

Table 3. Hazard ratios and 95% CIs of incidence of subtypes of stroke with gender difference by salt preference categories.

	Salt preference category		
	Favor	So-so	Disfavor
Men			
Cerebral hemorrhage			
N	18	17	12
HR-age	0.96 (0.49 - 1.87)	1.00	0.92 (0.44 - 1.91)
HR-all*	0.84 (0.41 - 1.70)	1.00	0.86 (0.40 - 1.88)
Cerebral infarction			
N	54	58	38
HR-age	0.85 (0.59 - 1.24)	1.00	0.84 (0.56 - 1.26)
HR-all*	0.80 (0.54 - 1.17)	1.00	0.86 (0.56 - 1.32)
Subarachnoid hemorrhage			
N	9	1	3
HR-age	8.09 (1.02 - 63.84)	1.00	4.12 (0.42 - 39.78)
HR-all*	7.10 (0.88 - 56.84)	1.00	2.62 (0.24 - 29.10)
Women			
Cerebral hemorrhage			
N	15	14	18
HR-age	1.79 (0.87 - 3.71)	1.00	1.42 (0.70 - 2.85)
HR-all†	1.59 (0.74 - 3.44)	1.00	1.59 (0.78 - 3.27)
Cerebral infarction			
N	36	42	36
HR-age	1.40 (0.89 - 2.19)	1.00	0.93 (0.59 - 1.45)
HR-all†	1.07 (0.65 - 1.78)	1.00	0.94 (0.59 - 1.49)
Subarachnoid hemorrhage			
N	8	18	17
HR-age	0.78 (0.34 - 1.81)	1.00	1.10 (0.56 - 2.14)
HR-all†	0.65 (0.27 - 1.56)	1.00	1.05 (0.54 - 2.07)

HR-age: hazard ratios adjusted for age. HR-all*: hazard ratios adjusted for age, smoking status and drinking status, history of hyperlipidemia, and education years. HR-all†: hazard ratios adjusted for age, smoking status and drinking status, MI, and HDL-cholesterol, and education years.

women. HRs for stroke were 1.21 (0.99 - 1.49) for men and 1.22 (1.00 - 1.49) for women. It is possible that the discrepancies in the results between the JACC Study and our study were due to differences in the number of participants, follow-up period, and examination end points. Our study suggested the possibility that salt preference was associated with the stage of CVD incidence rather than mortality, with gender differences.

High salt preference may result in a long-term, high-sodium intake, then leading to high blood pressure and an increased risk of CVD. Several previous studies reported positive associations between salt preference and salt intake [12] [17] [18] and between salt intake and the incidence of CVD or mortality [3]-[6]. Several explanations for the associations between sodium intake and CVD have been put forward. High salt intakes influence

CVD by altering left ventricular mass [19] or increasing blood flow and vascular reactivity [20] [21]. In our study, the incidence of CVD was high for women. Our targets among women were almost local residents. So, the incidence of CVD may be slightly higher than the previous study. For women, high salt preference tended to be less well educated. Therefore, subjects with high salt preference may have behavioral risk factors, leading to higher risk of CVD in the women. Accordingly, women with a high salt preference may intake much more salt than those with a low salt preference. Further investigations are necessary to clarify sex difference in cardiovascular risk factors.

In our study, favor salt preference was positively associated with smoking and alcohol drinking in both men and women. The men in the favor salt preference group tended to be younger and more highly educated, whereas the women in the salt preference group tended to be older, less well educated, and more likely to have a higher BMI and lower serum concentration of HDL-C. Despite these results, salt preference was not associated with CVD risk factors such as SBP, DBP, and a history of hypertension. Our results suggest that salt preference may be one of the risk factors of premature CVD. It is also possible that some people with a high salt preference developed hypertension that led to CVD during the follow-up period. Among the women, salt preference was associated with the incidence of CVD after age adjustment. After adjustment for smoking status, alcohol drinking status, BMI, HDL-C, and years of education, the risk of CVD was attenuated. Accordingly, the influence of common risk factors on CVD incidence was strong for women, and salt preference may reflect accumulation of confounding risk factors except for age. These common factors can be self-managed and self-controlled. People indicating a high salt preference in the detailed interview during health check-ups should be recommended to practice adequate health behavior for the prevention of CVD in daily life, especially for women.

