/dL (n=5,373)	121.3 (56.3)	106.5 (31.0)	<0.001
TG, mg/dl	139.2 (80.0)	119.7 (71.6)	<0.001
LDL-C, mg/dL	124.8 (31.8)	126.0 (33.0)	0.51
HDL-C, mg/dl	55.3 (15.6)	58.8 (14.5)	<0.001
Proteinuria ≥ +, %	2.5	1.3	0.08
Current smoker, %	34.7	22.2	<0.001
Current drinker, %	41.4	36.1	0.05
Family history of CVD, %	36.7	30.1	0.01

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

was calculated as the duration until the occurrence of CVD, death, or failure to follow-up, whichever occurred first. During follow-up, 380 (4.7%) participants moved out of their community. Baseline characteristics were compared between participants with or without CVD using a *t*-test or chi-square test. We calculated the HRs and 95% confidence intervals (CIs) of CVD according to three risk categories of each risk factor using Cox proportional hazards models with reference to the low-risk group. In model 1, we adjusted for age (years), sex, and area. In model 2, we further adjusted for BMI (non-overweight [< 25 kg/m^2] and overweight [≥ 25 kg/m^2]), smoking status (never, former, current smoker [<20 and ≥ 20 cigarettes per day]), alcohol intake (never, former, current drinker [<23, 23–<46, 46–<69, and ≥ 69 g/day]), family history of CVD, and other conventional risk factors of CVD (blood pressure, serum glucose, LDL-C, HDL-C, TG, and proteinuria). The linear trend for HRs across the three risk categories was tested using an order variable (0, 1, and 2 for three risk categories). We calculated the PAF with the following formula: PAF = pd × (HR − 1)/HR, where pd is the ratio of the incidence of each risk category to the total incidence and HR is the multivariate HR of each risk category with 95% CI for PAFs[22, 23]. We further stratified the participant according to non-overweight or overweight status and calculated the HRs (95% CIs) and PAFs of CVD according to three risk categories of each risk factor with reference to the non-overweight low-risk group.

We previously reported that LDL-C calculated using the Friedewald formula is applicable to persons with TG <781 mg/dL[4], although the Friedewald formula is recommended for persons with TG <400 mg/dL. For confirmation, we conducted a sensitivity analysis excluding participants with TG ≥ 400 mg/dL.

SAS (version 9.4; SAS Institute, Cary, NC, USA) was used for all analyses. All statistical analyses were performed using a two-tailed test, and $P<0.05$ was considered statistically significant.

Ethical Considerations

Informed consent was obtained from representatives in communities and was implied by individual participation in health checkups, on the basis of the guidelines of the Council for International Organizations of Medical Science[24]. This study was approved by the Ethics Committee of the Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka University and the University of Tsukuba.

Results

After the follow-up for 109,294 person-years (median 14.1 years), we confirmed 327 incident cases of CVD (188 in men and 139 in women), including 223 stroke cases (117 in men and 106 in women) and 111 CHD cases (76 in men and 35 in women).

Table 2 shows the baseline characteristics for our study population without clinical treatment, stratified by developing CVD or remaining free of CVD. The

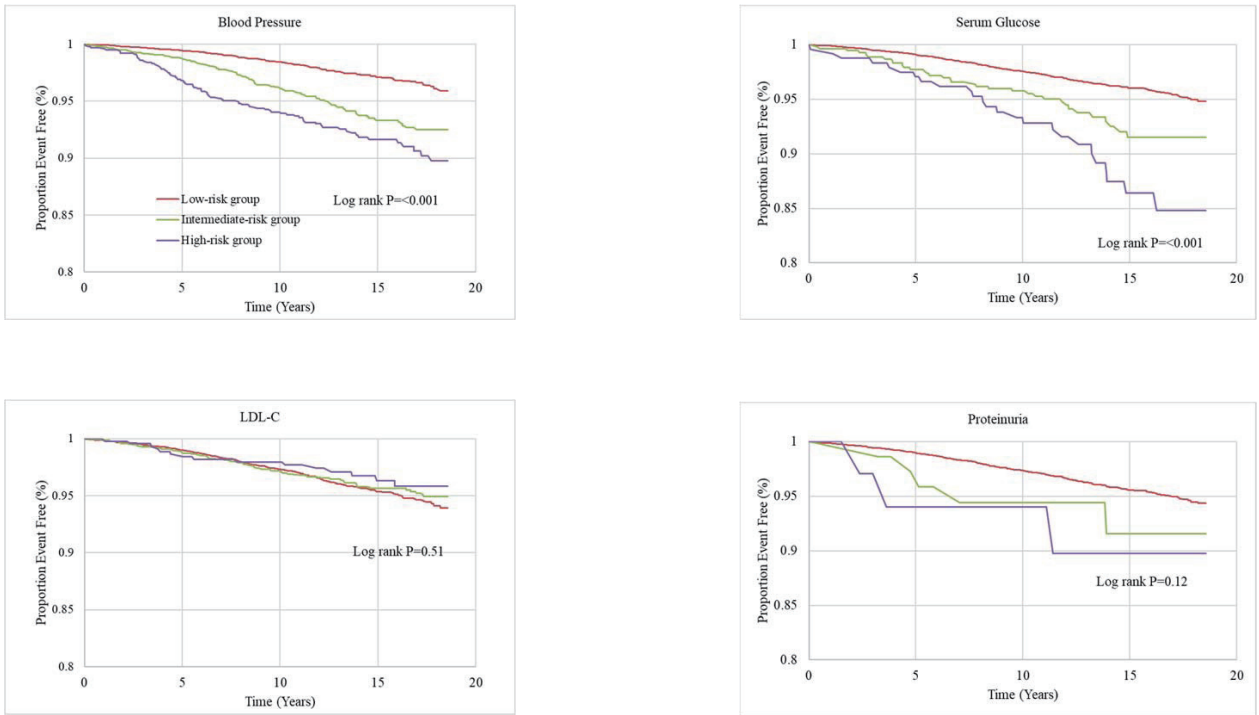

Fig. 1. Kaplan–Meier curves for each risk factor category for the incidence of cardiovascular disease

participant with CVD had higher mean values of age, SBP, DBP, fasting serum glucose, non-fasting serum glucose, and TG, as well as the proportions of current smoker and family history of CVD, and lower mean values of HDL-C and lower proportion of women.

