In the present study, we demonstrated a clear log-linear association between blood pressure levels and the risks of CVD, stroke, and all-cause death, regardless of kidney function status. These findings are consistent with the results of other studies conducted in the general population.[9,10] Recent publications of prospective cohort data suggest, however, that individuals with a reduced GFR and a systolic blood pressure below 120 mm Hg may be at increased risk of stroke or death.[12,13] Other post hoc analyses of trials conducted on individuals with coronary heart disease[24] and with diabetic nephropathy[25] suggest an increased risk of coronary events at the lower achieved blood pressures. In the present study, however, no evidence of an increased risk of myocardial infarction was observed at the lower blood pressure level. One possible explanation for the J-curve association observed in the previous studies may be the phenomenon of reverse causality,[26] in which extensive vascular disease or subclinical cardiac dysfunction is associated with lower blood pressure levels and reduced GFR and is associated independently with a relatively high risk of CVD, rather than with any adverse effects of low blood pressure itself.

Several limitations of the present study should be noted. First, the generalizability of our findings to some populations at high risk for CVD may be limited. The participants excluded from the analysis due to missing baseline examination data or event data were likely to have a higher cardiovascular risk, because they were older (mean 63 years), had higher blood pressure levels (mean 138/80 mm Hg), and had a greater prevalence of diabetes (8.7%) than the study population. This bias has the potential to alter our findings, which may therefore be conservative. Second, the present GFR estimates, which were made with a simplified prediction equation, may not be sufficiently correct, which possibly could lead to a certain number of misclassifications of estimated kidney function status. Such misclassifications would weaken the association found in the present study, biasing the results toward the null hypothesis. Third, we were unable to obtain information regarding the use of antihypertensive drugs, medication compliance, or blood pressure control during the follow-up period. The lack of this information may reduce the accuracy of our findings to some extent. Fourth, the applicability of the present results to populations with severe kidney dysfunction is limited, because very few of our subjects (0.1%) had a GFR <30 mL · min^{-1} · 1.73 m^{-2}. Moreover, the absence of data on proteinuria in the present study makes it impossible to assess the effects of the earliest stages of kidney disease on the risk of CVD. Finally, creatinine measurement was conducted locally rather than at a central laboratory, which introduces a certain amount of variability that may reduce the reliability of the results.

In conclusion, the present findings suggest that a reduced GFR is associated significantly with a high risk of CVD in the general Japanese population. Furthermore, we observed a continuous relationship between blood pressure levels at baseline and the risk of CVD, regardless of kidney function status. The optimization of blood pressure control in individuals with kidney dysfunction is therefore likely to substantially reduce the burden of CVD in the general population.

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Disclosures

None.

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CLINICAL PERSPECTIVE

There have been several studies reporting a strong association between reduced kidney function and cardiovascular risk. The findings, however, have been inconsistent in Asian populations, and there has been no attempt to date to review the evidence. Hence, we conducted an overview of individual participant data from Japanese community-based cohort studies to reliably assess the impact of reduced kidney function on cardiovascular risk in the general Japanese population. Our findings suggest a clear association between reduced kidney function and a 57% greater risk of cardiovascular disease in the Japanese population, as well as a log-linear relationship between blood pressure levels and cardiovascular risk in individuals with reduced kidney function. The optimization of blood pressure control in individuals with reduced kidney function is therefore likely to substantially reduce the burden of cardiovascular disease in the general population. Given that the prevalence of reduced kidney function is ≈10% in the general population, we believe that these novel findings are significant in the areas of clinical and public health.

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LDL Cholesterol and the Development of Stroke Subtypes and Coronary Heart Disease in a General Japanese Population

The Hisayama Study

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Background and Purpose—Although the relation between serum LDL cholesterol level and coronary heart disease (CHD) is well established, its relation with stroke subtypes is less clear.

Methods—A total of 2351 inhabitants age ≥40 years in a Japanese community were followed up for 19 years.

Results—During follow-up, 271 subjects developed stroke and 144 developed CHD. Whereas the age- and sex-adjusted incidences of CHD significantly increased with increasing LDL cholesterol levels (P for trend <0.001), the associations between LDL cholesterol level and the incidences of ischemic or hemorrhagic stroke were not significant. The age- and sex-adjusted incidences of atherothrombotic infarctions (ATIs) and lacunar infarctions (LIs) significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATIs and=0.02 for LIs), but no such association was observed for cardioembolic infarction. After multivariate adjustment, the positive associations of LDL cholesterol level with the risks of ATI and CHD remained significant (P for trend=0.02 for ATIs and=0.03 for CHD), whereas the association with LIs was not significant. The risk of ATI significantly increased in the fourth quartile of LDL cholesterol compared with the first quartile (multivariate-adjusted hazard ratio=2.84; 95% CI, 1.17 to 6.93). The multivariate-adjusted risks for developing nonembolic infarction (ATIs and LIs) and CHD were significantly elevated in the groups with elevated LDL cholesterol values with and without the metabolic syndrome.

Conclusions—Our findings suggest that an elevated LDL cholesterol level is a significant risk factor for developing ATI as well as CHD, and these associations are independent of the metabolic syndrome. (***Stroke*. 2009;40:382-388.)**

Key Words: epidemiology ■ cholesterol ■ lipoproteins ■ risk factors

Increased blood cholesterol levels are causally related to an increased risk of coronary heart disease (CHD).[1] In contrast, the relation between total cholesterol levels and the risk of stroke remains unclear because of conflicting results reported in the literature.[2,3] The inconsistent results may be due to several reasons. First, because stroke is a heterogeneous syndrome of different etiologic origins, lipid abnormalities may be important for some subtypes of stroke but not for others. An inverse association has been observed between total cholesterol and hemorrhagic stroke,[2,4] and there is a positive association between total cholesterol and ischemic stroke.[2,5] Furthermore, the association may be different for ischemic stroke subtypes.[6] Second, lipoprotein subfractions are considered to exert varying influence on stroke risk.[7] It is possible that the protective effect of HDL cholesterol against stroke weakens the positive association between total cholesterol and stroke in instances where lipoprotein subfractions are counted together. The association between cholesterol and stroke, therefore, needs to be discussed on the basis of stroke subtypes and lipoprotein subfractions.

Together with the results from prospective studies, the positive association between LDL cholesterol level and the risk of CHD has been confirmed by lipid-lowering randomized trials.[8] On the other hand, whereas statins significantly reduced the risk of stroke,[8] the risk reduction for stroke in trials in which subjects were treated with nonstatins was not significant,[9] suggesting that statins involve mechanisms other than cholesterol lowering for the prevention of stroke. Therefore, the true association between LDL cholesterol and the risk of stroke remains unknown. The purpose of this study was to evaluate the association between LDL cholesterol

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level and the development of stroke by its subtypes as well as of CHD in a prospective study of a general Japanese population.

Subjects and Methods

Study Population

Since 1961, we have been conducting a long-term, prospective cohort study of cardiovascular disease (CVD) in the town of Hisayama, a suburb of Fukuoka city in southern Japan. In 1983, a screening survey for the present study was performed in the town. A total of 2548 residents age ≥40 years (80.7% of the total population of this age group) consented to participate in the examination. Of these, 197 subjects were excluded for the following reasons: past history of stroke or myocardial infarction (MI; n=89), blood samples not being collected or collected after a meal (n=86), and excessively high value of triglycerides (≥4.48 mmol/L) for which the Friedewald formula loses its validity[10] (n=22). The remaining 2351 subjects (991 men, 1360 women) were included in this study.

Follow-Up Survey

This population was followed up prospectively for 19 years, from November 1983 through October 2002, by annual health examinations. For subjects who did not undergo regular examinations or who moved out of Hisayama, health status was checked yearly by mail or telephone. We also established a daily monitoring system, which connected us with local physicians and the members of the Health and Welfare Office for the town, and through the system we gathered information on new events of CVD, including suspected cases. When stroke or CHD occurred or was suspected, physicians in the study team examined the subject and evaluated his/her detailed clinical information. The clinical diagnosis of stroke or CHD was based on the patient's history, physical and neurologic examinations, and ancillary laboratory examinations. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 1 subject was lost to follow-up, 707 subjects died, and 555 subjects (78.5%) underwent autopsy examination.

Definition of Cardiovascular Events

The diagnosis and classification of stroke were determined on the basis of clinical information, including brain computed tomography and magnetic resonance imaging, cerebral angiography, echocardiography, carotid duplex imaging, or autopsy findings. In principle, stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficits persisting for >24 hours, and the stroke was then classified as either hemorrhagic or ischemic. Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. Ischemic stroke was further divided into 4 clinical categories: atherothrombotic infarction (ATI), lacunar infarction (LI), cardioembolic infarction (CEI), and undetermined subtype of ischemic stroke (UND), based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke,[11] as well as on the basis of the diagnostic criteria of the Trial of Org10172 in Acute Stroke Treatment (TOAST) Study[12] and the Cerebral Embolism Task Force.[13]

Details of the diagnostic criteria for ischemic stroke subtypes have been described previously.[14] In brief, ATI was diagnosed when the subjects had significant stenosis (>50%) or occlusion of a major cerebral artery with infarct size ≥1.5 cm on brain imaging or autopsy. LI was diagnosed as the presence of a relevant brainstem, basal ganglia, or subcortical hemispheric lesion with a diameter <1.5 cm demonstrated on brain imaging or autopsy and no evidence of cerebral cortical or cerebellar impairment. The diagnosis of CEI was made on the basis of primary and secondary clinical features suggestive of CEI as reported by the Cerebral Embolism Task Force.[13] The category of UND included all ischemic stroke cases for which the subtype could not be determined because of insufficient clinical or morphologic information. We considered morphologic findings to be significant and used clinical features as reference information. Cases with cerebrovascular diseases with distinct pathology, such as collagen disease, hematologic disorder, trauma, chronic subdural hematoma, or moyamoya disease, were excluded from the evaluation.

