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Impact of Metabolic Syndrome Compared With Impaired Fasting Glucose on the Development of Type 2 Diabetes in a General Japanese Population

The Hisayama study

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OBJECTIVE — We examined whether metabolic syndrome predicts incident type 2 diabetes more effectively than impaired fasting glucose (IFG) in a general Japanese population.

RESEARCH DESIGN AND METHODS — A total of 1,935 nondiabetic subjects aged 40–79 years were followed-up prospectively for a mean of 11.8 years.

RESULTS — During the follow-up, 286 subjects developed type 2 diabetes. Compared with those without metabolic syndrome, the multivariate-adjusted hazard ratio (HR) for incident type 2 diabetes was significantly higher in subjects of both sexes with metabolic syndrome, even after adjustment for confounding factors, age, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise (men: HR 2.58 [95% CI 1.85–3.59]; women: 3.69 [2.58–5.27]). The multivariate-adjusted HR of metabolic syndrome for type 2 diabetes was slightly lower in men and similar in women compared with that of IFG. The multivariate-adjusted HR for type 2 diabetes rose progressively as the number of metabolic syndrome components increased in both subjects with and without IFG. In stratified analysis, the multivariate-adjusted risk of type 2 diabetes was significantly higher in subjects with metabolic syndrome alone (2.37 [1.45–3.88]) or IFG alone (3.49 [2.57–4.74]) and markedly increased in subjects with both metabolic syndrome and IFG (6.76 [4.75–9.61]) than in subjects with neither metabolic syndrome nor IFG. Furthermore, the multivariate-adjusted risk for type 2 diabetes was also significantly higher in subjects with both metabolic syndrome and IFG than in those with either one alone (both $P < 0.001$).

CONCLUSIONS — Our findings suggest that metabolic syndrome significantly increases the risk of incident type 2 diabetes, independent of IFG, and is therefore a valuable tool to identify individuals at high risk of type 2 diabetes.

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Metabolic syndrome consists of a clustering of cardiovascular risk factors, such as central obesity, elevated blood pressure, glucose intolerance, and dyslipidemia, and individuals with this condition have an elevated risk of developing cardiovascular diseases (1–5) and type 2 diabetes in different ethnic populations (1–4,6–11). Thus, the concept of metabolic syndrome could be used to reduce the incidence of these diseases worldwide. However, a number of experts in the field of diabetes have questioned whether the idea of metabolic syndrome is useful and valuable (12–14). Because all of the criteria sets for metabolic syndrome have included the component of impaired fasting glucose (IFG), which is a powerful predictor of type 2 diabetes, detractors have questioned whether the more complex definition of metabolic syndrome is better than a simple measurement of fasting plasma glucose (FPG). However, reported findings concerning this issue are controversial: a cohort study has shown that the ability of metabolic syndrome to predict type 2 diabetes was superior to that of IFG alone (3), whereas in other studies, the value of metabolic syndrome was comparable or inferior to that of IFG alone (2,6,7). Furthermore, most of these epidemiological studies were performed in Western populations, and this subject has not been assessed sufficiently in Asian populations.

The purpose of the present study was to investigate the association between metabolic syndrome and the development of type 2 diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors. In addition, we compared which of the two measures, metabolic syndrome or IFG, better predicted incident type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population and follow-up survey

A population-based prospective study of cardiovascular disease and its risk factors has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. In 1988, a screening survey for the present study was performed in the town. A detailed description of this survey was published previously (15). In brief, of the total of 3,227 residents aged 40–79 years based on the town registry, 2,587 residents (participation rate,

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80.2%) consented to take part in a comprehensive assessment. After exclusion of 82 subjects who had already had breakfast, 10 subjects who were receiving insulin therapy, and 15 subjects who complained of nausea or general fatigue during the ingestion of glucose, a total of 2,480 subjects completed a 75-g oral glucose tolerance test. Among these, 297 subjects with diabetes, 52 subjects for whom there was no measurement of waist circumference, and 2 subjects who died before the start of follow-up were excluded, and the remaining 2,129 subjects (894 men and 1,235 women) were enrolled in the baseline examination.

The baseline subjects were followed-up prospectively from December 1988 to November 2002 by repeated health examinations. Of the baseline subjects, 1,935 subjects (793 men and 1,142 women) who underwent reexaminations were finally selected for the present study (follow-up rate, 90.9%; mean follow-up period, 11.8 years; mean frequency of follow-up examinations, 6.9 times). One subject who developed overt type 1 diabetes clinically during the follow-up period was censored at the time.

Table 1—*Baseline characteristics of subjects by the presence or absence of incident type 2 diabetes, 1988*

	No developed diabetes	Developed diabetes
n	1,649	286
Age (years)	57 ± 10	56 ± 9
Men (%)	39.3	50.7
FPG (mmol/l)	5.4 ± 0.5	5.9 ± 0.6
Two-hour postload glucose (mmol/l)	6.4 ± 1.5	7.5 ± 1.8
Family history of diabetes (%)	6.3	14.0
Waist circumference (cm)	80.8 ± 9.0	85.0 ± 8.7
Total cholesterol (mmol/l)	5.35 ± 1.06	5.39 ± 1.07
HDL cholesterol (mmol/l)	1.32 ± 0.30	1.26 ± 0.30
Triglycerides (mmol/l)	1.09 (0.40–2.98)	1.43 (0.45–4.49)
Systolic blood pressure (mmHg)	130 ± 19	137 ± 19
Diastolic blood pressure (mmHg)	77 ± 11	82 ± 12
Elevated blood pressure (%)	48.8	67.8
Current drinking (%)	28.6	39.2
Current smoking (%)	21.6	31.8
Regular exercise (%)	11.3	6.6

Data are means ± SD, %, or geometric means (95% CI) for triglycerides (because of the skewed distribution). Elevated blood pressure was defined as blood pressure ≥130/85 mmHg and/or current use of antihypertension agents.

Clinical evaluation and laboratory measurements

In the baseline and follow-up examinations, the study subjects underwent an oral glucose tolerance test between 8:00 and 10:30 A.M. after an overnight fast of at least 12 h. Blood for the glucose assay was obtained by venipuncture into tubes containing sodium fluoride at fasting and at 2-h postload. Plasma glucose concentrations were determined by the glucose oxidase method. According to the American Diabetes Association criteria in 2003 (16), diabetes was defined as FPG concentrations of ≥7.0 mmol/l and/or 2-h postload glucose concentrations of ≥11.1 mmol/l and/or the use of antidiabetes medication. Total and HDL cholesterol and triglycerides were determined enzymatically.

At the baseline examination, waist circumference was measured by a trained staff member at the umbilical level with the subject standing. Blood pressure was obtained three times using a mercury sphygmomanometer with the subject in a sitting position; the average values were used in the analyses. Each participant completed a self-administered questionnaire covering medical history, antidiabetes and antihypertension treatments, alcohol intake, smoking habits, and physical activity at the screening. Diabetes in first- or second-degree relatives was taken to indicate a family history of diabetes. Alcohol intake and smoking habits were classified as either current use or not. Subjects engaging in sports at least three times per week during their leisure time were defined as the regular-exercise group.

Definition of metabolic syndrome

The criteria set for metabolic syndrome used in this study was defined by the updated 2005 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (17). By this definition, metabolic syndrome includes the presence of at least three of five factors: elevated FPG (≥5.6 mmol/l), central obesity for Asians (waist circumference ≥90 cm in men and ≥80 cm in women), elevated triglycerides (≥1.68 mmol/l), reduced HDL cholesterol (<1.03 mmol/l for men and <1.29 mmol/l for women), and elevated blood pressure (blood pressure ≥130/85 mmHg and/or current use of antihypertension agents).

Statistical analysis

The SAS software package (version 8.2; SAS Institute, Cary, NC) was used to perform all statistical analyses. Serum triglycerides were transformed into logarithms to improve the skewed distribution. Multivariate-adjusted hazard ratios (HRs) and their 95% CIs were estimated with the use of the Cox proportional hazards model. $P < 0.05$ was considered statistically significant in all analyses.

Ethical considerations

This study was conducted with the approval of the Ethics Committee of the Faculty of Medicine, Kyushu University, and written informed consent was obtained from all participants.

RESULTS— During the follow-up, 286 subjects (145 men and 141 women) developed type 2 diabetes. The baseline clinical characteristics of subjects by the presence or absence of incident type 2 diabetes are shown in Table 1. The mean values of fasting and 2-h postload glucose, waist circumference, triglycerides, and systolic and diastolic blood pressures and the frequencies of men, family history of diabetes, elevated blood pressure, alcohol intake, and smoking habits were higher in subjects who developed type 2 diabetes than in those who did not develop it, and subjects with incident type 2 diabetes had lower HDL cholesterol and lower frequency of regular exercise. The mean values for age and total cholesterol did not differ between the groups.