The Kaplan–Meier curves showed that the high-risk group according to blood pressure and serum glucose, but not LDL-C and proteinuria, had an increased risk of CVD **(Fig. 1)**.

The intermediate- and high-risk groups of blood pressure had a higher risk of CVD **(Table 3)**. The multivariable HRs (95% CIs) of CVD were 1.7 (1.3–2.2) in the intermediate-risk group and 2.3 (1.7–3.1) in the high-risk group. The high-risk group of serum glucose also had a higher risk of CVD, with HRs (95% CIs) of 1.2 (0.8–1.7) in the intermediate-risk group and 2.1 (1.4–3.1) in the high-risk group. Such associations were not observed for LDL-C and proteinuria. There was an interaction of borderline significance between overweight and blood pressure in relation to CVD (P for interaction = 0.06), but not between overweight and other cardiovascular risk factor (P for interaction = 0.16 for serum glucose; 0.39 for LDL-C; and 0.23 for proteinuria). The PAFs of CVD in the intermediate-risk group were 14.5% (8.7 to 19.1) for blood pressure and 1.5% (–2.5 to 4.2) for serum glucose; in the high-risk group, these values were 13.7% (10.2 to 16.3) and 3.9% (2.0 to 5.2) for blood pressure and serum glucose, respectively. The intermediate- and high-risk groups of blood pressure had higher risk of stroke, with HRs (95% CIs, PAFs) of 1.8 (1.3–2.5, 15.4%) in the intermediate-risk group and 2.8 (2.0–4.0, 18.0%) in the high-risk group. The HRs and PAFs of CHD were statistically significant in the intermediate-risk group of blood pressure [HR (95% CI), PAF: 1.5 (1.0–2.4), 12.0%] and high-risk group of serum glucose [HR (95% CI), PAF: 2.9 (1.6–5.3), 7.1%]. There was an interaction of borderline significance between overweight and blood pressure (P for interaction = 0.07), serum glucose (P for interaction = 0.06) and LDL-C (P for interaction = 0.05) in relation to stroke, and LDL-C (P for interaction = 0.08) in relation to CHD.

After participants were stratified by non-overweight or overweight status, the high-risk group of blood pressure and serum glucose had a higher risk of CVD in both non-overweight and overweight participants **(Table 4)**. Furthermore, the HRs and PAFs of incident CVD according to the high-risk categories of blood pressure and serum glucose were not different between the non-overweight and overweight groups when we used the non-overweight low-risk group as reference **(Table 4)**. According to the risk categories of blood pressure, the multivariable HRs (95% CIs, PAFs) of CVD were 2.0 (1.5–2.6, 12.5%) in the non-overweight intermediate-risk

Table 3. Hazard ratios and population-attributable fractions (95% confidence intervals) of incident cardiovascular disease (CVD) according to each risk factor category among men and women without clinical treatment

	Low	Intermediate	High	*P* for trend
CVD				
Blood pressure				
Person-years	69356	26642	13295	
No. at risk	5030	2006	1015	
No. of cases	135	113	79	
Age-, sex- and area-adjusted HR	1.0	1.7 (1.3-2.2)	2.3 (1.8-3.1)	<0.001
Multivariable HR	1.0	1.7 (1.3-2.2)	2.3 (1.7-3.1)	<0.001
PAF (%)	-	14.5 (8.7 to 19.1)	13.7 (10.2 to 16.3)	
Serum glucose				
Person-years	99461	6806	3027	
No. at risk	7272	538	241	
No. of cases	268	34	25	
Age-, sex- and area-adjusted HR	1.0	1.3 (0.9-1.8)	2.3 (1.5-3.4)	<0.001
Multivariable HR	1.0	1.2 (0.8-1.7)	2.1 (1.4-3.1)	0.002
PAF (%)	-	1.5 (-2.5 to 4.2)	3.9 (2.0 to 5.2)	
LDL-C				
Person-years	74054	28857	6383	
No. at risk	5509	2086	456	
No. of cases	229	83	15	
Age-, sex- and area-adjusted HR	1.0	1.0 (0.8-1.3)	1.0 (0.6-1.7)	0.98
Multivariable HR	1.0	1.0 (0.8-1.3)	0.9 (0.5-1.5)	0.69
PAF (%)	-	-0.4 (-8.0 to 5.5)	-0.6 (-4.3 to 1.5)	
Proteinuria				
Person-years	107925	948	421	
No. at risk	7943	73	35	
No. of cases	319	5	3	
Age-, sex- and area-adjusted HR	1.0	1.6 (0.7-3.9)	1.9 (0.6-6.1)	0.13
Multivariable HR	1.0	1.2 (0.5-2.9)	1.6 (0.5-5.0)	0.41
PAF (%)	-	0.2 (-1.7 to 1.0)	0.3 (-0.9 to 0.7)	
Stroke				
Blood pressure				
No. of cases	84	77	62	
Age-, sex- and area-adjusted HR	1.0	1.9 (1.4-2.5)	2.9 (2.1-4.1)	<0.001
Multivariable HR	1.0	1.8 (1.3-2.5)	2.8 (2.0-4.0)	<0.001
PAF (%)	-	15.4 (8.2 to 20.6)	18.0 (14.0 to 20.8)	
Serum glucose				
No. of cases	182	28	13	
Age-, sex- and area-adjusted HR	1.0	1.6 (1.1-2.4)	1.8 (1.0-3.2)	0.004
Multivariable HR	1.0	1.4 (0.9-2.1)	1.6 (0.9-2.8)	0.03
PAF (%)	-	3.7 (-0.8 to 6.7)	2.1 (-0.7 to 3.8)	
LDL-C				
No. of cases	163	51	9	
Age-, sex- and area-adjusted HR	1.0	0.8 (0.6-1.1)	0.8 (0.4-1.5)	0.19
Multivariable HR	1.0	0.8 (0.6-1.2)	0.7 (0.3-1.4)	0.14
PAF (%)	-	-4.7 (-15.2 to 3.0)	-1.9 (-7.7 to 1.0)	
Proteinuria				
No. of cases	217	4	2	
Age-, sex- and area-adjusted HR	1.0	1.9 (0.7-5.1)	1.9 (0.5-7.8)	0.14
Multivariable HR	1.0	1.4 (0.5-3.9)	1.4 (0.3-5.8)	0.44
PAF (%)	-	0.5 (-1.7 to 1.3)	0.3 (-1.7 to 0.7)	