During the follow-up period, we identified 271 first-ever stroke events. All of the stroke cases underwent morphologic evaluation that included brain imaging and autopsy; 269 subjects (99.3%) underwent brain imaging studies, and autopsies were performed on 128 subjects of 157 deceased stroke cases (81.5%), including 2 subjects who were not examined by brain imaging. When sufficient clinical and morphologic information was obtained, a diagnosis of cerebral infarction subtype was defined as "definite." When the amount of either type of information was insufficient, the diagnosis level was defined as "probable." On the basis of the aforementioned criteria, stroke cases were divided into 80 hemorrhagic strokes and 191 ischemic strokes (51 ATIs, 93 LIs, 46 CEIs, and 1 UND). Among 191 ischemic strokes, 182 were defined as definite and 9 as probable. In this study, we present the data regarding definite and probable stroke cases together, because these combined data were almost identical to those for definite cases only.

The criteria for the diagnosis of CHD included first-ever acute MI, silent MI, sudden cardiac death within 1 hour after the onset of acute illness, coronary artery angioplasty, and bypass grafting. The diagnosis of MI was based on detailed clinical information and at least 2 of the following findings: typical clinical symptoms, ECG evidence of MI, elevated cardiac enzymes, or morphologic findings including echocardiographic, scintigraphic, or angiographic abnormalities compatible with myocardial injury. Silent MI was defined as myocardial scarring without any historical indication of clinical symptoms and/or abnormal cardiac enzyme changes.[15] During the follow-up period, we identified 144 first-ever events of CHD.

Risk Factors

Blood samples were drawn after an overnight fast of at least 12 hours. All measurements were done within 24 hours after venipuncture in the central study laboratory (Japan Medical Laboratory Inc, Fukuoka, Japan), which participated in the Centers for Disease Control and Prevention Lipid Standardization Program. Total cholesterol and triglyceride levels were measured enzymatically. Measurement of HDL cholesterol was performed after precipitation of VLDL and LDL with dextran sulfate and magnesium. LDL cholesterol concentration was calculated with the Friedewald formula.[10] Plasma glucose levels were determined by the glucose oxidase method. Sitting blood pressure (BP) was measured with a sphygmomanometer 3 times at the right upper arm after at least 5 minutes of rest, and the mean of the 3 measurements was used in the analysis. Hypertension was defined as a BP ≥140/90 mm Hg and/or current treatment with antihypertensive agents. ECG abnormalities were defined as left ventricular hypertrophy (Minnesota code 3-1), ST-segment depression (Minnesota codes 4-1,2,3), or atrial fibrillation (Minnesota code 8-3). Body height and weight were measured in light clothing without shoes, and body mass index (BMI; kg/m^2) was calculated. Information on alcohol consumption, smoking habits, and physical activity during leisure time was obtained by the use of a questionnaire. Alcohol consumption and smoking habits were classified as either current use or not. Those subjects who engaged in sports or other forms of exertion ≥3 times per week during their leisure time were designated the regular-exercise group. We defined the presence of the metabolic syndrome according to the National Cholesterol Education Program Expert Panel criteria[16] with a minor modification. The presence of the metabolic syndrome was based on the existence of 3 or more of the following components: (1) BMI ≥25 kg/m^2 as a substitute for waist circumference[17]; (2) fasting triglyceride concentration ≥1.68 mmol/L; (3) HDL cholesterol concentration <1.03 mmol/L in men and <1.29 mmol/L in women; (4) BP ≥130/85 mm Hg or use of antihypertensive drugs; and (5) fasting plasma glucose value ≥6.1 mmol/L or current use of antidiabetic drugs.

Statistical Analysis

To analyze LDL cholesterol level as a categorical variable, we classified the subjects into 4 groups according to quartiles of LDL

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Table 1. Age- and Sex-Adjusted Mean Values or Frequencies of Risk Factors for CVD According to LDL Cholesterol Quartiles at Baseline

	Quartile of LDL Cholesterol Levels, mmol/L				
Risk Factor	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Men, %	57.4	44.1	39.2	31.5	<0.001
Age, y	56±11	57±11	57±11	59±11	<0.001
Total cholesterol, mmol/L	4.03±0.57	4.81±0.41	5.40±0.43	6.45±0.68	<0.001
HDL cholesterol, mmol/L	1.36±0.42	1.35±0.36	1.34±0.37	1.31±0.33	<0.001
Triglycerides, mmol/L	1.15±0.75	1.07±0.51	1.12±0.53	1.32±0.58	<0.001
Fasting blood glucose, mmol/L	4.66±0.92	4.75±0.96	4.76±0.93	4.96±1.14	<0.001
Systolic BP, mm Hg	132±22	132±21	135±22	138±21	<0.001
Diastolic BP, mm Hg	81±12	81±12	82±11	83±10	<0.001
Hypertension, %	39.7	41.4	43.8	48.5	0.01
ECG abnormalities,* %	20.6	19.4	21.0	18.4	0.12
BMI, kg/m^2	21.9±3.0	22.2±3.1	23.0±3.1	23.5±3.1	<0.001
Current drinking, %	42.2	33.3	31.8	27.9	<0.001
Current smoking, %	30.7	28.5	28.3	26.5	<0.001
Regular exercise,† %	9.0	7.9	9.5	5.7	0.03

Data are mean±SD or percent. Percentage of men was age adjusted. Mean age was sex adjusted.

*Minnesota codes 3–1; 4–1, –2, –3; or 8–3.

†Engaging in sports or other forms of exertion regularly ≥3 times per week during leisure time.

cholesterol level: ≤2.65, 2.66 to 3.24, 3.25 to 3.88, and ≥3.89 mmol/L. Serum triglyceride levels were logarithmically transformed to improve the skewed distribution. Age- and sex-adjusted mean values of the possible risk factors were calculated by the ANCOVA method, and their trends across LDL cholesterol levels were tested by multiple-regression analysis. Frequencies of risk factors were adjusted for age and sex by the direct method and were examined for trends by the Cochran-Mantel-Haenszel test. The incidences of CVD were calculated by the person-year method and were adjusted for age and sex by the direct method according to 10-year age groups. Differences in age- and sex-adjusted incidences between LDL cholesterol quartiles were tested by Cox proportional-hazards regression analysis. The age- and sex-adjusted or multivariate-adjusted hazard ratios (HRs) and 95% CIs were also calculated by the Cox proportional-hazards model. All statistical analyses were performed with the SAS program package. $P<0.05$ was considered statistically significant in all analyses.

Results

The age- and sex-adjusted mean values or frequencies of risk factors for CVD are listed by quartiles of LDL cholesterol levels at baseline in Table 1. The frequencies of male sex, current drinking, current smoking, and regular exercise and the mean values of HDL cholesterol declined with increasing LDL cholesterol level, whereas mean values of age, total cholesterol, triglycerides, fasting blood glucose, systolic and diastolic BPs, BMI, and frequency of hypertension significantly increased with rising LDL cholesterol level. The frequency of ECG abnormalities was not different among serum LDL cholesterol levels.

Table 2 shows the age- and sex-adjusted incidences of CVD according to quartiles of LDL cholesterol levels. No significant associations were observed between LDL cholesterol levels and the incidences of stroke, whether ischemic or hemorrhagic. In regard to subtypes of ischemic stroke, the incidences of ATI and LI significantly increased with increasing LDL cholesterol level (P for trend=0.03 for ATI and=0.02 for LI), and there were significant differences between the first and fourth quartiles of LDL cholesterol for both subtypes (age- and sex-adjusted HR=2.31; 95% CI, 1.03 to 5.16; $P=0.04$ for ATI; age- and sex-adjusted HR=2.00; 95% CI, 1.05 to 3.80; $P=0.03$ for LI; Table 3). No such association was observed for CEI. The incidence of CHD also significantly increased with increasing LDL cholesterol level (P for trend <0.001), and compared with the first quartile, the incidence was significantly higher in the third (age- and sex-adjusted HR=1.77; 95% CI, 1.07 to 2.91; $P=0.03$; Table 3) and fourth (age- and sex-adjusted HR=2.00; 95% CI, 1.22 to 3.28; $P=0.006$) quartiles.