The multivariate-adjusted HRs for the development of type 2 diabetes associated with metabolic syndrome and its individual components were estimated by sex (Table 2). The multivariate analysis showed that metabolic syndrome was a

Table 2—*Multivariate-adjusted HRs for the development of type 2 diabetes associated with metabolic syndrome and its individual components*

	Population at risk (*n*)	No. events	Multivariate-adjusted HR (95% CI)	*P*
Men				
Updated 2005 NCEP ATP III				
(−)	597	82	1 (referent)	
(+)	196	63	2.58 (1.85–3.59)	<0.001
IFG				
(−)	401	35	1 (referent)	
(+)	392	110	3.76 (2.57–5.52)	<0.001
Central obesity				
(−)	667	103	1 (referent)	
(+)	126	42	2.28 (1.58–3.29)	<0.001
Reduced HDL cholesterol				
(−)	614	108	1 (referent)	
(+)	179	37	1.32 (0.90–1.95)	0.16
Elevated triglycerides				
(−)	579	84	1 (referent)	
(+)	214	61	2.05 (1.46–2.88)	<0.001
Elevated blood pressure				
(−)	338	41	1 (referent)	
(+)	455	104	2.17 (1.49–3.17)	<0.001
Women				
Updated 2005 NCEP APT III				
(−)	723	52	1 (referent)	
(+)	419	89	3.69 (2.58–5.27)	<0.001
IFG				
(−)	685	47	1 (referent)	
(+)	457	94	3.50 (2.45–5.00)	<0.001
Central obesity				
(−)	496	39	1 (referent)	
(+)	646	102	1.96 (1.35–2.85)	<0.001
Reduced HDL cholesterol				
(−)	631	64	1 (referent)	
(+)	511	77	1.55 (1.10–2.18)	0.01
Elevated triglycerides				
(−)	973	105	1 (referent)	
(+)	169	36	2.28 (1.54–3.37)	<0.001
Elevated blood pressure				
(−)	598	51	1 (referent)	
(+)	544	90	2.49 (1.74–3.58)	<0.001

Data are *n* or HR (95% CI). IFG, FPG levels of 5.6–6.9 mmol/l; central obesity, waist circumference of ≥90 cm in men and ≥80cm in women; reduced HDL cholesterol, HDL cholesterol levels of <1.03 mmol/l in men and <1.29 mmol/l in women; elevated triglycerides, triglyceride levels of ≥1.68 mmol/l; elevated blood pressure, blood pressure ≥130/85 mmHg and/or current use of antihypertension agents. Multivariate adjustment was made for age, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise.

significant risk factor for type 2 diabetes in men and women, even after adjustment for the following confounding factors: age, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise (men: multivariate-adjusted HR, 2.58 [95% CI 1.85–3.59], $P < 0.001$; women: 3.69 [2.58–5.27], $P < 0.001$). All components of metabolic syndrome in both sexes, except for reduced HDL cholesterol in men, were significantly associated with future type 2 diabetes. Among the individual components of metabolic syndrome, IFG was the strongest predictor of incident type 2 diabetes in both sexes (men: 3.76 [2.57–5.52], $P < 0.001$; women: 3.50 [2.45–5.00], $P < 0.001$). Compared with that of IFG, the multivariate-adjusted HR of metabolic syndrome for developing type 2 diabetes was slightly lower in men and similar in women. Furthermore, even when the cutoff point of waist circumference for U.S. individuals was used (>102 cm in men and >88 cm in women) in the metabolic syndrome criteria instead of the cutoff point for Asians, the HR of metabolic syndrome for incident type 2 diabetes was substantially unchanged (men: 2.48 [1.76–3.51], $P < 0.001$; women: 3.22 [2.27–4.55], $P < 0.001$).

Because IFG is a strong predictor of future type 2 diabetes, the associations between the number of the other metabolic syndrome components and the development of type 2 diabetes were examined among individuals with or without IFG in men and women together (Table 3). In subjects with normal FPG levels, the multivariate-adjusted HRs for type 2 diabetes rose significantly as the number of metabolic syndrome components increased (one component: multivariate-adjusted HR 1.76 [95% CI 0.88–3.50]; two components: 2.49 [1.22–5.06]; three components: 3.71 [1.72–8.02]; and four components: 5.90 [2.24–15.53]; $P_{trend} < 0.001$). Similar relationships were also observed in subjects with IFG (one component: 2.38 [1.30–4.35]; two components: 2.98 [1.62–5.47]; three components: 4.61 [2.48–8.56]; and four components: 4.22 [2.01–8.83]; $P_{trend} < 0.001$).

Finally, we examined the combined as well as separate effects of metabolic syndrome and IFG on the development of type 2 diabetes. In this analysis, metabolic syndrome was defined as the presence of at least three metabolic syndrome components, not including the component of elevated FPG. As shown in the Figure 1, the multivariate-adjusted HR for future type 2 diabetes was significantly higher in subjects with metabolic syndrome alone and in those with IFG alone than in those with neither metabolic syndrome nor IFG; the former was slightly lower than the latter, but there was no significant difference between the two (metabolic syndrome alone: multivariate-adjusted HR 2.37 [95% CI 1.45–3.88], $P < 0.001$; IFG alone: 3.49 [2.57–4.74], $P < 0.001$). Furthermore, the subjects who had both metabolic syndrome and IFG had a markedly higher HR for the development of type 2 diabetes (6.76 [4.75–9.61], $P < 0.001$). The risk of future type 2 diabetes was also significantly higher in subjects with both metabolic syndrome and IFG than in subjects with metabolic syndrome alone (2.82 [1.74–4.57], $P < 0.001$) as well as in those with IFG alone (1.94 [1.44–2.62], $P < 0.001$).

Table 3—*Multivariate-adjusted HRs for the development of type 2 diabetes associated with the number of metabolic syndrome components excluding IFG by the presence or absence of IFG*

FPG levels	No. of metabolic syndrome components excluding IFG	Population at risk (*n*)	No. events	Multivariate-adjusted HR (95%CI)	P_{trend}
Normal	0	285	12	1 (referent)	
	1	399	26	1.76 (0.88–3.50)	
	2	236	22	2.49 (1.22–5.06)	
	3	126	15	3.71 (1.72–8.02)	
	4	40	7	5.90 (2.24–15.53)	<0.001
IFG	0	122	13	1 (referent)	
	1	278	61	2.38 (1.30–4.35)	
	2	243	62	2.98 (1.62–5.47)	
	3	153	51	4.61 (2.48–8.56)	
	4	53	17	4.22 (2.01–8.83)	<0.001

Data are *n* or HR (95% CI). Multivariate adjustment was made for age, sex, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise. Normal, FPG levels of <5.6 mmol/l; IFG, FPG levels of 5.6–6.9 mmol/l.

CONCLUSIONS— Using data from a 14-year follow-up study of a defined general Japanese population, we demonstrated that metabolic syndrome determined by the updated 2005 NCEP ATP III criteria was an independent risk factor for the development of type 2 diabetes in both sexes even after adjustment for comprehensive risk factors. The HR of metabolic syndrome for developing type 2 diabetes was slightly lower in men and similar in women compared with that of IFG. When subjects were stratified by the presence or absence of IFG, the risk of future type 2 diabetes rose significantly as the number of metabolic syndrome components increased in both FPG level groups. Furthermore, metabolic syndrome that did not include the IFG component was also a significant risk factor for developing type 2 diabetes, and the coexistence of metabolic syndrome and IFG greatly increased the risk of future type 2 diabetes. These findings suggest that the diagnosis of metabolic syndrome as well as that of IFG is a valuable tool to identify individuals at increased risk of type 2 diabetes.

In Japan, there has been only one prospective study to date that found a significant association between metabolic syndrome determined by the World Health Organization definition and incident type 2 diabetes among Japanese male workers (18). To our knowledge, the present study is the first report to indicate that metabolic syndrome was associated significantly with future type 2 diabetes for individuals of both sexes in a general Japanese population. Several epidemiological studies examined the relationship between metabolic syndrome determined by the updated 2005 NCEP ATP III criteria and incident diabetes (3,4,9–11), and the risks of incident diabetes associated with metabolic syndrome have differed among these investigations. In the Framingham Offspring Study, subjects with metabolic syndrome had an 8.6-fold higher risk of future type 2 diabetes than those without metabolic syndrome (4). The San Antonio Heart Study, which consisted predominantly of Hispanics, also showed that the diabetes risk was 6.9-fold higher in subjects with metabolic syndrome than that in subjects without metabolic syndrome (3). A similar increased risk of diabetes was observed among subjects with metabolic syndrome in an Ital-

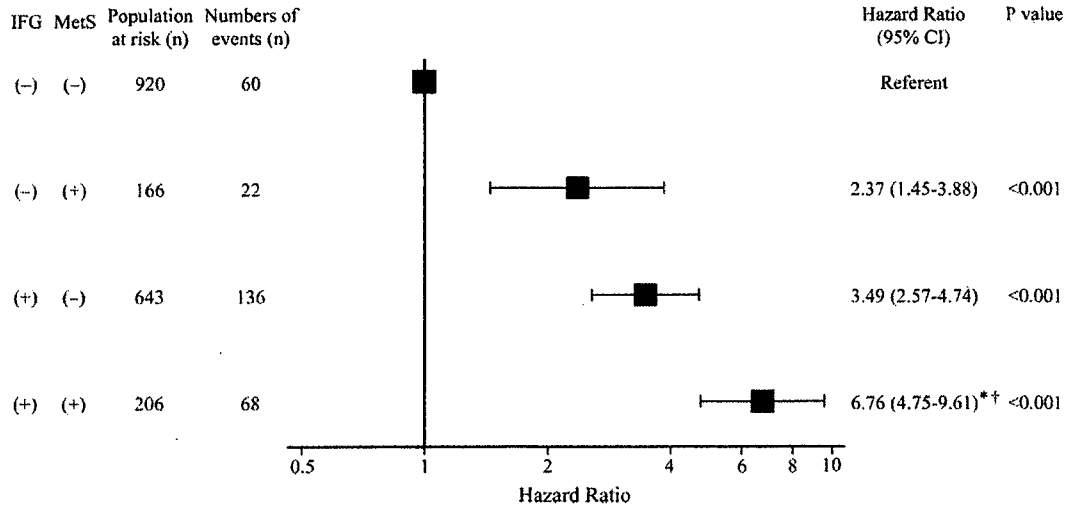

Figure 1—*Multivariate-adjusted HRs for the development of type 2 diabetes according to the presence or absence of metabolic syndrome and IFG. Metabolic syndrome (MetS) was defined as the presence of at least three metabolic syndrome components other than that related to FPG. Multivariate adjustment was made for age, sex, family history of diabetes, total cholesterol, alcohol intake, smoking habits, and regular exercise. The centers of the boxes are placed at the estimates of HRs. Error bars indicate 95% CIs. IFG indicates FPG levels of 5.6–6.9 mmol/l. *P < 0.001 vs. IFG (–) and MetS (+). †P < 0.001 vs. IFG (+) and MetS (–).*

