

Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women

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Abstract

Aims/hypothesis. The aim of this study was to examine the relationship between type 2 diabetes and risk of ischaemic stroke in Asian populations.

Methods. We conducted a 17-year prospective cohort study in 10,582 Japanese individuals (4287 men and 6295 women) aged 40–69 years living in five communities in Japan. All subjects were free of stroke and CHD at baseline. Diabetes was defined as a fasting glucose level of ≥ 7.0 mmol/l, a non-fasting glucose of ≥ 11.1 mmol/l, or receiving medication for diabetes.

Results. The risk of non-embolic ischaemic stroke was approximately two-fold higher in diabetic subjects than in subjects with normal glucose levels. The multivariate relative risk after adjustment for age, community, hypertensive status, BMI, triceps and subscapular skinfold thickness (TSF and SSF), and other known cardiovascular risk factors was 1.8 (95% CI 1.0–3.2) for men and 2.2 (1.2–4.0) for women. This excess risk was primarily observed among non-hypertensive subjects and

individuals with higher values for measures of adiposity (BMI, TSF and SSF values above the median), particularly those with higher values for SSF. The association between non-embolic ischaemic stroke and glucose abnormality was particularly strong among non-hypertensive subjects with higher SSF values: the multivariate relative risk was 1.9 (1.0–3.7) for borderline diabetes and 4.9 (2.5–9.5) for diabetes.

Conclusions/interpretation. In this cohort, type 2 diabetes was a significant risk factor for non-embolic ischaemic stroke, particularly in non-hypertensive and non-lean individuals. Due to the nationwide decrease in blood pressure and increase in mean BMI among the Japanese population, with current levels approaching those observed in Western countries, the impact of glucose abnormalities on risk of ischaemic stroke represents a forthcoming public health issue in Japan.

Keywords Adiposity · BMI · Follow-up studies · Ischaemic stroke · Japanese · Type 2 diabetes · Skinfold thickness.

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Abbreviations: CT, computerised tomography · MRI, magnetic resonance imaging · RR, relative risk · SSF, subscapular skinfold thickness · TSF, triceps skinfold thickness

Introduction

Previous studies in Western countries and Japanese Americans have shown that diabetes, IFG and IGT are significant risk factors for ischaemic stroke [1, 2, 3]. However, data on Japanese people living in Japan and on other Asian populations are extremely limited [4]. Due to the lower prevalence of diabetes in Asia compared with that in Western countries [5], the majority of existing cohort studies in Asia may have a low statistical power for detecting an association between diabetes and risk of ischaemic stroke.

Since the 1960s, the prevalence of diabetes [5] and the mean BMI had increased in Japan, while blood

pressure levels have decreased [6]. Because hypertension is a primary risk factor for ischaemic stroke [1, 4], we postulated that the increased prevalence of diabetes and obesity and the decreased blood pressure levels may increase the relative contribution of diabetes to the development of ischaemic stroke. To investigate whether diabetes is a significant predictor of ischaemic stroke in Japanese men and women, particularly in non-hypertensive and non-lean individuals, we analysed data from a large prospective study of 10,000 middle-aged men and women in five Japanese communities.

Subjects and methods

Study population. The study population included residents of five communities who participated in one of three cardiovascular risk surveys. The first was performed between 1975 and 1980 in two northeast rural communities (the towns of Ikawa and Ishizawa, Akita Prefecture) and in a southwest rural community (the town of Noichi, Kochi Prefecture). The second was carried out between 1981 and 1986 in a central rural community (the town of Kyowa, Ibaraki Prefecture). The third was conducted between 1975 and 1984 in a southwest urban suburb (the city of Yao, Osaka Prefecture). Subjects were aged 40–69 years, and the overall participation rate at baseline was 67%. After excluding individuals with a history of CHD ($n=66$) and stroke ($n=135$) were excluded, 10,582 individuals (4287 men and 6295 women) remained in the analyses. Subjects were followed-up through 2000 to determine the incidence of stroke endpoints. A total of 632 (6%) subjects moved out of the communities during the follow-up period, as determined by the municipal office records on emigration, and 1750 (17%) died. For these subjects, follow-up was censored at the date of moving out or the date of death. The average follow-up period was 16.9 years. Informed consent was obtained from the participants and the study was approved by the Ethics Committee of the University of Tsukuba.