(Cont. Table 3)

	Low	Intermediate	High	*P* for trend
CHD				
Blood pressure				
No. of cases	54	38	19	
Age-, sex- and area-adjusted HR	1.0	1.4 (0.9-2.2)	1.4 (0.8-2.3)	0.13
Multivariable HR	1.0	1.5 (1.0-2.4)	1.4 (0.8-2.4)	0.10
PAF (%)	-	12.0 (0.1 to 19.8)	4.8 (-3.9 to 9.9)	
Serum glucose				
No. of cases	91	8	12	
Age-, sex- and area-adjusted HR	1.0	0.8 (0.4-1.7)	2.9 (1.6-5.4)	0.01
Multivariable HR	1.0	0.8 (0.4-1.7)	2.9 (1.6-5.3)	0.01
PAF (%)	-	-1.7 (-11.3 to 2.9)	7.1 (3.9 to 8.8)	
LDL-C				
No. of cases	71	34	6	
Age-, sex- and area-adjusted HR	1.0	1.5 (1.0-2.2)	1.6 (0.7-3.7)	0.06
Multivariable HR	1.0	1.4 (0.9-2.1)	1.4 (0.6-3.2)	0.15
PAF (%)	-	8.2 (-3.5 to 15.9)	1.5 (-3.9 to 3.7)	
Proteinuria				
No. of cases	109	1	1	
Age-, sex- and area-adjusted HR	1.0	0.9 (0.1-6.2)	1.9 (0.3-13.4)	0.67
Multivariable HR	1.0	0.7 (0.1-5.0)	2.0 (0.3-15.0)	0.76
PAF (%)	-	-0.4 (-8.6 to 0.7)	0.5 (-2.4 to 0.8)	

CHD, coronary heart disease; HR, hazard ratio; PAF, population-attributable fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol. Multivariable HRs were adjusted for age, sex, area, body mass index, smoking status, alcohol intake, family history of CVD, and the above-mentioned other conventional risk factors (blood pressure, serum glucose, LDL-C, high-density lipoprotein cholesterol, triglyceride, and proteinuria).

group, 2.0 (1.4–2.9, 7.0%) in the non-overweight high-risk group, 1.1 (0.7–1.6, 0.6%) in the overweight low-risk group, 1.3 (0.9–2.0, 2.2%) in the overweight intermediate-risk group, and 2.9 (1.9–4.3, 6.8%) in the overweight high-risk group. According to the risk categories of serum glucose, the corresponding HRs (95% CIs, PAFs) were 1.5 (1.0–2.2, 2.6%), 2.0 (1.2–3.4, 2.5%), 1.1 (0.8–1.4, 1.7%), 0.7 (0.3–1.5, –1.0%), and 2.2 (1.1–4.3, 1.5%) in the non-overweight intermediate-risk, non-overweight high-risk, overweight low-risk, overweight intermediate-risk, and overweight high-risk groups, respectively.

In the risk categories of blood pressure, the HRs and PAFs of incident stroke associated with high blood pressure did not differ materially between the non-overweight and overweight groups although they were not statistically significant for incident CHD in all risk categories. In the risk categories of serum glucose, the HRs and PAFs of stroke were statistically significant in the intermediate- and high-risk groups with non-overweight, but not in any risk groups with overweight. Those for CHD were statistically significant only in the high-risk group of serum glucose with overweight. In the risk categories of LDL-C, the HR and PAF for CHD were statistically significant only in the intermediate-risk group with non-overweight.

These results did not change substantially when we excluded the participants with non-fasting blood sample (33% of total participants were at fasting; **Supplemental Tables 1 and 2**) and those with TG ≥ 400 mg/dL (data not shown).

Discussion

In our long-term prospective cohort study of the general population, we found a twofold excess risk of incident CVD associated with the non-treated high-risk categories of blood pressure and serum glucose. Among the four cardiovascular risk factors, high blood pressure had the largest impact of incident CVD and stroke, and high serum glucose had the largest impact of incident CHD. When we stratified participants by overweight status, the HRs and PAFs of incident CVD associated with high blood pressure and serum glucose did not differ materially between the non-overweight and overweight groups.