As shown in Table 3, the positive associations between LDL cholesterol level and risk of ATI and CHD remained significant even after adjustment for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise (P for trend=0.02 for ATI and=0.03 for CHD). Compared with the first quartile, the risk of ATI was significantly high in the fourth quartile after adjustment for the aforementioned confounding factors (multivariate-adjusted HR=2.84; 95% CI, 1.17 to 6.93; $P=0.02$). On the other hand, the negative association between LDL cholesterol and the risk of CEI appeared to be significant after multivariate adjustment (P for trend=0.03), and the risk of CEI was significantly lower in the fourth quartile than in the first quartile (multivariate-adjusted HR=0.34; 95% CI, 0.12 to 0.96; $P=0.04$). A similar association was observed when LDL cholesterol was examined on a continuous scale.

Because not only LDL cholesterol but also other metabolic factors may be strong risk factors for CVD, we examined the combined as well as the separate effects of elevated LDL cholesterol level and the metabolic syndrome on the development of selected CVDs. As shown in the Figure, we

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Table 2. Age- and Sex-Adjusted Incidences (per 1000 Person-Years) of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L				
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend
Stroke					
No. of events	56	62	74	79	
Age- and sex-adjusted incidence	7.4	8.1	10.1	10.2	0.13
Ischemic stroke					
No. of events	37	47	47	60	
Age- and sex-adjusted incidence	4.9	6.3	6.8	7.9	0.07
Atherothrombotic					
No. of events	9	12	9	21	
Age- and sex-adjusted incidence	1.2	1.6	1.2	3.3*	0.03
Lacunar					
No. of events	14	21	25	33	
Age- and sex-adjusted incidence	2.0	2.6	2.9	3.8*	0.02
Cardioembolic					
No. of events	14	14	12	6	
Age- and sex-adjusted incidence	1.7	2.1	2.4	0.8	0.07
Hemorrhagic stroke					
No. of events	19	15	27	19	
Age- and sex-adjusted incidence	2.6	1.8	3.3	2.3	0.95
CHD					
No. of events	25	28	43	48	
Age- and sex-adjusted incidence	3.4	3.4	5.5*	6.6†	<0.001

*$P<0.05$, †$P<0.01$ vs lowest quartile.

estimated the HRs for the occurrence of nonembolic infarction, including ATI and LI, as well as of CHD, by dividing the subjects into 4 groups according to the presence or absence of high LDL cholesterol levels (the fourth quartile, ≥3.89 mmol/L for nonembolic infarction; the third and fourth quartiles, ≥3.25 mmol/L for CHD) and the metabolic syndrome after adjustments for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Compared with a reference group with neither high LDL cholesterol levels nor the metabolic syndrome, the risk of developing nonembolic infarction was significantly high in the group with high LDL cholesterol levels alone and in the group with both high LDL cholesterol levels and the metabolic syndrome, whereas it was marginally significant for the group with the metabolic syndrome alone. Similarly, the risk for the development of CHD was elevated in both the group with high LDL cholesterol without the metabolic syndrome and the group with high LDL cholesterol and the metabolic syndrome. The risk of CHD was also significant for the group with the metabolic syndrome alone.

Discussion

In a long-term, prospective study of a general Japanese population, we demonstrated positive and significant associations between serum LDL cholesterol level and risk for the development of ATI and CHD. These associations remained unchanged even after adjustment for other lipid fractions as well as other confounding factors, namely, age, sex, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. In addition, the impact of high LDL cholesterol on CVD appeared to be similar to that of the metabolic syndrome. On the other hand, the association between LDL cholesterol level and the risk of CEI was negative and significant after adjusting for the aforementioned risk factors. To our knowledge, this is the first prospective cohort study to investigate the association between LDL cholesterol and the development of subtypes of ischemic stroke.

Several prospective studies have investigated the association between LDL cholesterol and ischemic stroke, but the results were not unanimous. The Cardiovascular Health Study[18] reported a positive association between LDL cholesterol and the risk of ischemic stroke, whereas the Atherosclerosis Risk in Communities Study[19] and the Framingham Study[20] found no clear associations. In the present analysis, LDL cholesterol level was not clearly associated with the risks of stroke and ischemic stroke, but these associations were heterogeneous across ischemic stroke subtypes. Because LI and CEI seem to have a less potent relation with elevated LDL cholesterol,[21,22] inclusion of those subtypes may mask the positive association between LDL cholesterol and ATI. This heterogeneity in the associations of LDL cholesterol level and ischemic stroke subtypes may be a reason for the controversial results obtained from previous studies that investigated the outcome of "total" ischemic stroke.

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Table 3. Age-, Sex-, and Multivariate-Adjusted HRs and 95% CIs for the Development of CVD According to LDL Cholesterol Quartiles

	Quartile of LDL Cholesterol Levels, mmol/L					
	≤2.65 (n=586)	2.66 to 3.24 (n=591)	3.25 to 3.88 (n=585)	≥3.89 (n=589)	*P* Value for Trend	Continuous Scale
Stroke						
No. of events	56	62	74	79		
Age- and sex-adjusted HR (95% CI)	1.0	0.96 (0.66–1.37)	1.12 (0.84–1.69)	1.23 (0.86–1.75)	0.13	1.08 (0.95–1.23)
Multivariate-adjusted HR (95% CI)	1.0	0.94 (0.64–1.38)	1.15 (0.79–1.67)	1.23 (0.84–1.81)	0.16	1.07 (0.93–1.24)
Ischemic stroke						
No. of events	37	47	47	60		
Age- and sex-adjusted HR (95% CI)	1.0	1.08 (0.70–1.67)	1.17 (0.75–1.80)	1.45 (0.95–2.21)	0.07	1.15 (0.99–1.35)
Multivariate-adjusted HR (95% CI)	1.0	1.05 (0.66–1.66)	1.05 (0.66–1.68)	1.35 (0.85–2.14)	1.19	1.11 (0.94–1.31)
Atherothrombotic						
No. of events	9	12	9	21		
Age- and sex-adjusted HR (95% CI)	1.0	1.14 (0.48–2.71)	0.98 (0.39–2.50)	2.31 (1.03–5.16)*	0.03	1.51 (1.14–1.99)§
Multivariate-adjusted HR (95% CI)	1.0	1.35 (0.54–3.35)	1.19 (0.45–3.17)	2.84 (1.17–6.93)*	0.02	1.60 (1.19–2.16)§
Lacunar						
No. of events	14	21	25	33		
Age- and sex-adjusted HR (95% CI)	1.0	1.29 (0.65–2.54)	1.56 (0.81–3.05)	2.00 (1.05–3.80)*	0.02	1.23 (1.00–1.53)
Multivariate-adjusted HR (95% CI)	1.0	1.19 (0.57–2.50)	1.41 (0.69–2.89)	1.69 (0.83–3.43)	0.11	1.13 (0.90–1.43)
Cardioembolic						
No. of events	14	14	12	6		
Age- and sex-adjusted HR (95% CI)	1.0	0.83 (0.39–1.75)	0.80 (0.37–1.75)	0.39 (0.15–1.04)	0.07	0.71 (0.51–1.00)
Multivariate-adjusted HR (95% CI)	1.0	0.75 (0.34–1.63)	0.59 (0.25–1.38)	0.44 (0.12–0.96)*	0.03	0.64 (0.44–0.94)‡
Hemorrhagic stroke						
No. of events	19	15	27	19		
Age- and sex-adjusted HR (95% CI)	1.0	0.69 (0.35–1.36)	1.24 (0.68–2.24)	0.83 (0.43–1.59)	0.95	0.94 (0.74–1.20)
Multivariate-adjusted HR (95% CI)	1.0	0.71 (0.35–1.47)	1.41 (0.75–2.65)	1.01 (0.50–2.05)	0.53	1.02 (0.79–1.33)
CHD						
No. of events	25	28	43	48		
Age- and sex-adjusted HR (95% CI)	1.0	1.02 (0.60–1.76)	1.77 (1.07–2.91)*	2.00 (1.22–3.28)†	<0.001	1.29 (1.08–1.53)§
Multivariate-adjusted HR (95% CI)	1.0	1.01 (0.56–1.80)	1.68 (0.99–2.84)	1.57 (0.91–2.73)	0.03	1.15 (0.95–1.39)

Multivariate adjustment was made for age, sex, HDL cholesterol, triglycerides, systolic BP, ECG abnormalities, fasting blood glucose, BMI, current drinking, current smoking, and regular exercise. For the continuous scale, HR is given for each 1-mmol/L increase in LDL cholesterol.
*$P<0.05$, †$P<0.01$ vs lowest quartile; ‡$P<0.05$, §$P<0.01$.

The atherogenesis of LDL cholesterol to large vessels, including coronary arteries and other peripheral arteries, is well known, and clinical studies have shown that an elevated LDL cholesterol level is also significantly related to the development of atherosclerotic lesions in extracranial or intracranial large vessels.[23,24] Because ATI is caused by atherosclerotic lesions of those large vessels, the significant association between elevated LDL cholesterol level and the risk of ATI observed in the present analysis is compatible with the evidence of the atherogenic role of LDL cholesterol.