Endpoint determination. The participants were followed-up to identify the number of incident strokes that occurred up to the end of 2000. The details of endpoint determination have been previously described elsewhere [7]. Briefly, to obtain histories of incident strokes, participants completed annual cardiovascular risk surveys. For subjects who had moved from the community or died, the incidence of stroke was determined by mailed questionnaire and by the use of death certificates respectively. Cases with stroke as an underlying cause of death (International Classification of Diseases, 9th Revision) were selected from the death certificates. We also used national insurance claims, ambulance records, reports by local physicians, and reports by public health nurses and health volunteers. To confirm the diagnosis, all living patients were either telephoned or visited to obtain their medical history, and their medical records were reviewed. For deaths, we obtained histories from families and reviewed medical records.

Stroke was defined as a focal neurological disorder with rapid onset, persisting for at least 24 h or until death. Using the clinical criteria, incident strokes were identified by a panel of three to four study physicians who were blinded to the data from the risk factor survey. Stroke events were classified as intraparenchymal haemorrhages, subarachnoid haemorrhages, ischaemic strokes (thrombotic or embolic), or strokes of undetermined type, primarily based on computerised tomography

(CT) and/or magnetic resonance imaging (MRI) [8]. Non-embolic ischaemic strokes were subclassified as lacunar infarctions or large-artery occlusive infarctions [8].

In the present study, the endpoints of interest were non-embolic ischaemic stroke and its subtypes. Embolic infarction was not included because atrial fibrillation, which is relevant to chronic hypertension but not glucose abnormality, was the embolic source in the majority of cases [9].

Baseline examination. At baseline (study entry), blood was drawn from seated participants into a plain, siliconised glass tube and the serum was separated. Fasting was not required prior to blood draw. The distribution of time since the last meal was: <2 h, 39%; 2 h, 43%; 3–7 h, 9%; and ≥ 8 h, 9%. Serum glucose was measured by the cupric-neocuproine method between 1975 and September 1986 and by the hexokinase method thereafter. Glucose values obtained using the first method were adjusted using the formula of the regression line estimated from 60 random samples of blood: $0.047 \times (\text{glucose concentration in mmol/l}) - 0.541$, $r^2=0.93$. Glucose values were subsequently divided into three categories (normal, borderline diabetes and diabetes) according to modified criteria of the Japan Diabetes Society [10]. Borderline diabetes was defined as a fasting glucose level of 6.1–6.9 mmol/l or a non-fasting glucose level of 7.8–11.0 mmol/l, without the use of medication for diabetes. Diabetes was defined as a fasting glucose level of ≥ 7.0 mmol/l, a non-fasting glucose level of ≥ 11.1 mmol/l, or the use of medication for diabetes. Unlike the original criteria [10] and those of American Diabetic Association [11], we relied on a single measurement and did not require the presence of symptoms (polyuria, polydipsia and unexplained weight loss) for the diagnosis of individuals with a non-fasting glucose level of ≥ 11.1 mmol/l, due to the fact that the symptoms could not be reliably assessed in the survey situation.

Serum total cholesterol was measured by the Liebermann–Burchard direct method using the Autoanalyzer II (Technicon, Tarrytown, N.Y., USA) at the Osaka Medical Center for Cancer and Cardiovascular Diseases (presently the Osaka Medical Center for Health Science and Promotion). The Osaka laboratory has been standardised by the Centers for Disease Control / National Heart, Lung, and Blood Institute (CDC-NHLBI) Lipid Standardization Program, and successfully met the criteria for precision and accuracy of triglyceride and cholesterol measurements [12].