ian population study (6.2-fold) (11). On the other hand, metabolic syndrome increased the risk of diabetes two- to fourfold in studies of Chinese populations (9,10). In the present analysis, the risk of developing type 2 diabetes was nearly threefold higher in men and fourfold higher in women with metabolic syndrome than in those without it, and these figures were much lower than the figures in Western populations but comparable to those of other Asian populations. Furthermore, even when the definition of waist circumference for U.S. individuals was used (>102 cm in men and >88 cm in women) in the metabolic syndrome criteria set, the risk of future type 2 diabetes among subjects with metabolic syndrome was hardly altered. Taken together, these findings suggest that metabolic syndrome is less strongly associated with increased risk of type 2 diabetes in Asian populations than in Western populations. Although the reason for this difference is unclear, the diversity of etiology for type 2 diabetes among races could explain it. That is, an epidemiological study has shown that the levels of insulin secretion and resistance differed among various ethnic groups in the U.S. (19); Asians had lower levels of insulin secretion than other ethnic groups, whereas whites, especially Hispanics, were more insulin resistant than Asians. In addition, Japanese diabetic individuals were found to have lower BMI levels than western diabetic individuals (20). Thus, we speculate that insulin resistance may play a lesser role than impaired insulin secretion in the development of type 2 diabetes among Asian populations. These findings may indicate one reason that the impact of metabolic syndrome, which has features of insulin resistance, on the development of type 2 diabetes is lower in Asian populations, including ours, than in Western populations.

There has been controversy over whether metabolic syndrome is better than IFG for detecting subjects at high risk of type 2 diabetes. The San Antonio Heart Study revealed that metabolic syndrome was a better predictor of diabetes than IFG (3), whereas other epidemiological studies including ours (2,6,7) showed that metabolic syndrome was comparable or inferior to IFG as a predictor of diabetes. This discrepancy also may result from the difference in the degree of insulin resistance among the populations, because the study subjects in the San Antonio Heart Study were more obese than those in other studies. Thus, metabolic syndrome might be less effective in predicting incident type 2 diabetes in relatively lean ethnic groups. In our study, however, the risk of type 2 diabetes rose progressively as the number of the other metabolic syndrome components increased, not only in subjects with IFG but also in those with normal FPG levels. Moreover, our stratified analysis indicated that metabolic syndrome defined without the FPG component was also a significant risk factor for future type 2 diabetes in individuals both with and without IFG. These results imply that metabolic syndrome excluding the FPG component is also an independent risk factor for incident type 2 diabetes. On the other hand, in our study, the coexistence of metabolic syndrome and IFG appeared to increase the risk of future type 2 diabetes compared with either one alone. Other epidemiological studies have also shown that type 2 diabetes prediction was greatly enhanced by adding information on metabolic variables to that of IFG (21–23). Thus, metabolic syndrome would provide additional information beyond that provided by IFG alone in regard to the development of type 2 diabetes.

In our study, reduced HDL cholesterol was not a significant risk factor for developing type 2 diabetes in men, although lower HDL cholesterol has often been shown to be a strong predictor of diabetes in other epidemiological studies (2,6,7,9,21–23). The reasons for this discrepancy are not precisely known, but a higher prevalence of drinking habits in our men (61%) relative to our women (9%) may contribute to this phenomenon. It is known that heavy alcohol intake augments the risk of diabetes (24), whereas it increases serum HDL cholesterol levels (25). These effects of alcohol intake could weaken the association between HDL cholesterol levels and the risk of diabetes.

The strengths of our study include a longitudinal population-based design, a long duration of follow-up, a sufficient number of type 2 diabetes events, a high follow-up rate, and the use of an oral glucose tolerance test for the diagnosis of diabetes. However, two limitations of the present study should be discussed. One is that the diagnosis of metabolic syndrome was based on a single measurement of its components at baseline, as was the case in other epidemiological studies. The risk factor levels might have changed during the follow-up because of modifications in lifestyle or medication. The other limitation is that the present study lacked information on antilipidemic drugs, such as fibrates and nicotinic acid, which could have affected the metabolism of HDL cholesterol and triglycerides, although these medications were rarely used in our country by 1988, the time of the baseline. These limitations may have led to misclassification of metabolic syndrome. These biases have the potential to underestimate the association between metabolic syndrome and incident type 2 diabetes, and thus the true impact of metabolic syndrome on the occurrence of type 2 diabetes may be stronger than that shown in our findings. For this reason, we believe that these limitations would not have substantially altered our conclusions.

In summary, the present analysis clearly demonstrated that metabolic syndrome was a significant risk factor for developing type 2 diabetes in both sexes in a general Japanese population. Although the ability of metabolic syndrome to predict type 2 diabetes was comparable or inferior to that of IFG, the effects of metabolic syndrome on the development of type 2 diabetes were independent of IFG. These findings suggest that the diagnosis of metabolic syndrome is useful and valuable for predicting type 2 diabetes even in relatively lean Asians. Further studies are needed to verify these findings in other populations.

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Hyperglycemia Increases Risk of Gastric Cancer Posed by *Helicobacter pylori* Infection: A Population-Based Cohort Study

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See related article, Wu C–Y et al, on page 427 in *CGH*.

Background & Aims: **Although diabetes mellitus and hyperglycemia are considered to be possible risk factors for various types of malignancy, the epidemiologic evidence concerning gastric cancer is scarce. The aim of this study was to evaluate the impact of hemoglobin A_{1c} (HbA_{1c}) levels on gastric cancer occurrence and their interaction with *Helicobacter pylori* infection.** ***Methods:*** **A total of 2603 Japanese subjects aged ≥40 years were stratified into 4 groups according to baseline HbA_{1c} levels (≤4.9%, 5.0%–5.9%, 6.0%–6.9%, and ≥7.0%) and followed up prospectively for 14 years.** ***Results:*** **During the follow-up, 97 subjects developed gastric cancer. The age- and sex-adjusted incidence of gastric cancer significantly increased in the 6.0%–6.9% (5.1 per 1000 person-years; $P < .05$) and ≥7.0% groups (5.5 per 1000 person-years; $P < .05$) compared with the 5.0%–5.9% group (2.5 per 1000 person-years), whereas it was slightly but not significantly high in the ≤4.9% group (3.6 per 1000 person-years). This association remained substantially unchanged even after adjusting for the confounding factors including *Helicobacter pylori* seropositivity, (multivariate-adjusted hazard ratio [HR], 2.13; 95% confidence interval [CI]: 1.30–3.47 for the 6.0%–6.9% group and HR, 2.69; 95% CI: 1.24–5.85 for the ≥7.0% group). Among subjects who had both high HbA_{1c} levels (≥6.0%) and *Helicobacter pylori* infection, the risk of gastric cancer was dramatically elevated (interaction term, $P = .004$).** ***Conclusions:*** **Our findings suggest that casual hyperglycemia is a risk factor for gastric cancer and is a possible cofactor increasing the risk posed by *Helicobacter pylori* infection.**

Despite the fact that the incidence of and mortality from gastric cancer have declined markedly worldwide over the past decades, gastric cancer is still the second most common cause of cancer-related death in the world.[1] Gastric cancer is considered a multifactorial disease, and various factors are involved in its development. Among the risk factors, *Helicobacter pylori* infection is a well-known and strong risk factor for gastric cancer, and its prevalence in Japan is higher than in other Western countries, especially in middle-aged and elderly individuals.[2] However, only a small percentage of people with *H pylori* infection develop gastric cancer, indicating that *H pylori* infection cannot be the only etiologic factor of gastric cancer.[3]

Although a possible association between diabetes mellitus and an increased risk of malignant neoplasms has been discussed for many years,[4] very few studies have evaluated the relation of diabetes mellitus or hyperglycemia to the development of gastric cancer specifically. We have previously revealed a significant association between fasting plasma glucose levels and subsequent occurrence of gastric cancer[5]; however, 2 other cohort studies failed to show a similar association.[6,7]

A hyperglycemic state has various indicators: of them, HbA_{1c} reflects long-term glycemic control and is a more stable measurement than fasting plasma glucose.[8] Although the associations between HbA_{1c} levels and incidence or mortality for malignancies have been shown in 2 cohort studies,[9,10] no studies have evaluated the impact of HbA_{1c} levels on the development of gastric cancer. In the present study, we conducted a prospective investigation of the relationship between HbA_{1c} levels and gastric cancer occurrence in a general Japanese population, taking *H pylori* infection as well as other risk factors into consideration.

Subjects and Methods

Study Population

A population-based prospective study has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area of Kyushu Island, Japan. The age and occupational distributions for Hisayama have been almost identical to those of Japan as a whole from 1961 to the present based on data from the national census. A screening survey for the present study

Abbreviations used in this paper: HbA_{1c}, hemoglobin A_{1c}.

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was performed in 1988. A detailed description of this survey has been published previously.[11,12] Briefly, of the 3390 Hisayama residents in 1988 who were 40 years or over according to the town registry, 2742 (80.9%) consented to take part in the comprehensive assessment, including an interview covering medical history. After excluding 132 individuals with a prior history of gastrectomy or gastric cancer, 2 individuals for whom HbA_{1c} levels were not measured, and 5 individuals who died during the screening period, a total of 2603 subjects (1070 men and 1533 women; mean age, 59 years) was enrolled in the study. This study protocol was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and written informed consent for medical research was obtained from the study subjects.