Salt preference and food intake are affected by socioeconomic and psychophysiological factors such as recent dietary habit, culture, and income [22] [23]. Taste preferences are acquired early in life through the process of choosing foods and actual salt intake [24]. Lampure *et al.* reported that as a new pathway without a common route that leads to CVD, salt preference was associated with uncontrolled eating behavior [25], which is the tendency to lose control over eating when hungry or when exposed to external stimuli. A previous study showed that binge eating was associated with a higher incidence of a new diagnosis of dyslipidemia, any metabolic syndrome component (hypertension, dyslipidemia, or type 2 diabetes), and two or more components of metabolic syndrome after 5 years of follow-up [26]. Thus, eating disorders such as uncontrolled eating behavior can result in a relationship between salt preference and the occurrence of CVD.

In our study, salt preference tended to be inversely associated with the incidence of MI in the men. Our results are similar to those of a previous study [11] although the reason for this cannot be fully explained. The decreased risk of MI associated with high salt preference might reflect the beneficial cardiovascular effects of the intake of $n - 3$ polyunsaturated fatty acids and isoflavones in the inhibition of platelet aggregation, lowering of blood pressure, and modulation of the inflammatory system [27] [28]. For the men in the present study, the low incidence of MI and the high incidence of SAH were based on a small number of incident cases. Thus, there was wide range of 95% CIs for the point estimates.

For women, salt preference may reflect common risk factors that will cause CVD in the future and other unknown factors such as eating behavior in an earlier stage of life. Especially in women, early assessment of salt preference may be effective in reducing the incidence of CVD. For subjects with high salt preference, early intervention may be able to prevent excessive salt intake and uncontrolled eating behavior in the future.

Our study has several strengths. First, it was conducted as a large-scale multicenter cohort study. In addition, we investigated the incidence of not only CVD but also stroke subtypes as endpoints. However, there were several limitations. First, the follow-up period was shorter, and second, the numbers of subjects with an incidence of CVD were less than those of a previous study [11]. Third, estimated salt intake is not measured quantitatively. It is unclear whether the salt preference questionnaire reflects the responder's actual salt intake. Fourth, the participants were recruited through a mass screening program, and therefore, their concern for health may exceed that of the general population, which could result in differences in salt intake and other behavioral profiles. Finally, we were unable to control for other potential confounders such as nutrient factors and income.

5. Conclusion

We found that salt preference was positively associated with an increased risk of the incidence of SAH in men after multivariate adjustment and in CVD in women after adjustment for age. As with other common risk factors

for CVD, assessing salt preference may lead to the prevention of CVD because such assessment may help to prevent excessive salt intake and uncontrolled eating behavior in the future. These tendencies may apply especially to women.

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Appendix

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Abbreviations

CVD: cardiovascular disease

JMS Cohort Study: Jichi Medical School Cohort Study

HDS: hazardratios

HR-all^{*}: hazard ratios adjusted for age, smoking status and drinking status, history of hyperlipidemia, and education years

HR-all[†]: hazard ratios adjusted for age, smoking status and drinking status, BMI, HDL-cholesterol, and education years

BMI: body mass index

SBP: systolic blood pressure

DBP: diastolic blood pressure

HDL-C: high density lipoprotein cholesterol

MI: myocardial infarction

SAH: subarachnoid hemorrhage

MONICA Project: Multinational Monitoring of Trends and Determinants in Cardiovascular Disease Project

JACC study: the Japan Collaborative Cohort Study for Evaluation of Cancer Risk



Original Article

Breakfast Skipping is Positively Associated With Incidence of Type 2 Diabetes Mellitus: Evidence From the Aichi Workers' Cohort Study

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ABSTRACT

Background: Skipping breakfast has been suspected as a risk factor for type 2 diabetes (T2DM), but the associations are not entirely consistent across ethnicities or sexes, and the issue has not been adequately addressed in the Japanese population.