Our study group reported that hypertension had

Table 4. Hazard ratios and population-attributable fractions (95% confidence intervals) of incident cardiovascular disease (CVD) according to each risk factor category among men and women without clinical treatment, stratified by overweight status

	Non-overweight (BMI <25 kg/m^2)			Overweight (BMI ≥ 25 kg/m^2)		
	Low	Intermediate	High	Low	Intermediate	High
CVD						
Blood pressure						
Person-years	55173	17831	8378	14184	8811	4917
No. at risk	4004	1355	644	1026	651	371
No. of cases	104	84	45	31	29	34
Age-, sex- and area-adjusted HR	1.0	1.9 (1.4-2.6)	2.1 (1.5-2.9)	1.2 (0.8-1.8)	1.5 (1.0-2.2)	3.1 (2.1-4.6)
Multivariable HR	1.0	2.0 (1.5-2.6)	2.0 (1.4-2.9)	1.1 (0.7-1.6)	1.3 (0.9-2.0)	2.9 (1.9-4.3)
PAF (%)	-	12.5 (8.1 to 15.9)	7.0 (4.1 to 9.0)	0.6 (-3.9 to 3.6)	2.2 (-1.3 to 4.5)	6.8 (5.0 to 8.0)
Serum glucose						
Person-years	74902	4484	1996	24559	2322	1031
No. at risk	5485	357	161	1787	181	80
No. of cases	190	27	16	78	7	9
Age-, sex- and area-adjusted HR	1.0	1.6 (1.0-2.3)	2.3 (1.4-3.8)	1.3 (1.0-1.7)	0.9 (0.4-2.0)	2.8 (1.4-5.4)
Multivariable HR	1.0	1.5 (1.0-2.2)	2.0 (1.2-3.4)	1.1 (0.8-1.4)	0.7 (0.3-1.5)	2.2 (1.1-4.3)
PAF (%)	-	2.6 (-0.2 to 4.5)	2.5 (0.9 to 3.5)	1.7 (-5.4 to 7.1)	-1.0 (-4.6 to 0.7)	1.5 (0.3 to 2.1)
LDL-C						
Person-years	57085	19837	4460	16968	9020	1923
No. at risk	4244	1444	315	1265	642	141
No. of cases	168	57	8	61	26	7
Age-, sex- and area-adjusted HR	1.0	1.1 (0.8-1.5)	0.8 (0.4-1.7)	1.3 (1.0-1.7)	1.0 (0.7-1.6)	1.6 (0.8-3.5)
Multivariable HR	1.0	1.1 (0.8-1.5)	0.7 (0.4-1.5)	1.0 (0.8-1.4)	0.9 (0.6-1.3)	1.2 (0.6-2.6)
PAF (%)	-	1.1 (-4.7 to 5.4)	-0.9 (-4.5 to 0.8)	0.7 (-5.9 to 5.5)	-1.3 (-6.2 to 1.9)	0.4 (-1.7 to 1.3)
Proteinuria						
Person-years	80448	674	260	27477	274	161
No. at risk	5930	52	21	2013	21	14
No. of cases	230	2	1	89	3	2
Age-, sex- and area-adjusted HR	1.0	0.9 (0.2-3.5)	0.9 (0.1-6.5)	1.2 (0.9-1.5)	4.0 (1.3-12.4)	5.0 (1.3-20.4)
Multivariable HR	1.0	0.6 (0.2-2.6)	0.9 (0.1-6.4)	1.0 (0.7-1.2)	2.5 (0.8-7.8)	2.5 (0.6-10.3)
PAF (%)	-	-0.3 (-3.3 to 0.4)	0.0 (-2.2 to 0.3)	-1.3 (-9.9 to 5.2)	0.5 (-0.3 to 0.8)	0.4 (-0.4 to 0.6)
Stroke						
Blood pressure						
No. of cases	64	59	35	20	18	27
Age-, sex- and area-adjusted HR	1.0	2.2 (1.5-3.1)	2.6 (1.7-4.0)	1.2 (0.7-2.0)	1.5 (0.9-2.5)	4.0 (2.5-6.2)
Multivariable HR	1.0	2.1 (1.5-3.1)	2.5 (1.7-3.9)	1.2 (0.7-1.9)	1.3 (0.8-2.3)	3.7 (2.3-5.9)
PAF (%)	-	14.0 (8.6 to 17.8)	9.5 (6.3 to 11.6)	1.3 (-3.9 to 4.4)	2.0 (-2.3 to 4.6)	8.8 (6.9 to 10.1)
Serum glucose						
No. of cases	125	22	11	57	6	2
Age-, sex- and area-adjusted HR	1.0	2.0 (1.3-3.2)	2.5 (1.4-4.7)	1.4 (1.0-1.9)	1.2 (0.5-2.8)	0.9 (0.2-3.8)
Multivariable HR	1.0	1.9 (1.2-2.9)	2.2 (1.2-4.1)	1.2 (0.9-1.7)	0.9 (0.4-2.1)	0.8 (0.2-3.1)
PAF (%)	-	4.5 (1.4 to 6.5)	2.7 (0.6 to 3.7)	4.5 (-3.8 to 10.4)	-0.3 (-4.2 to 1.4)	-0.3 (-4.0 to 0.6)
LDL-C						
No. of cases	124	32	2	39	19	7
Age-, sex- and area-adjusted HR	1.0	0.8 (0.5-1.1)	0.3 (0.1-1.0)	1.1 (0.8-1.6)	1.0 (0.6-1.6)	2.0 (0.9-4.3)
Multivariable HR	1.0	0.8 (0.5-1.2)	0.2 (0.1-0.9)	0.9 (0.6-1.3)	0.8 (0.5-1.3)	1.5 (0.7-3.2)
PAF (%)	-	-3.6 (-12.3 to 2.3)	-3.1 (-15.4 to -0.1)	-2.3 (-11.5 to 4.0)	-1.9 (-8.6 to 2.2)	1.0 (-1.5 to 2.2)
Proteinuria						
No. of cases	155	2	1	62	2	1
Age-, sex- and area-adjusted HR	1.0	1.3 (0.3-5.4)	1.3 (0.2-9.7)	1.2 (0.9-1.6)	4.0 (1.0-16.2)	3.9 (0.5-28.1)
Multivariable HR	1.0	0.9 (0.2-3.8)	1.1 (0.1-7.9)	1.0 (0.7-1.4)	2.9 (0.7-12.0)	1.9 (0.3-14.2)
PAF (%)	-	-0.1 (-3.1 to 0.7)	0.0 (-2.6 to 0.4)	-0.4 (-10.9 to 7.2)	0.6 (-0.4 to 0.8)	0.2 (-1.3 to 0.4)

