Table 3. Sex-specific HRs and 95% CIs for stage ≥3 CKD by BMI categories among diabetes-free and CVD risk factor-free at baseline

Sex and body mass index category (kg/m^2)	Number of subjects	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariable HR[c]	95% CI	*P* for trend
Diabetes[a]-free								
Men								
<18.5	1207	5426	19.5	**0.73**	**0.60, 0.90**	**0.80**	**0.65, 0.99**	
18.5–20.9	5352	26 978	19.4	**0.89**	**0.79, 0.99**	0.94	0.84, 1.05	
21.0–22.9	7247	38 202	19.9	1	(ref.)	1	(ref.)	
23.0–24.9	7255	37 952	23.1	**1.27**	**1.15, 1.40**	**1.21**	**1.09, 1.33**	<0.001
25.0–26.9	4601	23 495	23.0	**1.38**	**1.24, 1.55**	**1.26**	**1.12, 1.41**	
27.0–29.9	2227	11 013	22.2	**1.44**	**1.25, 1.67**	**1.24**	**1.07, 1.44**	
>30.0	359	1715	29.2	**2.02**	**1.52, 2.69**	**1.64**	**1.23, 2.19**	
Women								
<18.5	2492	12 512	19.4	**0.75**	**0.65, 0.86**	**0.80**	**0.70, 0.92**	
18.5–20.9	10 818	58 756	17.3	**0.86**	**0.79, 0.93**	**0.89**	**0.82, 0.96**	
21.0–22.9	15 336	85 182	19.8	1	(ref.)	1	(ref.)	
23.0–24.9	15 086	81 737	21.4	1.03	0.97, 1.11	1.00	0.93, 1.06	<0.001
25.0–26.9	10 024	53 502	24.4	**1.11**	**1.03, 1.19**	1.04	0.96, 1.11	
27.0–29.9	6182	31 475	27.2	**1.21**	**1.12, 1.32**	**1.09**	**1.00, 1.18**	
>30.0	1574	7272	33.7	**1.65**	**1.44, 1.89**	**1.41**	**1.23, 1.62**	
CVD risk factor[b]-free								
Men								
<18.5	501	2364	11.8	**0.63**	**0.42, 0.95**	**0.64**	**0.42, 0.96**	
18.5–20.9	1815	9989	12.0	0.83	0.65, 1.06	0.84	0.65, 1.08	
21.0–22.9	1945	10 918	12.4	1	(ref.)	1	(ref.)	
23.0–24.9	1528	8402	13.9	**1.29**	**1.01, 1.65**	**1.30**	**1.01, 1.67**	<0.001
25.0–26.9	757	4007	12.5	1.36	0.98, 1.88	1.30	0.93, 1.81	
27.0–29.9	232	1121	16.1	**1.85**	**1.13, 3.03**	**1.78**	**1.08, 2.93**	
>30.0	29	109	9.2	2.20	0.31, 15.75	1.94	0.27, 13.92	
Women								
<18.5	1304	6802	15.1	0.90	0.72, 1.12	0.92	0.74, 1.15	
18.5–20.9	5285	29 349	12.0	0.99	0.86, 1.14	1.01	0.87, 1.16	
21.0–22.9	6243	36 399	11.8	1	(ref.)	1	(ref.)	
23.0–24.9	4920	27 907	14.0	**1.17**	**1.02, 1.34**	**1.16**	**1.01, 1.33**	<0.001
25.0–26.9	2509	14 196	16.3	**1.27**	**1.08, 1.49**	**1.21**	**1.03, 1.42**	
27.0–29.9	1126	5989	19.2	**1.57**	**1.27, 1.92**	**1.47**	**1.2, 1.81**	
>30.0	222	1111	26.1	**2.15**	**1.47, 3.13**	**1.98**	**1.35, 2.89**	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio.
[a]Diabetes is defined as plasma glucose ≥6.1 mmol/L in a fasted state or ≥7.8 mmol/L in a non-fasted state, or being treated for diabetes mellitus.
[b]Cardiovascular disease risk factors are hypertension, dyslipidemia, and diabetes.
[c]Adjusted for age (years), systolic blood pressure (mm Hg), total cholesterol level (mmol/liter), high-density lipoprotein cholesterol level (mmol/liter), log-transformed triglyceride level (mmol/liter), proteinuria (yes or no), smoking status (never, ex-, current <20 cigarettes/day, or ≥20 cigarettes/day), and alcohol intake (never, sometimes, <56 g/day, or ≥56 g/day).

populations.[11,17,18] The Framingham Offspring Study, which included 2585 participants (mean age, 43 years) who were followed from 1978–2001 (mean follow-up, 18.5 years), showed a strong dose-response relationship between baseline BMI and risk of CKD (defined as eGFR using the MDRD Study equation: ≤64.25 mL/[min·1.73 m^2] in men and ≤59.25 mL/[min·1.73 m^2] in women).[11] The multivariable odds ratio of CKD was 1.23 (95% CI, 1.08–1.41) per one standard deviation of approximately 4 kg.[11] A Japanese community-based study, which followed 100 753 individuals (mean age, 49 years) for 17 years, revealed that a higher BMI at baseline was associated with an increased risk of end-stage renal disease in men but not women.[18] The multivariable-adjusted odds ratios of end-stage renal disease were 1.27 (95% CI, 1.21–1.45) in men and 0.95 (95% CI, 0.83–1.09) in women for each 2 kg/m^2 increment of BMI.[18] Although these authors did not examine the association between BMI and the risk of CKD among older adults, their results in middle-aged adults are consistent with our findings.

The association between obesity and stage ≥3 CKD may be mediated through multiple biological mechanisms, including hormonal factors, inflammation, oxidative stress, and endothelial dysfunction.[19,20] In obese individuals, the rennin-angiotensin-aldosterone system is commonly activated,[21] and it is a well-coordinated hormonal system that regulates adrenal, cardiovascular, and kidney function by controlling the fluid and electrolyte balance. Activation of this system leads to the development of hypertension via the production of angiotensin 2, which causes further damage to the kidneys.[22] Estrogen, a sex hormone that is secreted more in premenopausal women compared with men and post-menopausal women, decreases the expression of angiotensin

Table 4. Age and sex-specific HRs and 95% CIs for stage ≥3 CKD by BMI categories

Sex, age group, and BMI categories (kg/m^2)	Number of participants	Number of person-years	Incidence rates per 1000 person-years	Age-adjusted HR	95% CI	Multivariable HR[a]	95% CI	*P* for trend
Men								
Age 40–59 years								
<18.5	298	1373	2.9	0.44	0.16, 1.18	0.47	0.17, 1.28	
18.5–20.9	1948	10900	4.3	**0.63**	**0.45, 0.88**	**0.71**	**0.50, 0.99**	
21.0–22.9	3310	18194	6.7	1	(ref.)	1	(ref.)	
23.0–24.9	3762	20086	9.4	**1.41**	**1.12, 1.77**	1.22	0.97, 1.54	0.001
25.0–26.9	2676	14323	8.9	**1.34**	**1.05, 1.72**	1.10	0.85, 1.42	
27.0–29.9	1384	7130	10.9	**1.57**	**1.18, 2.09**	1.21	0.90, 1.63	
≥30.0	264	1241	16.9	**2.59**	**1.63, 4.11**	**1.83**	**1.14, 2.95**	
Age 60–79 years								
<18.5	1272	5688	24.3	**0.77**	**0.64, 0.92**	0.84	0.70, 1.01	
18.5–20.9	4769	22777	27.7	0.93	0.84, 1.03	0.99	0.89, 1.10	
21.0–22.9	5734	28828	28.3	1	(ref.)	1	(ref.)	
23.0–24.9	5335	26887	33.4	**1.25**	**1.13, 1.37**	**1.18**	**1.07, 1.30**	<0.001
25.0–26.9	3252	15847	35.5	**1.39**	**1.25, 1.55**	**1.26**	**1.13, 1.41**	
27.0–29.9	1515	6961	36.6	**1.46**	**1.27, 1.68**	**1.22**	**1.06, 1.41**	
≥30.0	219	1011	42.5	**1.83**	**1.34, 2.48**	**1.47**	**1.08, 2.01**	
Women								
Age 40–59 years								
<18.5	1209	6864	6.8	0.91	0.68, 1.23	0.98	0.72, 1.33	
18.5–20.9	6611	38770	6.7	0.91	0.78, 1.07	0.96	0.82, 1.12	
21.0–22.9	9324	56401	7.7	1	(ref.)	1	(ref.)	
23.0–24.9	8808	51514	8.4	1.04	0.91, 1.19	1.00	0.88, 1.15	0.291
25.0–26.9	5436	31685	9.2	1.10	0.95, 1.28	1.02	0.87, 1.18	
27.0–29.9	3219	17926	9.5	1.17	0.98, 1.39	1.02	0.85, 1.22	
≥30.0	928	4778	11.3	**1.46**	**1.10, 1.94**	1.19	0.90, 1.59	
Age 60–79 years								
<18.5	1637	7359	31.9	**0.75**	**0.65, 0.86**	**0.81**	**0.70, 0.93**	
18.5–20.9	5441	26910	33.9	**0.86**	**0.79, 0.93**	**0.89**	**0.82, 0.97**	
21.0–22.9	7822	38553	38.3	1	(ref.)	1	(ref.)	
23.0–24.9	8314	40906	39.1	1.04	0.97, 1.12	1.00	0.93, 1.07	<0.001
25.0–26.9	6123	29501	41.4	**1.09**	**1.01, 1.18**	1.02	0.95, 1.10	
27.0–29.9	4010	18422	45.8	**1.22**	**1.12, 1.33**	**1.10**	**1.00, 1.19**	
≥30.0	991	3982	62.3	**1.67**	**1.46, 1.90**	**1.44**	**1.26, 1.65**	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio.
[a]Adjusted for age (years), smoking status (never, ex-, current <20 cigarettes/day, or ≥20 cigarettes/day), alcohol intake (never, sometimes, <56 g/day, or ≥56 g/day), fasting status (yes or no), systolic blood pressure (mm Hg), antihypertensive medication use (yes or no), total cholesterol level (mmol/liter), high-density lipoprotein cholesterol level (mmol/liter), log-transformed triglyceride level (mmol/liter), lipid medication use (yes or no), blood glucose status (normal: <6.1 mmol/l during fasting or <7.8 mmol/l during nonfasting; border: 6.1–7.0 mmol/l during fasting or 7.8–11.1 mmol/l during nonfasting; hyperglycemic: 7.0 mmol/l during fasting or 11.1 mmol/l during nonfasting), diabetes medication use (yes or no), and proteinuria (yes or no).