Follow-up Survey

The subjects were followed prospectively for 14 years from December 1988 to November 2002 by repeated health examinations or by a daily monitoring system established by the study team and local physicians or members of the Health and Welfare Office of the town. Health status was checked once yearly by mail or telephone for any subjects who did not undergo a regular examination or who moved out of town. To identify new occurrences of gastric cancer in this cohort, 3 monitoring methods were performed. First, we interviewed subjects concerning their medical history of gastric cancer at every checkup and checked all records of the annual mass screenings for gastric cancer (performed by barium x-ray examination). Second, we also monitored all radiographic and endoscopic study records and endoscopic biopsy records for the stomach at local clinics or general hospitals in and around Hisayama. Third, to find any concealed gastric cancer, autopsies were performed on 442 (76.1%) of a total of 581 subjects who died during the follow-up period. The diagnosis of all cases of gastric cancer was confirmed by histologic examination of tissue obtained by surgery, including gastrectomy and endoscopic mucosal resection, or autopsy. Pathologic diagnosis and classification of identified gastric cancers were made according to the guidelines proposed by the Japanese Gastric Cancer Association[13] and the histologic classification of Laurén.[14] During the follow-up period, only 1 subject dropped out, and first-ever gastric cancer developed in 97 subjects (68 men and 29 women), including 3 (3.1%) concealed cases first diagnosed at autopsy. Among these positive cases, 8 subjects (8.2%) had double cancers with a total of 105 lesions.

Laboratory Testing and Risk Factor Measurement

At the baseline examination, HbA_{1c} was measured by high-performance liquid chromatography (HLC-723Hb; TOSOH Inc., Tokyo, Japan). Plasma glucose levels were determined by a glucose-oxidase method. Diabetes was determined by a 75-g oral glucose tolerance test (1998 World Health Organization criteria), fasting plasma glucose levels (≥7.0 mmol/L), or medical history of diabetes.

To assess the independent effect of HbA_{1c} on gastric cancer occurrence, the following baseline factors in addition to age and sex were used for analysis as confounding factors: (1) serum IgG antibodies to *H pylori* were assayed by means of a quantitative enzyme immunoassay, and the assay values were interpreted as either positive or negative based on the manufacturer's instructions; (2) information about history of peptic ulcer disease, alcohol intake, and smoking habits was obtained by means of a questionnaire administered to each subject, and the latter 2 items were categorized as in current use or not; (3) height and weight were measured with the subject in light clothes without shoes, and the body mass index was calculated (weight in kilograms/height in square meters); (4) serum cholesterol levels were determined by an enzymatic autoanalyzer; (5) data on dietary factors were obtained by the semiquantitative food frequency method, validated in a prior study[15]; and the daily nutrient intakes, including total energy, total fat, salt, vitamin A, vitamin B-1, vitamin B-2, vitamin C, and dietary fibers, were calculated using the 4th revision of the Standard Tables of Food Composition in Japan,[16] and the nutritional elements were adjusted for energy intake using the method of Willet and Stampfer.[17]

Statistical Analysis

According to the American Diabetes Association's guideline,[18] an HbA_{1c} level of 4.0%–6.0% is considered normal; an HbA_{1c} less than 7.0% is the recommended glycemic control level for adults with diabetes, and a more stringent glycemic goal is less than 6.0%. Therefore, dividing subjects with normal HbA_{1c} by 1.0% intervals, we classified all of the subjects into 4 groups according to baseline HbA_{1c} level: ≤4.9%, 5.0%–5.9%, 6.0%–6.9%, and ≥7.0% and considered the 5.0%–5.9% group as a reference based on the finding of the analysis with the spline model. Age- and sex-adjusted mean values of the possible risk factors were calculated by the analysis of covariance method, and their trends across HbA_{1c} levels were tested by multiple regression analysis. The frequencies of risk factors were adjusted for age by the direct method and were examined for trends by the Cochran-Mantel-Haenszel test. Age- and sex-adjusted incidence rates were calculated by the person-year method and the direct method and compared by the Cox proportional hazards model.[19] For age adjustment in direct method, all study subjects were used as the standard population. The age- and sex- or multivariate-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were also estimated using the Cox proportional hazards model. In the multivariate analysis, the possible risk factors for gastric cancer available in our cohort, namely, age, sex, *H pylori* seropositiv-

Table 1. Age- and Sex-Adjusted Mean Values or Frequencies of Risk Factors According to Hemoglobin A_{1c} Levels at Baseline

Variables	Hemoglobin A_{1c} level (%) ≤4.9 (n = 390)	5.0–5.9 (n = 1685)	6.0–6.9 (n = 427)	≥7.0 (n = 101)	*P* value for trend
Age (*y*)	55.3 ± 12.0	59.2 ± 11.9	62.2 ± 12.1	61.4 ± 10.1	<.001
Men (%)	39.1	38.9	53.3	52.8	<.001
Hemoglobin A_{1c} (%)	4.7 ± 0.3	5.4 ± 0.3	6.3 ± 0.3	8.3 ± 0.3	<.001
Diabetes (%)	5.3	6.7	28.1	94.2	<.001
Helicobacter pylori infection (%)	68.3	73.0	70.2	74.9	.97
History of peptic ulcer disease (%)	12.0	14.5	16.0	11.6	.40
Body mass index (*kg/m²*)	22.5 ± 3.1	22.9 ± 3.1	23.4 ± 3.1	23.8 ± 3.1	<.001
Total cholesterol (*mmol/L*)	5.08 ± 1.06	5.34 ± 1.05	5.60 ± 1.06	5.71 ± 1.06	<.001
Alcohol intake (%)	28.3	30.0	34.1	36.6	.010
Smoking habits (%)	21.1	24.2	28.2	25.5	.019
Total energy intake (*kJ/day*)	7055 ± 1585	7169 ± 1569	7046 ± 1571	7371 ± 1572	.16
Total fat intake (*g/day*)	48.0 ± 10.2	48.2 ± 10.1	48.5 ± 10.2	50.4 ± 10.1	.20
Salt intake (*g/day*)	13.1 ± 4.7	13.1 ± 4.7	13.1 ± 4.7	12.0 ± 4.7	.15
Vitamin A intake (*IU/day*)	2737 ± 1097	2935 ± 1086	2836 ± 1094	3087 ± 1088	.003
Vitamin B-1 intake (*mg/day*)	0.77 ± 0.40	0.82 ± 0.39	0.78 ± 0.39	0.78 ± 0.39	.06
Vitamin B-2 intake (*mg/day*)	1.11 ± 0.31	1.15 ± 0.30	1.17 ± 0.31	1.29 ± 0.31	<.001
Vitamin C intake (*mg/day*)	75.6 ± 32.7	78.0 ± 32.4	73.9 ± 32.7	84.6 ± 32.5	.012
Dietary fiber intake (*g/day*)	10.7 ± 3.3	10.7 ± 3.3	10.9 ± 3.3	12.2 ± 3.3	<.001

NOTE. Age is sex-adjusted; sex is age-adjusted; mean ± SD or percentage.

ity, history of peptic ulcer disease, body mass index, serum cholesterol, alcohol intake, smoking habits, and dietary factors, were included in the model all at once. These variables are known or suspected to modify the risk of gastric cancer.[3,11,20–23] Additionally, we examined the possibility of a nonlinear relation between HbA_{1c} levels and the occurrence of gastric cancer using a spline model with the model selection method proposed by Kawaguchi et al.[24] The effect of the interaction between HbA_{1c} and *H pylori* infection on the risk of gastric cancer was examined by the χ^2 test. All tests were 2-sided, and a *P* value of <.05 was considered statistically significant. Because there was no interaction between sex and HbA_{1c} levels (data not shown), we included men and women together in all analyses. Statistical analyses were conducted using Statistical Analysis Software (SAS) version 8 (SAS Institute, Cary, NC).

Results

Table 1 compares the age- and sex-adjusted mean values or frequencies of possible risk factors for gastric cancer among the HbA_{1c} groups. The mean age and frequency of male sex tended to increase with an increase in HbA_{1c} levels. The frequencies of diabetes, alcohol intake, and smoking habits and mean values of body mass index and total cholesterol also increased significantly with higher HbA_{1c} levels, but such tendencies were not observed for the frequencies of *H pylori* infection and history of peptic ulcer disease. Among relevant dietary factors, the mean values of vitamin A, vitamin B-2, vitamin C, and dietary fiber intakes showed positive relationships with HbA_{1c} levels.

The incidence of gastric cancer was 3.1 per 1000 person-years in our total subjects. Figure 1 shows the age- and sex-adjusted incidence of gastric cancer according to HbA_{1c} levels. The incidence of cancer was significantly higher in the 6.0%–6.9% and ≥7.0% groups compared with the 5.0%–5.9% group (both, $P < .05$), and it was slightly but not significantly higher in the ≤4.9% group. The age- and sex-adjusted HR of gastric cancer was 1.97 (95% CI: 1.23–3.16; $P = .005$) in the 6.0%–6.9% group and 2.51 (95% CI: 1.18–5.32, $P = .016$) in the ≥7.0% group (Table 2). This association remained substantially unchanged even after adjustment for age; sex; *Helicobacter pylori* seropositivity; history of peptic ulcer disease; body mass index; serum cholesterol; alcohol intake; smoking habits; and dietary factors, including intake of total en-

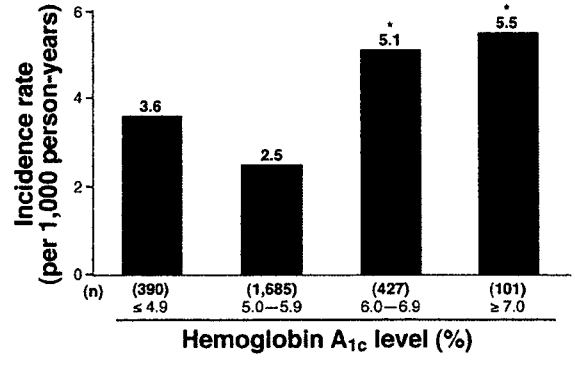

Figure 1. Age- and sex-adjusted incidence rate of gastric cancer according to hemoglobin A_{1c} levels. *$P < .05$ vs hemoglobin A_{1c} 5.0%–5.9%.