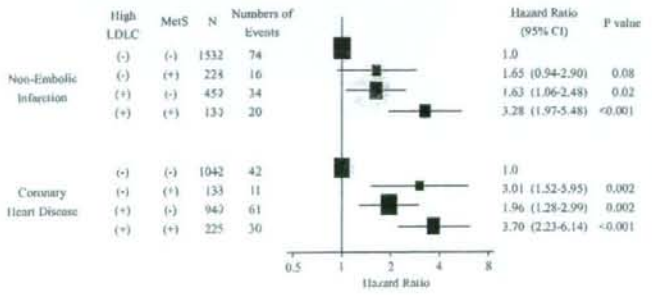

Figure. Multivariate-adjusted HRs for the development of nonembolic infarction and CHD according to the presence or absence of high LDL cholesterol and the metabolic syndrome. Multivariate adjustment was made for age, sex, ECG abnormalities, current drinking, current smoking, and regular exercise. Centers of the boxes are placed at the estimates of HRs. Horizontal lines indicate 95% CIs, and sizes of boxes are proportional to the numbers of events. LDLC indicates LDL cholesterol; MetS, metabolic syndrome.

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In our cohort, the association between LDL cholesterol and the risk of LI was no longer significant after multivariate adjustment, suggesting that elevated LDL cholesterol was not an independent risk factor for the development of LI. Our previous report showed that multiple risk factors were related to the occurrence of LI,[14] and case-control studies on the relation between LDL cholesterol level and LI have reported varied associations.[21,22,25] One study reported a significant association between elevated LDL cholesterol and the risk of LI,[25] another study observed lower LDL cholesterol levels in LI cases,[22] and another study found no significant association.[21] Lacunar infarcts occur as a result of multiple mechanisms, such as (1) lipohyalinosis and/or fibrinoid necrosis, (2) microatheroma, (3) atherosclerosis of the basilar and middle cerebral artery stem or proximal division of large vessels, or (4) cardioembolic occlusion.[26] Lipohyalinosis is a vasculopathy caused by hypertension,[26] whereas large-vessel atherosclerosis is affected by risk factors including LDL cholesterol,[23,24] but cardioembolism seems less related to elevated LDL cholesterol.[22,25] These heterogeneous roles for LDL cholesterol in the multiple pathogenesis of LI occurrence might account for the weak association between LDL cholesterol and the risk of LI.

An inverse relation between LDL cholesterol level and the risk of CEI was observed in our earlier population in the 1960s,[14] and the same association was found in the present investigation after adjustment for confounding factors. Although the reason for this association is unknown, a plausible explanation is that a lowered cholesterol level might increase the risk of CEI through the increased occurrence of atrial fibrillation,[27] a predominant risk factor for CEI. Additional clinical and experimental evidence is needed to elucidate the mechanism underlying this association.

The results of previous prospective studies of the association between LDL cholesterol and hemorrhagic stroke have been inconsistent; a significant inverse association was reported in women in the Framingham Study,[20] whereas a nonsignificant association was observed in the Cardiovascular Health Study.[18] Lipid-lowering trials recently conducted in Japan[28,29] and a meta-analysis of >90 000 subjects enrolled in statin trials[8] found no apparent increase in the risk of hemorrhagic stroke. A nonsignificant association between LDL cholesterol and the risk of hemorrhagic stroke observed in our data was in accord with the findings of a previous prospective study[18] and intervention trials.[8,28,29]

Several prospective studies conducted in Western countries have reported positive associations between LDL cholesterol and the risk of CHD.[30] Among Japanese, no study has investigated the association between LDL cholesterol level and the risk of CHD, but several prospective studies have shown that total cholesterol is a strong risk factor for CHD.[31,32] The findings obtained from the present analysis support the results from those prospective studies and, for the first time, have demonstrated a positive association between calculated LDL cholesterol and the risk of CHD in a general Japanese population.

The metabolic syndrome has been shown to be a clear risk factor for CVD,[33] but LDL cholesterol level is not involved in the definition of the metabolic syndrome. In the present analysis, comparable and independent effects were observed for elevated LDL cholesterol and the metabolic syndrome on the risks of nonembolic infarction and CHD. The highest risk was observed for the subgroup with both an elevated LDL cholesterol value and the metabolic syndrome. Similar results were found in a prospective study of a Danish cohort.[34] All of these results imply that management of LDL cholesterol as well as the metabolic syndrome is important for the prevention of ischemic stroke and CHD.

The strengths of our study include its longitudinal population-based study design, long duration of follow-up, almost perfect follow-up of subjects, sufficient number of cardiovascular events, and accuracy for diagnosis of CVD, including ischemic stroke subtypes. One limitation of our study is that our findings are based on a 1-time measurement of serum lipids. Subsequent use of cholesterol-lowering agents could have altered lipid levels in some participants; however, this source of variability could not account for the relation observed in the present study, because a random misclassification of such nature would tend to cause an underestimation of study findings and bias the results toward the null hypothesis. Therefore, the true association could be stronger than that observed in our study. Another limitation is that the value of LDL cholesterol was not directly assayed but was calculated by the Friedewald equation. This equation has been adopted in substantial epidemiologic and clinical studies of LDL cholesterol and CVD. It is unlikely that the bias of LDL cholesterol values that occurred through calculation, if any, would have strengthened the association between LDL cholesterol and ATI or CHD observed in the present analysis.

In conclusion, we have shown that elevated LDL cholesterol is a significant risk factor for developing ATI as well as CHD in a general Japanese population. Because LDL cholesterol level is independent of the metabolic syndrome for the development of CVD, lowering a patient's LDL cholesterol level should be considered together with treatment of other metabolic disorders for the prevention of CVD.

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Disclosures

None.

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厚生労働省科学研究費補助金(循環器疾患等生活習慣病対策総合研究)
分担研究報告書

耐糖能障害と大血管障害との関連 ―舟形研究(Funagata study)―

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研究要旨

糖尿病は大血管障害の危険因子であることは多くの研究より明らかにされている。糖尿病の予備軍といえる境界型の異常、言い換えれば、メタボリックシンドロームの構成因子といえる高血糖の状態、と大血管障害との関連についても近年注目されており、報告が多く成されているが、耐糖能の正確な評価が無い、大血管障害を、心血管障害と脳血管障害にわけて解析していない、等の問題点があった。今回、私達は山形県舟形町の 35 歳以上の住民を対象としたコホート追跡研究(n=2,938)にて耐糖能別の大血管障害への危険度について調べ、糖尿病は脳卒中、及び、心血管障害の危険因子だが、耐糖能障害(IGT)も大血管障害(OR:1.77, 95%CI:1.68-1.87)、特に、脳卒中(OR:1.87, 95%CI:1.73-2.03)の強い危険因子であることを明らかにした。

A. 研究目的

大血管障害は、主に、脳卒中と心血管障害(CHD)の2つの疾患を合わせた概念である。欧米での研究では、耐糖能障害(IGT)が CHD の危険因子であるとの報告は多数されているが、一方、脳卒中の危険因子であるかは明確にされていない。これは、欧米での脳卒中の発症率の低さ(CHD の 25-35%)に起因する検出力の低下に基づくものかもしれない。本邦では、脳卒中の発症率は CHD の 1.5-2.5 倍と報告されているので、本邦の症例を用いれば、より検出力の高い解析ができると思われる。そこで、私達のコホート(舟形コホート)を用いて、IGT と脳卒中、及び、CHD との関連を調べた。

B. 研究方法

1979 年より山形県舟形町の35歳以上の住民を対象に行っている舟形研究では、1990 年から参加者全員に糖負荷試験を行い、確実な耐糖能の評価を行いコホートとして追跡調査を行っている。第1コホート(1990-1992 年受検者)を対象に死亡をエンドポイントとした研究では、IGT でも大血管障害による死亡率が正常耐糖能と比して有意に高く、その程度は糖尿病に匹敵することを報告した(正常耐糖能に対するハザード比は糖尿病では2.3倍、IGTでは2.2倍)(Diabetes Care 22:920, 1999)が、この研究の脳卒中と CHD に分けての解析では、IGT はいずれに対しても有意な危険因子とならなかった。そこで、症例数を増やし、追跡期間も延ばし、さらに、死亡ではなく発症をエンドポイントとして、脳卒中および CHD の発症と耐糖能との関係を調べた。

第1コホートに第2コホート(1995-1997 年受検者)を加えて対象とし(n=3,482; 対象舟形住民人口は 3,806 で参加率は 91.5%)、エンドポイントには脳卒中および CHD の死亡のみならず発症を加えた。2002 年 12 月末までの脳卒中と CHD の発症有無については、個別のアンケート調査を

行い(2,938 名より有効回答)、死亡は死亡票のICD コードより把握した。対象者はベースラインでの耐糖能検査の結果により正常群、境界型群(IGT 及び空腹時過血糖(IFG))、糖尿病群(1999JDS criteria)に分けた。糖尿病で治療中のものは、糖負荷試験によらず糖尿病とした。各群の疾患発症状況の違いについて統計解析(人年法、生命表法、Cox 比例ハザードモデル)を行い比較した。

C. 研究結果

平均追跡期間は 116.5(最長 147)ヶ月。人年法解析では糖尿病および IGT 共に脳卒中およびCHD の有意な危険因子であった(脳卒中に対してのオッズ比は各々3.6 及び 1.9;CHD に対しては各々3.5 及び 1.5)が、IFG は危険因子ではなかった。また、COX 比例ハザードモデル解析では、IGT は脳卒中の有意な危険因子(ハザード比:1.51, p=0.039)であったが、CHD に対しては有意ではなかった(p=0.51)。IFG は脳卒中及びCHD のどちらに対しても有意な危険因子とは認められなかった。