Blood pressures were measured by trained observers using standard mercury sphygmomanometers on the right arm of seated participants after a 5 min rest [13]. Hypertension was defined as a systolic blood pressure ≥ 160 mm Hg, a diastolic blood pressure ≥ 95 mm Hg, or use of antihypertensive medication, while normotension was defined as a systolic blood pressure <140 mm Hg and a diastolic blood pressure <90 mm Hg without the use of antihypertensive medication. Subjects who did not meet either criterion were classified as having borderline hypertension. Height in stockinged feet and weight in light clothing were measured. BMI was calculated as weight (kg) / [height (m)]². Triceps skinfold thickness (TSF) and subcapular skinfold thickness (SSF) were measured to the nearest mm using Keys calipers. An interview was conducted to determine the number of cigarettes smoked per day, usual weekly intake of alcohol in *go* (a Japanese traditional unit of volume corresponding to 23 g of ethanol), and the menopausal status of the female subjects.

Statistical analysis. Due to the fact that a previous Japanese study [4] reported that the relationship between diabetes and risk of ischaemic stroke varied according to sex, we conducted sex-specific analyses in addition to sex-adjusted analyses.

Table 1. Age- and community-adjusted mean values or prevalences of risk factors at baseline according to serum glucose category

	Men				Women			
	Normal (n=3737)	Borderline (n=411)	Diabetes (n=139)	<i>p</i> value for difference	Normal (n=5882)	Borderline (n=285)	Diabetes (n=128)	<i>p</i> value for difference
Age (years)	53	53	55	0.04	53	56	58	<0.001
Serum glucose (mmol/l) ^a	5.42	8.54	12.1	<0.001	5.25	8.52	13.0	<0.001
Systolic blood pressure (mm Hg)	137	141	141	<0.001	134	139	140	<0.001
Diastolic blood pressure (mm Hg)	82	83	83	0.48	80	81	81	0.11
Antihypertensive medication (%)	13	16	22	0.001	13	16	24	<0.001
Hypertensive (%)	28	30	36	0.07	23	29	31	0.004
BMI (kg/m ²)	22.8	23.1	23.3	0.02	23.4	23.9	25.0	<0.001
TSF (mm)	7.3	8.3	7.8	<0.001	15.6	16.5	16.4	0.02
SSF (mm)	12.1	13.1	12.9	0.001	18.5	20.1	21.5	<0.001
Serum total cholesterol (mmol/l)	4.68	4.79	4.78	0.03	5.00	5.23	5.20	<0.001
HDL cholesterol (mmol/l)	1.45	1.44	1.45	0.86	1.48	1.48	1.39	0.08
Current smokers (%)	62	67	67	0.12	7	7	9	0.51
Ethanol intake (g/day)	26.6	30.8	30.8	0.003	1.8	1.5	0.9	0.62

^a Also adjusted for time since last meal

Age-adjusted mean values and the prevalence rates of covariates were calculated according to serum glucose category, and differences between categories were tested by analysis of covariance or the chi square test.

Person-years were calculated as the sum of individual follow-up time until the occurrence of incident stroke, death, emigration or the end of the year 2000. The Cox proportional hazards model was used to calculate the relative risks of ischaemic stroke and their respective 95% confidence intervals, using the risk of individuals in the normal glucose category as a reference value. A test for trend between the serum glucose category and risk of ischaemic stroke was also conducted by applying sex-specific median glucose values, adjusted for age, sex, time since last meal and community, to each glucose category. We adjusted for age and community, and for other potential confounding variables including hypertension status, sex-specific quartiles of BMI, triceps skinfold thickness (TSF), subscapular skinfold thickness (SSF), serum total and HDL cholesterol, smoking status, alcohol intake category, and for the menopausal status of women. We conducted stratified analyses by hypertension status, BMI, TSF and SSF to assess potential effect modification. The significance of the interaction between serum glucose category and hypertension status and adiposity was tested using cross-product terms of these variables in multivariate models. All analyses were conducted using the SAS statistical package, Version 8 (SAS Institute, Cary, N.C., USA). All *p* values for statistical tests were two-tailed, and a *p* value less than 0.05 was regarded as statistically significant.

Results

By the end of 2000, representing 178,828 person-years of follow-up, we had documented 400 incident non-embolic ischaemic strokes (219 in men, 181 in women; 80% confirmed by CT or MRI), 144 intraparenchymal haemorrhages (69 in men, 75 in women), 89 subarachnoid haemorrhages (30 in men, 59 in women), 39 embolic strokes (20 in men, 19 in women), and 36 unclassified strokes (17 in men, 19 in

women). Among the non-embolic ischaemic strokes we identified 254 lacunar strokes (131 in men, 123 in women) and 60 large-artery occlusive infarctions (33 in men, 27 in women); the remaining 86 cases (55 in men, 31 in women) were not further classified due to a lack of imaging studies.