type 1 receptors in the vasculature and kidneys[23] and reduces the expression and activity of angiotensin-converting enzymes.[24,25] These biological mechanisms may be underlying factors for the significant relationship between obesity and the development of stage ≥3 CKD among middle-aged women in our study.

The strength of our study is that stage ≥3 CKD was defined as an eGFR level <60 mL/min/1.73 m^2 reported at more than two successive annual surveys. Further, all of the blood samples were measured by the same laboratory, which was verified using a validated quality control system.[26] However, there are several limitations. First, we only examined generalized obesity and not abdominal obesity, because the measurements of central obesity were not available during the baseline examination. Second, potential residual confounders may not have been assessed, such as fat distribution, dietary lifestyle (ie protein and salt intake), and physical activity. Third, detailed information on use of medications such as statins and omega 3-fatty acids was not collected because of the nature of the community-based health checkup.

Obesity was associated with the risk of developing stage ≥3 CKD among men and older women. Compared with participants who had a normal BMI (21.0–22.9 kg/m^2), those with a BMI ≥30.0 kg/m^2 had a markedly high risk of developing stage ≥3 CKD. Weight management may be important for preventing CKD in obese men and women.

ONLINE ONLY MATERIAL

Abstract in Japanese.

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Conflicts of interest: None declared.

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Blood pressure, low-density lipoprotein cholesterol, and incidences of coronary artery disease and ischemic stroke in Japanese: the Suita study.
Tsukinoki R, Okamura T, Watanabe M, Kokubo Y, Higashiyama A, Nishimura K, Takegami M, Murakami Y, Okayama A, Miyamoto Y. Am J Hypertens. 2014 ;27(11):1362-9.

BACKGROUND: Blood pressure (BP) and low-density lipoprotein cholesterol (LDL-C) are risk factors for coronary artery disease (CAD) and ischemic stroke. However, the hazards of their coexistence are not fully understood in Asian populations. We investigated whether the relationship between BP and cardiovascular disease (CVD) outcomes are modified by LDL-C level in a Japanese population.
METHODS: Individuals aged 30-79 years (n = 5,151) were classified into 6 groups according to LDL-C levels (<140 and ≥140mg/dL or lipid medication) and BP levels (optimal BP, prehypertension, and hypertension; reference: low LDL-C and optimal BP). Hazard ratios (HRs) were calculated after adjusting for age, high-density lipoprotein cholesterol, diabetes, smoking status, and alcohol consumption. The effect modification of LDL-C on BP-CVD association was assessed using likelihood ratio tests.
RESULTS: There were 264 CAD and 215 ischemic stroke events during 13 years of follow-up. With low LDL-C, the HRs of prehypertension and hypertension for CAD were 2.01 and 4.71, respectively. Similar trends of HRs were observed with high LDL-C (optimal BP = 2.09, prehypertension = 3.45, hypertension = 5.94). However, the HRs for ischemic stroke did not differ between normal and high LDL-C levels at the same BP level. The apparent effect modification of LDL-C was not observed in the BP-CVD association in either CAD (P = 0.48) or ischemic stroke (P = 0.39).
CONCLUSIONS: The HRs for CAD in prehypertensive and hypertensive groups were higher than those in the optimal BP group at the same LDL-C levels in a Japanese population; however, there was no statistical effect modification of LDL-C on the BP-CAD association.

This study was also supported by a Health and Labour Sciences Research Grant (H23-Junkankitou (Seisyu)-Ippan-005) from the Ministry of Health, Labour and Welfare, Japan.

Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study. Nishimura K, Okamura T, Watanabe M, Nakai M, Takegami M, Higashiyama A, Kokubo Y, Okayama A, Miyamoto Y J Atheroscler Thromb. 2014;21(8):784-98.

AIM: The Framingham risk score (FRS) is one of the standard tools used to predict the incidence of coronary heart disease (CHD). No previous study has investigated its efficacy for a Japanese population cohort. The purpose of this study was to develop new coronary prediction algorithms for the Japanese population in the manner of the FRS, and to compare them with the original FRS.
METHODS: Our coronary prediction algorithms for Japanese were based on a large population-based cohort study (Suita study). The study population comprised 5,521 healthy Japanese. They were followed-up for 11.8 years on average, and 213 cases of CHD were observed. Multiple Cox proportional hazard model by stepwise selection was used to construct the prediction model.
RESULTS: Our coronary prediction algorithms for Japanese patients were based on a large populationbased cohort study (the Suita study). A multiple Cox proportional hazard model by stepwise selection was used to construct the prediction model. The C-statistics showed that the new model had better accuracy than the original and recalibrated Framingham scores. The net reclassification improvement (NRI) by the Suita score with the inclusion of CKD was 41.2% ($P < 0.001$) compared with the original FRS. The recalibration of the FRS slightly improved the efficiency of the prediction, but it was still worse than the Suita score with the CKD model. The calibration analysis suggested that the original FRS and the recalibrated FRS overestimated the risk of CHD in the Japanese population. The Suita score with CKD more accurately predicted the risk of CHD.
CONCLUSION: The FRS and recalibrated FRS overestimated the 10-year risk of CHD for the Japanese population. A predictive score including CKD as a coronary risk factor for the Japanese population was more accurate for predicting CHD than the original Framingham risk scores in terms of the C-statics and NRI.
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Non-high-density lipoprotein cholesterol and the development of coronary heart disease and stroke subtypes in a general Japanese population: The Hisayama Study

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ABSTRACT

Background and purpose: It has not been fully determined whether non-high-density lipoprotein cholesterol (non-HDLC) levels are involved in vascular events, especially stroke, in general Asian populations. We evaluated the association between non-HDLC levels and the risk of type-specific cardiovascular disease in a prospective cohort study in Japan.

Methods: A total of 2452 community-dwelling Japanese subjects aged ≥40 years were followed prospectively for 24 years.

Results: The age- and sex-adjusted incidence of coronary heart diseases (CHD) significantly increased with elevating non-HDLC levels (P for trend < 0.001), but no such association was observed for ischemic and hemorrhagic strokes. With regard to ischemic stroke subtypes, the age- and sex-adjusted incidence of lacunar infarction significantly increased with elevating non-HDLC levels (P for trend < 0.01), and such tendency was seen for atherothrombotic infarction (P for trend = 0.098), while a significant inverse association was observed for cardioembolic infarction (P for trend = 0.007). After adjustment for confounders, namely, age, sex, diabetes, body mass index, systolic blood pressure, electrocardiogram abnormalities, current drinking, current smoking, and regular exercise, the associations remained significant for CHD [adjusted hazard ratio (HR) for a 1 standard deviation of non-HDLC concentrations = 1.17, 95% confidence interval (CI) = 1.02 to 1.35], atherothrombotic infarction (adjusted HR = 1.39, 95% CI = 1.09 to 1.79), and cardioembolic infarction (adjusted HR = 0.64, 95% CI = 0.47 to 0.85).

Conclusions: Our findings suggest that elevated non-HDLC levels are a significant risk factor for the development of atherothrombotic infarction as well as CHD but reduce the risk of cardioembolic infarction in the general Japanese population.