Table 2. Age- and Sex-Adjusted and Multivariate-Adjusted Hazard Ratios and 95% Confidence Intervals of Gastric Cancer by Hemoglobin A_{1c} Levels

Hemoglobin A_{1c} level (%)	No. of population at risk	No. of events	Age- and sex-adjusted		Multivariate-adjusted[a]	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
≤4.9	390	14	1.49 (0.82–2.72)	.19	1.59 (0.85–3.00)	.15
5.0–5.9	1,685	47	1.00		1.00	
6.0–6.9	427	28	1.97 (1.23–3.16)	.005	2.13 (1.30–3.47)	.003
≥7.0	101	8	2.51 (1.18–5.32)	.016	2.69 (1.24–5.85)	.013
P value for trend			.025		.021	

HR, hazard ratio; CI, confidence interval.
[a]Adjusted for age, sex, *Helicobacter pylori* seropositivity, history of peptic ulcer disease, body mass index, serum total cholesterol, alcohol intake, smoking habits, and dietary factors (intake of total energy, total fat, salt, vitamin A, vitamin B-1, vitamin B-2, vitamin C and dietary fibers).

ergy; total fat, salt, vitamin A, vitamin B-1, vitamin B-2, vitamin C, and dietary fibers.

Furthermore, we examined the nonlinear relationship between HbA_{1c} levels and the risk of gastric cancer using the spline model after adjusting for other potential risk factors (Figure 2). Compared with reference HbA_{1c} level of 5.5%, the adjusted HRs of gastric cancer significantly increased at HbA_{1c} levels above this reference, whereas it plateaued at HbA_{1c} levels of >6.5%. The risk of the cancer was also higher at HbA_{1c} levels of <5.5%, but the increase was not significant.

The seroprevalence of *H pylori* was 71.9% for all subjects. The age- and sex-adjusted incidence of gastric cancer was 1.6 per 1000 person-years in *H pylori*-negative subjects and 3.8 in *H pylori*-positive subjects: the difference was statistically significant (age- and sex-adjusted HR, 2.09; 95% CI: 1.18–3.68; $P = .01$).

To clarify the combined effects of elevated HbA_{1c} levels and *H pylori* infection on gastric cancer occurrence, we estimated the age- and sex-adjusted or multivariate-adjusted HRs of gastric cancer among 4 groups divided into high (≥6.0%) or low (≤5.9%) HbA_{1c} levels, with or without *H pylori* infection (Figure 3). Compared with the reference group having neither high HbA_{1c} levels nor *H pylori* infection, the age- and sex-adjusted HRs of gastric cancer for the groups with high HbA_{1c} levels alone and *H pylori* infection alone were not significant, but the HR for the group having both high HbA_{1c} levels and *H pylori* infection was significantly high (HR, 3.48; 95% CI: 1.75–6.93; $P < .001$). This association remained significant even after adjustment for the above-mentioned risk factors (HR, 4.03; 95% CI: 1.89–8.58; $P < .001$); moreover, there was a significant interaction between high HbA_{1c} levels and *H pylori* infection ($P = .004$).

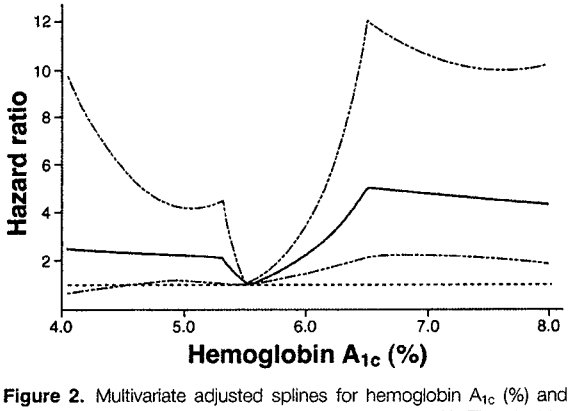

Figure 2. Multivariate adjusted splines for hemoglobin A_{1c} (%) and gastric cancer risk, relative to hemoglobin A_{1c} = 5.5%. The *double-dashed* lines are the 95% confidence intervals for the splines. The risk-changing points (shown by knots) are the hemoglobin A_{1c} values of 5.3%, 5.5%, and 6.5%. The risks are adjusted for age, sex, history of peptic ulcer disease, body mass index, serum total cholesterol, alcohol intake, smoking habits, and total dietary factors (intake of total energy, total fat, salt, vitamin A, vitamin B-1, vitamin B-2, vitamin C, and dietary fibers).

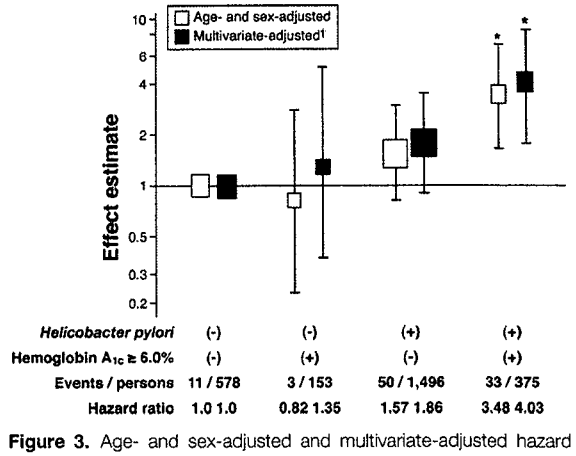

Figure 3. Age- and sex-adjusted and multivariate-adjusted hazard ratios and 95% confidence intervals of gastric cancer according to hemoglobin A_{1c} level and *Helicobacter pylori* status. †Adjusted for age, sex, history of peptic ulcer disease, body mass index, serum total cholesterol, alcohol intake, smoking habits and total dietary factors (intake of total energy, total fat, salt, vitamin A, vitamin B-1, vitamin B-2, vitamin C, and dietary fibers). *$P < .001$ vs hemoglobin A_{1c} ≤5.9% and *Helicobacter pylori* negative.

Discussion

Our findings indicated that elevated HbA_{1c} level was a significant risk factor for the development of gastric cancer. This association remained significant even after adjusting for other risk factors, namely, age, sex, *H pylori* seropositivity, history of peptic ulcer disease, body mass index, serum total cholesterol, alcohol intake, smoking habits, and dietary factors. Moreover, the coexistence of a high HbA_{1c} level and *H pylori* infection dramatically increased the risk of future gastric cancer. To our knowledge, this is the first epidemiologic study to reveal the association between HbA_{1c} levels and gastric cancer incidence, while taking into account the interaction between HbA_{1c} levels and *H pylori* status.

Diabetes and impaired glucose tolerance are thought to be possible risk factors, not only for cardiovascular events,[25] but also for malignancies.[4–7,26] Among the studies on this subject, few have examined the association between hyperglycemia and gastric cancer.[5–7] Our previous study showed that elevated fasting plasma glucose levels (≥5.3 mmol/L) were clearly associated with gastric cancer incidence.[5] Another prospective study revealed that only men who had a fasting plasma glucose level of 6.1–6.9 mmol/L or known diabetes had a significantly elevated risk of death from gastric cancer.[6] However, another prospective study did not show these relationships.[7] On the other hand, HbA_{1c} is a good time-integrated indicator of blood glucose concentrations over the preceding 1 to 3 months.[27] It is also a particularly convenient screening or monitoring tool for diabetes because it does not require subjects to fast. However, there have been no studies to date examining the association between HbA_{1c} levels and the risk of gastric cancer.

In the present study, we demonstrated that the incidence of gastric cancer significantly increased in the HbA_{1c} groups of ≥6.0% compared with the 5.0%–5.9% group. These findings suggest that a modest increase in casual blood glucose is a risk factor for the cancer. However, the risk of gastric cancer appeared to plateau at HbA_{1c} levels over 6.5% using the spline model. It is possible that the risk did not change at the higher HbA_{1c} levels or that this finding was a result of the competing effect of other diseases such as cardiovascular events. In fact, elevated HbA_{1c} levels were significantly associated with the increased cardiovascular mortality in our cohort (data not shown). Meanwhile, the spline model showed that the risk of gastric cancer was lowest at an HbA_{1c} level of around 5.5%. These observations indicate that an optimum HbA_{1c} level for prevention of gastric cancer may exist. Further studies are needed to confirm these findings.

The precise pathogenetic role of hyperglycemia in gastric carcinogenesis remains obscure so far. One possible explanation is that hyperglycemia and its related conditions may act directly as a carcinogenic factor. A clinical study with diabetic subjects and healthy volunteers has demonstrated that diabetes is associated with increased production of reactive oxygen species and greater oxidative damage to DNA.[28] In an experimental study, high glucose itself was also shown to induce DNA damage.[29] Thus, it is possible that increased production of reactive oxygen species or high glucose itself contributes to DNA damage, which may lead to mutational changes in oncogenes and tumor suppressor genes, and thereby to the development of gastric cancer. Another possible explanation is that hyperinsulinemia is related to gastric carcinogenesis. It is well-known that individuals with hyperglycemia are prone to insulin resistance, the effect of which is increased blood insulin levels. An experimental study has shown that insulin enhances the stimulatory effects of epidermal growth factor on the proliferation of cultured gastric epithelial cells obtained from guinea pigs.[30] It is speculated that an increase in cell proliferation predisposes gastric mucosa to genetic or epigenetic alterations and, therefore, to carcinogenesis. Another experimental study has also demonstrated that insulin-like growth factors, which increase in diabetic patients, may play an important role in the initiation, progression, and metastasis of gastric cancer.[31]

Numerous epidemiologic and experimental studies have shown a clear association between *H pylori* infection and the risk of gastric cancer.[11] Although the mechanisms for the increased risk of gastric cancer in the presence of *H pylori* are not clearly understood, it has been clarified that this infection contributes to modifications in epithelial cell proliferation,[32] which is considered to be the initial step in a cascade culminating in the development of gastric cancer. However, despite the increased risk of gastric cancer from *H pylori* infection, the majority of *H pylori*-infected subjects do not develop gastric cancer. This fact suggests that *H pylori* infection is not an absolute oncogenic factor for gastric cancer and that there must be other critical cofactors contributing to the risk posed by *H pylori* infection. Our stratified analysis showed a dramatically increased risk of gastric cancer occurrence only in subjects with both high HbA_{1c} levels and *H pylori* infection after adjustment for other comprehensive risk factors. On the other hand, the multivariate-adjusted risk of gastric cancer for the groups with high HbA_{1c} levels alone and *H pylori* infection alone were slightly but not significantly higher than that of the reference group. This might be due to the limited number of gastric cancer cases. However, the interaction term between high HbA_{1c} level and *H pylori* infection was significant, indicating their synergic effect on gastric carcinogenesis. This finding suggests that hyperglycemia is one of the possible cofactors increasing the carcinogenic effects of *H pylori* infection.