D. 考察

糖尿病は脳卒中および CHD の危険因子と考えられた。一方、IGT は、脳卒中の危険因子であると考えられたが、CHD の有意な危険因子であるとは示せなかった。IGT が日本人においてもCHD の危険因子であるかは、今後の研究課題である。私達の研究からは、IGT は CHD よりも脳卒中の危険因子としての程度がより強いと考えられた。本邦では、CHD の発症が増加しているとはいえ、まだまだ脳卒中の発症率の方が明らかに高いということを考慮すると、IGT は脳卒中の危険因子として強調すべきものと考えられた。

E. 結論

糖尿病は脳卒中および CHD の危険因子と考えられるが、IGT も脳卒中の危険因子と考えられた。

G.研究発表

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H.知的財産権の出願・登録状況

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Impaired glucose tolerance is a risk factor for stroke in a Japanese sample—the Funagata study

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Abstract

Impaired glucose tolerance (IGT) is a known risk factor for cardiovascular disease, which includes stroke as well as coronary heart disease (CHD). We investigated whether IGT is a risk factor for stroke. The incidence of stroke and CHD in a cohort population (n = 2938) consisting of participants of the 1990-1997 Funagata study was assessed through interviews with the participants and their family members and reviews of death certificates and residence transfer documents through 2002. Glucose tolerance at the baseline was classified according to the criteria of the 1998 World Health Organization (normal glucose tolerance, n = 2189; IGT, n = 320; and diabetes, n = 286). The cumulative incidences among the groups were compared using the Kaplan-Meier product-limit method, and the risks of these conditions were evaluated by person-year and Cox proportional hazard methods. During the 147-month (mean, 116.5 months) follow-up, 158 (normal glucose tolerance, IGT, and diabetes: 94, 35, and 29, respectively) participants experienced a stroke and 94 (54, 16, and 24, respectively) experienced CHD. By the person-year method, IGT and diabetes were shown to be significant risk factors for stroke and CHD (odds ratio, 1.87 [95% confidence interval, 1.73-2.03] and 3.57 [3.21-3.98] for stroke; 1.53 [1.31-1.78] and 3.47 [2.91-4.14] for CHD, respectively). Cox proportional hazard analysis showed that IGT was a risk factor for stroke (age-, sex-, and hypertension-adjusted hazard ratio: 1.51 [95% confidence interval, 1.02-2.24], $P = .039$) but not for CHD (1.21 [0.69-2.313], .509). Impaired glucose tolerance is a risk factor for future stroke in a Japanese population.
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1. Introduction

Abnormal glucose tolerances such as impaired glucose tolerance (IGT) as well as diabetes are well-established risk factors for cardiovascular disease (CVD) [1-5]. Because CVD includes several medical conditions, such as stroke and coronary heart disease (CHD), the observed risk for CVD is the combined outcomes of these medical conditions. Both diabetes and IGT seem to be well-established risk factors for CHD [6-9]. likewise, that diabetes is a risk factor for stroke has also been shown in many studies [9-11]. However, IGT does not seem to be a well-established risk factor for stroke.

A high prevalence of abnormal glucose tolerance, including IGT, in patients who have had a recent ischemic stroke has been reported [12,13]; and thus, IGT may also be a risk factor for stroke. In some studies of elderly subjects (mean age, ~75 years), IGT was shown to be a risk factor for stroke [14,15]. Furthermore, IGT has been reported as a risk factor for future stroke in patients having experienced a transient ischemic attack or minor ischemic stroke as well as in those with CHD [16,17]. Therefore, it is being established that IGT is a risk factor for stroke, at least in some high-risk populations. We conducted a cohort study of the participants of the community-based Funagata study to determine whether IGT is a risk factor for stroke in the general population as well.

2. Subjects and methods

2.1. Subjects

The Funagata study is a population-based longitudinal study held in Funagata, an agricultural area located about

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400 km north of Tokyo, Japan [18,19]. An original cohort of 2658 participants older than 40 years that registered from 1990 to 1992 and additional cohorts of 824 participants older than 35 years that registered from 1993 to 1997 (n = 3482) were enrolled for this study. The Funagata population older than 35 years in 1995 was 4183. Individuals (n = 377) with stroke or other disabilities who were unable to participate in the study were excluded at the baseline. Thus, the participation rate was estimated as 91.5% (3482 of 3806 [4183−377]). Through 2002, death certificates were reviewed annually; and medical conditions including stroke and CHD events (fatal and nonfatal) were evaluated at the end of 2002 by interviewing the participants and their family members by area public health nurses using questionnaires. Among the participants, 2938 completed the study (follow-up rate, 84.3%). Of them, 288 died and 44 moved away during the follow-up. The participants who moved away during the follow-up period were identified by residence transfer documents. Death certificates of the deceased participants were collected with the permission of the Management and Coordination Agency of the Japanese government once a year. The death code (*International Classification of Diseases, Ninth Revision* [1990-1994] or *International Statistical Classification of Diseases, 10th Revision* [1995-2002]), the date, and the place of death were reviewed. In this study period, the participants did not receive any interventions not only for diabetes mellitus but also for comorbid disease, except for ordinary advice for health promotion.

All participants, except those (n = 167) who had been identified by public health nurses and through contacts with outpatient clinics as receiving medication for diabetes mellitus and thus were classified as diabetic, completed a 75-g oral glucose tolerance test at the baseline. Glucose tolerance was classified by the 1998 criteria of the World Health Organization [20]. The cohort population was divided into 3 groups: normal glucose tolerance (NGT) (n = 2189), IGT (n = 429), and diabetes (n = 320). For an analysis in which the risk of impaired fasting glucose (IFG) was examined, fasting plasma glucose levels alone were used to classify glucose tolerance: NGT (n = 2520), IFG (n = 172), and diabetes (n = 246). Hypertension was defined as present if the subject was confirmed to be receiving medications for hypertension by a questionnaire. This study was approved by the Ethics Committee of Yamagata University School of Medicine, and informed consent to participate in this study was obtained from all participants.

2.2. Statistical methods

The clinical characteristics are given as the means ± SD. The statistical significance of the differences in the characteristic values between any 2 groups was assessed by analysis of variance. The Scheffe test was used for post hoc analysis. The statistical significance of the difference in the sex ratio was analyzed by χ^2 tests.

For age adjustment of the study groups, the person-year method was used, with stratification into 5-year age groups by sex: 35 to 39, 40 to 44, 45 to 49, and so on. The observed person-years and events in each column were counted. The odds ratios of IGT to NGT and of diabetes to NGT for CVD, CHD, and stroke were calculated. The cumulative incidences were compared among the NGT, IGT, and diabetic groups using the Kaplan-Meier product-limit method, in which all events (fatal or nonfatal) corresponding to CVD (either stroke or CHD) were adopted as the end point. Multivariable Cox regression models were used to estimate the hazard ratios (HRs) of age, sex, hypertension, IGT to NGT, and diabetes to NGT. The latter 2 variables were used one after the other. For example, the diabetic group was not used when calculating the HR of IGT to NGT. A P value less than .05 was considered significant. All analyses were conducted using Stat View for Windows, version 5.0 (SAS Institute, Cary, NC).

3. Results

3.1. Clinical characteristics of the study groups

The clinical characteristics of the study groups at the baseline are shown in Table 1. The mean age and the sex ratio of the NGT, IGT, and diabetic groups were significantly different among the groups; thus, these differences were considered in the interpretation of the comparison of cumulative incidences among the 3 groups.

3.2. IGT is a risk factor for stroke

As shown in Table 2, during the follow-up, 158 (5.4%) participants experienced a stroke (ischemic, hemorrhagic,

Table 1
Baseline characteristics of the cohort population by glucose tolerance status

	NGT	IGT	Diabetes
n	2189	429	320
Age (y)	55.4 ± 11.5	60.8 ± 10.8[a]	65.0 ± 10.5[a]
Sex (M/F)	987/1202	172/257[b]	134/190[b]
Height (cm)	155.6 ± 8.5	152.5 ± 8.7[a]	152.0 ± 8.1[a,c]
Body weight (kg)	56.6 ± 9.4	57.9 ± 10.6[a]	59.9 ± 10.3[a,c]
Fasting plasma glucose (mg/dL)	90.5 ± 8.5	101.7 ± 11.7[a]	130.2 ± 32.8[a,c]
2-h plasma glucose (mg/dL)	99.2 ± 21.5	150.2 ± 24.3[a]	244.0 ± 81.2[a,c]
Waist circumference (cm)	78.4 ± 9.1	83.2 ± 9.5[a]	86.7 ± 9.6[a,c]
Hip circumference (cm)	91.5 ± 5.6	93.0 ± 6.6[a]	95.3 ± 7.1[a,c]
Waist-to-hip ratio	0.856 ± 0.074	0.893 ± 0.071[a]	0.910 ± 0.071[a,c]
Body mass index (kg/m^2)	23.33 ± 3.06	24.81 ± 3.47[a]	25.89 ± 3.65[a,c]
Hypertension (%)	468 (21.4)	151 (35.2)[b]	166 (51.9)[b]

Data are means ± SD. P less than .05 was considered as significant.

