standard Cox's proportional hazard model for analyzing data [11, 12]. Hence, in the present study, competing risk analysis was used for determining the impact of the combination of type 2 diabetes and smoking on cancer mortality with consideration given to cardiovascular mortality as a competing risk in Japanese males.

Materials and methods

This study was approved by the Ethics Committee of Sapporo Medical University. Written informed consent was obtained from all participants in this study.

Study participants

We recruited participants in the Tanno-Sobetsu Study [13, 14], a study with a population-based prospective cohort design for the present analyses. In two towns, Tanno and Sobetsu, in Hokkaido, Japan, public health nurses in the local government recruited by mail all residents aged 20 years or more for annual medical examinations, including standard blood and urine tests and an electrocardiogram. We explained this cohort study to each resident who was going to receive the health checkup by a face-to-face interview onsite, and we included residents who consented to participate in this study.

In 1994, 1908 residents who were aged 30 years or older received health checkups (794 men and 1114 women). Because there were few individuals with type 2 diabetes and few ex-smokers and current smokers among the females (4.8, 2.2 and 8.8 %, respectively), we included only 794 males as study participants for this analysis.

Measurement items

All participants were examined in the morning after an overnight fast. Body weight and height were measured, and body mass index (BMI) was calculated as body weight divided by the square of body height (kg/m^2). After 5 min of rest, systolic and diastolic blood pressures (SBP and DBP) were measured twice in a sitting position using a mercury sphygmomanometer by a well-trained doctor, and average values were used for analysis. Total cholesterol (TC) and fasting plasma glucose (FPG) levels were measured by venous blood tests. TC and FPG levels were measured by the cholesterol oxidase and hexokinase method, respectively. Information on medical history including use of medications, smoking status and alcohol drinking status was obtained via interviews by public nurses.

In this study, smoking status was defined according to three categories: never smoker, ex-smoker and current smoker. Individuals with type 2 diabetes were defined as individuals with FPG $\geq$7.0 mmol/l and/or receiving medication for type 2 diabetes.

Follow-up

All participants were followed up from 1994 to 31 December 2007, and their vital status and emigration status and cause of death were annually ascertained using residence registry data, death certificates, medical records in hospitals and/or questionnaires. Out-migrate individuals were defined as censored cases at the time of move-out day.

Statistical analyses

To determine the impact of the combination of type 2 diabetes and smoking on cancer mortality, participants were divided into the following six groups: non-DM (NDM) and never smoker, NDM and ex-smoker, NDM and current smoker, DM and never smoker, DM and ex-smoker, and DM and current smoker.

Stata version 12.1 (StataCorp LP, USA) was used for statistical analysis. The significance level in all analyses was set at $p < 0.05$. All numerical values are expressed as mean $\pm$ SD. Dunnett's and Fisher's exact tests were used for examination of intergroup differences compared with the NDM and never-smoker group and for frequency comparison, respectively.

To assess the risk of cancer mortality in each of the six groups, we first calculated the hazard ratio (HR) and 95 % confidence interval (CI) using Cox's proportional hazard model. We then performed competing risk regression analyses because cardiovascular death is considered to be a competing risk event in this analysis. Competing risk regression analyses were conducted using the Fine and Gray method, and the subhazard ratio (SHR), with the NDM and never-smoker group being used as a reference group, was calculated in each group. In multivariate analysis, age, BMI, alcohol drinking and TC level were selected as covariates being confounding factors for cancer mortality.

As a sensitivity analysis, we conducted the same analysis as that described above after excluding events of cancer death within 3 years from baseline.

Results

Baseline characteristics in the six groups according to DM and smoking status are shown in Table 1. Mean age tended to be lower in the current smoker groups than in the never-smoker groups and was significantly lower in the NDM and

Table 1 Baseline characteristics in the six groups according to DM and smoking status

	NDM and never smoker ($n = 185$)	NDM and ex-smoker ($n = 151$)	NDM and current smoker ($n = 393$)	DM and never smoker ($n = 15$)	DM and ex-smoker ($n = 21$)	DM and current smoker ($n = 29$)	p value‡
Age (years)	60.9 ± 11.6	63.6 ± 12.5	57.8 ± 12.5*	65.9 ± 10.6	65.1 ± 11.8	64.7 ± 10.2	<0.001
BMI (kg/m^2)	23.7 ± 2.9	23.6 ± 3.2	23.0 ± 3.1	24.4 ± 2.6	23.3 ± 2.4	24.2 ± 4.0	0.06
SBP (mmHg)	133.7 ± 17.1	136.3 ± 19.2	131.2 ± 18.6	143.3 ± 18.6	142.4 ± 15.2	134.4 ± 19.7	0.003
DBP (mmHg)	79.5 ± 9.2	79.8 ± 9.6	77.6 ± 9.4	77.1 ± 7.5	81.9 ± 9.5	78.5 ± 8.6	0.045
TC (mmol/l)	5.1 ± 0.8	4.9 ± 0.9	4.7 ± 0.8	5.2 ± 0.8	4.9 ± 0.9	4.8 ± 0.9	0.199
FPG (mmol/l)	5.2 ± 0.5	5.4 ± 0.6	5.2 ± 0.6	8.4 ± 3.0*	8.1 ± 2.5*	8.0 ± 3.0*	<0.001
Alcohol drinking							<0.001
Never drinker (%)	31.4	20.5	18.1	33.3	28.6	31.0	
Ex-drinker (%)	5.4	17.2	8.4	6.7	38.1	3.4	
Current drinker (%)	63.2	62.3	73.5	60.0	33.3	65.5	
Medication for hypertension (%)	15.1	21.9	17.6	20.0	14.3	24.1	0.576
Medication for hypercholesterolemia (%)	1.6	0.0	0.8	0.0	0.0	3.4	0.297
Medication on DM (%)	0	0	0	73.3	66.7	69.0	<0.001

Values are expressed as mean ± SD

DM type 2 diabetes, *NDM* non-DM, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *FPG* fasting plasma glucose

* $p < 0.05$, vs. NDM and never smoker, Dunett's test

‡ Analysis of variance (ANOVA) and Fisher's exact test were used for mean comparison and frequency comparison, respectively

current smoker group than in the NDM and never-smoker group. BMI and blood pressure levels tended to be higher in the DM groups than in the NDM groups. Frequency of being an ex-drinker tended to be high in the ex-smoker groups. There were no significant differences in the frequency of medication for DM among the three DM groups.

The mean follow-up period was 11.3 ± 3.6 years, and 8914 person-years were totally observed. During the follow-up period, there were 169 all-cause deaths (62 cancer deaths and 40 CVD deaths). The 62 cancer deaths included 22 lung cancer, 11 gastric cancers, 8 liver cancers, 5 pancreatic cancers, 5 prostate cancers, 3 colorectal cancers and 8 other cancer deaths. Table 2 shows cancer mortality and CVD mortality rates in the six groups. Cancer mortality rates in the ex-smoker and current smoker groups were higher than those in the never-smoker groups both with and without DM. Cancer mortality rate also tended to be higher in the DM groups than in the NDM groups.

Table 3 shows the results of competing risk regression and Cox proportional hazard regression analysis for total cancer mortality. When using Cox regression analysis, HRs after adjustment for several confounding factors were higher in the ex-smoker and current smoker groups than in the never-smoker group, and HRs were also higher in the DM groups than in the NDM groups. HR in the DM and current smoker group was the highest among the six groups. When using competing risk regression analysis, SHRs were almost the same as the HRs of Cox regression analysis.