There is suggestive clinical evidence to explain the synergistic effects of hyperglycemia and *H pylori* infection on gastric carcinogenesis. A population study demonstrated that hyperglycemia was associated with gastric

mucosal atrophy,[33] which is considered to be a precursor of gastric cancer. It is possible that increased reactive oxygen-related damage to DNA and genetic or epigenetic alterations in gastric mucosa induced by hyperglycemia or associated hyperinsulinemia stimulate a modifying effect of *H pylori* on epithelial cell proliferation, which is the initial step in a cascade of gastric carcinogenesis. On the other hand, *H pylori* infection might affect insulin release from the pancreas through gut hormones. A clinical study showed that *H pylori*-related gastritis increases glucose- and meal-stimulated insulin release by increasing gastrin secretion.[34] *H pylori* infection can also increase pancreatic insulin secretion by decreasing the serum concentration of somatostatin,[35] which has an inhibiting effect on insulin release.[36] Moreover, a clinical study demonstrated an increased state of insulin resistance in subjects with *H pylori* infection.[37] Thus, the enhanced effect of hyperglycemia and *H pylori* infection on gastric cancer might be explained partially by hyperinsulinemia or insulin resistance. Another possible explanation is that hyperglycemia affects *H pylori* and that its infection status or stimulates its carcinogenic effects. However, the association between diabetes and *H pylori* infection is controversial. A higher prevalence of *H pylori* infection in diabetic than in control subjects has been reported in some studies,[38,39] whereas other studies have found no significant correlation between fasting plasma glucose levels and *H pylori* status.[40,41] In our subjects, no significant correlation was observed between HbA_{1c} levels and *H pylori* prevalence at baseline. Given the limited findings, these hypotheses require further consideration.

The incidence rate of gastric cancer in our cohort was higher than that of other reported data.[1,2,42] This discrepancy seemed to have occurred because of differences in the study design as well as in the age structure or regions examined. Most of the previous studies were registration studies, whereas ours was a prospective cohort study. In addition, even the representative cancer registry research in Japan covered only 20%–30% of the total population,[43] and few studies included concealed cancers.[44] On the other hand, we performed almost perfect follow-up of subjects, with only 1 subject dropping out of follow-up and 76% of subjects who died during the follow-up underwent autopsy. Furthermore, the diagnosis of all our cases of gastric cancer was confirmed by histologic examination. Therefore, it is considered that very few cases who developed gastric cancer were missed, resulting in the high incidence rate in our cohort.

There are some limitations in this study that merit discussion. First, changes in HbA_{1c} and other potentially confounding factors were not reassessed over time in our subjects, although this limitation is typical of most prospective studies. It is therefore possible that, as a result of treatment for diabetes, greater modification of HbA_{1c} and other risk factors occurred in diabetic than in nondiabetic subjects. In our subjects, however, the risk of gastric cancer increased even at relatively low elevations of HbA_{1c}, which do not require medical treatment. Therefore, biases of this kind should not have distorted the significant association between HbA_{1c} levels and the risk of gastric cancer; nonetheless, the estimates of effect that we have reported here are most likely conservative. Second, because we did not perform a screening survey of the stomach in each subject at baseline examination, it is undeniable that there were presymptomatic gastric cancer patients at the baseline of this study, although this limitation is also a major problem for other registration studies of gastric cancer. However, the prevalence of gastric cancer in healthy subjects was reported to be low (0.12%) by nationwide mass screening in Japan.[45] We performed the same analysis with all subjects, except for those who developed gastric cancer in the first 2 years of the follow-up period, and the risk of gastric cancer was substantially unchanged (data not shown). Thus, we believe that the influence of concealed cancer at the time of baseline examination is small enough that it can be neglected.

In conclusion, this is the first population-based cohort study to investigate the association between HbA_{1c} levels and gastric cancer incidence. Our findings suggest that an elevated HbA_{1c} level, namely, casual hyperglycemia, is an independent risk factor for gastric cancer occurrence and is a possible cofactor increasing the risk of cancer posed by *H pylori* infection. Although the mechanism by which hyperglycemia per se is involved in gastric carcinogenesis remains obscure, early identification of hyperglycemia and appropriate behavioral and therapeutic intervention may be beneficial for the prevention of gastric cancer, especially in countries such as Japan where the number of diabetic individuals is increasing rapidly, and the risk of gastric cancer is considerable. Further cohort studies and intervention trials with strict control of blood glucose-enrolling diabetic patients and/or hyperglycemic subjects, especially those with *H pylori* infection, are needed to clarify the role of hyperglycemia in the development of gastric cancer.

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Conflict of interest

The authors disclose no conflicts.

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Impact of blood pressure levels on different types of stroke: the Hisayama study

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Objective Clinical uncertainty remains whether the blood pressure classification and risk stratifications recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) are useful in predicting the risks of stroke and its subtypes in the general Japanese population.

Methods A total of 1621 stroke-free residents of a Japanese community aged at least 40 years were followed up for 32 years. Outcomes were total and cause-specific stroke (lacunar infarction, atherothrombotic infarction, cardioembolic infarction, cerebral haemorrhage and subarachnoid haemorrhage). Incidence was calculated by the pooling of repeated observations method.

Results The age-adjusted incidence of total stroke rose progressively with higher blood pressure levels in both sexes (both P for trend <0.0001). A similar pattern was observed for lacunar infarction in both sexes and for cerebral haemorrhage in men: the differences were significant between optimal blood pressure and grades 1–3 hypertension (all $P<0.05$). The age-adjusted incidence of atherothrombotic infarction in either sex and that of cardioembolic infarction and subarachnoid haemorrhage in women significantly increased in grade 3 hypertension (all $P<0.05$). These associations remained substantially unchanged even after adjustment for other risk factors. In regard to risk stratification, the age-adjusted incidence of stroke significantly increased with the level of risk in both sexes.

Conclusion Our findings suggest that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines are useful in predicting the risk of stroke in a general Japanese population, but the magnitude and patterns of the impact of blood pressure categories are different among stroke subtypes. *J Hypertens* 27:2437–2443 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: blood pressure, stroke, stroke subtype, prospective cohort study, risk factor

Abbreviations: JSH, Japanese Society of Hypertension; LVH, left ventricular hypertrophy; TOD, target organ damage

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Introduction

Recent guidelines for the management of hypertension recommend assessment of total cardiovascular risk using risk factors, target organ damage (TOD) and pre-existing cardiovascular disease, as well as blood pressure levels [1–3]. These classifications have primarily been established based on clinical and epidemiological studies that investigated the risks of coronary heart disease, stroke and other forms of cardiovascular diseases in Western populations. However, there has been shown to be significant heterogeneity in the incidences of stroke and the frequencies of stroke subtypes between Asian and Western populations: the stroke incidence is higher, as is the proportion of stroke due to parenchymatous small arterial lesions, in Asian populations than in Western populations [4–7]. Because of the heterogeneity in the pathogenesis of stroke subtypes, the impact of blood pressure levels should be evaluated separately for each stroke subtype. Despite clear evidence of the associations between blood pressure levels and the incidence of total stroke [1–3,7–10], clinical uncertainty remains about the impact of blood pressure on the risks of different types of stroke, particularly on the risks of cerebral infarction subtypes.

The Hisayama study is a prospective cohort study of cardiovascular disease conducted in the town of Hisayama, Japan [6,11,12]. During the study period, 93% of the first-ever stroke patients underwent morphological examinations by autopsy and/or brain imaging, and more than 80% of the total number of surviving patients participated in five repeated follow-up examinations. This characteristic study design provided us an

A free communication on a portion of this study was presented at the 18th Scientific Meeting of the European Society of Hypertension/the 22nd Scientific Meeting of the International Society of Hypertension held in Berlin in June 2008.

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opportunity to classify stroke into different types with a high degree of accuracy and to assess the stroke incidence, taking into account the dynamic transition of blood pressure. In the present article, we examined whether the blood pressure classification and risk stratifications recently recommended by the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [3] are useful in predicting the occurrence of stroke and its subtypes in Japanese.

Methods

Study population and follow-up survey

In 1961, 1621 stroke-free residents of the town of Hisayama, aged 40 years or over (participation rate 88%), were enrolled in the present study [6,11,12]. Members of this cohort have received follow-up evaluations for 32 years from 1 November 1961 through 30 October 1993. Health examinations were repeated in 1967, 1974, 1978, 1983 and 1988, and the participation rates for these examinations were 96, 87, 85, 81 and 98%, respectively.

For patients 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 of the town, and used this system to gather information on new events of stroke, inclusive of suspected cases [6,11,12]. When stroke occurred or was suspected, physicians in the study team examined the patients and evaluated their detailed clinical information. The clinical diagnosis of stroke was based on the patient's history, physical and neurological examinations, and ancillary laboratory examinations. During the follow-up period, 1063 patients died, and 861 of these (81%) underwent autopsy to pathologically verify the cause of death and type of stroke. Only two patients were lost to follow-up.