[a] Mean value was significantly different from that of the NGT group (Scheffe F test).

[b] Sex distribution was significantly different from the NGT group (χ^2 test).

[c] Data were not obtained from the subjects (n = 167) who had been diagnosed as diabetic before the baseline examination.

Table 2
Odds ratio of CVD, stroke, and CHD by glucose tolerance status (person-year method)

	NGT	IGT	Diabetes
n	2189	429	320
CVD			
No. (%) of events			
Total	147 (6.7)	51 (11.9)	51 (15.9)
Fatal and nonfatal	47 (2.1), 100 (4.6)	20 (4.7), 31 (7.2)	23 (7.2), 28 (8.8)
Observed person-years	21139.7	4147.1	2934.4
Odd ratio (95% CI)	1	1.77 (1.68~1.87)	2.55 (2.35~2.75)
Stroke			
No. (%) of events			
Total	94 (4.3)	35 (8.2)	29 (9.1)
Fatal and nonfatal	28 (1.3), 66 (3.0)	13 (3.0), 22 (5.1)	10 (3.1), 19 (5.9)
Observed person-years	21319.3	4176.8	3100.9
Odds ratio (95% CI)	1	1.87 (1.73~2.03)	3.57 (3.21~3.98)
CHD			
No. (%) of events			
Total	54 (2.5)	16 (3.7)	24 (7.5)
Fatal and nonfatal	19 (0.9), 35 (1.6)	7 (1.6), 9 (2.1)	13 (4.1), 11 (3.4)
Observed person-years	21393	4249.8	2994.2
Odds ratio (95% CI)	1	1.53 (1.31~1.78)	3.47 (2.91~4.14)

The NGT group was used as a reference.

and unclassified: 104, 45, and 7, respectively) and 94 (3.2%) participants experienced CHD. Among them, one of the NGT group and two of the diabetes group had 2 events (ischemic stroke and CHD) simultaneously; and thus, these participants were counted for these 2 events. By the person-year method, both IGT and diabetes were shown to be

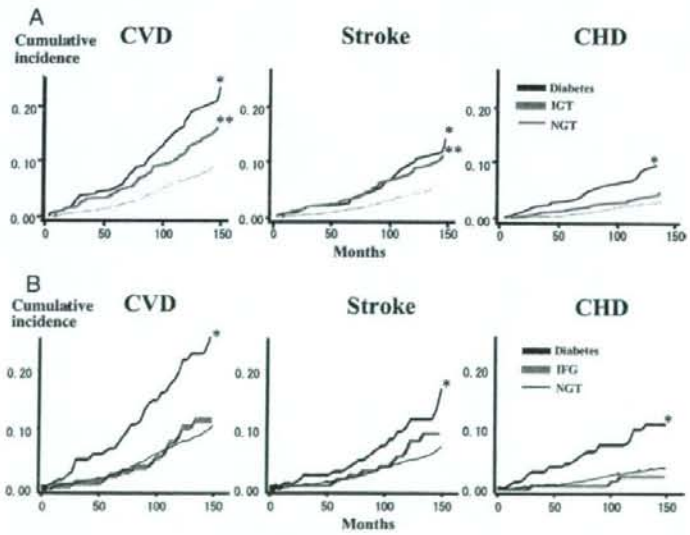

Fig. 1. Cumulative incidence of CVD, CHD, and stroke by glucose tolerance status. A, The participants were divided into 3 groups based on the 1998 criteria of the World Health Organization for glucose tolerance: NGT, IGT, and diabetes. B, Fasting plasma glucose levels alone were used to classify their glucose tolerance: NGT, IFG, and diabetes. The significances of the differences between each groups at the end of the follow-up are indicated by * and **, respectively. The cumulative incidence of stroke for the IGT group was significantly higher than that for NGT, whereas that for IFG was not significant. *P* less than .05 was considered as significant.

significant risk factors for both stroke and CHD, as the odds ratios of those incidences for IGT to NGT and diabetes to NGT were significantly more than 1.0 (Table 2).

As shown in Fig. 1A, at the end of the follow-up (longest and mean follow-up periods: 147 and 116.5 months, respectively), the cumulative incidences of CVD, stroke, and CHD for diabetes (0.159, 0.091, and 0.075, respectively) were significantly higher than those for NGT (0.067, 0.043, and 0.025, respectively). The cumulative incidences of CVD and stroke for IGT (0.117 and 0.082, respectively) were significantly higher than those for NGT, whereas the cumulative incidence of CHD for IGT (0.037) was not significantly higher than that for NGT.

Afterward, Cox proportional hazard model analyses were used to adjust the differences in several clinical characteristics among the groups, which could account for the observed differences in the cumulative incidences. The variables included in this model were age, sex, and the presence of hypertension, which are known as strong risk factors for stroke. As shown in Table 3, IGT was associated with increased risk for stroke (HR, 1.51; 95% confidence interval [CI], 1.02-2.24), but not for CHD (1.21, 0.69-2.13), whereas diabetes was significantly associated with CHD ($P = .010$) and CVD ($P = .017$). Association of IGT with increased risk for CVD was marginal ($P = .054$) (Table 3). All of these results indicate that IGT is a significant risk factor for stroke in a Japanese population.

3.3. IFG is not a risk factor for stroke

As shown in Fig. 1B, at the end of the follow-up, the cumulative incidences of CVD, stroke, and CHD for IFG (0.110, 0.091, and 0.034, respectively) were not significantly higher than those for NGT (0.101, 0.069, and 0.022, respectively). Furthermore, Cox proportional hazard model analyses with age, sex, and the presence of hypertension as the covariables did not show the risk of IFG for CVD (HR, 0.88; 95% CI, 0.52-1.50), stroke (1.11, 0.61-2.02), and CHD (0.50, 0.16-1.60). These results indicate that IFG is not a substantial risk factor for stroke in a Japanese population.

Table 3
Risk for CVD, stroke, and CHD by glucose tolerance status

	HR	95% CI	P
CVD			
Age (1 y)	1.06	1.05~1.08	<.001
Sex (female)	0.54	0.42~0.70	<.001
Hypertension	1.62	1.25~2.11	<.001
IGT (vs NGT)	1.37	0.99~1.89	.054
Diabetes (vs NGT)	1.50	1.08~2.10	.017
Stroke			
Age (1 y)	1.06	1.05~1.08	<.001
Sex (female)	0.63	0.46~0.86	.004
Hypertension	1.25	1.03~1.54	.025
IGT (vs NGT)	1.51	1.02~2.24	.039
Diabetes (vs NGT)	1.47	0.96~2.25	.079
CHD			
Age (1 y)	1.07	1.05~1.09	<.001
Sex (female)	0.45	0.29~0.68	<.001
Hypertension	1.05	0.80~1.41	.679
IGT (vs NGT)	1.21	0.69~2.13	.509
Diabetes (vs NGT)	1.97	1.18~3.28	.010

Cox hazard model was applied. Calculation was done vs NGT group.

4. Discussion

Both diabetes and IGT are well-established risk factors for CVD [1-5], which includes several medical conditions such as stroke and CHD. The incidence of stroke is much lower (25%-35% of CHD) than that of CHD in the United States and Europe [2,21,22]. Therefore, in previous studies, the observed risk for CVD seemed to be attributed primarily to the risk for CHD. Here, we evaluated separately the risks of IGT for stroke and CHD using a cohort study of a Japanese population. The incidence of stroke is higher (1.5-2.5 times more) than that of CHD in Japan [23-25]; therefore, the risk for stroke was evaluated more precisely in the present study. However, even in a previous study of Japanese subjects, IGT was shown to be a risk factor for CVD but not for stroke [26]. In the previous study, the follow-up period (5 years) was substantially shorter than ours (mean, 116.5 months); and this difference may account for the insignificant result. We have clearly shown here that IGT was a significant risk factor for stroke in a community-based Japanese sample.

Increased risk of IGT for future stroke has been shown [16,17]. However, the study populations used were those with transient ischemic attacks or minor ischemic stroke or those with CHD; and thus, these studies indicated that IGT is a risk factor for stroke in some high-risk populations. Recently, in an English population-based male cohort study, *glucose intolerance*, defined as 96 to 199 mg/dL of 2-hour plasma glucose after 50-g oral glucose tolerance test, was shown to be a risk factor for stroke mortality (HR, 1.47; 95% CI, 1.16-1.88) [21]. In that study [21], however, nonfatal stroke events were not monitored; thus, the risk for stroke seemed to be evaluated less precisely. Both fatal and nonfatal stroke events were monitored in the present study.

Although IGT was shown to be a significant risk factor for stroke, diabetes was not shown to be a significant risk factor for stroke in the present study. The above-mentioned study similarly showed that diabetes was not a risk factor for stroke mortality (HR, 1.16; 95% CI, 0.29-4.64) [21]. However, these results may not be appreciated. As is typical of population-based studies, the samples were uneven. In this case, the number of the diabetic subjects was considerably smaller than that with IGT. This fact may have decreased the statistical power to assess the risk for diabetes in the present study and may explain the lack of significance in the results.