Methods: We followed 4631 participants (3600 men and 1031 women) in a work-site cohort of participants aged 35–66 years in 2002 through 2011 for T2DM development. Frequency of eating breakfast was self-reported and was subsequently dichotomized to breakfast skippers, who eat breakfast 3–5 times/week or less, and to eaters. Cox proportional hazards models were used to adjust for potential confounding factors, including dietary factors, smoking and other lifestyles, body mass index (BMI), and fasting blood glucose (FBG) at baseline.

Results: During 8.9 years of follow-up, 285 T2DM cases (231 men and 54 women) developed. Compared to participants who reported eating breakfast every day, maximally-adjusted hazard ratios and 95% confidence intervals (CI) of those with the frequency of almost every day and 3–5, 1–2, and 0 days/week were: 1.06 (95% CI, 0.73–1.53), 2.07 (95% CI, 1.20–3.56), 1.37 (95% CI, 0.82–2.29), and 2.12 (95% CI, 1.19–3.76), respectively. In a dichotomized analysis, breakfast skipping was positively associated with T2DM incidence (maximally-adjusted hazard ratio 1.73; 95% CI, 1.24–2.42). The positive associations were found in both men and women, current and non-current smokers, normal weight and overweight (BMI ≥ 25 kg/m²), and normal glycemic status and impaired fasting glycemic status (FBG 110 to <126 mg/dL) individuals at baseline (*P*s for interaction all >0.05).

Conclusions: The present study in middle-aged Japanese men and women suggests that skipping breakfast may increase the risk of T2DM independent of lifestyles and baseline levels of BMI and FBG.

Key words: breakfast; diabetes mellitus; cohort study; Japan

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major cause of morbidity and mortality globally.¹ Indeed, the prevalence of diabetes in Japanese aged 40–69 was reported to be as high as 10.2% in male workers and 4.7% in female workers in large-scale companies in 2008–2010 and 15.0% in men and 8.0% in women in the National Health and Nutrition Survey in 2011.^{2,3} Diabetes was also the 14th highest cause of disability-

adjusted life years (DALYs) in Japan in 2010.⁴ It is estimated that diabetes prevalence will remain roughly stable in the next 20 years.⁵

At the same time, skipping breakfast has been suggested to be associated with the incidence of several diseases or conditions, such as obesity,⁶ insulin insensitivity,⁷ cardiovascular diseases,⁸ and T2DM.^{9–11} However, the associations of breakfast skipping with T2DM are not entirely consistent across different ethnicities or sexes, and

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the issue has not been adequately addressed in the Japanese population. Furthermore, breakfast skipping is becoming common in Japan, as the 2011 National Health and Nutrition Survey indicated that 14.4% men and 11.1% women start their day without having breakfast.³ Since breakfast eating habit is modifiable, examining the possible causal relationship has public health significance in the prevention of T2DM.

Therefore, we designed the present study to examine the association between breakfast skipping and the incidence of T2DM in a large-scale prospective cohort of middle-aged Japanese men and women, and to find out whether the association would be independent of diet and lifestyles, body mass index (BMI), and fasting blood glucose (FBG) levels at baseline.

METHODS

Study population

We used data obtained from the Aichi workers' cohort study. The cohort included 6648 Japanese civil servants in Aichi prefecture, an urban and suburban area located in central Japan. Participants were between 35 and 66 years old at recruitment in 2002. Most workers in the cohort were engaged in clerical work. Police officers, firefighters, and public school teachers were not included in the cohort, but health professionals working in prefectural hospitals were included. The baseline survey conducted in 2002 included a self-administered questionnaire concerning their lifestyle and medical history, as well as a health checkup. Written informed consent was obtained in advance separately for the lifestyle questionnaire and the use of annual health checkup data.

We excluded the following participants: (1) those who did not agree to our use of the annual health checkup results ($n = 1045$); (2) those with missing information for frequency of eating breakfast ($n = 8$), energy intake ($n = 83$), and smoking status ($n = 48$); (3) prevalent cases of diabetes mellitus, defined as self-reported medication use ($n = 570$) or baseline glucose level ≥ 126 mg/dL ($n = 128$); and (4) those modifying their diet under physicians' or dietitians' suggestion ($n = 135$). After these exclusions, 4631 participants (3600 men and 1031 women) were available for the present analysis.