Numerous studies have demonstrated that increased levels of low-density lipoprotein cholesterol (LDLC) are causally related to an increased risk of cardiovascular disease [1]. Aggressive LDLC lowering has therefore been the main strategy of lipid therapy. Even after achieving target LDLC levels, however, a significant number of subjects continue to have cardiovascular events. Thus, the residual risk of cardiovascular events in lipid management should be considered and identified in clinical settings. In the third report of the US National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATPIII) [2], high non-high-density lipoprotein cholesterol (non-HDLC) levels were introduced as a secondary target for the prevention of coronary heart disease (CHD). Prior prospective studies have found a positive association between non-HDLC levels and the risk of CHD [1,3,4], but it has not been fully determined whether non-HDLC levels are involved in vascular events in general Asian populations, who have lower adiposity and insulin resistance than Western populations. In addition, several prospective studies have investigated the association between non-HDLC levels and the risk of stroke, and the results differed among the studies [5–7].

The purpose of this prospective study of a general Japanese population was to evaluate the association between non-HDLC

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Original Article

A Low Ankle Brachial Index is Associated with an Increased Risk of Cardiovascular Disease: The Hisayama Study

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Aim: Peripheral artery disease (PAD), defined as a decreased ankle brachial index (ABI), is a risk factor for cardiovascular disease; however, few studies have assessed the relationship between a low ABI and cardiovascular risks in Asian populations. We herein examined the relationship between the ABI and the development of cardiovascular disease in a Japanese community.
Methods: A total of 2,954 community-dwelling Japanese individuals without prior cardiovascular disease ≥ 40 years of age were followed up for an average of 7.1 years. The subjects' ABIs were categorized into the three groups: low (≤ 0.90), borderline (0.91-0.99) and normal (1.00-1.40). We estimated the relationship between the ABI and cardiovascular risk using a Cox proportional hazards model.
Results: During the follow-up period, 134 subjects experienced cardiovascular events. The incidence of cardiovascular disease across the ABI values was significantly different ($p<0.001$). After adjusting for confounding factors, namely age, sex, systolic blood pressure, use of anti-hypertensive drugs, diabetes, total cholesterol, high-density lipoprotein cholesterol, obesity, smoking, alcohol intake and regular exercise, individuals with a low ABI were at 2.40-fold (95% confidence interval [CI] 1.14-5.06) greater risk of cardiovascular disease and 4.13-fold (95% CI 1.62-10.55) greater risk of coronary heart disease.
Conclusions: Our findings suggest that individuals with an ABI of ≤ 0.90 have an increased risk of cardiovascular events, independent from traditional risk factors, in the general Japanese population.

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Key words: Peripheral artery disease, Ankle brachial index, Cardiovascular disease, Prospective study, Epidemiology

Introduction

Peripheral artery disease (PAD) of the lower extremities is an atherosclerotic disease that can cause intermittent claudication, limb ischemia, gangrene, amputations and subsequent decrements in the patient's functional capacity and quality of life[1,2]. In addition, the presence of PAD is an indicator of systemic atherosclerosis in other vascular territories, such as the coronary, carotid and cerebrovascular arteries[3]. Some epidemiological evidence suggests that individuals with PAD are at an increased risk of cardiovascular mortality and morbidity, such as that involving coronary heart disease and brain infarction[4-9]. The manifestations of PAD are thus attended by significant personal, social and economic burdens, and PAD is increasingly being recognized as a health problem

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worldwide.

Screening to identify individuals with asymptomatic PAD is important, not only for preventing complications directly related to PAD, but also inhibiting the development of cardiovascular disease (CVD). However, the findings of clinical examinations (e.g., skin color and temperature, peripheral pulse and bruits) have poor sensitivity for the detection of asymptomatic PAD[10]. The ankle brachial index (ABI), which is calculated as the ratio of the ankle systolic blood pressure (SBP) to the brachial SBP, is a simple, noninvasive and relatively cost-effective measurement for assessing individuals with asymptomatic PAD[11].

Several epidemiological studies have demonstrated that a lower ABI is associated with a higher cardiovascular risk[4-9]. Meta-analyses of population-based cohort studies conducted in Western countries have also suggested that individuals with an ABI below 0.90 have a significantly greater risk of coronary heart disease, stroke and cardiovascular death[12, 13]. Recent guidelines from the European Society of Cardiology, European Society of Hypertension, American College of Cardiology Foundation (ACC) and American Heart Association (AHA) recommend estimating the ABI to detect and manage asymptomatic PAD[14-16]. However, the relationship between the ABI and the incidence of CVD has not been fully addressed in general Asian populations. It is important to determine whether the cut-off values for the ABI used in epidemiological studies conducted in Western populations are applicable to Asian populations. We herein present the findings of a prospective cohort study that investigated the relationship between the ABI and the incidence of CVD in a general Japanese population.

Methods

Study Population

The Hisayama Study is an ongoing prospective cohort study for CVD and its risk factors in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. The population of the town is approximately 8,000, and full community surveys of the residents have been repeated since 1961[17]. In 2002 and 2003, a screening survey for the present study was performed. The detailed description of this survey has been published previously[18]. Briefly, a total of 3,328 residents 40 years of age or older (77.6% of the total population of this age group) participated in the examination and underwent a comprehensive assessment. We excluded 30 subjects who did not consent to participate in the study, 190 subjects who had a medical history of CVD and 152 subjects with no data for the ABI. Two subjects with an ABI of >1.40 who were considered to have incompressible calcified arteries in the legs[19] were also excluded because the number of subjects was too small to perform a reliable risk estimation. Finally, the remaining 2,954 participants (1,262 men and 1,692 women) were enrolled.

Follow-Up

The subjects were followed up prospectively from the date of undergoing a comprehensive assessment until November 2009 using annual health examinations. The patient's health status was checked yearly by mail or telephone for any subjects who did not undergo the annual examination in a given year or who moved out of the town. A daily monitoring system was also established among the study team, local physicians and the staff of the health and welfare office in the town. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University.

ABI Measurement

The ABI was measured with the subject in the supine position after at least five minutes of rest using an automatic oscillometric apparatus (BP-203PRE II form PWV/ABI; Omron Healthcare, Kyoto, Japan). Four oscillometric cuffs were wrapped on both brachia and ankles. The cuffs were connected to a central unit that contained four pressure control pumps and four pressure sensors to automatically determine the blood pressure on the four limbs. The ABI was defined as the ankle SBP/brachial SBP ratio, for which the higher value of the brachial SBP between the right and left arms was used. Two readings of the ABI were measured as the same time on the right side and left side, and the lower value was used in the present study. We categorized the ABIs into three groups: low (≤ 0.90), borderline (0.91-0.99) and normal (1.00-1.40), according to the guidelines of the ACC Foundation and AHA[16].

Risk Factor Measurement

Self-administered questionnaires concerning the subject's current use of anti-hypertensive agents, insulin and oral glucose-lowering agents, as well as smoking habits and alcohol intake were checked by trained interviewers at the time of screening. These variables were classified as being either habitual or not. The subjects engaging in sports or other forms of exertion ≥ 3 times a week during their leisure time made up a regular exercise group. Blood pressure was measured three times using an automated sphygmomanometer

with the subject in the sitting position after at least five minutes of rest. The mean of three readings was used in this study. Hypertension was defined as a blood pressure of ≥ 140/90 mmHg and/or the current use of anti-hypertensive agents. The plasma glucose levels were measured according to the glucose oxidase method. Diabetes was defined as a fasting plasma glucose level of ≥ 7.0 mmol/L (126 mg/dL), two-hour post-loaded or casual glucose level of ≥ 11.1 mmol/L (200 mg/dL) and/or the current use of insulin or oral glucose-lowering agents. The serum total and high-density lipoprotein (HDL) cholesterol concentrations were determined enzymatically. Body height and weight were measured with the subject in light clothing without shoes, and the body mass index (BMI) was calculated as body weight/body height^2 (kg/m^2). Obesity was defined as a BMI of ≥ 25.0 kg/m^2. All clinical examinations and blood tests were conducted on the same day as the ABI measurements.

Definition of Cardiovascular Disease

The main outcomes of this study were first-ever events of CVD and its subtypes (coronary heart disease, ischemic stroke and hemorrhagic stroke). Coronary heart disease was defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within one hour after the onset of acute illness or the use of coronary interventions (coronary artery bypass surgery and angioplasty). Acute myocardial infarction was diagnosed when a subject met at least two of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain, (2) abnormally high levels of cardiac enzymes confirmed more than twice, (3) evolving diagnostic electrocardiographic changes and (4) morphological changes, including local asynergy of the cardiac wall motion on electrocardiography, persistent perfusion defects on cardiac scintigraphy or myocardial necrosis and/or the presence of scars measuring 1 cm or longer accompanied by coronary atherosclerosis at autopsy.

Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal changes in cardiac enzymes. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficits that continued for >24 hours and subclassified as either ischemic or hemorrhagic. All cardiovascular events were assessed based on the findings of a physical examination, review of all available clinical data, including medical records and brain imaging, and an autopsy by a panel of study members who remained blind to the information of the ABI values of the subjects.