We have shown here that IGT is a risk factor for future stroke independent of age, sex, and the presence of hypertension. Blood pressures were not measured for all the participants, and hypertension was defined on the basis of medications. Therefore, those who were hypertensive but not

on medications were not defined as hypertensive, which may discount the significance of the results. Except for the factors described above, there are several other known risk factors for stroke, such as smoking, atrial fibrillation, and hyperlipidemia [27-30]. A meta-analysis with 32 separate studies showed the overall relative risk of stroke associated with cigarette smoking (relative risk, 1.5) [28]. In the Framingham Study, the following have been shown: the risk of stroke was increased as the number of cigarettes smoked increased, and the relative risk of stroke in heavy smokers (greater than 40 cigarettes per day) was twice that of light smokers (fewer than 10 cigarettes per day)[27]; compared with subjects free of the conditions, the age-adjusted incidence of stroke was more than trebled in the presence of hypertension and a near 5-fold excess when atrial fibrillation was present [29]. A study to examine the relation between the serum total cholesterol level and the risk of death from stroke in 350977 men showed a positive association between the serum cholesterol level and death from nonhemorrhagic stroke [30]. Therefore, these factors appeared to be the established risk factors for stroke and thus should have been included in this study; however, we could not obtain such information under conditions reliable enough for analysis. Information about smoking habits was obtained from only some of the participants, and none of the participants gave information about the presence of atrial fibrillation. Information related to hyperlipidemia such as serum total cholesterol and triglyceride levels was obtained for most participants (n = 2830). However, no information about medication for hyperlipidemia was available; and thus, precise diagnosis for hyperlipidemia was not possible. Nevertheless, when we added the information about hyperlipidemia (serum cholesterol levels ≥240 mg/dL and/or triglyceride levels ≥150 mg/dL) as one of the covariates for the multivariate Cox regression analysis shown in Table 3, IGT was still shown to be a significant risk factor for stroke (1.53, 1.03-2.27, $P = .036$). Therefore, although this result may not be accurate, it raises the possibility that the risk of IGT for stroke may be independent of hyperlipidemia as well. Whether IGT is a risk factor for stroke independent of other factors such as hyperlipidemia, smoking habits, and atrial fibrillation has yet to be proven.

Many epidemiologic studies have shown that IGT is a risk factor for CVD, whereas IFG is not [1-9,18,31-33]. However, whether IGT and/or IFG is a risk factor for stroke has not been well established to date. Several studies in which intima-media thickness has been used as a condition related to carotid atherosclerosis, which seemed to lead to the development of stroke, have shown that IGT was associated with intima-media thickness, but IFG was not [34-36], although a controversy exists [37]. These facts may indicate that IGT is a risk factor for stroke, whereas IFG is not. We examined here also the risk of IFG for CVD, stroke, and CHD and found that IFG was not a risk factor for these conditions. These results indicate that IFG is not a risk factor for stroke as well as for CVD.

In conclusion, IGT is an independent risk factor for future stroke in a Japanese population.

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The metabolic syndrome and retinal microvascular signs in a Japanese population: the Funagata study

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ABSTRACT

Aims: To determine the relationship of metabolic syndrome and its components with retinopathy and other retinal microvascular signs in a Japanese population.

Methods: The Funagata study recruited 1961 (53.3% of eligible) Japanese aged 35 or older. The metabolic syndrome was diagnosed primarily using definitions of the International Diabetes Federation. Retinopathy and retinal microvascular signs were assessed from fundus photographs. Retinal arteriolar and venular diameters were measured using a computer-assisted programme.

Results: Data were available for analysis in 1638 persons for retinopathy and retinal microvascular signs and 921 persons for retinal vessel diameters. Various components of the metabolic syndrome were associated with retinal microvascular signs: a larger waist circumference was associated with wider venular diameter and retinopathy lesions; a higher blood pressure level was associated with focal arteriolar narrowing, arteriovenous nicking, enhanced arteriolar wall reflex and narrower arteriolar diameter; and a higher triglyceride level was associated with enhanced arteriolar wall reflex. Overall, persons with the metabolic syndrome were more likely to have retinopathy (odds ratio 1.64, 95% CI: 1.02 to 2.64) and wider venular diameter 4.69 μm (95% CI: 1.20 to 8.19 μm) than persons without the metabolic syndrome.

Conclusion: We report associations of metabolic syndrome components with retinopathy and wider venular diameter in Japanese adults. These data suggest that metabolic abnormalities, indicated by metabolic syndrome components, are associated with microvascular changes in the retina. There was no synergistic effect of the metabolic syndrome on retinal microvascular changes beyond its individual components.

The metabolic syndrome, consisting of central obesity, dyslipidaemia, high blood pressure and hyperglycaemia, is increasingly seen as a major public health problem affecting a large proportion of adult persons worldwide, including Japan.[1] The metabolic syndrome is associated with a high risk of cardiovascular disease and premature mortality.[1 2] In addition to large-vessel diseases, there is increasing evidence that metabolic syndrome, like diabetes, may also impact on the microvasculature.[3] Recent studies have shown that individual components of the metabolic syndrome are associated with various retinal microvascular changes. For example, narrower retinal arteriolar diameter has been associated with hypertension,[4–9] and wider venular diameter with diabetes,[6] dyslipidaemia[8 10 11] and obesity.[6 11]

However, to the best of our knowledge, there has been only one study that has directly examined the relationship of the metabolic syndrome with retinal microvascular signs. The Atherosclerosis Risk In Community (ARIC) study, which examined Caucasian white and African–American populations in the United States,[12] showed that metabolic syndrome had a range of effects on the retinal vasculature. It is unclear whether such associations are also present in Asian populations. It has been suggested, for example, that waist circumference is different in Asian versus Caucasian populations.[13]

In the current study, we report the associations of the metabolic syndrome, and its components, with retinal microvascular signs in population-based samples of adult Japanese, the Funagata study.

METHODS

Study population

The Funagata study is a population-based study of Japanese aged 35 years or older.[14] The study population and methods have been described in detail previously.[14 15] All data are based on the examinations between 2000 and 2002. A total of 4160 residents in the Funagata town, Yamagata, Japan were invited to this study. We excluded individuals with severe disabilities as well as those under treatment for diabetes, because our screening included a 75-g oral glucose test to detect newly diagnosed diabetes. We excluded 484 individuals leaving 3676 persons identified as eligible. Of these, 1961 (53.3% of those eligible) participated in examinations. Comparing the demographics of participants and non-participants, women were more likely to participate (57.6% vs 51.5%, $p = 0.002$). Of the 1961 who participated, 1786 (48.6%) had retinal photographs taken, and 1638 (91.7% of 1,786) had adequate quality for grading retinal signs. These were included in the assessment of retinal microvascular signs including arteriolar wall signs (focal arteriolar narrowing, arteriovenous nicking and enhanced arteriolar wall reflex) and presence of retinopathy lesions. There were 921 (25.1%) who had retinal photographs with good quality and appropriate field definition so that retinal vessel diameters could be measured. Compared with these 921 individuals, persons who were excluded were older and had a shorter height and a lower weight.[14] There was no statistically significant difference between systolic/diastolic blood pressures, body mass index, waist circumference, triglyceride and HDL cholesterol level between these two groups.[14] Institutional review boards at the Yamagata University Faculty of Medicine (Yamagata, Japan) and at the Johns

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Hopkins University Bloomberg School of Public Health (Baltimore, MD) approved this study. Informed consent was obtained from all participants, and the study was conducted according to the recommendations of the Declaration of Helsinki.

Data collection

All participants had a standardised examination. Anthropometric measurements were taken, with each subject wearing light clothing and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Waist circumference was measured at the level of the umbilicus. Blood samples were collected after at least a 10-h overnight fast. Fasting plasma glucose (FPG) was measured by the glucose oxidase method (GA1160, Arkray, Kyoto, Japan). HDL cholesterol was measured using selective inhibition (TBA 80FR, Toshiba Medical System, Tokyo). Triglyceride (TG) was measured by the glycerol phosphate oxidase method (TBA 80FR, Toshiba Medical System, Tokyo). Blood pressure was measured once in a sitting position, after 5 minutes' rest using a mercury sphygmomanometer.

Definition of the metabolic syndrome

We adopted the International Diabetes Federation (IDF) definition of the metabolic syndrome;[16] a person had metabolic syndrome if central obesity (defined by ethnicity- and gender-specific waist circumference), plus any of two of four additional factors, was present:

- high TG level: ≥1.7 mmol/l (150 mg/l);
- low HDL cholesterol: <1.03 mmol/l (40 mg/dl) in men and <1.29 mmol/l (50 mg/dl) in women or participants who were on treatment specifically for these lipid abnormalities;
- high blood pressure: systolic blood pressure ≥130 or diastolic blood pressure ≥85 mm Hg at examinations (or participants with a previous diagnosis of hypertension and who were on treatment for hypertension;
- high FPG: FPG ≥5.6 mmol/l (100 mg/dl) at examinations or participants with a previous diagnosis of type 2 diabetes.