Table 1 shows the age-adjusted means and percentages of selected cardiovascular risk factors at baseline according to serum glucose category. The prevalence of borderline diabetes was 9.6% among the men and 4.5% among the women, and the corresponding values for diabetes were 3.2% and 2.0% respectively. Abnormal glucose levels were positively associated with age, systolic and diastolic blood pressure, hypertension, BMI, and serum total cholesterol levels in both sexes. Glucose abnormality was positively associated with ethanol intake in men alone and was inversely associated with HDL cholesterol levels in women alone.

Compared with those in the normal glucose category, the age- and community-adjusted risk of non-embolic ischaemic stroke was two-fold higher in men in the diabetic category and two-and-half-fold higher in women in the diabetic category (Table 2). We observed a dose-response relationship between serum glucose category and the risk of ischaemic stroke among the women. Further adjustment for known cardiovascular risk factors reduced the excess risk of ischaemic stroke with diabetes; however, the association remained statistically significant for both sexes. Lacunar infarction comprised 64% of non-embolic ischaemic strokes and was similarly associated with glucose abnormality in terms of risk. Analysis of the combined data for men and women revealed that serum glucose category was not significantly associated with the risk of intraparenchymal haemorrhage (multivariate relative risk [RR]=0.90, 95% CI 0.33–2.46,

Table 2. Serum glucose category and sex-specific risk of non-embolic ischaemic stroke

	Men				Women			
	Normal	Borderline	Diabetes	<i>p</i> value for trend	Normal	Borderline	Diabetes	<i>p</i> value for trend
Person-years	60,800	6730	1947		102,476	4860	2015	
Ischaemic stroke								
No. of cases	185	21	13		155	14	12	
Age- and community-adjusted RR (95% CI)	1.0	1.0 (0.6–1.6)	1.9 (1.1–3.4)	0.07	1.0	1.3 (0.8–2.3)	2.6 (1.4–4.6)	0.001
Multivariate RR (95% CI) ^a	1.0	0.9 (0.6–1.5)	1.8 (1.0–3.2)	0.14	1.0	1.3 (0.8–2.3)	2.2 (1.2–4.0)	0.008
Lacunar infarction								
No. of cases	109	14	8		104	11	8	
Age- and community-adjusted RR (95% CI)	1.0	1.2 (0.7–2.0)	2.1 (1.0–4.2)	0.07	1.0	1.6 (0.9–3.0)	2.8 (1.4–5.8)	0.002
Multivariate RR (95% CI) ^a	1.0	1.1 (0.6–1.9)	2.1 (1.0–4.3)	0.08	1.0	1.6 (0.9–3.1)	2.4 (1.1–5.0)	0.008

^a Adjusted for age (5-year categories), community, hypertension status (normotension, borderline hypertension and hypertension), sex-specific quartiles of BMI (kg/m²), TSF (mm), SSF (mm), serum total cholesterol (mmol/l) and HDL cholesterol (mmol/l), smoking status (never, former and current: 1–19 and ≥20 cigarettes per day), alcohol intake (never, former, and current: <46, 46–68 and ≥69 g/day ethanol) and, for women, menopausal status (pre- and post-menopausal)

terol (mmol/l), smoking status (never, former and current: 1–19 and ≥20 cigarettes per day), alcohol intake (never, former, and current: <46, 46–68 and ≥69 g/day ethanol) and, for women, menopausal status (pre- and post-menopausal)

$p=0.39$ for trend) or subarachnoid haemorrhage (RR=0.76, 95% CI 0.19–3.12, $p=0.89$ for trend).