Statistical Analysis

We analyzed the linear trends in the mean values and frequencies of the risk factors across the ABI groups using a linear regression analysis and logistic regression analysis, respectively. The event-free survival rates for CVD based on the ABI group were calculated according to the Kaplan-Meier method and compared using a log-rank test. We calculated the incidence of CVD using the person-year method. The hazard ratios (HRs) with 95% confidential intervals (CIs) of cardiovascular events according to the ABI were estimated using a Cox proportional hazards model. The SAS software package (SAS Institute, Cary, NC) was used to perform all statistical analyses. Two-sided p values of <0.05 were considered to be significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from all participants.

Results

The baseline characteristics of the study population according to the ABI are shown in **Table 1**. The prevalence of low, borderline and normal ABI values were 1.4% ($n=40$), 7.3% ($n=216$) and 91.3% ($n=2,698$), respectively. The subjects with a low ABI were significantly older than those with borderline or normal ABI values. The mean SBP and frequency of diabetes were significantly increased among the subjects with a low ABI.

During the average 7.1-year follow-up period, 134 subjects experienced cardiovascular events, including 85 stroke events and 54 coronary heart disease events. The event-free survival rates for CVD according to the ABI are shown in **Fig. 1A**. The cardiovascular event-free survival rates across the ABI values were significantly different (log-rank $p<0.001$). The subjects with a low ABI had a 5.41-fold (95% CI: 2.64-11.08) higher risk of cardiovascular events compared to those with a normal ABI, whereas there was no evidence of any differences between the subjects with borderline and normal ABI values ($p=0.51$) (**Table 2**). This relationship remained substantially unchanged after adjusting for age and sex (HR 2.90 [95% CI: 1.39-6.05]) as well as potential confounding factors, namely, age, sex, systolic blood pressure, anti-hypertensive agents, diabetes, serum total cholesterol, serum HDL cholesterol, obesity, smoking habits, alcohol intake and regular exercise (HR 2.40 [95% CI: 1.14-

Table 1. Baseline characteristics of the study population according to the ABI (ankle brachial index)

Variables	ABI level			*P* for trend
	Normal (1.00-1.40) *n* = 2,698	Borderline (0.91-0.99) *n* = 216	Low (≤ 0.90) *n* = 40	
Age, years	60 (11)	59 (14)	69 (14)	<0.001
Male, %	43.4	34.7	42.5	0.07
Systolic blood pressure, mmHg	131.5 (20.3)	128.8 (24.1)	145.1 (27.9)	<0.001
Diastolic blood pressure, mmHg	78.8 (11.6)	76.9 (13.4)	78.9 (16.2)	0.08
Anti-hypertensive agents, %	21.4	19.4	35.0	0.43
Hypertension, %	41.5	36.1	62.5	0.59
Diabetes, %	16.3	21.8	37.5	<0.001
Serum total cholesterol, mmol/L	5.28 (0.91)	5.43 (0.97)	5.16 (0.86)	0.05
Serum HDL cholesterol, mmol/L	1.63 (0.42)	1.59 (0.42)	1.50 (0.39)	0.06
Body mass index, kg/m^2	23.2 (3.3)	23.1 (4.0)	22.3 (2.6)	0.19
Obesity, %	27.0	27.3	15.0	0.33
Alcohol intake, %	45.6	37.0	47.5	0.48
Smoking habit, %	22.9	22.2	17.5	0.11
Regular exercise, %	10.8	9.3	12.5	0.80

ABI, ankle brachial index; HDL, high-density lipoprotein.
The values are presented as the mean (standard deviation) or percentage.

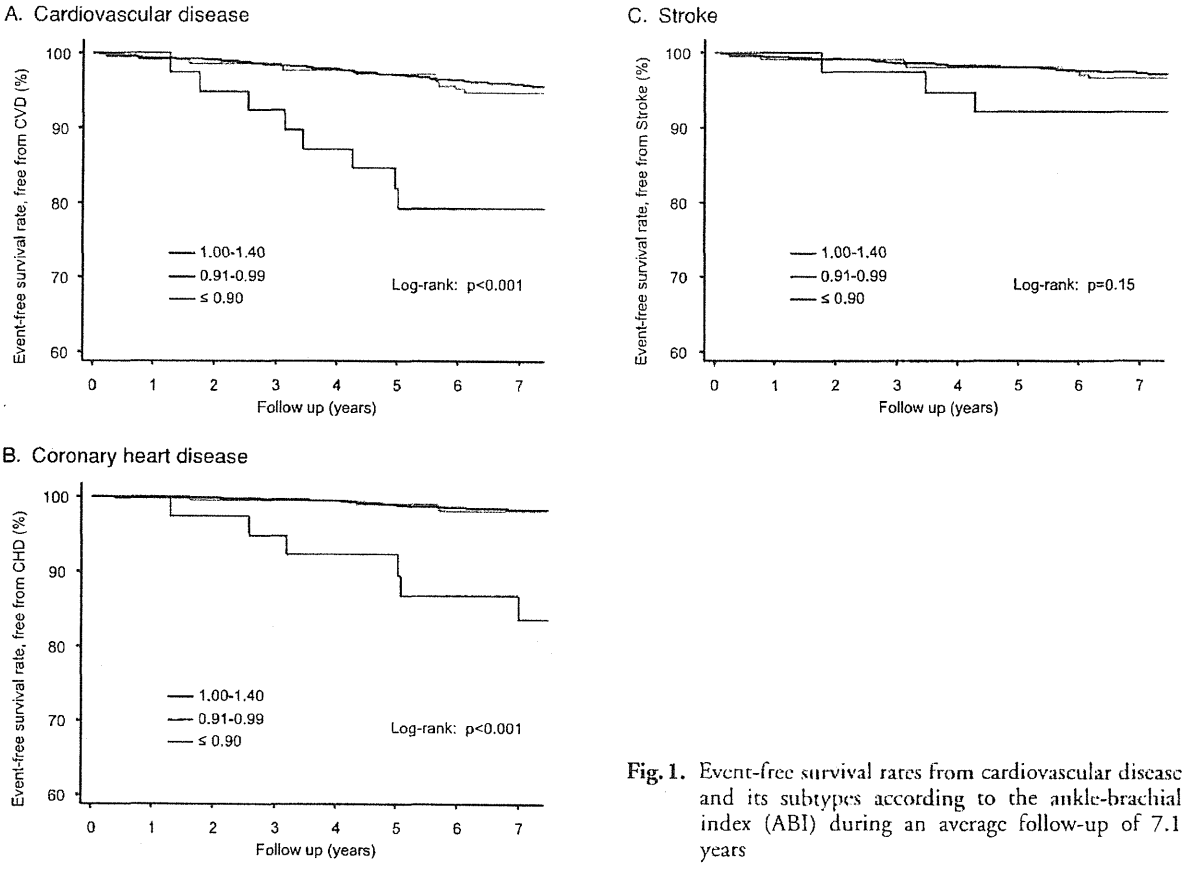

Fig. 1. Event-free survival rates from cardiovascular disease and its subtypes according to the ankle-brachial index (ABI) during an average follow-up of 7.1 years

Table 2. Relationships between ankle brachial index (ABI) and the development of cardiovascular disease, stroke and coronary heart disease during the 7.1-year average follow-up period

ABI level	Median of ABI	No. of events	Incidence[a] (/10³ PYs)	Unadjusted			Age- and sex-adjusted			Multivariable-adjusted[b]		
				HR (95%CI)	*p*	*p* for trend	HR (95%CI)	*p*	*p* for trend	HR (95%CI)	*p*	*p* for trend
Cardiovascular disease												
Normal (1.00-1.40)	1.10	115	6.1	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	11	7.6	1.23 (0.66-2.29)	0.51	<0.001	1.27 (0.68-2.36)	0.45	0.009	1.09 (0.58-2.05)	0.78	0.054
Low (≤ 0.90)	0.81	8	32.8	5.41 (2.64-11.08)	<0.001		2.90 (1.39-6.05)	0.005		2.40 (1.14-5.06)	0.02	
Coronary heart disease												
Normal (1.00-1.40)	1.10	44	2.3	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	4	2.7	1.17 (0.42-3.24)	0.77	<0.001	1.24 (0.45-3.47)	0.68	0.001	0.95 (0.34-2.70)	0.93	0.018
Low (≤ 0.90)	0.81	6	23.7	10.50 (4.47-24.64)	<0.001		5.34 (2.20-12.97)	<0.001		4.13 (1.62-10.55)	0.003	
Stroke												
Normal (1.00-1.40)	1.10	75	4.0	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	7	4.7	1.21 (0.56-2.62)	0.63	0.12	1.23 (0.57-2.67)	0.60	0.37	1.11 (0.50-2.42)	0.80	0.68
Low (≤ 0.90)	0.81	3	11.8	2.96 (0.93-9.38)	0.07		1.60 (0.49-5.16)	0.43		1.23 (0.38-4.02)	0.73	
Ischemic stroke												
Normal (1.00-1.40)	1.10	46	2.4	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	6	4.0	1.69 (0.72-3.97)	0.22	0.33	1.70 (0.73-3.99)	0.22	0.07	1.48 (0.62-3.51)	0.38	0.16
Low (≤ 0.90)	0.81	3	11.8	4.84 (1.50-15.55)	0.008		2.48 (0.75-8.23)	0.14		2.07 (0.62-6.93)	0.24	
Hemorrhagic stroke												
Normal (1.00-1.40)	1.10	29	1.52	1.00 (reference)			1.00 (reference)			NA		
Borderline (0.91-0.99)	0.97	1	0.58[c]	0.38(0.05-2.77)	0.34[c]	NA	0.35 (0.05-2.60)	0.31[c]	NA	NA		
Low (≤ 0.90)	0.81	0										

PYs, person-years; HR, hazard ratio; CI, confidence interval; NA, not analyzed.
[a]Values were unadjusted.
[b]The risk estimates were adjusted for age, sex, systolic blood pressure, anti-hypertensive agents, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, obesity, smoking habits, alcohol intake and regular exercise.
[c]The borderline and low groups were combined.