As a sensitivity analysis, we conducted the same analysis as that described above after excluding events of cancer death within 3 years from baseline (Table 4). Although there were some differences in HRs and SHRs and slightly larger 95 % CIs, the DM and ex-smoker group and the DM and current smoker group showed the same tendency of higher HRs and SHRs as shown in Table 3.

Discussion

The main findings of this study are (1) both type 2 diabetes and smoking status were strong risk factors for all-cause cancer mortality, and the combination of type 2 diabetes and smoking status was a stronger risk than type 2 diabetes alone or smoking status alone; (2) when using competing risk analysis, there were no remarkable attenuations of SHR compared with Cox regression analysis.

There has been an accumulation of evidence indicating that type 2 diabetes is related to cancer morbidity and mortality [1–8], and the American Diabetes Association (ADA) and American Cancer Society (ACS) jointly published a consensus report on the association between

Table 2 Cancer mortality and CVD mortality in the DM and smoking groups

	Number of cancer deaths	Number of CVD deaths	Person-years	Cancer mortality (/1000 person-year)	CVD mortality (/1000 person-year)
NDM and never smoker ($n = 185$)	4	7	2153	1.9	3.3
NDM and ex-smoker ($n = 150$)	10	10	1647	6.1	6.1
NDM and current smoker ($n = 390$)	37	17	4463	8.3	3.8
DM and never smoker ($n = 15$)	1	1	152	6.6	6.6
DM and ex-smoker ($n = 21$)	4	3	206	19.4	14.6
DM and current smoker ($n = 29$)	6	2	293	20.5	6.8

CVD cardiovascular disease, *DM* type 2 diabetes, *NDM* non-DM

Table 3 Competing risk and Cox proportional hazard regression analyses for total cancer mortality among DM and smoking status categories

	Competing risk			Cox proportional hazard		
	SHR	95 % CI	*p* value	HR	95 % CI	*p* value
NDM and never smoker ($n = 185$)	1.00 (ref)	–	–	1.00 (ref)	–	–
NDM and ex-smoker ($n = 150$)	2.42	0.71–8.17	0.157	2.36	0.72–7.74	0.155
NDM and current smoker ($n = 390$)	5.01	1.77–14.21	0.002	4.89	1.72–13.91	0.003
DM and never smoker ($n = 15$)	2.77	0.27–28.42	0.391	2.54	0.28–23.10	0.406
DM and ex-smoker ($n = 21$)	6.06	1.39–26.51	0.017	7.88	1.91–32.55	0.004
DM and current smoker ($n = 29$)	10.12	2.69–38.07	<0.001	10.61	2.99–37.66	<0.001

Both HR and SHR were adjusted for age, body mass index, alcohol drinking and total cholesterol level

DM type 2 diabetes, *NDM* non-DM, *SHR* subhazard ratio assessed by competing risk regression, *HR* hazard ratio assessed by Cox proportional hazard model, *95 % CI* 95 % confidence interval

Table 4 Competing risk and Cox proportional hazard regression analyses for total cancer mortality among DM and smoking status categories after excluding events of cancer death within 3 years from baseline

	Competing risk			Cox proportional hazard		
	SHR	95 % CI	*p* value	HR	95 % CI	*p* value
Non-DM and never smoker ($n = 185$)	1.00 (ref)	–	–	1.00 (ref)	–	–
Non-DM and ex-smoker ($n = 150$)	2.63	0.67–10.35	0.166	2.61	0.68–10.06	0.164
Non-DM and current smoker ($n = 390$)	5.93	1.78–19.74	0.004	5.78	1.75–19.11	0.004
DM and never smoker ($n = 15$)	3.73	0.34–41.40	0.283	3.46	0.35–33.74	0.286
DM and ex-smoker ($n = 21$)	5.81	1.07–31.54	0.041	8.00	1.56–41.03	0.013
DM and current smoker ($n = 29$)	8.64	1.78–41.94	0.007	9.41	2.10–42.06	0.003

Both HR and SHR were adjusted for age, body mass index, alcohol drinking and total cholesterol level

DM type 2 diabetes, *NDM* non-DM, *SHR* subhazard ratio assessed by competing risk regression, *HR* hazard ratio assessed by Cox proportional hazard model, *95 % CI* 95 % confidence interval

diabetes and cancer in 2010 [15, 16]. The Japan Diabetes Society (JDS) and Japanese Cancer Association (JCA) also published a report of the JDS/JCA Joint Committee on Diabetes and Cancer in 2013 [17]. In these two reports, both type 2 diabetes and smoking are common risk factors for cancer, and individuals with DM are recommended to stop smoking. However, the impact of a combination of type 2 diabetes and smoking on cancer is not mentioned in these two reports, and this issue is still unclear because smoking status was likely to have been used as a confounding factor for the relationship between type 2 diabetes and cancer in previous studies. There are a few reports on the interaction of DM and smoking for pancreatic cancer. Two case-control studies showed that the combination of DM and smoking was a stronger risk for pancreatic cancer than DM alone or ever smoking alone [18, 19]. We assessed the interaction between type 2 diabetes and smoking on cancer mortality by using both a Cox model

and a Fine and Gray model into which type 2 diabetes (yes/no), smoking status (current and ex/never) and the interaction term (type 2 diabetes × smoking status) were added as covariates in the analysis before dividing participants into six categories according to DM and smoking status (data not shown). *P* values of the interaction term were 0.489 and 0.678 in the Cox model and the Fine and Gray model, respectively, and we could not find a significant interaction between type 2 diabetes and smoking status. However, the results of this study showed that the highest SHR for all cancer mortality was in the DM and current smokers (Table 3), and this large risk for cancer mortality may enhance the motivation of patients with type 2 diabetes to stop smoking.

Mechanisms of this effect of the combination of type 2 diabetes and smoking on cancer mortality could not be explored in this analysis, but some mechanisms can be considered. Hyperinsulinemia due to insulin resistance [20–22], oxidative stress accompanied by hyperglycemia [23, 24] and chronic inflammation [25, 26] are considered to lead to development and progression of cancer in type 2 diabetes patients. The combination of these various mechanisms and the effect of smoking is easily considered to play a pleiotropic and synergistic role in the development of cancer. As another mechanism of the interaction, a recent meta-analysis [27] showed that the circulating soluble receptor for the advanced glycation end product (sRAGE) was inversely associated with the risk of developing cancer, and smoking status explained some part of the heterogeneity for the association of circulating sRAGE with cancer risk using a meta-regression analysis. The AGE-RAGE system may be related to the synergistic interaction between type 2 diabetes and smoking for cancer mortality.

In this study, when using competing risk analysis, there were no remarkable attenuations in SHRs of the DM and ex-smoker group and the DM and current smoker group compared with the results of Cox regression analysis. One possible reason for this is the change in specific causes of death in type 2 diabetes patients over the past few decades in Japan. The most common cause of death among Japanese patients with diabetes was cardiovascular disease from 1979 to 1989, but cancer death became the most common cause of death in the 1990s with the extension of life expectancy among patients with diabetes [28]. Therefore, the change in specific causes of death among patients with diabetes may have affected the results of this study, which were intended for mortality.

One of the clinical implications of this study is that the impact of the combination of type 2 diabetes and smoking on cancer mortality may help medical staff in the situation of education for patients with type 2 diabetes and a smoking habit. These patients may be motivated to stop smoking by the tenfold higher risk of cancer mortality than for non-DM and never smokers. Another clinical implication is that the results of this study may be useful in education for community-dwelling smokers by public health workers. Smoking is one of the risk factors for future occurrence of type 2 diabetes as well as occurrence of cancer [29, 30]. Community-dwelling smokers, therefore, are at high risk for future occurrence of both type 2 diabetes and cancer. Moreover, if they acquire type 2 diabetes in the near future and become patients with type 2 diabetes who have a smoking habit, their relative risk for cancer mortality might increase from five- to tenfold. This information may help to motivate community-dwelling smokers to stop smoking.