Participants were followed until the end of follow-up (March 31, 2011), censoring, or ascertainment of diabetes, whichever came first. Participants were censored when they retired, except for those who provided their postal address to the researchers. The number of participants who were censored due to retirement was 919. The study protocol was approved by the Ethics Review Committee of Nagoya University School of Medicine.

Ascertainment of incident T2DM

We ascertained incidence of T2DM by two methods. First, we

defined the incidence as the year when FBG level reached ≥ 126 mg/dL. We arbitrarily set the date of onset as July 1st for the analysis, considering that the checkups were usually carried out from October to December and that T2DM would generally be a chronic state without a definite onset. Second, we utilized data from self-administered questionnaire surveys on medical history, which were conducted in 2004, 2007, and 2011. In the surveys, participants reported medical histories of T2DM and other pre-specified conditions. Those who had T2DM history provided information about the onset (year of diabetes diagnosis) as well as the name and address of their present or past physician. We obtained written consent to access participants' medical records via their specified physicians. We previously confirmed the accuracy (95%) of self-reports by reviewing the medical records from cases with written consent, and the details of the validation study have been reported elsewhere.¹² Health checkups were provided annually during their employment. After retirement, participants were followed only by the questionnaire. Health checkup results of retired participants were not systematically collected.

Frequency of eating breakfast

In this study, we assessed frequency of eating breakfast using a self-administered questionnaire. Breakfast eating frequency was assessed using the following five categories: every day, almost every day with occasional skips, 3–5 days/week, 1–2 days/week, and none. We later reclassified the participants into two groups as breakfast eaters (those who reported their breakfast eating frequency as every day and almost every day with occasional skips) and breakfast skippers (those who classified themselves in the breakfast eating categories of 3–5 days/week, 1–2 days/week, and none). The reproducibility (Spearman's correlation coefficient) of the breakfast eating frequency question over a 9-month period has been reported to be 0.62.¹³ In addition, 752 out of the present 4631 participants also reported breakfast eating frequency 5 years after the baseline (in 2007). The agreement between these two surveys was still fair (Spearman's correlation coefficient: 0.55).

Other dietary factors

The self-administered brief-type dietary history questionnaire (BDHQ) was used for the assessment of diet, including intakes of nutrients, alcohol, and total energy.^{14,15} Intakes of fish, fruits, vegetables, whole-grain cereals, coffee, sugar-sweetened beverages, and snacks obtained by the BDHQ were adjusted for total energy intake by the nutrient density method.¹⁴ Eating speed was self-reported in the BDHQ as very fast, relatively fast, medium, relatively slow, and slow. The last two categories were combined in the analysis. In addition to the information obtained by the BDHQ, information about participants' habit of eating to satiety was also obtained.

Anthropometric measurements and biochemical analysis

Height was measured to the nearest 0.1 cm with participants standing upright against a stadiometer without shoes. Body weight was measured to the nearest 0.1 kg with the participants in typical indoor clothing. BMI was calculated as weight (kg) divided by the square of height (m). Venous blood samples were drawn after the participants fasted for 8 h or more (or overnight), and serum samples were frozen at -80°C until the biochemical assay. Blood glucose was enzymatically determined by the hexokinase method. Insulin concentration was measured by solid-phase radioimmunoassay (RIABEAD II; Dinabot Co., Ltd., Chiba, Japan).

Other variables

Smoking status was classified into three categories (current, former, and never). The number of days engaged in leisure-time physical activity for 60 minutes or more was self-reported and classified into two categories: ≥ 3 days/week or < 3 days/week. Work-time physical activity was assessed by the question "Are you engaged in physical labor?" and classified into two categories (yes or no). Work schedule was classified into four categories: with shiftwork including night shifts, with shiftwork but without night shifts, without shiftwork but with night work, and without shiftwork or night work. Sleep duration was classified into two categories: < 7 h or ≥ 7 h. Strength of perceived stress was self-reported by the following four categories: very much, much, ordinary, and little. Family history of diabetes among first-degree relatives was self-reported and used as a dichotomized variable (yes or no) in the analysis.