5.06]).

With regard to the subtype of CVD, the event-free survival rate for coronary heart disease was significantly different across the ABI groups (log-rank $p<0.001$), whereas that for stroke was not (log-rank $p=0.15$) (**Fig. 1B, C**). The multivariable-adjusted risk of coronary heart disease was significantly increased (by 4.13-fold; 95% CI: 1.62-10.55) in the subjects with a low ABI compared to that observed in the subjects with a normal ABI, while there was no evidence of a significant relationship between the ABI values and the risk of stroke. Among the stroke subtypes, however, the univariate analysis revealed that those with a low ABI were at an increased risk of ischemic stroke (HR 4.84; 95% CI: 1.50-15.55), although the significance of the relationship disappeared after adjusting for the above-mentioned confounding factors. No clear relationships between the ABI values and hemorrhagic stroke were observed when the borderline and low ABI groups were combined, as the number of events was zero in the low ABI group.

Discussion

The present results clearly demonstrated that an ABI of 0.90 or lower is significantly associated with an increased risk of cardiovascular events. This relationship remained significant after adjusting for potential confounding factors. To the best of our knowledge, this is the first study to prospectively investigate the relationship between the ABI and cardiovascular events in a community-based cohort study of a general Asian population.

The ABI has been investigated as a risk factor in several population-based cohort studies, primarily in North America and Europe[4-8]. Almost all of these studies found that an ABI of ≤ 0.90 is significantly associated with an increased risk of total mortality[4-6], cardiovascular mortality[4-6] and incident coronary heart disease[4, 7]. The ABI Collaboration, an individ-

ual-based meta-analysis of 16 community-dwelling cohorts conducted in Western countries, clearly demonstrated that a lower ABI (≤ 0.90) approximately doubles the risk of total mortality, cardiovascular mortality and major coronary events compared to an ABI of 1.11-1.20, independent of the Framingham risk score[13].

With regard to Asian populations, a significant relationship between the ABI and cardiovascular risks has been found in several hospital-based prospective studies conducted among patients with risk factors such as metabolic syndrome, ischemic heart disease and chronic kidney disease[20-22]. For example, the China ABI Cohort Study, a hospital-based study of 3,210 Chinese patients with two or more cardiovascular risk factors, showed that the multivariable-adjusted risk of cardiovascular mortality increased significantly (by 2.0 times) in the subjects with an ABI below 0.90 compared to that observed in the subjects with an ABI above 0.90[20]. However, limited studies have addressed this issue in the general Asian population. Our findings suggest that an ABI of ≤ 0.90 is an independent risk factor for the incidence of CVD in a community-based Asian population.

In the ABI Collaboration[13], subjects with an ABI from 0.91 to 1.10 and those with a high ABI (> 1.40), which may be related to poor arterial compressibility resulting from stiffness and calcification, were at slightly increased absolute risks of total mortality, cardiovascular mortality and major coronary events. These results suggest that subjects with an ABI of 0.91 to 1.10 or greater than 1.40 may have slightly higher risks of these outcomes than those with a normal ABI, although the widely accepted high-risk cut-off value of 0.90 is reasonable[11]. Based on these findings, the ACC/AHA practice guidelines define ABI categories as low ABI (severe and mild to moderate), borderline ABI, normal ABI and high ABI[16]. In the present study, however, we did not find that borderline ABI was related to the risk of cardiovascular events, likely due to the limited statistical power. Likewise, we were unable to address the relationship between an ABI of >1.40 and cardiovascular risk, because only two subjects had an ABI of >1.40. The relationship between a borderline or high ABI and the risk of cardiovascular events should be addressed in large samples of Asian populations.

When we investigated the subtypes of cardiovascular events, we observed that, after adjusting for confounding factors, a low ABI was significantly related to an increased risk of coronary heart disease events, but not the risk of stroke. Several epidemiological studies conducted in Western countries have shown a low ABI to be a significant risk factor for stroke events[5, 19, 23]. The Atherosclerosis Risk in Communities Study also found that a low ABI is associated with a higher incidence of ischemic stroke after adjusting for age, race, sex and center; however, this significant relationship disappeared after adjusting for other confounding factors[8]. These results are similar to the present findings, although the relationship in the present study did not reach a level of statistical significance and was largely attenuated compared to that observed in previous studies, possibly because lacunar stroke is the dominant type of ischemic stroke in Japan, whereas large-artery atherothrombotic brain infarction is more prevalent in Western countries[24]. Given the etiology of each stroke subtype, the risk of atherothrombotic brain infarction, as well as coronary heart disease, may be expected to increase in subjects with a low ABI because PAD is an atherosclerotic disease of the large arteries. Atherosclerotic changes in cerebral arteries, as well as coronary arteries, may already be advanced among subjects with PAD defined as an ABI of ≤ 0.9, as PAD is attributable to atherosclerotic remodeling of lower extremity peripheral arteries. The risk of atherothrombotic brain infraction may thus be expected to increase in subjects with a low ABI. Large-scale studies are therefore required to elucidate the relationship between a low ABI and the risk of stroke subtypes.

Several limitations of the present study should be noted. First, the generalizability of our findings may be limited, as 152 subjects without available ABI data were excluded from the study. Compared to the subjects who were included, the excluded subjects were older (mean age: 81 years for the excluded subjects vs. 60 years for the included subjects) and more likely to have hypertension (73.7% vs. 43.0%) or a history of cardiovascular events (21.5% vs. 4.5%). This bias would lead to underestimation of the relationship between the ABI and cardiovascular risks. Second, only a single ABI measurement was obtained at the baseline examination. This may have caused the misclassification of subjects into the wrong ABI group. Such misclassification, if present, would weaken the relationship found in this study, biasing the results toward the null hypothesis. Third, we were unable to obtain information regarding the subjects' medical treatment during the follow-up period. The lack of this information may have reduced the accuracy of our findings to some extent. In addition, we used an automatic device to measure blood pressure in the four limbs and the oscillometric method instead of the standard doppler method. The standard doppler method is recommended in the ACC/AHA guidelines

because some devices using oscillometric blood pressure have been found to overestimate the actual ankle blood pressure, especially in subjects with a very low ankle blood pressure[25]. However, the precision of our device has been validated in both Japanese and European populations[26, 27], and thus, although this limitation may have reduced the precision of the ABI values to some extent, it is unlikely to have altered the findings substantially.

In conclusion, the present findings indicate that, in a general Japanese population, the subjects with an ABI of ≤ 0.90 had an increased risk of cardiovascular events, independent of traditional cardiovascular risk factors. Because the ABI is a noninvasive and user-friendly method for estimating the extent of systemic atherosclerotic disease, it may be applied more broadly in general practice to identify individuals at a high risk of developing CVD.

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Disclosures

I. Kojima is a former employee of Omron Healthcare Co., Ltd. There are no other conflicts of interest to declare.

Conflicts of Interest

The first author, Iwao Kojima is a former employee for Omron Healthcare, Co., Ltd., which produces the device used to measure the ABI. All remaining authors report no conflicts of interest.

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Midlife and late-life handgrip strength and risk of cause-specific death in a general Japanese population: the Hisayama Study

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ABSTRACT

Background Decreased handgrip strength has been reported to be a risk factor for all-cause death among the elderly. However, it is unclear whether handgrip strength measured in midlife is associated with risk of all-cause and cause-specific death in the general population.

Methods We followed, prospectively, a total of 2527 community-dwelling Japanese (1064 men and 1463 women) aged ≥40 years for 19 years. Participants were divided into three groups according to the age-specific and sex-specific tertiles of handgrip strength (T1, lowest; T3, highest).

Results During the follow-up period, 783 participants died, of whom 235 died of cardiovascular disease, 249 of cancer, 154 of respiratory disease and 145 of other causes. In the middle-aged group (40–64 years), multivariable-adjusted HRs (95% CIs) for all-cause death were 0.75 (0.56 to 0.99) in T2 and 0.49 (0.35 to 0.68) in T3 compared with T1 as a reference. Corresponding HRs (95% CI) in the elderly group (≥65 years) were 0.50 (0.40 to 0.62) and 0.41 (0.32 to 0.51), respectively. As regards the cause of death, higher levels of handgrip strength were significantly associated with decreased risks of cardiovascular death, respiratory death and death from other causes, but not of cancer, in the middle-aged and the elderly.