There were several limitations to this study. First, we could not assess cancer morbidity. Therefore, the results mainly reflect the effect of type 2 diabetes and smoking on cancers with high mortality. Second, we could not assess site-specific cancer mortality because of the small number of cancer deaths. To clarify the effect of the combination of type 2 diabetes and smoking for site-specific cancer mortality, further large-scale studies are needed. Third, we could not completely exclude the possibility that cancer-bearing individuals were recruited in this study at baseline. However, that possibility is not high since exclusion of events of cancer death within 3 years from baseline did not significantly change the results (Table 4). Fourth, because of the small numbers of individuals with type 2 diabetes and smokers in women, we could not assess the gender differences in the effect of the combination of type 2 diabetes and smoking on cancer mortality, and further large-scale studies also are needed to clarify gender differences. Fifth, we could not assess treatments for diabetes in detail, but some medications such as metformin [31, 32] may have confounded the results of this study.

In conclusion, the combination of type 2 diabetes and smoking is a strong risk factor for total cancer mortality in Japanese men, and it may motivate smokers both with and without type 2 diabetes to stop smoking.

Acknowledgments No potential conflicts of interest relevant to this article were reported. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent or a substitute for it was obtained from all participants for being included in the study. The authors sincerely thank the public health nurses and staff in the Tanno and Sobetsu Town Offices for their help in the recruitment of study participants and data collection.

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Defecation frequency and cardiovascular disease mortality in Japan: The Ohsaki cohort study

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ABSTRACT

Background: It has been suggested that constipation is associated with cardiovascular disease (CVD). The association between defecation frequency and CVD mortality in a large population has not been reported hitherto. The aim of this study was to examine whether defecation frequency is related to CVD mortality.
Methods and results: A total of 45,112 eligible Japanese men and women aged 40–79 years participated in the Ohsaki Cohort study. Defecation frequency was evaluated at the baseline using a self-administered questionnaire. Hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular disease mortality were calculated according to defecation frequency (≥1 time/day, 1 time/2–3 days, ≤1 time/4 days) by the Cox proportional hazards model. During 13.3 years of follow-up, 2028 participants died due to CVD. Compared with those in the ≥1 time/day group, the risk of overall CVD mortality was significantly higher in the 1 time/2–3 days and ≤1 time/4 days groups; the multivariate HR (95%CI) for 1 time/2–3 days and ≤1 time/4 days was 1.21 (95% CI: 1.08–1.35) and 1.39 (95% CI: 1.06–1.81), respectively.
Conclusion: A lower defecation frequency was associated with risk of CVD mortality in this Japanese population. Future studies, aiming at elucidating the mechanisms underlying the associations between chronic constipation and risk of CVD mortality, may be facilitated by our findings.
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1. Introduction

Constipation is a common problem, with a reported prevalence of approximately 20%, varying between 2% and 28% depending on the diagnostic criteria employed [1–7]. One study has suggested that chronic constipation is associated with shorter life span [8,9]. Other studies have reported that the concentration of intestinal microbiota differs between patients with constipation and non-constipated controls [10–14]. The intestinal microbial imbalance has an association with blood pressure [15], and its metabolism may be related to the risk of atherosclerosis and cardiovascular disease (CVD) [16,17]. Other studies have reported that oxidative stress might be associated with both constipation and CVD [18–20]. Valsalva-like breath-holding as a result of defecation-associated straining is suggested to cause circulatory changes and increase the risk of rupture of intracranial aneurysms [21–27].

However, epidemiological data on the association between constipation and CVD have been limited. Only one cohort study has reported that the subjective severity of constipation is related to a higher risk of CVD incidence among postmenopausal women [28]. To our knowledge, the association between quantitative indices of constipation, such as defecation frequency, and the risk of CVD has never been reported.

The aim of this cohort study was to examine whether defecation frequency is related to CVD mortality.

2. Methods

2.1. Study population

The present data were derived from the Ohsaki Cohort Study, a large prospective population-based study, the design of which was reported previously [29,30]. The subjects were all National Health Insurance (NHI) beneficiaries, aged 40–79 years, who were living in the catchment area of the Ohsaki Public Health Center, Miyagi

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Living situations associated with poor dietary intake among healthy Japanese elderly: the Ohasama Study.

Tsubota-Utsugi M[1], Kikuya M, Satoh M, Inoue R, Hosaka M, Metoki H, Hirose T, Asayama K, Imai Y, Ohkubo T.

Abstract

BACKGROUND:

Rapid increases in life expectancy have led to concurrent increases in the number of elderly people living alone or those forced to change living situations. Previous studies have found that poor dietary intake was common in elderly people living alone. However, there have been few studies about the dietary intake in elderly people living in other situations, particularly those living with family other than a spouse (nonspouse family), which is common in Japan.

OBJECTIVE:

To examine the differences in dietary intake by different living situations in elderly Japanese people. We analyzed the data of 1542 healthy residents in the town of Ohasama aged 60 years and over who had completed self-administered questionnaires.

METHODS:

The dietary intake was measured using a validated 141-item food frequency questionnaire. Multiple regression models with robust (White-corrected) standard errors were individually fitted for nutrients and foods by living situation.

RESULTS:

In men, although the presence of other family was correlated with significantly lower intake of protein-related foods, e.g., legumes, fish and shellfish, and dairy products, these declines were more serious in men living with nonspouse family. Conversely, in men living alone the intake of fruits and vegetables was significantly lower. In women, lower intakes of fruit and protein-related foods were significantly more common in participants living with nonspouse family than those living with only a spouse.

CONCLUSION:

These findings revealed that elderly people living alone as well as those living with family other than a spouse had poor dietary intake, suggesting that strategies to improve food choices and skills for food preparation could promote of healthy eating in elderly Japanese people.

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Association between N-terminal pro B-type natriuretic peptide and day-to-day blood pressure and heart rate variability in a general population: the Ohasama study.

Satoh M[1], Hosaka M, Asayama K, Kikuya M, Inoue R, Metoki H, Tsubota-Utsugi M, Hara A, Hirose T, Obara T, Totsune K, Hoshi H, Mano N, Node K, Imai Y,Ohkubo T.

Abstract

BACKGROUND:

In addition to day-to-day variability in blood pressure (BP) or heart rate (HR), N-terminal pro B-type natriuretic peptide (NT-proBNP) has been reported to be a predictor of cardiovascular disease. Here, we tested the hypothesis that day-to-day BP or HR variability calculated as the intraindividual standard deviation (SD) of home BP or HR is associated with elevated NT-proBNP in a cross-sectional study.

METHODS:

Among 664 participants (mean age, 61.9 years; female, 70.5%) from a general Japanese population without a history of heart disease, 86 (13.0%) had NT-proBNP at least 125pg/ml.

RESULTS:

Each 1 SD increase in the SD of home systolic BP (SBP) [odds ratio (OR), 1.82; P<.0001) and in the SD of home HR (OR, 1.44; P=0.008) were significantly associated with the prevalence of NT-proBNP at least 125pg/ml after adjustment for possible confounding factors including home SBP and HR. Among the four groups defined by the median SD of home SBP and of home HR, the group with higher SDs in home SBP (≥8.0mmHg) and HR (≥5.0bpm) had the greatest OR for the prevalence of NT-proBNP at least 125pg/ml (OR, 4.80; P=0007 vs. a reference group with lower SDs of home SBP and HR).