The relationship between blood glucose category stratified according to hypertension status or BMI and risk of non-embolic ischaemic stroke is shown in Table 3. The association between the risk of ischaemic stroke and diabetes was primarily observed in non-hypertensive subjects. The excess risk of ischaemic stroke was greater in individuals with higher adiposity (BMI, TSF and SSF values above the median), particularly those with higher SSF values. The interaction with glucose category was statistically significant for hypertension status ($p=0.006$) and for SSF ($p=0.02$), of borderline significance for TSF ($p=0.07$), and was not significant for BMI ($p=0.97$). Similar associations were found between glucose category stratified by hypertension status, BMI, TSF or SSF and risk of lacunar infarction (data not shown).

The multivariate relative risks of non-embolic ischaemic stroke associated with glucose category stratified by hypertension status and adiposity combined are shown in Table 3. To analyse the combined effects of glucose abnormality, hypertension and adiposity on the risk, we also determined the age- and sex-adjusted incidence (per 1000 person-years) of non-embolic ischaemic stroke in each category (Fig. 1). There was a strong association between glucose abnormality and risk of non-embolic ischaemic stroke among non-hypertensive subjects with higher values for measures of adiposity. The calculated relative risks were 3.6 (95% CI 1.8–7.4), 3.6 (95% CI 1.7–7.4) and 4.9 (95% CI 2.5–9.5) for non-hypertensive diabetic subjects with higher BMI, higher TSF and higher SSF values respectively.

The varied association between the glucose category subdivided according to hypertension/adiposity and

the risk of non-embolic ischaemic stroke was paralleled by the mean glucose levels in three glucose categories. In diabetic subjects, the mean glucose value (\pm SEM) adjusted for sex, age, time since last meal and community was 12.8 \pm 0.1 mmol/l in non-hypertensive subjects with higher BMI values, 12.2 \pm 0.1 mmol/l in non-hypertensive subjects with lower BMI values, 12.5 \pm 0.1 mmol/l in hypertensive subjects with higher BMI values, and 12.4 \pm 0.2 mmol/l for hypertensive subjects with lower BMI values ($p<0.001$ for difference between groups). The respective glucose values for hypertension and TSF categories were 12.8 \pm 0.1 mmol/l, 12.2 \pm 0.1 mmol/l, 12.4 \pm 0.1 mmol/l and 12.5 \pm 0.2 mmol/l ($p<0.001$ for difference between groups), and those for hypertension and SSF categories were 12.5 \pm 0.1 mmol/l, 12.6 \pm 0.1 mmol/l, 12.6 \pm 0.1 mmol/l and 12.0 \pm 0.2 mmol/l ($p=0.01$ for difference between groups).

Discussion

In the present study, the age-adjusted risk of non-embolic ischaemic stroke, more specifically lacunar stroke, was two-fold higher in Japanese diabetic patients (both men and women) than in individuals with normal glucose levels. This excess risk remained statistically significant for both sexes after further adjustment for established cardiovascular risk factors. The magnitude of the excess risk of ischaemic stroke associated with diabetes was similar to that reported in previous studies in Western countries (RR=1.5–3.6) [1, 2, 3].

The excess risk of ischaemic stroke associated with diabetes was primarily observed in non-hypertensive subjects and those with higher adiposity, particularly

Table 3. Serum glucose category stratified by hypertension status and adiposity, separately and combined, and risk of non-embolic ischaemic stroke for the study population