Conclusions Our findings suggest that handgrip strength levels in midlife and late life are inversely associated with the risks of all-cause and non-cancer death in the general Japanese population.

INTRODUCTION

Handgrip strength, one of various indicators which reflect whole-body muscle strength, has been measured in many epidemiologic studies because it is a simple, easy and inexpensive way to evaluate muscle strength. Some population-based prospective studies have shown that handgrip strength levels were inversely associated with increased risks of all-cause death[1–13] and cardiovascular death.[1 2] Similarly, in a meta-analysis of observational studies, higher handgrip strength was associated with a lower risk of all-cause mortality.[14] In general, handgrip strength reaches its peak in the decade between the ages of 30 and 39 years, and then decreases with age after the age of 40 years.[15 16] Therefore, the association of handgrip strength levels with mortality risk may differ between midlife and late life. However, most previous studies have reported the influence of late-life handgrip strength in an elderly population (approx ≥65 years),[2–8 17] and only a small number of studies have examined the association between midlife handgrip strength and mortality risk.[1 10–13 18] Moreover, the influence of midlife handgrip strength on the risk of cause-specific death is still unclear.

The aims of the present study were to investigate the association of levels of handgrip strength with the risks of all-cause and cause-specific death in a general Japanese population, and to compare the influence of handgrip strength in the middle-aged (40–64 years old) and in the elderly (≥65 years old).

METHODS

Study participants

A population-based prospective study of cardiovascular and malignant diseases has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area of Kyushu Island in southern Japan. In 1988, a baseline examination for the present study was performed in this town. A total of 2742 residents aged ≥40 years (80.9% of the total population in this age group) participated in the examination. Excluded from the study were 168 individuals with a history of stroke, coronary heart disease, or cancer; 45 individuals in whom handgrip strength was not measured; and two individuals who died before follow-up; the remaining 2527 participating individuals (1064 men and 1463 women) were enrolled in the present study.

Baseline examination

At baseline examination, handgrip strength was measured using the Smedley Hand Dynamometer (MIS, Tokyo, Japan) according to instructions provided by a public health nurse. The width of the handle was adjusted such that the second phalanx was against the inner stirrup. The participants were encouraged to exert maximal handgrip strength. Two trials were allowed for each hand alternately, and the maximum value among four measurements was used for the analyses.

Each participant completed a self-administrated questionnaire covering medical history, treatments for hypertension and diabetes, smoking status, alcohol intake and leisure-time physical activity. Smoking status was classified into never smokers, former smokers, current light smokers (<20 cigarettes/day), and current heavy smokers (≥20 cigarettes/day). Alcohol intake was categorised into never drinkers, former drinkers, current light

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Trends in the prevalence of type 2 diabetes and prediabetes in community-dwelling Japanese subjects: The Hisayama Study

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ABSTRACT

Aims/Introduction: We examined secular trends in the prevalence of type 2 diabetes and prediabetes in community-dwelling Japanese subjects.

Materials and Methods: A total of 2,490 subjects in 1988 and 2,852 subjects in 2002 aged 40–79 years underwent a 75-g oral glucose tolerance test, and their glucose tolerance status was defined by the 1998 World Health Organization criteria.

Results: The age-adjusted prevalence of type 2 diabetes increased significantly from 1988 to 2002 in men (14.6% in 1988 to 20.8% in 2002, $P < 0.001$) and women (9.1% in 1988 to 11.2% in 2002, $P = 0.002$). A significant rise in the age-adjusted prevalence of prediabetes was also observed in both sexes (26.2% in 1988 to 35.3% in 2002, $P < 0.001$ for men; 22.5% in 1988 to 25.1% in 2002, $P = 0.04$ for women). In age-stratified analysis, the prevalence of type 2 diabetes increased markedly over time in men aged 60–69 and 70–79 years (both $P < 0.001$) and women aged 70–79 years ($P = 0.02$). The prevalence of overall and central obesity increased significantly in men aged 60–69 and 70–79 years, and women aged 70–79 years from 1988 to 2002, whereas the frequency of regular exercise decreased significantly in men aged 70–79 years between the surveys.

Conclusions: Our findings suggest that the prevalence of type 2 diabetes and prediabetes increased significantly in both sexes from the 1980s to the 2000s in a general Japanese population, and that the increasing prevalence of obesity and the decline in physical activity exerted an influence on this rising trend.

INTRODUCTION

The number of individuals with type 2 diabetes has been rapidly growing worldwide, especially in Asia, probably owing to economic development, population growth, aging and a Westernized lifestyle[1,2]. The burden of type 2 diabetes and its complications, including macro- and microvascular diseases, are increasingly recognized as a global health priority. Reliable estimates of secular trends in the prevalence of type 2 diabetes are required to develop effective strategies for prevention and management of type 2 diabetes. Several epidemiological studies have examined trends in the prevalence of type 2 diabetes and prediabetes, which were defined by a 75-g oral glucose tolerance test (OGTT) in Asian populations[3–6], as well as in Western populations[7,8], but there are no reliable data on this issue in Japan, where the number of patients with type 2 diabetes has increased steeply[9,10]. Meanwhile, some epidemiological studies in Western populations have shown that the rise in the prevalence of type 2 diabetes was mainly driven by increasing levels of obesity[7,11,12]. In the general Asian community, however, there are limited data assessing factors that contribute to the trends in the prevalence of type 2 diabetes[13,14].

The purpose of the present study was to investigate secular trends in the prevalence of type 2 diabetes and prediabetes, defined by the OGTT, and their risk factors over a 14-year period from 1988 to 2002 in community-dwelling Japanese subjects.

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MATERIALS AND METHODS

Study Population

A population-based prospective study of cardiovascular disease and its risk factors has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. The population of the town has been stable for 50 years, and was approximately 8,000 in 2010. The age and occupational distributions, and nutritional intake of the population were almost similar to those of Japan as a whole based on data from the national census and nutrition survey[15]. As a part of the study, two cross-sectional diabetes surveys have been carried out on Hisayama residents in a similar manner in 1988 and 2002. A detailed description of these surveys was published previously[15,16]. Briefly, of a total of 3,227 residents in 1988 aged 40–79 years based on the town registry, 2,587 (participation rate, 80.2%) consented to taking part in a comprehensive assessment, including the 75-g OGTT. After excluding 82 subjects who had already had breakfast, 10 who were on insulin therapy and 15 because of complaints of nausea or general fatigue during the ingestion of glucose, a total of 2,480 subjects completed the 75-g OGTT. Among the excluded subjects, 10 who were on insulin therapy for type 2 diabetes, who had been diagnosed by their attending physicians, were included in the analysis; thus, the final 1988 study group comprised 2,490 participants (1,077 men and 1,413 women). In 2002, of a total of 3,896 residents aged 40–79 years, 3,000 (participation rate, 77.0%) consented to participating in the examination, and underwent a comprehensive assessment. Of these, a total of 2,822 participants completed the OGTT after excluding 46 who had already eaten breakfast, 32 who were on insulin therapy and 100 who refused the OGTT. Among the participants who received insulin therapy, two with a clinical diagnosis of type 1 diabetes were excluded, and the remaining 30 subjects who were on insulin therapy were included in the analysis. Consequently, 2,852 participants (1,257 men and 1,595 women) made up the final 2002 study group.

Clinical Evaluation and Laboratory Measurements

In both the 1988 and 2002 surveys, clinical evaluation and laboratory measurements were carried out in a similar manner. The study participants underwent the OGTT between 08.00 h and 10.30 h after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h postload, and was separated into plasma and blood cells within 20 min. Plasma glucose concentrations were determined by the glucose-oxidase method. Glucose tolerance status was defined by the 1998 World Health Organization criteria[17]; namely, for normal glucose tolerance, fasting plasma glucose (FPG) <6.1 and 2-h postload glucose (PG) <7.8; for impaired fasting glycemia (IFG), FPG 6.1–6.9 and 2-h PG <7.8; for impaired glucose tolerance (IGT), FPG <7.0 and 2-h PG 7.8–11.0; and for diabetes, FPG ≥7.0 mmol/L or 2-h PG ≥11.1 mmol/L or both, or the use of antidiabetic medications. Prediabetes was defined as either IFG or IGT. Total and high-density lipoprotein (HDL) cholesterols and triglycerides were determined enzymatically.

The height and weight were measured with the participant in light clothes without shoes, and the body mass index (BMI; kg/m^2) was calculated. Overall obesity was defined as a BMI ≥25.0 kg/m^2. Waist circumference was measured at the umbilical level with the participant standing by a trained staff member, and central obesity was defined as a waist circumference ≥90 cm in men and ≥80 cm in women. Blood pressure was obtained three times using a mercury sphygmomanometer in 1988 and an automated sphygmomanometer (BP-203RV III; Colin, Tokyo, Japan) in 2002 with the participant in a sitting position after rest for at least 5 min; the average values were used in the analyses. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or current treatment with antihypertensive agents.