CONCLUSION:

These results suggest that day-to-day variability in BP and HR may be associated with target-organ damage or complications, which can lead to an elevated NT-proBNP level. An elevated NT-proBNP level may be involved in the prognostic significance of day-to-day variability in BP or HR.

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Long-Term Stroke Risk Due to Partial White-Coat or Masked Hypertension Based on Home and Ambulatory Blood Pressure Measurements: The Ohasama Study.

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Abstract

The prognostic significance of white-coat hypertension (WCHT) is controversial, and different findings on self-measured home measurements and 24-h ambulatory monitoring make identifying WCHT difficult. We examined whether individuals with partially or completely defined WCHT, as well as masked hypertension, as determined by different out-of-office blood pressure measurements, have a distinct long-term stroke risk. We followed 1464 participants (31.8% men; mean age, 60.6±10.8 years) in the general population of Ohasama, Japan, for a median of 17.1 years. A first stroke occurred in 212 subjects. Using sustained normal blood pressure (events/n=61/776) as a reference, adjusted hazard ratios for stroke (95% confidence intervals; events/n) were 1.38 (0.82-2.32; 19/137) for complete WCHT (isolated office hypertension), 2.16 (1.36-3.43; 29/117) for partial WCHT (either home or ambulatory normotension with office hypertension), 2.05 (1.24-3.41; 23/100) for complete masked hypertension (both home and ambulatory hypertension with office normotension), 2.08 (1.37-3.16; 38/180) for partial masked hypertension (either home or ambulatoryhypertension with office normotension), and 2.46 (1.61-3.77; 42/154) for sustained hypertension. When partial WCHT and partial maskedhypertension groups were further divided into participants only with home hypertension and those only with ambulatory hypertension, all subgroups had a significantly higher stroke risk (adjusted hazard ratio ≥1.84, P≤0.04). In conclusion, impacts of partial WCHT as well as partial maskedhypertension for long-term stroke risk were comparable to those of complete masked hypertension or sustained hypertension. We need both home and 24-h ambulatory blood pressure measurements to evaluate stroke risk accurately.

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ORIGINAL ARTICLE

Dietary carbohydrate intake, presence of obesity and the incident risk of type 2 diabetes in Japanese men

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Keywords
Cohort study, Dietary carbohydrates, Incidence

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ABSTRACT

Aims/Introduction: The present cohort study assessed the risk among Japanese men for developing type 2 diabetes, based on the percentage of energy intake from carbohydrates and degree of obesity.

Participants and Methods: The participants were 2,006 male factory employees, and the macronutrient intake of each patient was measured using a self-administered diet history questionnaire. The incidence of diabetes was determined in annual blood examinations over a 10-year period.

Results: During the study, 232 participants developed diabetes. The crude incidence rates (/1,000 person-years) for different levels of carbohydrate intake as a percentage of calories consumed (<50.0, 50.0–57.4, 57.5–65.0, >65.0% of energy intake) were 16.5, 14.4, 12.7 and 17.6. Overall, carbohydrate intake was not associated with the risk of diabetes. However, there was significant interaction between carbohydrate intake and degree of obesity on the incidence of diabetes (*P* for interaction = 0.024). Higher carbohydrate intake was associated with elevated risk for diabetes among participants with a body mass index ≥25.0 kg/m^2 (*P* for trend = 0.034). For obese participants, the multivariate-adjusted hazard ratio for those with carbohydrate intakes >65% energy was 2.01 (95% confidence interval 1.08–3.71), which was significantly higher than that of participants with carbohydrate intakes 50.0–57.4% energy.

Conclusions: Higher carbohydrate intake was associated with higher risk of diabetes in obese participants, but not in non-obese participants. Obese participants with carbohydrate intakes >65% energy should reduce their intakes to levels within the desirable carbohydrate energy proportion for Japanese (50–65% energy) to prevent development of type 2 diabetes.

INTRODUCTION

The prevalence of type 2 diabetes is similar in Asian and Western countries, although the prevalence of obesity is lower in Asia[1]. The high incidence of diabetes in the comparatively lean Asian populations might be explained, at least in part, by the presence of more abdominal fat in Asians, compared with Caucasians of a similar body mass index (BMI)[2,3]. In addition, non-obese Asians with low pancreatic B-cell function also have an elevated risk of diabetes[4–6].

Dietary factors could also play a role in the high incidence of diabetes in Asian populations. The traditional Japanese diet, characterized by a high intake of rice, soy-based foods and fish,

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could improve cardiovascular health. However, the trend over recent years (partially as a result of an economic transition) has been the increasing consumption of a Western-style diet. The average energy intake from fat increased from 10.6% in 1960 to 23.6% in 1980, and 25.5% in 2011.[7] Meanwhile, the average energy intake from carbohydrates decreased from 76.1% in 1960 to 61.5% in 1980 and 59.7% in 2011.[7] These dietary changes might partially explain the increasing prevalence of type 2 diabetes in Japanese populations.

In previous studies carried out in Western countries, carbohydrate intake was not associated with the incidence of type 2 diabetes.[8–13] In contrast, a study of Chinese women showed that a diet consisting of a higher percentage of carbohydrates and lower percentage of fat was associated with an elevated risk of type 2 diabetes.[14] An international study of associations between macro- and micronutrient levels and blood pressure showed that carbohydrate intake was higher in East Asian countries, including China and Japan, than in Western countries[15,16], and these differences in macronutrient intake might affect the association between carbohydrate intake and diabetes. However, although decreased average carbohydrate intake has been correlated with increased prevalence of diabetes in these East Asian countries, it is unclear how dietary carbohydrate affects the incidence of diabetes in these populations.

In the present 10-year prospective study of Japanese men, we investigated the relationship between dietary carbohydrate intake and the risk for developing type 2 diabetes.

MATERIALS AND METHODS

Participants

The study participants were employees of a factory that produces zippers and aluminum sashes in Toyama Prefecture, Japan. Detailed information on the study population has been reported previously[6,17–19]. The Industrial Safety and Health Law in Japan requires employers to carry out annual health examinations for all employees. A test for diabetes mellitus was carried out during annual medical examinations between 2003 and 2013. In 2003, 2,275 (89%) out of 2,543 male employees aged 35–55 years received health examinations and responded to the dietary survey. Of these potential participants, 269 (12%) were excluded: 165 because they were diabetic or had high fasting plasma glucose (≥126 mg/dL) or high glycated hemoglobin (HbA1c; National Glycohemoglobin Standardization Program [NGSP] ≥6.5%) at the time of the baseline examination, nine because their total daily calorie intakes were below 500 kcal or above 5,000 kcal, 24 because of histories of cancer, 23 because of histories of cardiovascular disease and 48 because they did not participate in consecutive follow-up annual health examinations. Therefore, a total of 2,006 participants were enrolled in the study.

Data Collection

The annual health examination was carried out by trained staff, and included a medical history, physical examination, anthropometric measurements, and the measurement of fasting plasma glucose, HbA1c and serum lipid levels. Height was measured without shoes to the nearest 0.1 cm using a stadiometer. Weight was measured with participants wearing only light clothing and no shoes to the nearest 0.1 kg using a standard scale. BMI was calculated as weight/height^2 (kg/m^2). Blood pressure was measured using a mercury sphygmomanometer after the participant had rested for 5 min in a seated position.