The ethics committee of Kyushu University approved this study, participants provided written informed consent, and the procedures followed were in accordance with national guidelines.

Risk factor assessment

At each examination, blood pressure was measured three times using a standard sphygmomanometer after resting for at least 5 min in a supine position. Korotkoff phase 5 was taken as the diastolic blood pressure unless the sounds persisted at zero, in which case Korotkoff phase 4 was recorded. The mean of three measurements was used in the present analysis. We collected medical history and lifestyle information and conducted physical and neurological examinations. Information on antihypertensive treatment, smoking habits and alcohol intake was obtained using a standard questionnaire, and these factors were classified as being either habitually used or not used. Left ventricular hypertrophy (LVH; Minnesota code 3-1), ST depression (4-1, 2, 3 except for 3-1) and atrial fibrillation (8-3) on electrocardiography (ECG) were separately evaluated. Body weight and height were measured, and body mass index (BMI, kg/m^2) was calculated. Proteinuria was tested by the sulfosalicylic acid method in 1961 and 1967, and by the test paper method in 1974, 1978, 1983 and 1988. Serum cholesterol levels were determined by the Zak-Henly method, including a modification by Yoshikawa, in 1961 and 1967; by the Zurkowski method in 1974; and by the enzymatic method in 1978, 1983, and 1988 [13,14]. Glucose intolerance was determined by an oral glucose tolerance test in patients with glycosuria in 1961 and 1967, casual blood glucose levels in 1974, 1978 and 1983, and a 75-g oral glucose tolerance test in 1988, as well by reference to any medical history of diabetes at each examination [15,16].

Blood pressure classification and risk stratification

The JSH 2009 guidelines propose the following blood pressure categories: optimal blood pressure (systolic blood pressure < 120 mmHg and diastolic blood pressure < 80 mmHg), normal blood pressure (120–129/80–84 mmHg), high normal blood pressure (130–139/85–89 mmHg), grade 1 hypertension (140–159/90–99 mmHg), grade 2 hypertension (160–179/100–109 mmHg) and grade 3 hypertension (≥180/110 mmHg) [3]. The guidelines also recommend a risk stratification system that determines the whole cardiovascular risk using blood pressure categories and the presence or absence of other risk factors and TOD. In this study, risk factors were defined as age (≥65 years), dyslipidemia (total cholesterol >5.7 mmol/l), glucose intolerance and obesity (BMI ≥ 25 kg/m^2), and TOD was defined as electrocardiographic LVH (Minnesota code 3-1) and 1+ or more positive proteinuria. On the basis of the risk stratification system of the JSH 2009 guidelines, we classified patients into four risk groups. Specifically, the no additive risk group included patients with optimal and normal blood pressure and those with high-normal blood pressure who did not have risk factors or TOD. The low-risk group included patients with grade 1 hypertension who did not have risk factors or TOD. The moderate-risk group included patients with high-normal blood pressure and grade 1 hypertension who had one to two risk factors and those with grade 2 hypertension who did not have risk factors or TOD. The high-risk group included patients with high-normal blood pressure and grade 1 hypertension who had three or more risk factors, glucose intolerance or TOD, patients with grade 2 hypertension who had 1 or more risk factors, glucose intolerance or TOD and patients with grade 3 hypertension.

Stroke definition

The diagnosis of stroke was based on clinical information and the autopsy findings [6]. In principle, stroke was defined as a sudden onset of nonconvulsive and focal

neurological deficits persisting for more than 24 h, and the stroke was then classified as cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage or undetermined type of stroke. Cerebral infarction was further divided into four clinical categories: lacunar infarction, atherothrombotic infarction, cardioembolic infarction or undetermined type of cerebral infarction, based on the Classification of Cerebrovascular Disease III proposed by the National Institute of Neurological Disorders and Stroke [17], the criteria for the type of stroke of the TOAST study [18] and the Cerebral Embolism Task Force [19].

During the follow-up period, a total of 410 patients (200 men and 210 women) developed a first-ever stroke, and 381 of these (93%) underwent morphological examinations, including an examination of the cerebrospinal fluid, cerebral angiography, recent brain imaging including computed tomography and magnetic resonance imaging, echocardiography, carotid duplex imaging, and autopsy. Autopsies were performed on 303 stroke cases (74%). Of the 410 stroke cases that developed, 374 (181 men and 193 women) who participated in a follow-up examination within the 7 years previous to the stroke occurrence were eligible for the present study. These stroke cases were divided into 270 cases of cerebral infarction (128 men and 142 women), 68 of cerebral haemorrhage (45 and 23), 32 of subarachnoid haemorrhage (6 and 26) and four of an undetermined type of stroke (2 and 2). The cerebral infarction cases were further subdivided into 153 cases of lacunar infarction (72 and 81), 58 of atherothrombotic infarction (26 and 32), 51 of cardioembolic infarction (28 and 23) and eight of an undetermined type of cerebral infarction (2 and 6).

Statistical analysis

The incidence of stroke and its subtypes was calculated by the pooling of repeated-observations method [12,20,21]. This technique is a generalized person-years approach that incorporates all repeated examinations. It treats each examination interval as a mini follow-up study, in which the nearest risk factor measurements are employed to predict an event in the interval. Observations over multiple intervals are pooled into a single sample to predict the short-term risk of an event. The incidence was compared and the hazard ratios were estimated by the time-dependent Cox's proportional hazards model, in which risk factors other than age and sex were allowed to change in accordance with data from the five follow-up examinations. $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Table 1 shows the mean values or frequencies of risk factors for stroke at each examination by sex. The mean age was 56 years for men and 57 years for women at

Table 1 Means (±SD) or frequencies of risk factors at each examination among men and women

	Men						Women					
Risk factors	1961 ($n=707$)	1967 ($n=559$)	1974 ($n=396$)	1978 ($n=341$)	1983 ($n=278$)	1988 ($n=259$)	1961 ($n=914$)	1967 ($n=768$)	1974 ($n=599$)	1978 ($n=546$)	1983 ($n=436$)	1988 ($n=442$)
Age (years)	56±11	60±10	66±9	68±7.3	72±7	75±6	57±12	61±10	67±9	69±8	72±7	75±6
Systolic blood pressure (mmHg)	135±26	141±28	145±26	139±23	142±24	140±23	135±26	137±27	146±26	145±23	148±24	143±25
Diastolic blood pressure (mmHg)	79±14	82±14	80±12	79±11	80±12	77±12	77±13	79±13	79±12	79±11	79±11	75±11
Blood pressure category (%)												
Optimal (<120/80 mmHg)	30.0	24.5	17.7	20.2	15.5	18.9	32.4	29.0	15.0	13.9	11.2	15.6
Normal (120–129/80–84 mmHg)	18.3	13.8	13.9	14.7	16.2	16.2	16.1	13.9	13.4	13.2	10.8	15.4
High-normal (130–139/85–89 mmHg)	13.3	14.0	13.6	18.8	14.4	15.4	14.3	12.1	14.0	15.0	15.4	14.3
Grade 1 (140–159/90–99 mmHg)	19.4	22.2	27.5	27.0	31.3	30.9	19.4	25.4	30.2	32.1	31.2	30.8
Grade 2 (160–179/100–109 mmHg)	10.6	14.7	15.4	13.2	15.5	11.6	10.9	11.5	16.2	18.9	22.5	16.5
Grade 3 (≥180/110 mmHg)	8.5	10.9	11.9	6.2	7.2	7.0	6.9	8.1	11.2	7.0	8.9	7.5
Antihypertensive agent (%)	2.1	15.4	13.6	19.8	24.1	23.9	2.2	18.1	12.0	17.6	23.6	25.1
Left ventricular hypertrophy (%)[a]	22.0	17.5	19.4	19.1	23.3	18.2	10.3	10.2	10.2	15.0	21.9	14.8
ST depression (%)[b]	2.1	1.1	5.3	2.6	3.0	3.9	3.8	2.6	7.5	5.3	6.0	6.4
Atrial fibrillation (%)[c]	0.7	1.1	3.3	3.2	3.7	4.3	0.7	0.8	1.3	1.3	1.0	2.1
Glucose intolerance (%)	12.2	15.2	20.7	21.4	22.3	25.9	4.8	5.1	9.8	11.7	13.8	25.2
Body mass index (kg/m^2)	21.5±2.4	21.5±2.4	21.2±2.7	21.4±3.0	21.3±3.2	21.5±3.0	21.7±2.9	22.1±3.3	22.2±3.5	22.2±3.4	22.0±3.4	22.1±3.5
Total cholesterol (mmol/l)	3.9±0.9	4.1±0.8	4.6±0.9	4.6±1.0	4.8±1.0	4.6±1.0	4.2±1.0	4.6±1.0	5.1±0.9	5.3±1.0	5.4±1.0	5.4±1.1
Proteinuria (%)	7.1	3.8	16.4	6.3	13.6	8.5	9.4	3.6	13.4	4.8	9.4	7.8
Smoking habits (%)	76.2	70.2	67.0	60.7	52.5	45.2	17.1	14.9	12.2	11.3	8.3	10.9
Alcohol intake (%)	69.3	61.7	61.5	55.1	54.0	52.1	8.3	4.7	5.2	6.4	6.4	6.1

[a] Minnesota code 3-1. [b] Minnesota codes 4-1, 2, 3 except for 3-1. [c] Minnesota code 8-3.

baseline. The mean systolic blood pressure levels and frequency of hypertension (grades 1–3) slightly increased from 1961 to 1988 for both men and women. The frequency of patients taking antihypertensive agents increased from 2.1% in 1961 to 23.9% in 1988 among men and from 2.2 to 25.1% among women. The frequency of glucose intolerance and mean total cholesterol levels also increased from 1961 to 1988 in both sexes.