(Cont. Table 4)

	Non-overweight (BMI < 25 kg/m²)			Overweight (BMI ≥ 25 kg/m²)		
	Low	Intermediate	High	Low	Intermediate	High
CHD						
Blood pressure						
No. of cases	43	26	12	11	12	7
Age-, sex- and area-adjusted HR	1.0	1.4 (0.9-2.3)	1.3 (0.7-2.5)	1.0 (0.5-2.0)	1.5 (0.8-2.8)	1.5 (0.7-3.3)
Multivariable HR	1.0	1.5 (0.9-2.5)	1.3 (0.7-2.5)	0.8 (0.4-1.6)	1.4 (0.7-2.7)	1.4 (0.6-3.2)
PAF (%)	-	8.0 (-2.0 to 14.0)	2.5 (-5.2 to 6.4)	-2.0 (-13.5 to 3.8)	2.9 (-4.5 to 6.7)	1.7 (-4.2 to 4.3)
Serum glucose						
No. of cases	69	7	5	22	1	7
Age-, sex- and area-adjusted HR	1.0	1.0 (0.5-2.2)	1.7 (0.7-4.3)	1.0 (0.6-1.6)	0.3 (0.0-2.5)	5.8 (2.6-12.5)
Multivariable HR	1.0	1.0 (0.5-2.2)	1.8 (0.7-4.4)	0.8 (0.5-1.4)	0.3 (0.0-2.0)	4.4 (2.0-9.9)
PAF (%)	-	0.1 (-7.3 to 3.5)	1.9 (-1.9 to 3.5)	-4.0 (-19.6 to 5.4)	-2.4 (-22.8 to 0.5)	4.9 (3.1 to 5.7)
LDL-C						
No. of cases	48	27	6	23	7	0
Age-, sex- and area-adjusted HR	1.0	2.0 (1.2-3.2)	2.6 (1.1-6.1)	1.7 (1.0-2.7)	1.1 (0.5-2.4)	-
Multivariable HR	1.0	1.9 (1.1-3.0)	2.3 (0.9-5.4)	1.4 (0.8-2.4)	0.9 (0.4-1.9)	-
PAF (%)	-	11.2 (3.1 to 16.2)	3.0 (-0.3 to 4.4)	6.2 (-3.9 to 12.1)	-1.0 (-10.1 to 3.1)	-
Proteinuria						
No. of cases	81	0	0	28	1	1
Age-, sex- and area-adjusted HR	1.0	-	-	1.0 (0.7-1.6)	3.0 (0.4-21.5)	6.1 (0.8-43.8)
Multivariable HR	1.0	-	-	0.9 (0.5-1.3)	1.6 (0.2-11.9)	3.7 (0.5-28.4)
PAF (%)	-	-	-	-4.3 (-21.2 to 6.5)	0.3 (-3.3 to 0.8)	0.7 (-1.0 to 0.9)

CHD, coronary heart disease; BMI, body mass index; HR, hazard ratio; PAF, population-attributable fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol. Multivariable HRs were adjusted for age, sex, area, smoking status, alcohol intake, family history of CVD, and the above-mentioned other conventional risk factors (blood pressure, serum glucose, LDL-C, high-density lipoprotein cholesterol, triglyceride, and proteinuria).

the largest impact on CVD, especially on stroke, among the CVD risk factors (PAF = 46% for stroke)[25], despite a downward trend of blood pressure levels and a decreasing prevalence of hypertension[26]. We also reported that the impact of diabetes on incident CVD in the community had increased from the 1990s to the 2000s, and the PAF for diabetes in 2000–2003 was especially large (16.2%) for CHD[3]. The present study further extended these previous findings; i.e., non-treated severe hypertension had a large impact on incident stroke and CVD (PAF = 18.0% for stroke and 13.7% for CVD), and so did non-treated severe diabetes on incident CHD (PAF = 7.1%).

More importantly, the PAF of incident CVD for blood pressure and serum glucose did not differ materially between the non-overweight high-risk group and the overweight high-risk group. We reported that the prevalence of non-overweight hypertensive persons was still higher than that of overweight hypertensive persons from 1963–1966 to 2009–2013 among both men and women in a Japanese rural community[26]. The risk of type 2 diabetes increases at a lower BMI in Asians than in Caucasians[27] probably because East Asians have a lower insulin secretion ability than have Caucasians[28].

The lack of association between LDL-C and risk of CVD in the present study was probably due to the higher proportions of intracerebral hemorrhage and lacunar infraction[29] with which LDL-C levels were not associated[30] and the lower proportions of atherothrombotic infraction and ischemic heart disease[29, 31] with which LDL-C levels were positively associated[30], compared with those in the western population. The lack of association between proteinuria and risk of CVD was due in part to the small number of CVD cases in the intermediate- and high-risk categories. The attributable risk of the non-treated high-risk group of proteinuria for incident CVD was small.