Plasma glucose levels were measured enzymatically using an Abbott glucose UV test (Abbott Laboratories, Chicago, IL, USA). HbAlc was measured by high-velocity liquid chromatography using a fully automated analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Quality control of HbA1c measurements was confirmed using the standards certified by the Japanese Diabetes Society (JDS), and HbA1c values were converted into NGSP values using the formula provided by the JDS: HbA1c (NGSP) = 1.02 × HbA1c (JDS) + 0.25[20]. Total cholesterol and triglycerides were assessed using an enzyme assay, and high-density lipoprotein cholesterol was measured using direct methods.

A questionnaire was used to identify voluntary health-related behaviors, such as alcohol consumption, smoking and regular exercise habits. An additional self-administered questionnaire was used to collect information regarding medical history of hypertension, dyslipidemia, diabetes, the use of antidiabetic medication and any family history of diabetes. High blood pressure and dyslipidemia were defined using the Japanese criteria for metabolic syndromes:[21] high blood pressure was defined as a systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥85 mmHg, or the use of antihypertensive medication; and dyslipidemia was defined as serum triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL or the use of medication for dyslipidemia. The questionnaire also explored whether participants sometimes worked night shifts.

Dietary Assessment

At baseline examination, dietary habits during the month preceding the health examination were assessed using a self-administered diet history questionnaire (DHQ)[22]. The DHQ was developed to estimate the dietary intakes of macro- and micronutrients for epidemiological studies in Japan. Detailed descriptions of the methods used for calculating dietary intakes and the validity of the DHQ have been reported previously[23–25]. Estimates of the dietary intake of 147 food and beverage items, and their corresponding energy and nutrients were calculated using an *ad hoc* computer algorithm developed for the DHQ that was based on the Standard Tables of Food Composition in Japan[26]. Dietary fiber level was determined by assessing the intakes of 86 fiber-containing foods listed in the DHQ. The results from previous studies of middle-aged Japanese women showed that the relative differences between the mean intake levels obtained from the DHQ and from the 3-day diet records were 0.7% for total energy, 3.3% for carbohydrate, −1.4% for fat and 0.5% for protein intake[22].

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Diagnosis of Diabetes

Fasting plasma glucose and HbA1c were measured during the annual medical examinations. Based on the definition of the American Diabetes Association[27] and the JDS[28], the diagnosis of diabetes was confirmed by at least one of the following observations: a fasting plasma glucose concentration of ≥126 mg/dL, HbA1c value ≥6.5% and/or treatment with insulin or an oral hypoglycemic agent.

Statistical Analysis

According to the Dietary Reference Intakes for Japanese (2015), to prevent lifestyle-related diseases in adults, the desirable percentage of energy intake (% energy) from carbohydrates is 50–65%[29]. We divided the participants into four categories according to carbohydrate intake: <50, 50–57.4% (median values for the ideal range), 57.5–65.0 and >65.0% energy. Similarly, participants were divided into four groups by carbohydrate intake (g/day), adjusted for total energy intake using residual methods. To compare baseline characteristics among the groups, continuous variables were subjected to covariance analysis. The Kruskal–Wallis test was used to compare non-parametric variables, and the χ^2-test to compare categorical variables. We calculated the incidence rates and hazard ratios (HRs) for diabetes according to the level of carbohydrate intake. The Cox proportional hazards model was used to calculate HRs. Adjustment for possible confounders was carried out sequentially as follows: age (model 1); also for a family history of diabetes (no, yes), smoking status (never smoker, ex-smoker or current smoker), alcohol consumption as determined by the DHQ (non-drinker, occasional drinker, consumption <20 g/day, consumption ≥20 g/day), habitual exercise (no, yes) and performance of shift work (no, yes; model 2); also for total energy intake (kcal/day) and dietary fiber intake (g/day; model 3); also for hypertension (no, yes) and dyslipidemia (no, yes) at baseline (model 4a); or BMI (model 4b); or fasting plasma glucose level (model 4c). The HRs for diabetes were calculated separately for BMI (<25, ≥25 kg/m^2). Statistical analyses were carried out using the Statistical Package for the Social Sciences (IBM SPSS statistics version 22.0; IBM Corporation, New York, USA). A *P*-value of <0.05 was deemed statistically significant.

Ethical Considerations

Written informed consent was not obtained from the participants. The occupational safety and health committee of the

Table 1 | Baseline characteristics of study participants by level of dietary carbohydrate intake (% energy) in 2,006 Japanese men

	Carbohydrate intake (% energy)				*P*†
	<50.0	50.0–57.4	57.5–65.0	>65.0	
n	368	615	640	383	
Age (years)	45.1 ± 5.9	46.0 ± 5.9	46.0 ± 6.0	46.2 ± 6.0	0.060
Body mass index (kg/m^2)	23.6 ± 2.9	23.3 ± 2.8	23.3 ± 2.9	23.5 ± 3.1	0.392
Fasting plasma glucose (mg/dL)	93.8 ± 10.2	93.1 ± 9.5	92.2 ± 9.7	92.0 ± 9.4	0.022
HbA1c, NGSP (%)	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.3	0.524
Total energy intake (kcal/day)	2,365 (955–4,516)	2,171 (873–4,897)	1,996 (671–4,742)	1,886 (653–4,707)	<0.001
Total fiber intake (g/day)	10.4 (2.0–40.4)	10.9 (2.0–28.0)	10.2 (1.7–29.9)	9.2 (2.4–30.3)	<0.001
Fat (% energy)	27.0 (6.4–51.1)	24.3 (8.9–36.5)	21.3 (4.4–32.4)	15.7 (2.3–23.3)	<0.001
Protein (% energy)	12.7 (4.4–24.3)	12.4 (5.6–18.4)	11.6 (5.7–16.1)	10.2 (5.7–15.0)	<0.001
Family history of diabetes (%)	12.6	13.7	14.4	12.6	0.823
Smoking status (%)					
Non-smoker	61.4	57.2	49.2	54.6	<0.001
Ex-smoker	17.7	14.1	14.7	9.9	
Current smoker	20.9	28.6	36.1	35.5	
Alcohol consumption (%)					
Never	6.8	13.8	26.6	51.4	<0.001
Occasional	0.8	1.1	2.0	4.7	
Drink <20 g/day	13.9	33.2	41.1	31.6	
Drink ≥20 g/day	78.5	51.9	30.3	12.3	
Regular exercise (%)	49.7	55.1	53.0	48.8	0.179
Shift worker (%)	16.6	16.7	20.9	30.0	<0.001
Presence of hypertension (%)	41.8	35.6	31.4	32.4	0.006
Presence of dyslipidemia (%)	32.1	28.1	28.0	30.5	0.457

Values are presented as *n*, mean ± standard deviation, medians (with ranges) or %. †Covariance analysis was used for continuous variables, the Kruskal–Wallis test was used to compare non-parametric variables and the χ^2-test was used to compare categorical variables. HbA1c, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program.

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subject company, which consisted of employee representatives, approved the design of the present study. Employees were informed of the study design and of their right to refuse to participate. Hence, participants who answered the questionnaire were considered to have consented to the survey. The company ensured that individuals were not identifiable by providing linkable anonymous data to the researchers. The institutional Review Committee of Kanazawa Medical University for Ethical Issues approved the study.