Incidence and adjusted hazard ratio for stroke and its subtypes

Tables 2 and 3 show the age-adjusted incidence of total stroke and its subtypes according to the blood pressure categories of the JSH 2009 guidelines [3] by sex. The incidence of total stroke and its subtypes, except for that of subarachnoid haemorrhage, was higher in men than in women. In both sexes, the stroke incidence increased steeply with elevation in blood pressure levels (both P for trend <0.0001); the differences between optimal blood pressure and grades 1–3 hypertension were statistically significant (all $P < 0.01$). These associations remained significant even after controlling for age, LVH, ST depression and atrial fibrillation on ECG, glucose intolerance, BMI, total cholesterol, smoking habits and alcohol intake in either sex (both P for trend <0.0001). Similar patterns were observed for cerebral infarction in both sexes and for cerebral haemorrhage in men (all P for trend <0.0001). For women, the incidence of cerebral haemorrhage significantly increased in grade 2 hypertension ($P = 0.02$), as did the incidence of subarachnoid haemorrhage in grade 3 hypertension ($P = 0.01$). For men, subarachnoid haemorrhage did not show a clear relationship with the blood pressure categories, probably due to the small number of events. With regard to subtypes of cerebral infarction, the incidence of lacunar infarction increased with elevation of blood pressure levels in both sexes (both P for trend <0.0001). In contrast, the incidence of atherothrombotic infarction sharply increased in grade 3 hypertension for both sexes (both $P < 0.05$), and the incidence of cardioembolic infarction significantly increased in grade 3 hypertension for women ($P = 0.04$). Comparable associations were observed between blood pressure categories and stroke even after excluding patients taking antihypertensive agents at each examination.

Risk stratification

Figure 1 shows the age-adjusted incidence of stroke by risk groups defined by the risk stratification system proposed by the JSH 2009 guidelines [3] among men and women. The stroke incidence increased steeply with the elevation of risk levels for men and women (both P for trend <0.0001): compared to the no-additive risk group, the stroke incidence was significantly higher in the moderate and high-risk groups for both sexes (all $P < 0.05$) and also in the low-risk group for women ($P = 0.008$).

Table 2 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among men

Type of stroke		Optimal	Normal	High-normal	Hypertension			P trend
					Grade 1	Grade 2	Grade 3	
Total stroke								
	Age-adjusted incidence (per 1000 person-years)	3.1	5.3	5.4	10.0**	20.9**	54.2**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.64 (0.76–3.56)	1.52 (0.70–3.31)	3.31 (1.73–6.32)**	4.22 (2.16–8.25)**	5.75 (2.93–11.30)**	<0.0001
Cerebral infarction								
	Age-adjusted incidence (per 1000 person-years)	2.4	2.8	3.8	6.9**	8.9**	19.5**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.38 (0.54–3.48)	1.37 (0.55–3.41)	3.10 (1.47–6.55)**	3.29 (1.50–7.21)**	4.88 (2.24–10.65)**	<0.0001
Lacunar								
	Age-adjusted incidence (per 1000 person-years)	1.4	1.1	1.8	4.8**	6.4**	11.2**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.11 (0.29–4.15)	1.49 (0.45–4.96)	3.09 (1.13–8.47)*	3.26 (1.14–9.30)*	4.66 (1.63–13.32)**	0.0003
Atherothrombotic								
	Age-adjusted incidence (per 1000 person-years)	0.0	1.0	0.4	1.0	1.1	6.1*	0.0001
	Multivariate-adjusted hazard ratio (95% CI)	–	1 (reference)	0.46 (0.04–4.94)	2.27 (0.48–10.87)	2.48 (0.47–12.97)	5.08 (1.04–24.89)*	0.0004
Cardioembolic								
	Age-adjusted incidence (per 1000 person-years)	1.0	0.7	1.6	1.1	1.2	1.5	0.18
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.89 (0.19–4.12)	0.81 (0.18–3.79)	1.52 (0.44–5.21)	0.99 (0.24–4.14)	1.39 (0.32–6.06)	0.57
Cerebral haemorrhage								
	Age-adjusted incidence (per 1000 person-years)	0.4	0.9	1.2	3.0*	7.4**	34.3**	<0.0001
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	2.22 (0.37–13.34)	2.95 (0.53–16.38)	5.59 (1.21–25.75)*	9.30 (1.98–43.61)**	12.04 (2.47–58.66)**	<0.0001
Subarachnoid haemorrhage								
	Age-adjusted incidence (per 1000 person-years)	0.3	1.6	0.0	0.1	0.5	0.3	0.66
	Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.28 (0.28–38.13)	–	1.16 (0.07–19.67)	1.90 (0.09–41.01)	3.41 (0.15–76.27)	0.83

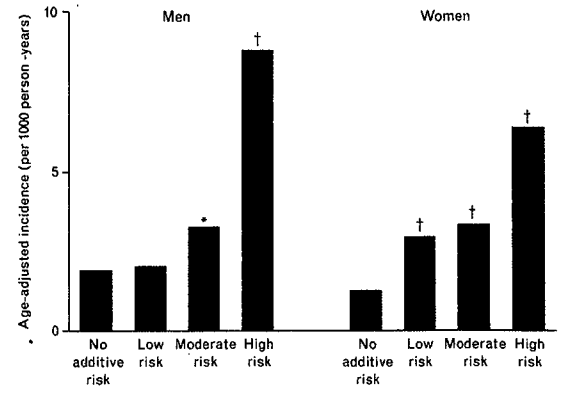
Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P < 0.05$, ** $P < 0.01$ vs. normal blood pressure for atherothrombotic infarction and vs. optimal blood pressure for other types of stroke.

Table 3 Incidence and adjusted hazard ratio for total stroke and its types by blood pressure categories among women

Type of stroke	Optimal	Normal	High-normal	Hypertension			P trend
				Grade 1	Grade 2	Grade 3	
Total stroke							
Age-adjusted incidence (per 1000 person-years)	2.0	2.5	3.9	6.3**	11.8**	22.4**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.53 (0.60–3.89)	2.19 (0.93–5.16)	3.92 (1.84–8.35)**	4.89 (2.24–10.67)**	7.51 (3.39–16.64)**	<0.0001
Cerebral infarction							
Age-adjusted incidence (per 1000 person-years)	1.4	2.1	2.0	4.6**	6.1**	14.3**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	1.78 (0.58–5.47)	1.91 (0.65–5.65)	3.91 (1.52–10.06)**	4.38 (1.66–11.57)**	7.14 (2.68–19.05)**	<0.0001
Lacunar							
Age-adjusted incidence (per 1000 person-years)	0.6	1.8	2.0	2.5*	3.3**	6.8**	<0.0001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.71 (0.76–18.00)	4.68 (1.01–21.62)	4.82 (1.11–20.90)*	6.25 (1.41–27.76)*	8.28 (1.82–37.70)**	0.002
Atherothrombotic							
Age-adjusted incidence (per 1000 person-years)	0.6	0.3	0.0	0.9	1.4	5.3*	0.002
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	0.50 (0.05–5.59)	–	2.26 (0.48–10.64)	1.92 (0.37–9.87)	3.68 (0.71–19.07)	0.02
Cardioembolic							
Age-adjusted incidence (per 1000 person-years)	0.2	0.0	0.0	1.1	1.1	1.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	–	4.26 (0.50–36.59)	4.73 (0.49–45.67)	11.09 (1.18–104.43)*	0.0008
Cerebral haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.2	0.5	0.6	0.5	4.6*	2.4	0.01
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	3.27 (0.29–36.62)	4.76 (0.48–47.33)	4.33 (0.47–39.71)	13.11 (1.45–18.55)*	7.40 (0.59–92.52)	0.02
Subarachnoid haemorrhage							
Age-adjusted incidence (per 1000 person-years)	0.4	0.0	1.3	1.0	1.0	5.4*	0.001
Multivariate-adjusted hazard ratio (95% CI)	1 (reference)	–	2.22 (0.36–13.67)	3.62 (0.73–17.93)	4.03 (0.71–22.97)	10.50 (1.86–59.20)**	0.0009

Hazard ratios are adjusted for age, sex, left ventricular hypertrophy, ST depression, atrial fibrillation, glucose intolerance, body mass index, total cholesterol, smoking habits and alcohol intake. * $P < 0.05$, ** $P < 0.01$ vs. optimal blood pressure.

Fig. 1



Age-adjusted incidence of total stroke by risk groups among men and women. *$P < 0.05$, †$P < 0.01$ vs no additive risk.

Discussion

The present analysis demonstrated strong associations between the blood pressure categories defined by the JSH 2009 guidelines [3] and the incidence of stroke among general Japanese patients. The incidence of total stroke increased with elevation of blood pressure categories and became significantly higher in patients with grades 1–3 hypertension than in those with optimal blood pressure levels. There were also strong associations between the JSH 2009 blood pressure categories and most of the stroke subtypes. These associations did not change even after adjustment for other cardiovascular risk factors. The incidence of stroke also increased with elevation of the risk levels defined by the risk stratification system recommended by the guidelines. A cohort study conducted in Japan has also demonstrated the validity of the risk stratification system of the JSH 2009 guidelines [22]. These findings support the hypothesis that the blood pressure classification and risk stratifications recommended by the JSH 2009 guidelines [3] are useful in predicting the risk of stroke among Japanese.

The incidence of stroke in each blood pressure category in the present analysis was similar to that obtained from other observational studies conducted in Japan [23,24], but was higher than that observed in Western populations [25,26]. These findings are consistent with those of previous epidemiological and clinical studies that demonstrated heterogeneous risks of stroke between Asian and Western populations [5,7,27].

Large-scale cohort studies have clearly demonstrated that blood pressure levels predicted future stroke events in Japan [10,12,23,24,28–32] as well as other countries around the world [7,8]. A number of cohort studies have demonstrated separately significant effects of blood