Each participant completed a self-administered questionnaire covering medical history, antidiabetic and antihypertensive treatments, alcohol intake, smoking habits, and physical activity. Alcohol intake and smoking habits were classified as either current use or not. Participants engaging in sports at least three times per week during their leisure time were defined as the regular exercise group.

Statistical Analysis

The SAS software package version 9.3 (SAS Institute, Cary, NC, USA) was used to carry out all statistical analyses. The prevalences of type 2 diabetes and each diabetes-related factor were adjusted for the age distribution of the world standard population[18] by using the direct method with 10-year age groupings. The age-adjusted mean values of diabetes-related factors were calculated using the analysis of covariance method with age included as a continuous variable. The statistical significance of the difference in the prevalence or mean of each factor between the surveys was assessed using the logistic or linear regression model fit by the generalized estimating equations, respectively, to take into account the individuals who participated in the two surveys[19,20]. Serum triglyceride values were transformed into logarithms to improve the skewed distribution. A value of $P < 0.05$ was considered statistically significant in all analyses.

Ethical Considerations

The present study was carried out with the approval of the Kyushu University Institutional Review Board for Clinical Research, and written informed consent was obtained from the participants.

RESULTS

The age-adjusted mean values or frequencies of diabetes-related factors in 1988 and 2002 are shown by sex in Table 1. The mean values of age, FPG, 2-h PG and HDL cholesterol, and the frequency of alcohol intake significantly increased from 1988 to 2002 in both sexes. In men, the mean values of BMI, waist circumference and diastolic blood pressure, and the prev-

alence of overall and central obesity significantly rose over time, whereas the frequency of smoking habits declined. In women, the mean values of total cholesterol, triglycerides and systolic blood pressure, and the prevalence of central obesity significantly decreased with time. The frequencies of hypertension and regular exercise did not differ over the study period for either sex.

The secular trends in the crude and age-adjusted prevalence of type 2 diabetes, IGT and IFG are shown by sex in Figure 1. The crude prevalence of type 2 diabetes and IFG increased significantly, and that of IGT tended to increase in both sexes from 1988 to 2002. The increasing trends in the prevalence of type 2 diabetes remained significant even after adjustment for age in both sexes (14.6% in 1988 to 20.8% in 2002, $P < 0.001$ for men; 9.1% in 1988 to 11.2% in 2002, $P = 0.002$ for women). The age-adjusted prevalence of IFG increased significantly in both men and women (7.9% in 1988 to 15.1% in 2002, $P < 0.001$ for men; 4.6% in 1988 to 6.3% in 2002, $P = 0.049$ for women), whereas the increase in that of IGT was not significant in either sex (18.3% in 1988 to 20.2% in 2002, $P = 0.30$ for men; 17.9% in 1988 to 18.8% in 2002, $P = 0.26$ for women). When IFG and IGT were grouped together as prediabetes, a significant rise in the age-adjusted prevalence of prediabetes was found over time in both sexes (26.2% in 1988 to 35.3% in 2002, $P < 0.001$ for men; 22.5% in 1988 to 25.1% in 2002, $P = 0.04$ for women).

Figure 2 shows the prevalence of type 2 diabetes according to age groups in the two surveys by sex. In 1988, the prevalence of type 2 diabetes increased with age and reached a peak at 50–59 years-of-age for men and at 60–69 years-of-age for women, and then it decreased thereafter. In contrast, in 2002, it increased consistently with age and peaked in the oldest age group in both sexes (both P for trend <0.001). Compared with that in 1988, the prevalence of type 2 diabetes in 2002 rose markedly in men aged 60–69 and 70–79 years (both $P < 0.001$), and in women aged 70–79 years ($P = 0.02$).

To investigate factors contributing to the increased prevalence of type 2 diabetes, the mean values or frequencies of risk factors for type 2 diabetes were estimated according to age groups in 1988 and 2002 by sex (Table 2). During the study period, the mean values of BMI clearly increased in men aged 60–69 and 70–79 years and in women aged 70–79 years (all $P < 0.001$). Similar trends were observed for the mean value of waist circumference, and the prevalence of overall and central obesity in the same age groups. Meanwhile, in men aged 40–49 and 50–59 years and women aged 60–69 years, these parameters of adiposity were almost unchanged between the two surveys, whereas women aged 40–49 and 50–59 years in 2002 had lower levels of adiposity than in 1988. The frequency of regular exercise decreased only in men aged 70–79 years in 2002 compared with that in 1988 ($P = 0.02$).

Table 1 | Age-adjusted mean values or frequencies of diabetes-related factors in 1988 and 2002 by sex

Variable	Men			Women		
	1988 (n = 1,077)	2002 (n = 1,257)	P-value	1988 (n = 1,413)	2002 (n = 1,595)	P-value
Age (years)	57 (10)	59 (10)	<0.001	58 (10)	59 (11)	<0.001
Fasting plasma glucose (mmol/L)	5.9 (1.3)	6.3 (1.4)	<0.001	5.7 (1.3)	5.9 (1.1)	<0.001
2-h postload glucose (mmol/L)	7.8 (3.9)	8.5 (4.2)	<0.001	7.5 (3.3)	7.7 (3.5)	0.003
Body mass index (kg/m^2)	22.8 (2.9)	23.6 (3.0)	<0.001	23.0 (3.2)	23.1 (3.5)	0.40
Overall obesity (%)	25.2	30.8	<0.001	24.6	24.2	0.27
Waist circumference (cm)	82.1 (8.1)	84.0 (8.1)	<0.001	81.5 (10.0)	81.0 (9.9)	0.07
Central obesity (%)	17.6	23.2	<0.001	56.4	48.5	0.007
Total cholesterol (mmol/L)	5.10 (1.07)	5.08 (0.88)	0.33	5.57 (1.05)	5.45 (0.90)	<0.001
HDL cholesterol (mmol/L)	1.26 (0.31)	1.48 (0.38)	<0.001	1.34 (0.29)	1.73 (0.41)	<0.001
Triglycerides (mmol/L)	1.33 (0.41–4.30)	1.35 (0.43–4.31)	0.33	1.07 (0.42–2.77)	1.03 (0.39–2.70)	<0.001
Systolic blood pressure (mmHg)	135 (20)	134 (20)	0.27	132 (21)	128 (21)	<0.001
Diastolic blood pressure (mmHg)	81 (11)	82 (11)	0.008	76 (11)	76 (12)	0.15
Hypertension (%)	42.9	42.0	0.60	32.7	30.0	0.87
Current drinking (%)	63.4	73.1	<0.001	9.7	30.3	<0.001
Current smoking (%)	51.0	48.0	0.009	6.7	8.4	0.19
Regular exercise (%)	11.2	10.7	0.32	8.6	8.4	0.81

Age is not age-adjusted. Triglycerides are shown by geometric means and 95% confidence intervals due to the skewed distribution. All other values are given as the mean (standard deviations) or as a percentage. Overall obesity was defined as a body mass index ≥25.0 kg/m^2.Central obesity was defined as a waist circumference ≥90 cm in men and ≥80 cm in women. Hypertension was defined as blood pressure ≥140/90 mmHg and/or current use of antihypertensive agents. Regular exercise was defined as engaging in sports at least three times per week during leisure time. HDL, high-density lipoprotein.

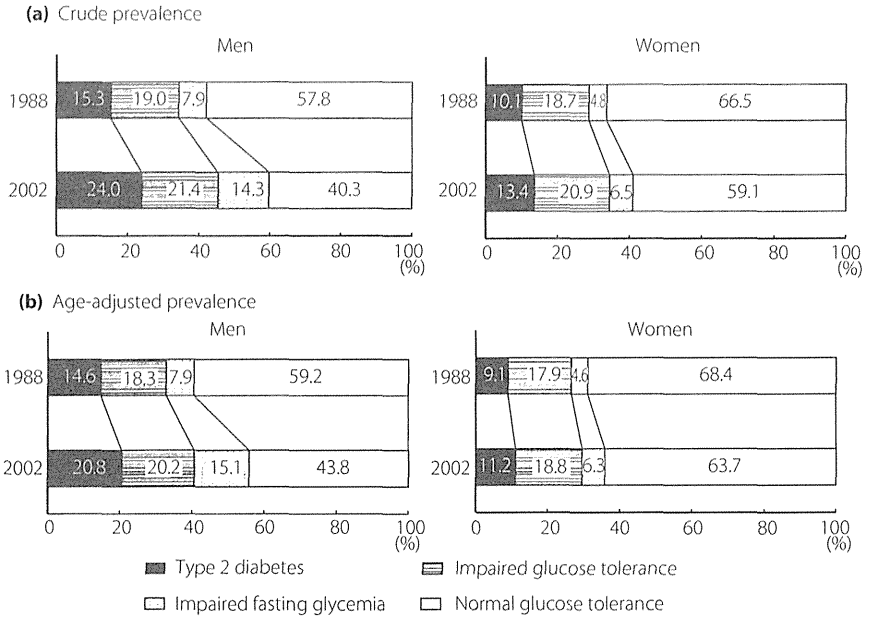

Figure 1 | Secular trends in the (a) crude and (b) age-adjusted prevalence of type 2 diabetes, impaired glucose tolerance, and impaired fasting glycemia in 1988 and 2002 by sex.