RESULTS

The mean participant age at baseline was 45.9 years, and the mean BMI was 23.4 kg/m^2. The baseline characteristics of the participants according to carbohydrate intake level are shown in Table 1 (carbohydrate energy ratio) and Table 2 (carbohydrate intake adjusted for total energy intake using residual methods). A higher carbohydrate intake was associated with a significantly lower total energy intake, lower fiber intake, higher prevalence of current smokers, lower percentage of excess alcohol consumption, a higher percentage of shift workers and lower prevalence of hypertension. Among the participants, 557 (27.0%) were obese (BMI ≥25.0 kg/m^2). A higher carbohydrate intake was associated with a significantly lower total energy intake, and lower percentage of excess alcohol consumption for both non-obese and obese participants. For non-obese participants, a higher carbohydrate intake was associated with a significantly lower fiber intake, higher prevalence of current smokers and lower prevalence of hypertension (Table S1). Similar associations were observed when carbohydrate intake was expressed as an amount of daily intake (g/day; Table S2).

During the 10-year follow up (15,593 person-years), we documented 232 cases of type 2 diabetes. Among these, 121 diagnoses were based on high fasting plasma glucose levels, 75 on elevated HbA1c, 30 on both high fasting plasma glucose and elevated HbA1c levels, and six participants were being treated with hypoglycemic medications.

The crude incidence rates (per 1,000 person-years) across the categories of carbohydrate intake (% energy) from lowest to highest were 16.5, 14.4, 12.7 and 17.6, respectively (Table 3). Dietary carbohydrate intake was not associated with higher HRs for diabetes after adjustment for dietary factors and other lifestyle factors. The crude incidence rates across the quintiles of carbohydrate intake (g/day), from lowest to highest, were

Table 2 | Baseline characteristics of 2,006 Japanese men by quartile of dietary carbohydrate intake (g/day)

	Carbohydrate intake, g/day (quartile)				*P*†
	<285.7	285.8–313.8	313.9–341.7	≥341.8	
n	502	501	502	501	
Age (years)	45.3 ± 5.9	46.0 ± 6.1	46.0 ± 6.0	46.3 ± 5.9	0.060
Body mass index (kg/m^2)	23.6 ± 2.8	23.3 ± 2.8	23.2 ± 2.8	23.5 ± 3.1	0.055
Fasting plasma glucose (mg/dL)	93.4 ± 9.9	93.4 ± 9.9	92.0 ± 9.1	92.2 ± 9.8	0.021
HbA1c, NGSP (%)	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.4	5.3 ± 0.3	0.510
Total energy intake (kcal/day)	2,308 (873–4,553)	1,986 (653–4,206)	1,971 (658–3,890)	2,188 (1,124–4,897)	<0.001
Total fiber intake (g/day)	10.5 (2.0–40.4)	10.1 (1.7–27.9)	9.6 (2.5–29.9)	10.8 (2.4–30.3)	<0.001
Fat (% energy)	26.8 (6.4–51.1)	23.6 (4.4–36.5)	21.4 (5.4–32.4)	17.2 (2.3–29.7)	<0.001
Protein (% energy)	12.7 (4.4–24.3)	12.1 (5.9–18.2)	11.6 (5.7–17.8)	10.7 (5.7–16.1)	<0.001
Family history of diabetes (%)	12.3	14.9	13.1	13.7	0.693
Smoking status (%)					
Non-smoker	61.2	56.5	51.4	50.7	<0.001
Ex-smoker	16.1	14.0	15.3	11.2	
Current smoker	22.7	29.5	33.3	38.1	
Alcohol consumption (%)					
Never	8.4	15.0	28.1	43.7	<0.001
Occasional	0.8	1.6	2.2	3.6	
<20 g/day	18.1	36.7	38.0	34.5	
≥20 g/day	72.7	46.7	31.7	18.2	
Regular exercise (%)	51.8	51.1	53.2	52.9	0.904
Shift worker (%)	16.3	15.0	19.7	31.3	<0.001
Presence of hypertension (%)	39.8	34.7	33.3	31.3	0.032
Presence of dyslipidemia (%)	30.3	29.3	27.3	30.1	0.710

Values are presented as *n*, means ± standard deviations, medians (with ranges) or %. †Covariance analysis was used to compare continuous variables, the Kruskal–Wallis test to compare nonparametric variables and the χ^2-test to compare categorical variables. HbA1c, glycated hemoglobin; NGSP, National Glycohemoglobin Standardization Program.

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Table 3 | Incidence of and adjusted hazard ratios for type 2 diabetes development, by dietary carbohydrate intake, in Japanese men

	Carbohydrate intake				*P* for trend
Carbohydrate intake (% energy)	<50.0	50.0–57.4	57.5–65.0	>65.0	
n	368	615	640	383	
Cases (*n*)	46	68	65	53	
Person-years of follow up	2781	4708	5099	3004	
Incidence (/1,000 person-years)	16.5	14.4	12.7	17.6	
Adjusted hazard ratio (95% CI)					
Model 1	1.20 (0.83–1.74)	1.00 (reference)	0.88 (0.63–1.23)	1.20 (0.84–1.72)	0.851
Model 2	1.12 (0.76–1.66)	1.00 (reference)	0.94 (0.66–1.33)	1.34 (0.90–1.99)	0.569
Model 3	1.11 (0.75–1.65)	1.00 (reference)	0.95 (0.67–1.35)	1.38 (0.93–2.06)	0.457
Model 4a	1.04 (0.70–1.54)	1.00 (reference)	0.97 (0.68–1.38)	1.32 (0.88–1.97)	0.397
Model 4b	1.08 (0.73–1.60)	1.00 (reference)	0.96 (0.68–1.37)	1.43 (0.95–2.14)	0.344
Model 4c	0.88 (0.58–1.31)	1.00 (reference)	0.87 (0.61–1.23)	1.18 (0.80–1.76)	0.383
Carbohydrate intake (g/day, quartile)	<285.7	285.8–313.8	313.9–341.7	≥341.8	
n	502	501	502	501	
Cases (*n*)	58	54	52	68	
Person-years of follow up	3819	3827	4025	3922	
Incidence (/1,000 person-years)	15.2	14.1	12.9	17.3	
Adjusted hazard ratio (95% CI)					
Model 1	1.12 (0.77–1.62)	1.00 (reference)	0.91 (0.62–1.33)	1.21 (0.84–1.72)	0.742
Model 2	1.03 (0.70–1.51)	1.00 (reference)	0.95 (0.64–1.39)	1.32 (0.90–1.94)	0.272
Model 3	1.02 (0.69–1.51)	1.00 (reference)	0.95 (0.64–1.40)	1.31 (0.89–1.94)	0.283
Model 4a	0.99 (0.67–1.47)	1.00 (reference)	0.96 (0.65–1.42)	1.27 (0.86–1.88)	0.273
Model 4b	0.99 (0.67–1.46)	1.00 (reference)	0.97 (0.65–1.42)	1.32 (0.89–1.95)	0.204
Model 4c	0.95 (0.64–1.41)	1.00 (reference)	0.96 (0.65–1.42)	1.19 (0.80–1.76)	0.331

Model 1, adjusted for age; Model 2, adjusted for age, a family history of diabetes, smoking (yes), alcohol consumption, regular exercise and performance of shift work; Model 3, adjusted for the variables of model 2 plus total energy intake (kcal) and total fiber intake (g/day); Model 4a–c, adjusted for the variables of model 3 plus the presence of hypertension and hyperlipidemia at baseline (model 4a), body mass index (model 4b) or fasting plasma glucose level (model 4c). CI, confidence interval.

15.2, 14.1, 12.9 and 17.3, respectively, and carbohydrate intake was not associated with the risk of diabetes (Table 3).