The strengths of this study include (1) the use of standardized methods for the measurement of serum lipid and risk characteristics and (2) the almost complete CVD surveillance and the high percentage of stroke events confirmed by imaging studies.

This study has several limitations. First, we measured serum and proteinuria only once at the

baseline survey, which may have caused a regression dilution bias because of temporal changes and random errors in the measurement of exposure variables. Thus, the estimates we reported might have been underestimated. Second, about 67% of the participants were non-fasting, which is likely to have led to underestimation of LDL-C calculation when the Friedewald formula was used. According to a validation study conducted by our lipid reference standardization laboratory, the LDL-C level calculated using the Friedewald formula was underestimated by 4 mg/dl among non-fasting participated[4]. Third, we could not consider the treatment status after the baseline survey in analyses. Because a part of participants did not participate in health checkups every year, we could not obtain the information whether the individuals were really left untreated (before a CVD onset) during the follow-up period. Therefore, further studies are needed to consider the effects of changes in treatment conditions on incident CVD. Fourth, although we adjusted for major covariates, there remain possible residual confounding factors such as socioeconomic status, physical activity, and nutrient intake.

Conclusion

Persons with non-treated severe hypertension and diabetes had a higher risk of CVD regardless of overweight status, and the PAF of incident CVD associated with non-treated severe blood pressure and serum glucose did not differ materially between the non-overweight and overweight groups. Our long-term observational study implies that targeting these high-risk groups is prioritized to prevent CVD regardless of overweight status.

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Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Supplemental Table 1. Hazard ratios and population-attributable fractions (95% confidence intervals) of incident cardiovascular disease (CVD) according to each risk factor category among men and women who were collected fasting blood sample and without clinical treatment

	Low	Intermediate	High	*P* for trend
CVD				
Blood pressure				
Person-years	25051	9163	4759	
No. at risk	1697	644	337	
No. of cases	49	31	24	
Age-, sex- and area-adjusted HR	1.0	1.4 (0.9-2.3)	2.1 (1.3-3.5)	0.002
Multivariable HR	1.0	1.6 (1.0-2.6)	2.3 (1.3-3.9)	0.002
PAF (%)	-	11.7 (0.7 to 18.6)	13.1 (5.9 to 17.2)	
Serum glucose				
Person-years	35299	2619	1056	
No. at risk	2413	189	76	
No. of cases	88	7	9	
Age-, sex- and area-adjusted HR	1.0	0.7 (0.3-1.6)	2.8 (1.4-5.6)	0.06
Multivariable HR	1.0	0.6 (0.2-1.3)	2.3 (1.1-4.8)	0.31
PAF (%)	-	-5.3 (-20.6 to 1.4)	4.9 (0.7 to 6.8)	
LDL-C				
Person-years	23796	12140	3038	
No. at risk	1644	830	204	
No. of cases	73	26	5	
Age-, sex- and area-adjusted HR	1.0	0.7 (0.4-1.1)	0.7 (0.3-1.7)	0.12
Multivariable HR	1.0	0.6 (0.4-1.0)	0.5 (0.2-1.3)	0.03
PAF (%)	-	-15.1 (-38.9 to -0.2)	-4.4 (-18.5 to 1.2)	
Proteinuria				
Person-years	38494	291	187	
No. at risk	2640	23	15	
No. of cases	100	2	2	
Age-, sex- and area-adjusted HR	1.0	2.0 (0.5-8.1)	2.9 (0.7-11.9)	0.09
Multivariable HR	1.0	1.6 (0.4-7.0)	2.4 (0.6-10.4)	0.18
PAF (%)	-	0.7 (-3.3 to 1.6)	1.1 (-1.5 to 1.7)	
Stroke				
Blood pressure				
No. of cases	29	20	18	
Age-, sex- and area-adjusted HR	1.0	1.5 (0.9-2.7)	2.7 (1.5-4.9)	0.001
Multivariable HR	1.0	1.8 (1.0-3.2)	3.1 (1.7-6.0)	<0.001
PAF (%)	-	12.9 (-1.0 to 20.5)	18.3 (10.7 to 22.4)	
Serum glucose				
No. of cases	59	6	2	
Age-, sex- and area-adjusted HR	1.0	1.0 (0.4-2.4)	1.0 (0.2-4.0)	0.98
Multivariable HR	1.0	0.8 (0.3-2.0)	0.9 (0.2-4.1)	0.72
PAF (%)	-	-2.3 (-18.9 to 4.4)	-0.2 (-10.7 to 2.3)	
LDL-C				
No. of cases	47	17	3	
Age-, sex- and area-adjusted HR	1.0	0.7 (0.4-1.2)	0.6 (0.2-1.9)	0.14
Multivariable HR	1.0	0.7 (0.4-1.2)	0.5 (0.2-1.8)	0.14
PAF (%)	-	-11.0 (-39.9 to 5.1)	-4.0 (-23.5 to 1.9)	
Proteinuria				
No. of cases	65	1	1	
Age-, sex- and area-adjusted HR	1.0	1.6 (0.2-11.8)	2.4 (0.3-17.3)	0.34
Multivariable HR	1.0	1.3 (0.2-10.1)	1.9 (0.2-15.1)	0.51
PAF (%)	-	0.3 (-8.0 to 1.3)	0.7 (-4.5 to 1.4)	

(Cont. Supplemental Table 1)