	Normal	Borderline	Diabetes	<i>p</i> for trend	Normal	Borderline	Diabetes	<i>p</i> for trend
	Non-hypertensive				Hypertensive			
Person-years	125,984	8188	2549		37,292	3401	1413	
No. of cases	156	21	14		184	14	11	
Multivariate RR (95% CI)	1.0	1.7 (1.0–2.6)	3.1 (1.8–5.5)	<0.001	1.0	0.7 (0.4–1.2)	1.2 (0.7–2.3)	0.94
	Lower BMI				Higher BMI			
Person-years	82,087	5569	1620		81,189	6021	2341	
No. of cases	153	13	8		187	22	17	
Multivariate RR (95% CI)	1.0	0.9 (0.5–1.6)	1.9 (0.9–3.9)	0.21	1.0	1.2 (0.8–1.9)	2.2 (1.3–3.6)	0.004
	Lower TSF				Higher TSF			
Person-years	69,608	4163	1553		93,668	7426	2408	
No. of cases	155	10	8		185	25	17	
Multivariate RR (95% CI)	1.0	0.9 (0.5–1.7)	1.4 (0.7–2.9)	0.53	1.0	1.2 (0.8–1.8)	2.3 (1.4–3.9)	0.002
	Lower SSF				Higher SSF			
Person-years	79,092	4927	1592		84,185	6662	2370	
No. of cases	174	11	5		166	24	20	
Multivariate RR (95% CI)	1.0	0.7 (0.4–1.4)	0.8 (0.3–2.0)	0.44	1.0	1.4 (0.9–2.1)	2.8 (1.8–4.5)	<0.001
	Non-hypertensive with lower BMI				Non-hypertensive with higher BMI			
Person-years	68,644	4380	1140		57,340	3809	1409	
No. of cases	78	9	5		78	12	9	
Multivariate RR (95% CI)	1.0	1.5 (0.7–3.0)	2.5 (1.0–6.3)	0.03	1.0	1.8 (0.9–3.3)	3.6 (1.8–7.4)	<0.001
	Hypertensive with lower BMI				Hypertensive with higher BMI			
Person-years	13,443	1189	481		23,849	2212	933	
No. of cases	75	4	3		109	10	8	
Multivariate RR (95% CI)	1.0	0.5 (0.2–1.5)	1.0 (0.3–3.2)	0.51	1.0	0.8 (0.4–1.6)	1.5 (0.7–3.1)	0.60
	Non-hypertensive with lower TSF				Non-hypertensive with higher TSF			
Person-years	55,978	3116	1047		70,006	5073	1501	
No. of cases	72	8	5		84	13	9	
Multivariate RR (95% CI)	1.0	1.5 (0.7–3.1)	3.0 (1.1–7.8)	0.01	1.0	1.8 (1.0–3.3)	3.6 (1.7–7.4)	<0.001
	Hypertensive with lower TSF				Hypertensive with higher TSF			
Person-years	13,631	1048	507		23,662	2354	907	
No. of cases	83	2	3		101	12	8	
Multivariate RR (95% CI)	1.0	0.4 (0.1–1.5)	0.6 (0.2–2.1)	0.90	1.0	0.9 (0.5–1.7)	1.8 (0.9–3.8)	0.26
	Non-hypertensive with lower SSF				Non-hypertensive with higher SSF			
Person-years	64,990	3760	1083		60,994	4428	1465	
No. of cases	88	9	3		68	12	11	
Multivariate RR (95% CI)	1.0	1.3 (0.7–2.7)	1.5 (0.5–5.0)	0.23	1.0	1.9 (1.0–3.7)	4.9 (2.5–9.5)	<0.001
	Hypertensive with lower SSF				Hypertensive with higher SSF			
Person-years	14,102	1167	509		23,191	2234	905	
No. of cases	86	2	2		98	12	9	
Multivariate RR (95% CI)	1.0	0.3 (0.1–1.1)	0.4 (0.1–1.6)	0.05	1.0	1.0 (0.5–1.9)	1.8 (0.9–3.7)	0.17

Multivariate adjustments: sex and the same variables listed in Table 2, except for the stratified variable. Adiposity category was divided by the sex-specific median value: BMI,

22.7 kg/m² for men and 23.1 kg/m² for women; TSF, 6 mm for men and 15 mm for women; and SSF, 11 mm for men and 18 mm for women

those with higher values for SSF, which is an indicator of central obesity. Compared with those in the corresponding subgroups of the normal glucose category, diabetic non-hypertensive subjects with higher BMI or TSF values had a four-fold increased risk of non-embolic ischaemic stroke, and diabetic non-hypertensive

subjects with higher SSF values had a five-fold increased risk. Non-hypertensive subjects with higher values for measures of adiposity and borderline diabetes had a two-fold increased risk compared with those in the corresponding subgroups of the normal glucose category. The strong association between glucose ab-