Next, we analyzed the association between carbohydrate intake and the incidence of diabetes in subgroups based on BMI (Table 4). A significant interaction between obesity and carbohydrate intake (% energy) levels was observed on the association with risk for diabetes (*P* for interaction = 0.024). Carbohydrate intake was not associated with the risk for diabetes in non-obese participants. However, higher carbohydrate intake was associated with higher risk for diabetes in obese participants (*P* for trend = 0.034), and the risk of diabetes was significantly higher in participants with carbohydrate intakes >65% compared with 50.0–57.4% of total energy. Compared with the non-obese participants with carbohydrate intakes of 50.0–57.4% energy, a significantly higher risk of diabetes was observed for obese participants with carbohydrate intakes 50.0–57.4% of total energy (HR 1.86, 95% CI 1.08–3.22), those with carbohydrate intakes 57.5–65.0% of total energy (HR 2.18, 95% CI 1.34–3.55) and those with carbohydrate intakes >65.0% of total energy (HR 3.57, 95% CI 2.11–6.03; Figure 1). Carbohydrate intake (g/day) was also associated with the risk of diabetes development in obese participants (*P* for trend = 0.050); however, the association was somewhat weaker than that between the risk and carbohydrate intake expressed as % total energy (Table 4 and Figure 1).

DISCUSSION

We assessed the association between dietary carbohydrate intake and the incidence of type 2 diabetes in middle-aged Japanese men, and found that the association between these parameters varied with BMI: a carbohydrate intake higher than the desirable proportion for Japanese adults (50–65% energy)[29] was associated with increased risk of type 2 diabetes in obese participants, but not non-obese participants.

In previous studies from Western countries, carbohydrate intake was not associated with the incidence of type 2 diabetes[8–13]. In contrast, both the results of the present study and those from a study of Chinese women[14] showed that higher carbohydrate intake was associated with an increased risk of diabetes in participants with BMI ≥25 kg/m^2. The difference in insulin secretory capacity between Asian and Western subjects[4–6] might affect the results. Higher insulin demand as a result of both obesity-related insulin resistance and excessive carbohydrate consumption could render compensatory insulin

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Table 4 | Incidence of and adjusted hazard ratios for type 2 diabetes development, by dietary carbohydrate intake, in the obese

	Carbohydrate intake				*P* for trend
Carbohydrate intake (% energy)	<50.0	50.0–57.4	57.5–65.0	>65.0	
Body mass index <25.0 kg/m^2					
n	261	443	478	267	
Cases (*n*)	32	39	36	24	
Person-years of follow up	1984	3412	3852	2151	
Incidence (/1,000 person-years)	16.1	11.4	9.3	11.2	
Adjusted hazard ratio (95% CI)†					
Model 2	1.26 (0.77–2.06)	1.00 (reference)	0.86 (0.54–1.36)	1.08 (0.62–1.87)	0.446
Model 3	1.23 (0.75–2.02)	1.00 (reference)	0.87 (0.55–1.38)	1.09 (0.63–1.90)	0.537
Body mass index ≥25.0 kg/m^2					
n	107	172	162	116	
Cases (*n*)	14	29	29	29	
Person-years of follow up	798	1296	1247	853	
Incidence (/1,000 person-years)	17.5	22.4	23.3	34.0	
Adjusted hazard ratio (95% CI)†					
Model 2	0.91 (0.47–1.75)	1.00 (reference)	1.17 (0.68–2.00)	1.86 (1.02–3.41)	0.046
Model 3	0.92 (0.48–1.79)	1.00 (reference)	1.19 (0.69–2.04)	2.01 (1.08–3.71)	0.034
Carbohydrate intake, g/day (quartile)	<285.7	285.8–313.8	313.9–341.7	≥341.8	
Body mass index <25.0 kg/m^2					
n	353	364	383	349	
Cases (*n*)	37	32	29	33	
Person-years of follow up	2698	2823	3080	2799	
Incidence (/1,000 person-years)	13.7	11.3	9.4	11.8	
Adjusted hazard ratio (95% CI)†					
Model 2	1.08 (0.66–1.77)	1.00 (reference)	0.89 (0.50–1.70)	1.16 (0.69–1.95)	0.944
Model 3	1.04 (0.63–1.72)	1.00 (reference)	0.88 (0.53–1.46)	1.10 (0.65–1.88)	0.988
Body mass index ≥25.0 kg/m^2					
n	149	137	119	152	
Cases (*n*)	21	22	23	35	
Person-years of follow up	1121	1004	945	1123	
Incidence (/1,000 person-years)	18.7	21.9	24.3	31.2	
Adjusted hazard ratio (95% CI)†					
Model 2	0.92 (0.50–1.70)	1.00 (reference)	1.12 (0.61–2.04)	1.64 (0.91–2.94)	0.059
Model 3	0.97 (0.52–1.80)	1.00 (reference)	1.14 (0.62–2.10)	1.76 (0.97–3.21)	0.050

†Hazard ratios were adjusted for age, a family history of diabetes, smoking (yes), alcohol consumption, regular exercise and performance of shift work (model 2); plus total energy intake (kcal/day) and total fiber intake (g/day; model 3). CI, confidence interval.

secretion inadequate only in Asian people because of their lower insulin secretory capacity compared with Western people[4–6].

Carbohydrate intake is higher among Asians than Westerners[15,16]. The difference in sources of carbohydrate between Asian and Western populations might also contribute to the differences in the relationship between carbohydrate intake and risk of type 2 diabetes. White rice is the main source of carbohydrates for East Asian people, and it constitutes ~70% of the carbohydrates consumed by Japanese people[7,16]. In contrast, carbohydrate sources in Western populations frequently vary, and can include rice, bread, pasta and potatoes[16]. Diets high in refined grains[30] and white rice[31], or with an otherwise high glycemic index/glycemic load[17,32], can all increase the risk of diabetes. As such, the increased carbohydrate intake predominantly from white rice might increase the risk for type 2 diabetes in East Asian populations.

Although average carbohydrate intake has decreased in the past few decades[7], the prevalence of diabetes has increased in Japan and other East Asian countries. These ecological observations might not be compatible with our results that high carbohydrate intake was associated with higher risk for diabetes in obese Japanese men. However, the prevalence of obesity has increased in Japanese men, and the rise in the numbers of such subjects who are at high risk for diabetes because of their carbohydrate intake might be reflected in an increase in actual diabetes cases.

We found linear trends in the associations between the carbohydrate energy ratio (% energy) and the total carbohydrate intake (g/day), and the incidence of diabetes in obese subjects.

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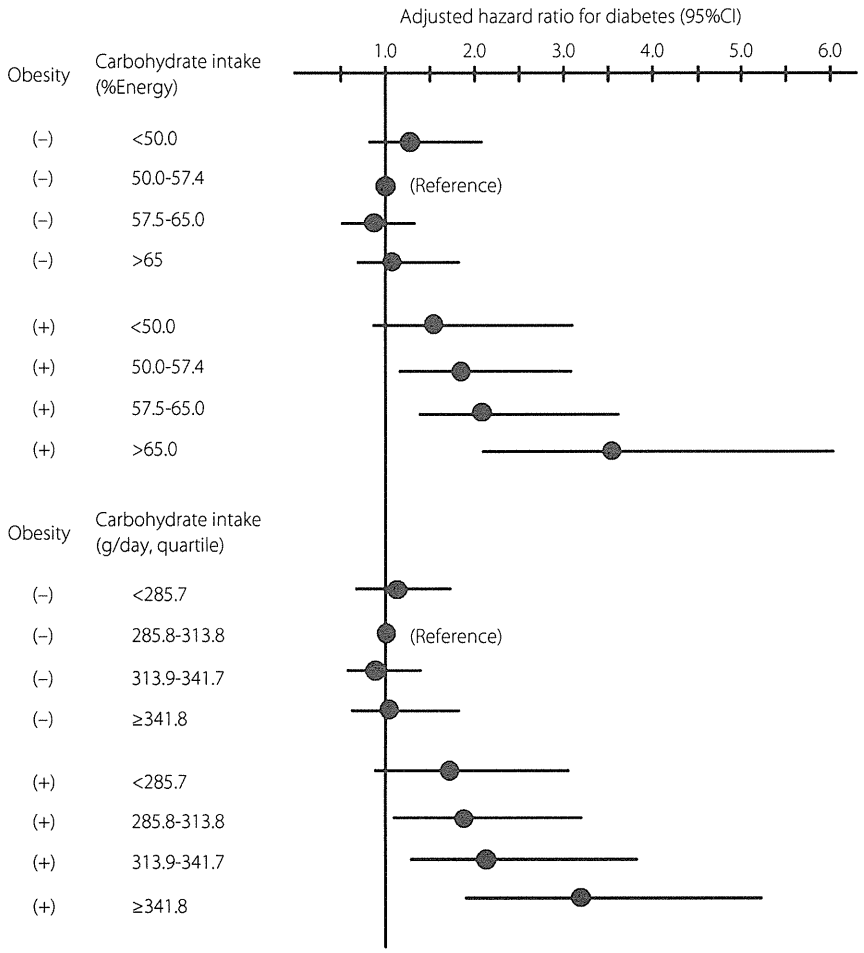