	Low	Intermediate	High	*P* for trend
CHD				
Blood pressure				
No. of cases	22	11	6	
Age-, sex- and area-adjusted HR	1.0	1.2 (0.6-2.4)	1.2 (0.5-2.9)	0.68
Multivariable HR	1.0	1.1 (0.5-2.3)	0.8 (0.3-2.4)	0.77
PAF (%)	-	1.8 (-29.6 to 16.2)	-2.8 (-35.7 to 8.9)	
Serum glucose				
No. of cases	29	3	7	
Age-, sex- and area-adjusted HR	1.0	1.0 (0.3-3.3)	6.1 (2.6-14.0)	<0.001
Multivariable HR	1.0	0.9 (0.3-3.1)	4.5 (1.8-11.5)	0.008
PAF (%)	-	-0.8 (-21.8 to 5.2)	14.0 (7.9 to 16.4)	
LDL-C				
No. of cases	27	10	2	
Age-, sex- and area-adjusted HR	1.0	0.8 (0.4-1.6)	0.8 (0.2-3.3)	0.48
Multivariable HR	1.0	0.6 (0.3-1.2)	0.5 (0.1-2.1)	0.10
PAF (%)	-	-19.5 (-70.4 to 4.4)	-5.6 (-41.9 to 2.7)	
Proteinuria				
No. of cases	37	1	1	
Age-, sex- and area-adjusted HR	1.0	2.6 (0.4-19.2)	3.7 (0.5-28.0)	0.12
Multivariable HR	1.0	2.6 (0.3-20.6)	3.2 (0.4-26.7)	0.18
PAF (%)	-	1.6 (-5.5 to 2.4)	1.8 (-4.2 to 2.5)	

CHD, coronary heart disease; HR, hazard ratio; PAF, population-attributable fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol. Multivariable HRs were adjusted for age, sex, area, body mass index, smoking status, alcohol intake, family history of CVD, and the above-mentioned other conventional risk factors (blood pressure, serum glucose, LDL-C, high density lipoprotein cholesterol, triglyceride, and proteinuria).

Supplemental Table 2. Hazard ratios and population-attributable fractions (95% confidence intervals) of incident cardiovascular disease (CVD) according to each risk factor category among men and women who were collected fasting blood sample and without clinical treatment, stratified by overweight status

	Non-overweight (BMI < 25 kg/m^2)			Overweight (BMI ≥ 25 kg/m^2)		
	Low	Intermediate	High	Low	Intermediate	High
CVD						
Blood pressure						
Person-years	20295	6070	2859	4756	3093	1900
No. at risk	1375	437	203	322	207	134
No. of cases	37	23	12	12	8	12
Age-, sex- and area-adjusted HR	1.0	1.7 (1.0-2.9)	1.8 (0.9-3.4)	1.5 (0.8-2.9)	1.2 (0.6-2.6)	3.3 (1.7-6.3)
Multivariable HR	1.0	2.1 (1.2-3.5)	2.2 (1.1-4.4)	1.4 (0.7-2.8)	1.4 (0.6-3.0)	3.0 (1.5-6.3)
PAF (%)	-	11.3 (3.6 to 15.8)	6.4 (1.4 to 8.9)	3.6 (-4.0 to 7.4)	2.0 (-5.0 to 5.1)	7.7 (3.6 to 9.7)
Serum glucose						
Person-years	26871	1713	641	8428	906	415
No. at risk	1844	126	45	569	63	31
No. of cases	62	6	4	26	1	5
Age-, sex- and area-adjusted HR	1.0	1.0 (0.4-2.2)	2.1 (0.8-5.8)	1.4 (0.9-2.2)	0.4 (0.1-3.0)	4.7 (1.9-11.7)
Multivariable HR	1.0	0.9 (0.4-2.1)	2.0 (0.7-5.7)	1.2 (0.7-2.0)	0.2 (0.0-1.5)	3.1 (1.1-8.8)
PAF (%)	-	-0.8 (-10.0 to 3.0)	1.9 (-1.5 to 3.2)	4.1 (-9.1 to 12.3)	-4.0 (-37.5 to 0.3)	3.3 (0.4 to 4.3)
LDL-C						
Person-years	18588	8528	2108	5208	3612	930
No. at risk	1283	591	141	361	239	63
No. of cases	53	17	2	20	9	3
Age-, sex- and area-adjusted HR	1.0	0.7 (0.4-1.2)	0.4 (0.1-1.7)	1.4 (0.8-2.4)	0.9 (0.4-1.8)	1.4 (0.4-4.6)
Multivariable HR	1.0	0.6 (0.4-1.1)	0.3 (0.1-1.3)	1.1 (0.6-1.9)	0.6 (0.3-1.4)	1.0 (0.3-3.2)
PAF (%)	-	-9.3 (-28.6 to 1.8)	-4.1 (-23.4 to 0.5)	1.1 (-12.8 to 9.0)	-4.9 (-20.2 to 2.3)	-0.1 (-7.1 to 2.0)
Proteinuria						
Person-years	28919	197	108	9576	94	79
No. at risk	1990	16	9	650	7	6
No. of cases	70	1	1	30	1	1
Age-, sex- and area-adjusted HR	1.0	1.4 (0.2-10.5)	2.0 (0.3-14.9)	1.3 (0.9-2.1)	4.0 (0.6-28.9)	6.4 (0.9-47.0)
Multivariable HR	1.0	1.3 (0.2-9.8)	1.9 (0.2-14.5)	1.1 (0.7-1.8)	2.4 (0.3-19.9)	3.8 (0.5-31.1)
PAF (%)	-	0.2 (-4.6 to 0.9)	0.5 (-2.9 to 0.9)	2.5 (-13.5 to 12.4)	0.6 (-2.4 to 0.9)	0.7 (-1.1 to 0.9)
Stroke						
Blood pressure						
No. of cases	23	16	10	6	4	8
Age-, sex- and area-adjusted HR	1.0	1.9 (1.0-3.6)	2.4 (1.2-5.1)	1.2 (0.5-2.9)	1.0 (0.3-2.8)	3.4 (1.5-7.6)
Multivariable HR	1.0	2.1 (1.1-4.1)	2.9 (1.3-6.3)	1.3 (0.5-3.3)	1.2 (0.4-3.7)	4.1 (1.7-9.9)
PAF (%)	-	12.7 (2.3 to 18.1)	9.8 (3.7 to 12.6)	2.1 (-8.2 to 6.2)	1.0 (-9.0 to 4.3)	9.0 (4.8 to 10.7)
Serum glucose						
No. of cases	42	5	2	17	1	0
Age-, sex- and area-adjusted HR	1.0	1.3 (0.5-3.2)	1.7 (0.4-6.9)	1.3 (0.7-2.3)	0.6 (0.1-4.7)	-
Multivariable HR	1.0	1.2 (0.5-3.2)	2.0 (0.5-8.8)	1.3 (0.7-2.4)	0.3 (0.0-2.5)	-
PAF (%)	-	1.3 (-8.9 to 5.2)	1.5 (-3.4 to 2.6)	5.6 (-11.2 to 14.7)	-3.4 (-38.8 to 0.9)	-
LDL-C						
No. of cases	38	11	0	9	6	3
Age-, sex- and area-adjusted HR	1.0	0.6 (0.3-1.2)	-	0.9 (0.4-1.8)	0.8 (0.3-1.9)	1.8 (0.5-5.8)
Multivariable HR	1.0	0.7 (0.3-1.3)	-	0.8 (0.4-1.8)	0.7 (0.3-1.7)	1.5 (0.4-5.3)
PAF (%)	-	-8.6 (-33.8 to 4.0)	-	-3.5 (-24.2 to 5.8)	-4.2 (-23.7 to 3.7)	1.6 (-5.7 to 3.6)