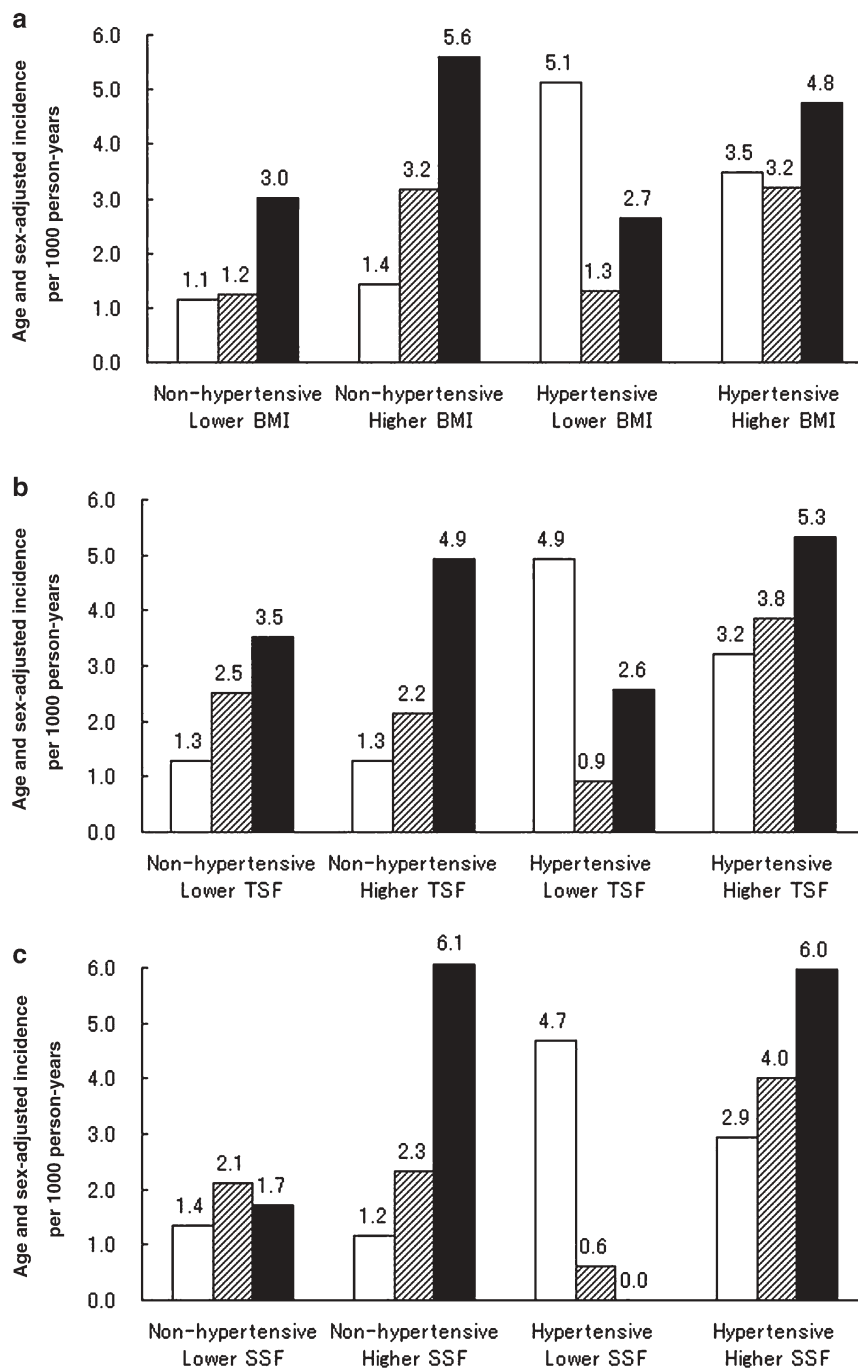


Fig. 1. Age- and sex-adjusted incidence of non-embolic ischaemic stroke (per 1000 person-years) according to serum glucose category stratified by hypertension and (a) BMI, (b) TSF and (c) SSF. Open bars, normal glucose category; hatched bars, borderline diabetes category; filled bars, diabetes category

normality and risk of ischaemic stroke in non-hypertensive subjects with higher adiposity was explained in part by the higher glucose levels observed in the diabetic patients in this subgroup compared with those in diabetic subjects in other subgroups. This finding suggests that the diabetic subjects in the non-hypertensive/higher adiposity subgroup had more advanced

diabetes. Secondly, the susceptibility of non-hypertensive subjects to glucose abnormalities may be indicative of non-hypertensive mechanisms (e.g. microvascular disease) linked to ischaemic stroke. The fact that a greater proportion of the ischaemic stroke cases were lacunar strokes (64%) rather than large-artery occlusive infarctions suggests that this may be the case. In hypertensive subjects, glucose abnormalities may not play a prominent role in the pathogenesis of stroke because hypertension is the predominant risk factor for stroke [3, 7]. Alternatively, it is possible that this finding was due to chance alone. To rule out this possibility, further studies are required to confirm the findings of these subgroup analyses.