We primarily used the IDF ethnicity-specific definitions of larger waist circumference for Japanese (men ≥85 cm and women ≥90 cm). For comparison, we repeated analyses with the definition by the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP-ATPIII).[17] This latter defines metabolic syndrome in a person with any three or more of the same five categories as in the IDF definition, except the cut-off for FPG is higher at 6.1 mmol/l (110 mg/dl) and central obesity (larger waist circumference) is not required as a mandatory component.

Assessment for retinal microvascular signs

The procedures for retinal photography and the grading of retinal microvascular signs are described in detail elsewhere.[14] In brief, one eye underwent retinal photography using a non-stereoscopic 45° non-mydriatic fundus camera (CR5-NM45, Canon, Tokyo; TRC, Topcon, Tokyo). Photographs were graded for retinal microvascular signs and retinal vessel diameters at the Centre for Vision Research, University of Sydney. Grading was performed by a trained grader in a masked fashion following standardised protocols as in the Blue Mountains Eye Study. Retinal microvascular signs assessed included retinal arteriolar wall signs (focal arteriolar narrowing, arteriovenous nicking and enhanced arteriolar wall reflex), retinopathy lesions (microaneurysms, retinal haemorrhages and exudates) and arteriolar/venular diameters.

Focal arteriolar narrowing was assessed in arterioles at least one half-disc diameter away from the optic disc margin and was graded as absent, questionable, mild or severe. Arteriovenous nicking was defined as a decrease in venular width on both sides of the crossing by an arteriole above the venule and was graded as absent, questionable, mild, moderate or severe.[5] Enhanced arteriolar wall reflex was assessed by comparing the central light reflex on major retinal arteriolar walls with standard slides with regard to the width, density and consistency of the reflex.[18]

Signs of narrower arteriolar diameter or wider venular diameter were assessed by measuring arteriolar and venular diameters using a computer-assisted program. Details of the digital image preparation are described elsewhere.[14] In brief, retinal photographs on 35-mm film were converted to digital images by scanner (LS2000, Nikon, Tokyo), and vessel diameters were measured using specific software. The average retinal arteriolar or venular diameter of each eye was calculated using the Parr–Hubbard formula and was summarised as the central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE).[4] All grading findings were adjudicated by a senior researcher, as well as a retinal specialist (PM), if significant pathology was found. Moderate to high intra-grader reproducibility was previously reported (Kappa values 0.55–0.86).[14]

Statistical analysis

The Mann–Whitney U test was used to compare continuous variables, and the chi-square test was used to compare categorical variables for demographic characteristics. Multiple logistic regression models were used to determine the likelihood (odds ratios) of having each retinal microvascular sign by the presence versus the absence of the metabolic syndrome and its components. The metabolic syndrome using the IDF and NCEP-ATP III definitions, and each of its five components (larger waist circumference, higher blood pressure; higher triglyceride, lower HDL cholesterol and higher glucose) were categorised as binary variables (present or absent). Retinal microvascular signs were categorised as binary outcomes (present versus absent): severe focal arteriolar narrowing; moderate to severe arteriovenous nicking; severe enhanced arteriolar wall reflex; and presence of any retinopathy lesions. Multiple linear regression models were used to estimate mean differences (μm) in CRAE and CRVE between those with and without the metabolic syndrome or its components.

Using logistic regression, we report findings of unadjusted estimates, estimates adjusted for age, gender and smoking status as co-variables (model 1), and estimates after adjusting for age, gender, smoking status and other components of the metabolic syndrome as co-variables (model 2). In regression analyses, the reference group was persons without the metabolic syndrome or its component. We also estimated the odds ratio and mean difference in vessel diameter associated with each additional metabolic syndrome component increase in the same subject, and persons who have four or more metabolic syndrome components versus persons without any metabolic syndrome components. Following the recommendation by Liew *et al*,[19] models for CRVE were also adjusted for CRAE and vice versa in adjusted models. All data were analysed using Stata for Windows (version9.2, StataCorp, College Station, TX).

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RESULTS

The demographic characteristics of the study population, and of persons with and without the metabolic syndrome defined by the IDF waist circumference criteria for Japanese, are shown in table 1. Persons with metabolic syndrome were significantly older, more likely to be men and smokers compared with persons without the metabolic syndrome.

The prevalence of retinal microvascular signs was higher in persons with a larger waist circumference, higher blood pressure, higher TG, higher FPG and metabolic syndrome than in persons without these component conditions. Persons with lower HDL cholesterol were less likely to have focal arteriolar narrowing, arteriovenous nicking and enhanced retinal arteriolar reflex, although the differences were not significant (table 2).

After adjusting for age, gender and smoking status (table 2, Model 1), persons with a larger waist circumference, or with higher fasting plasma glucose levels, were significantly more likely to have retinopathy lesions; persons with higher triglyceride levels were significantly more likely to have enhanced arteriolar wall reflex, and those with higher blood pressure levels were significantly more likely to have severe focal arteriolar narrowing, severe arteriovenous nicking or an enhanced arteriolar wall reflex. After further adjusting for other components of the metabolic syndrome in the model (table 2, Model 2), significant associations were persistent except for the association between higher fasting plasma glucose and retinopathy. After adjusting for age, gender, smoking status (table 3, Model 1), persons with a high blood pressure level were also significantly more likely to have a narrower CRAE, and persons with a larger waist circumference, higher triglycerides or higher fasting plasma glucose levels were significantly more likely to have a wider CRVE. After further adjusting for other components of the metabolic syndrome (table 3, Model 2), two associations remained significant: higher blood-pressure level with CRAE, and larger waist circumference with CRVE.

In this study population, 496 (30.3%) had one, 386 (23.6%) had two, 207 (12.6%) had three and 90 (5.5%) had four or more metabolic syndrome components. Persons with each additional coexisting metabolic syndrome component were 16–27% more likely to have retinal microvascular signs, or have 1.10 μm narrower arteriolar diameter and 1.75 μm wider venular diameter (tables 4 and 5). Persons with four or more metabolic syndrome components had two- to threefold increased odds of having retinal vascular signs except for focal arteriolar narrowing compared with persons without any metabolic syndrome components. Persons with metabolic syndrome were more likely to have retinopathy lesions (odds ratio 1.64, 95% confidence interval (CI): 1.02 to 2.64), and have an average CRVE 4.69 μm wider than that of persons without metabolic syndrome (95% CI: 1.2 to 8.19 μm) (tables 4 and 5). The association between metabolic syndrome and wider CRVE persisted, regardless of the different waist circumference cut-offs (provided by the IDF definition) or NCEP-ATPIII definitions of metabolic syndrome (data not shown). We further repeated these analyses in subgroups stratified by diabetes and by hypertension, and did not find any substantial difference in theses associations in persons with and without diabetes (n = 241 and n = 1,075, respectively), in those with and without hypertension (n = 496 and n = 820, respectively), or in those with both diabetes and hypertension (n = 129) and with neither diabetes nor hypertension (n = 708) (data not shown).

DISCUSSION

In this Japanese population, we found associations of metabolic syndrome and its individual components with a range of retinal microvascular signs. We confirmed positive associations between higher blood pressure level and focal arteriolar narrowing, arteriovenous nicking, enhanced arteriolar wall reflex and narrower arteriolar diameter, after adjusting for age, gender, smoking and other metabolic syndrome components. We also found that a larger waist circumference was associated with the presence of retinopathy lesions and with a wider venular diameter; higher TG levels were associated with an enhanced arteriolar wall reflex and a wider venular diameter. The associations between individual metabolic syndrome components and various retinal microvascular signs found in this Japanese sample are consistent with findings from mainly white populations, including studies in the United States,[4 5 6 9 12 20] Australia,[6 7] and the Netherlands.[11] We found that a larger waist was associated with retinopathy and wider venular diameter. The associations between obesity and retinopathy have been shown among persons with type 1[21] and type 2 diabetes,[22] as well as in persons without diabetes.[23] The association between obesity (larger waist circumference,[12] waist-to-hip ratio,[11] and body mass index[8]) and wider venular

Table 1 Demographics of participants with or without metabolic syndrome, defined with the International Diabetes Federation (IDF) criteria

	Metabolic syndrome	
	Present	Absent
	N = 202	N = 1436
	Mean (SD)	Mean (SD)
Age (years)	62.5 (11.5)	59.6 (12.0)
Gender (% male)	77.7	22.3
Current smoker (%)	25.7	18.1
Systolic blood pressure (mm Hg)	137.1 (14.5)	125.8 (16.7)
Diastolic blood pressure (mm Hg)	82.1 (9.2)	75.1 (9.7)
Height (cm)	159.6 (9.5)	154.8 (8.9)
Weight (kg)	69.3 (10.2)	55.8 (9.5)
Body mass index (kg/m^2)	27.3 (4.0)	23.2 (3.0)
Total cholesterol (mg/dl)	208.7 (34.8)	201.4 (33.0)
Triglyceride (mg/dl)	184.1 (107.0 to 204.5)*	110.1 (65.0 to 123.0)*
HDL cholesterol (mg/dl)	49.6 (13.9)	59.8 (13.8)
Fasting plasma glucose (mg/dl)	104.5 (16.9)	93.7 (13.9)

Data presented are mean and standard deviation (SD) unless otherwise stated.
*The inter-quartile range is shown for triglyceride because of the highly skewed distribution.