DISCUSSION

Using data from two cross-sectional surveys in a Japanese community, we showed that the age-adjusted prevalence of type 2 diabetes and prediabetes defined by the OGTT increased significantly in both sexes from 1988 to 2002. In 2002, the age-adjusted prevalence of type 2 diabetes was 20.8% in men and 11.2% in women, and that of prediabetes was 35.3 and 25.1%, respectively, indicating that, in recent years, the prevalence rate of hyperglycemia has been approximately 60% in men and 40% in women in community-dwelling Japanese subjects aged 40–79 years. To our knowledge, the present study is the first report to show that the prevalence of type 2 diabetes and prediabetes, determined by the OGTT, increased significantly over time in Japanese. In the age-stratified analysis, a marked rise in the prevalence of type 2 diabetes with time was observed in the elderly population for both sexes. These findings suggest that the increasing prevalence of type 2 diabetes is a serious concern, especially among older adults in Japan.

The prevalence of type 2 diabetes and prediabetes in our 2002 survey was higher than the data from the National Health and Nutrition Survey of Japan (individuals strongly suspected of having diabetes, 15.7% for men and 7.6% for women; individuals in whom diabetes cannot be ruled out, 17.3% for men and 15.4% for women, in 2011)[21] and another epidemiological study in a rural area of Japan (diabetes, 11.5%; prediabetes, 18.6%, in 2000–2002)[22]. This diversity might be attributable to a difference in the definition of diabetes and prediabetes among the studies. The National Health and Nutrition Survey of Japan used a measurement of glycated hemoglobin (HbA_{1c}) and medical history, not of glucose, for determining glucose tolerance status, whereas the OGTT was used in the other study and in the present study. Recent epidemiological studies have shown that the prevalence of diabetes and prediabetes defined by HbA_{1c} levels alone are lower than those defined by the OGTT in different populations[23,24]. In addition, the participation rate in our 2002 survey (77.0%) was higher than those in the other studies (nearly 50–60%). These might be reasons for the relatively high prevalence of diabetes and prediabetes in the present study. Several population-based studies in other Asian populations have investigated the prevalence of diabetes defined by the OGTT in the 2000s. The prevalence of diabetes was 10.6% for men and 8.8% for women in a nationwide survey in China in 2007–2008[4], 12.5% for men and 11.9% for women in a study carried out in urban India in 2000[25], and 12.3% for men and 10.4% for women in a national study in Singapore in 2010[6]. Considering the findings in our 2002 survey (20.8% for men and 11.2% for women), the prevalence of type 2 diabetes in the Japanese population was much higher in men, and similar or higher in women compared with those in other Asians. Furthermore, based on our prevalence estimates, if the OGTT is used for determining glucose tolerance status, it was calculated that among middle-aged and old-aged adults in Japan, there were at least 11.7 million persons with type 2 diabetes and 20.0 million persons with prediabetes, and these figures were higher than those noted in the latest data from the International Diabetes Federation in 2011 (10.7 million persons and 13.6 million persons, respectively)[10]. These findings sug-

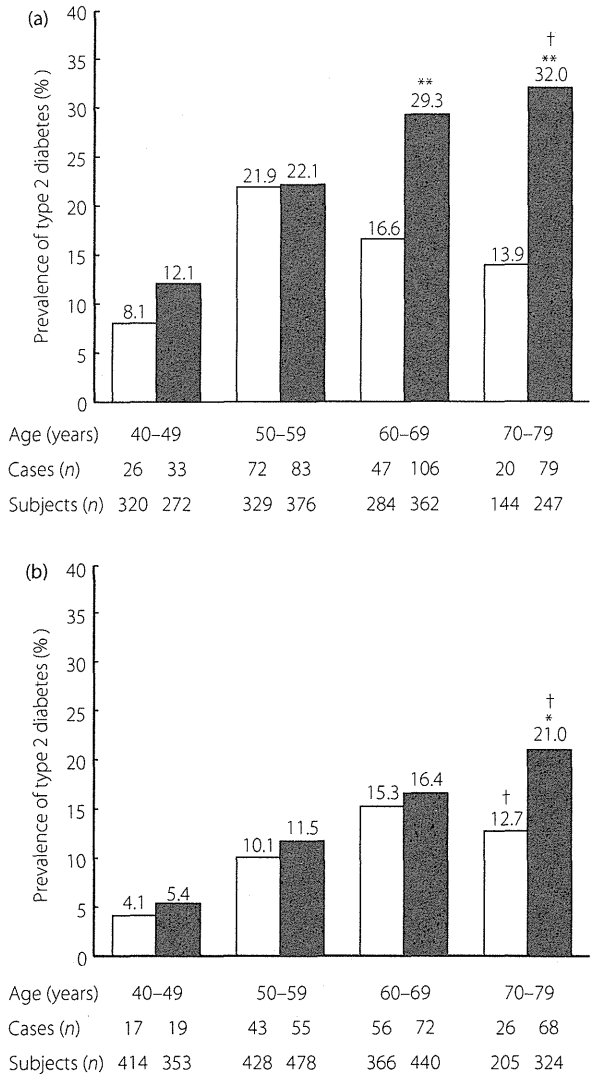

Figure 2 | Secular trends in the prevalence of type 2 diabetes according to age groups in 1988 and 2002 by sex. (a) Men. (b) Women. *P < 0.05, **P < 0.001 vs 1988, †P for trend <0.001. □, 1988; ■, 2002.

gest that type 2 diabetes and prediabetes might actually be more prevalent in Japan than was previously thought.

In the present study, the prevalence of type 2 diabetes increased 1.4-fold in men and 1.2-fold in women from 1988 to 2002, and that of prediabetes rose 1.3-fold in men and 1.1-fold in women; all these changes were statistically significant. Other Asian population studies, which used the OGTT for determining glucose tolerance status, showed that the prevalence of diabetes increased 3.9-fold (2.5% in 1994 to 9.7% in 2007–2008) in a Chinese population[3,4], 1.7-fold (8.3% in 1988–1989 to 14.3% in 2003–2004) in Asian Indians[5] and 2.4-fold (4.7% in 1984–1985 to 11.3% in 2010) in a Singapore population[6,26]. Furthermore, in these studies, a rising trend in the prevalence of prediabetes was also observed during the study period (1.2–16.0-fold)[3–6,26]. In contrast, in a national survey in the USA[8], there was a 1.2-fold increase (14.4 to 17.4%) in the prevalence of diabetes, but no change (35.9 to 35.4%) in that of prediabetes between 1988–1994 and 2005–2006. Taken together, these findings imply that the Japanese had a similar rate of increase in the prevalence of type 2 diabetes compared with the Americans, whereas other Asians showed a more rapid increase. Currently, at the start of the 2000s, China and India are experiencing an economic boom, whereas Japan and the USA are facing an era of slow growth. Thus, the pace of increase in the prevalence of type 2 diabetes by each country or area might be correlated with the economic growth rate.

In our age-stratified analysis, in 1988, the prevalence of type 2 diabetes increased with age, and reached its peak at 50–59 years-of-age for men and at 60–69 years-of-age for women, followed by a decline in older ages; whereas in 2002, it rose with age, reaching peak levels in the oldest age-groups in both sexes. These patterns were nearly mirrored by the patterns of the parameters of adiposity according to age groups. We speculate that changes from traditional to Westernized lifestyles occurred in the younger age group earlier, and then, as this group advanced in age, the Westernized lifestyle spread to the older age groups. In addition, a sedentary lifestyle was significantly more prevalent in men aged 70–79 years. Overall obesity, central obesity and the decline in physical activity have been shown to be associated with elevated risk of incident type 2 diabetes, independent of one another[16,27,28], and therefore, it is reasonable to suppose that the increase in overall and central obesity, and decreased frequency of physical activity contributed to the steep increment in the prevalence of type 2 diabetes among the elderly in the present study. Another possible explanation is that higher intake of animal fat is related to the rise in the prevalence of type 2 diabetes[1,29]. Our previous study reported that the percentage of energy intake from fat among Hisayama residents was unchanged at approximately 25% between 1985 and 2004, but the proportion of animal fat to total fat intake tended to increase from 42.3 to 47.5% during this period[30]. Other possible factors, such as an increase in the incidence of type 2 diabetes and improved survival in individuals with type 2 diabetes, might also be linked to the increasing prevalence of type 2 diabetes.

The strengths of the present study include the high participation rates and the use of an OGTT for determining glucose tolerance status in both surveys. However, some limitations of the present study should be discussed. First, the diagnosis of glucose tolerance status was based on a single measurement of glucose levels, as was the case in most other epidemiological studies. This limitation might have led to misclassification of glucose tolerance categories. However, we believe that the extent of misclassification of glucose tolerance categories would be similar across the surveys, and therefore such misclassification would not have substantially altered our conclusions. Second,