(Cont. Supplemental Table 2)

	Non-overweight (BMI <25 kg/m^2)			Overweight (BMI ≥ 25 kg/m^2)		
	Low	Intermediate	High	Low	Intermediate	High
Proteinuria						
No. of cases	47	1	1	18	0	0
Age-, sex- and area-adjusted HR	1.0	2.3 (0.3-17.0)	3.3 (0.4-24.7)	1.2 (0.7-2.0)	-	-
Multivariable HR	1.0	1.8 (0.2-14.2)	2.7 (0.3-22.2)	1.1 (0.6-2.0)	-	-
PAF (%)	-	0.6 (-5.4 to 1.4)	0.9 (-3.0 to 1.4)	2.0 (-18.5 to 13.3)	-	-
CHD						
Blood pressure						
No. of cases	16	7	2	6	4	4
Age-, sex- and area-adjusted HR	1.0	1.2 (0.5-3.0)	0.7 (0.2-2.9)	1.7 (0.7-4.4)	1.4 (0.5-4.3)	2.4 (0.8-7.2)
Multivariable HR	1.0	1.3 (0.5-3.2)	0.7 (0.2-3.3)	1.4 (0.5-3.8)	1.2 (0.4-3.8)	1.3 (0.3-4.6)
PAF (%)	-	3.6 (-18.7 to 12.3)	-1.8 (-26.1 to 3.6)	4.7 (-12.7 to 11.3)	1.6 (-17.7 to 7.6)	2.1 (-19.4 to 8.0)
Serum glucose						
No. of cases	20	3	2	9	0	5
Age-, sex- and area-adjusted HR	1.0	1.5 (0.4-5.1)	2.9 (0.7-12.6)	1.4 (0.7-3.2)	-	13.7 (5.1-36.7)
Multivariable HR	1.0	1.5 (0.4-5.3)	2.4 (0.5-10.8)	1.2 (0.5-2.8)	-	10.6 (3.0-37.5)
PAF (%)	-	2.5 (-10.6 to 6.2)	3.0 (-4.3 to 4.7)	3.9 (-20.8 to 14.7)	-	11.6 (8.5 to 12.5)
LDL-C						
No. of cases	16	7	2	11	3	0
Age-, sex- and area-adjusted HR	1.0	1.0 (0.4-2.4)	1.4 (0.3-6.4)	2.5 (1.2-5.4)	1.0 (0.3-3.6)	-
Multivariable HR	1.0	0.7 (0.3-1.8)	0.8 (0.2-3.7)	1.7 (0.7-4.1)	0.6 (0.2-2.3)	-
PAF (%)	-	-7.0 (-43.9 to 7.9)	-1.1 (-22.9 to 3.8)	12.0 (-10.0 to 21.3)	-4.7 (-38.4 to 4.3)	-
Proteinuria						
No. of cases	25	0	0	12	1	1
Age-, sex- and area-adjusted HR	1.0	-	-	1.5 (0.7-3.0)	10.1 (1.4-75.2)	19.0 (2.5-146.4)
Multivariable HR	1.0	-	-	1.2 (0.5-2.5)	8.1 (0.9-74.0)	8.5 (0.8-89.7)
PAF (%)	-	-	-	4.1 (-26.1 to 18.3)	2.2 (-0.3 to 2.5)	2.3 (-0.6 to 2.5)

CHD, coronary heart disease; BMI, body mass index; HR, hazard ratio; PAF, population-attributable fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol.
Multivariable HRs were adjusted for age, sex, area, smoking status, alcohol intake, family history of CVD, and the above-mentioned other conventional risk factors (blood pressure, serum glucose, LDL-C, high density lipoprotein cholesterol, triglyceride, and proteinuria).