Figure 1 | Adjusted hazard ratio for type 2 diabetes based on dietary carbohydrate intake by the presence of obesity in Japanese men. Hazard ratios were adjusted for age, family history of diabetes, smoking, alcohol drinking, habitual exercise, total energy intake and total fiber intake. CI, confidence interval.

The association between the diabetes incidence and the carbohydrate energy ratio was stronger. As is true also of total energy intake, an appropriate carbohydrate intake depends on BMI and the level of physical activity. The carbohydrate energy ratio might be a more suitable index of dietary quality when diet is to be modified to prevent diabetes development in a general population. The Dietary Reference Intakes for Japanese (2015) show that the desirable energy intake from carbohydrates is 50–65%[29]. However, this value is based on the general Japanese diet. We found that carbohydrate intake was associated with the risk of diabetes development in a Japanese population; diets with desirable proportions of carbohydrates (50–65% energy) might effectively prevent the development of type 2 diabetes in obese Japanese subjects.

The present study had several strengths, including a relatively large sample size. In addition, although several previous cohort studies have used information collected from self-administered questionnaires, our conclusions are based on more reliable data, including formal medical examinations, and fasting blood glucose and HbA1c measurements. However, the study also had several limitations. The study population only included participants who were employed. Because poor health might exclude some individuals from working, the prevalence of obesity and the incidence of diabetes might be lower in the present study than in the general Japanese population. Another limitation was that an observational study cannot evaluate the impact of fat intake on the association between carbohydrate intake and the incidence of diabetes. Carbohydrate intake is strongly and inversely associated with fat intake. Furthermore, subjects consuming high-carbohydrate/low-fat diets might include those on special diets, which could independently increase the risk of diabetes. Previous studies showed that a higher carbohydrate intake *per se* increased the risk of diabetes[14,17,30–32]. An interventional study is required to clarify whether a high-carbohydrate or a

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low-fat diet more strongly affects the incidence of diabetes. In addition, we did not distinguish between type 1 and type 2 diabetes. However, because the study participants were middle-aged and the condition was detected during annual medical examinations, it is unlikely that many cases were type 1 diabetes.

In conclusion, the present results show that the association between carbohydrate intake and risk of diabetes varies with BMI, and that higher carbohydrate intake was associated with a greater risk of diabetes in obese subjects, but not in those who were not obese. Obese subjects with carbohydrate intake >65% energy should reduce their intakes to within the desirable energy proportions for Japanese people (50–65% energy), to prevent the development of type 2 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1| Baseline characteristics of study participants by dietary carbohydrate intake (% energy) and obesity status.
Table S2| Baseline characteristics of study participants by dietary carbohydrate intake (g/day) and obesity status.

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Low-grade albuminuria and incidence of cardiovascular disease and all-cause mortality in nondiabetic and normotensive individuals.

Tanaka F, Komi R, Makita S, Onoda T, Tanno K, Ohsawa M, Itai K, Sakata K, Omama S, Yoshida Y, Ogasawara K, Ishibashi Y, Kuribayashi T, Okayama A, Nakamura M; Iwate-Kenco Study Group.

BACKGROUND: Recent studies indicate that, in people with diabetes or hypertension and in the general population, low-grade albuminuria (LGA) below the microalbuminuria threshold is a predictor for incidence of cardiovascular disease (CVD) and mortality. However, it remains unclear whether LGA predicts the risk of CVD incidence and death in nondiabetic and normotensive individuals.
METHODS: A total of 3599 individuals aged not less than 40 years from the general population who are free of CVD in nondiabetic and normotensive individuals with preserved glomerular filtration rate were followed for CVD incidence and all-cause death. LGA was defined as urinary albumin to creatinine ratio (UACR) less than 30 mg/g. It was examined whether there is an association between LGA and CVD incidence or all-cause death.
RESULTS: During the average 5.9 years of follow-up, 61 individuals had first CVD events, and 85 individuals died. The hazard ratios (HRs) for CVD incidence and all-cause death after full adjustment by potential confounders increased significantly in the top tertile of LGA (UACR ≥ 9.6 mg/g for men, ≥ 12.0 mg/g for women) compared with the first tertile [HR = 2.79, 95% confidence interval (CI), 1.41-5.52, HR = 1.69, 95% CI, 1.00-2.84, respectively]. Population-attributable fractions of the top tertile of LGA for CVD incidence and all-cause death were 37.9 and 20.1%, respectively.
CONCLUSION: In apparently healthy individuals with optimal blood pressure and no diabetes, LGA independently predicts CVD incidence and all-cause death, particularly with the large contribution to the excessive incidence of CVD.

2. J Epidemiol. 2016 Jan 23. [Epub ahead of print]

Standardized Prevalence Ratios for Atrial Fibrillation in Adult Dialysis Patients in Japan.

Ohsawa M, Tanno K, Okamura T, Yonekura Y, Kato K, Fujishima Y, Obara W, Abe T, Itai K, Ogasawara K, Omama S, Turin TC, Miyamatsu N, Ishibashi Y, Morino Y, Itoh T, Onoda T, Kuribayashi T, Makita S, Yoshida Y, Nakamura M, Tanaka F, Ohta M, Sakata K, Okayama A.

BACKGROUND: While it is assumed that dialysis patients in Japan have a higher prevalence of atrial fibrillation (AF) than the general population, the magnitude of this difference is not known.
METHODS: Standardized prevalence ratios (SPRs) for AF in dialysis patients (n = 1510) were calculated compared to data from the general population (n = 26 454) living in the same area.
RESULTS: The prevalences of AF were 3.8% and 1.6% in dialysis patients and the general population, respectively. In male subjects, these respective values were 4.9% and 3.3%, and in female subjects they were 1.6% and 0.6%. The SPRs for AF were 2.53 (95% confidence interval [CI], 1.88-3.19) in all dialysis patients, 1.80 (95% CI, 1.30-2.29) in male dialysis patients, and 2.13 (95% CI, 0.66-3.61) in female dialysis patients.
CONCLUSIONS: The prevalence of AF in dialysis patients was twice that in the population-based controls. Since AF strongly contributes to a higher risk of cardiovascular mortality and morbidity in the general population, further longitudinal studies should be conducted regarding the risk of several outcomes attributable to AF among Japanese dialysis patients.