In our study population, the proportion of strokes attributable to diabetes was only 2.5% in men and 2.3% in women, due to the low prevalence of diabetes (3.2% in men and 2.0% in women). These estimates increased to 10% for men and 8% for women when we used the recently published prevalence rates of diabetes in Japan (13.4% in men and 6.8% in women aged 40–69 years [14]). However, these figures are still low compared with those reported for Western countries (20–30%) where the prevalence of diabetes in middle-aged and older adults is approximately 20% [1, 2, 3]. This implies that the public health burden of diabetes-associated stroke is still lesser in Japan than it is in Western countries.

However, in Japan, the mean BMI consistently increased in men between 1970 and 2000, according to a national survey [15], and population-based surveys have revealed that the prevalence of diabetes has increased in both men and women [5]. Conversely, blood pressure levels decreased in both men and women between 1970 and 2000, which contributed to a decline in stroke mortality [15]. These trends may increase the relative importance of diabetes in the development of stroke in the Japanese population.

In the present study, lacunar infarctions comprised 64% of non-embolic ischaemic strokes and diabetes doubled the risk of lacunar infarction in both men and women. Our finding adds to existing evidence that diabetes raises the risk of lacunar infarction in both sexes, since a previous Japanese study showed a significant independent association only among men [4]. It is plausible that glucose abnormality or insulin resistance causes microangiopathy, with arteriosclerosis in small penetrating arterioles of the cerebral basal ganglia, leading to lacunar infarction [16]. We were not able to examine the relationship between glucose abnormality and risk of large-artery occlusive infarction because of the small number of cases ($n=1$ among diabetic participants). The high proportion of large-artery occlusive infarctions among ischaemic strokes (approximately 60–70%) [17], and the positive association between diabetes and the risk of ischaemic stroke among Western populations, suggest that diabetes also increases the risk of large-artery occlusive infarction. The results of a retrospective, case-controlled study indicate that this is also the case in the Japanese population [18].

The strengths of the present study include the large population-based sample of middle-aged Japanese men and women, and the use of standardised methods for the measurement of serum glucose and cardiovascular risk factors. Data collection on incident strokes was complete, and a high percentage of events were confirmed using imaging studies. These study characteristics allowed us to conduct analyses for ischaemic stroke subtype (lacunar infarction) and permitted stratification of subjects according to variable constitutional factors (i.e. hypertension and adiposity).

One of the limitations associated with the present study is that we relied on a single glucose measurement, and did not require the presence of symptoms in persons with a non-fasting glucose level ≥ 11.1 mol/l. Our classification system is more likely to identify false positives in terms of diabetes, thus weakening the association between diabetes and risk of ischaemic stroke. Consequently, the true association would be stronger than that reported in the present study.

Furthermore, we did not measure fasting serum insulin at baseline, which meant that the relationship between insulin resistance and risk of ischaemic stroke in non-diabetic individuals could not be examined. Two previous cohort studies of whites showed a significant independent relationship between serum insulin levels and risks of total [19] and ischaemic [20] strokes among non-diabetic individuals, while other studies in whites [20, 21] did not show an independent relationship.

In conclusion, in the present study, diabetes was a significant risk factor for non-embolic ischaemic stroke in Japanese men and women, particularly non-hypertensive and non-lean individuals. In Japan, there has been a nationwide decrease in blood pressure levels in both men and women, and an increase in BMI in men over the last three decades. If the nationwide prevalence of diabetes increases in Japan, as indicated by population-based surveys [5], the impact of glucose abnormality on the absolute risk of ischaemic stroke may increase and thereby become a public health issue.

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