Statistical analysis

FBG values were log-transformed to approximately normalize their distribution prior to the analyses and are presented as geometric means and their 95% confidence intervals (CIs). Other continuous variables were summarized as means and standard deviations (SD), while percentages were used for categorical variables. One-way analysis of variance or χ^2 tests were used, as appropriate, to compare baseline characteristics of breakfast eaters and breakfast skippers.

Multivariable adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs of the risk of T2DM according to breakfast eating frequency and in breakfast skippers relative to breakfast eaters. Model 1 was adjusted for age, sex, total energy intake, smoking status, alcohol consumption, leisure-time physical activity, work-time physical activity, family history of diabetes mellitus, eating speed, perceived stress, sleep duration, work schedule, habit of eating to satiety, and intakes of fruits and vegetables, fish, whole-grain cereals, coffee, sugar-sweetened beverages and snacks. In model 2, BMI (continuous) was included in addition to all the variables in model 1. We adjusted for FBG (continuous) in model 3 together with the variables in model 2.

We then performed the above analyses stratified by sex, smoking status (current, never, or former) and baseline values of BMI ($< 25 \text{ kg/m}^2$ or $\geq 25 \text{ kg/m}^2$) and FBG ($< 110 \text{ mg/dL}$ or $\geq 110 \text{ mg/dL}$). We also conducted sensitivity analyses by excluding incident cases who were followed up for less than 3 years ($n = 119$) and those who were night shift workers ($n = 53$). Furthermore, we carried out an analysis by censoring all the participants at the age of 60 (retirement age) because not all the retired participants were followed up (n of participants who were followed up after retirement = 881).

We also performed an analysis by updating breakfast skipping information with the data obtained after 5 years from baseline when available (approximately 70%) using time-dependent Cox regression model. For those who did not have such information, we carried forward the 2002 frequency.

Another ancillary analysis changing the outcome to impaired fasting glucose (IFG) or diabetes defined as FBG $\geq 110 \text{ mg/dL}$ was performed in an attempt to examine similarity and discrepancy of our findings to a prior study that used such outcome.¹⁶

All statistical analyses were conducted with IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp, Armonk, NY, USA). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Out of the 4631 participants included in our analysis, 90.4% were breakfast eaters. Compared with breakfast eaters, breakfast skippers seem to have worse lifestyles. For example, breakfast skippers were more likely to be current smokers, consumed more alcohol and sugar-sweetened beverages, and had less intakes of fruits and vegetables (all $P < 0.05$) (Table 1).

During a median of 8.9 years of follow-up, 285 cases of T2DM (231 men and 54 women) developed (crude incidence rate: 8.2 per 1000 person-years). Participants who reported eating breakfast 3–5 days/week, 1–2 days/week, and 0 days/week had higher T2DM incidence than those who consumed breakfast every day (model 3 HRs ranging from 1.37 to 2.12) (Table 2). However, the point estimates fluctuated and were not always statistically significant, and there was no apparent positive trend in the T2DM incidence according to the number of days breakfast was skipped. In addition, T2DM incidence of those who skipped breakfast only occasionally was not higher than every day eaters (model 3 HR 1.06). In the subsequent dichotomized analysis, T2DM incidence of breakfast skippers was significantly higher than that of breakfast eaters (crude incidence rate: 13.9/1000 person-years vs 7.5/1000 person-years; model 3 HR 1.73). The positive associations between breakfast skipping and T2DM were similar in both men and women, current and non-current smokers, and normal weight and overweight individuals, as well as those with normal glyceamic status and those with

Table 1. Participants' demographic, lifestyle, dietary habits, and metabolic risk factor characteristics according to breakfast consumption status at baseline, Aichi, 2002

	Breakfast eaters ^a	Breakfast skippers ^b	P value ^c
<i>n</i> , %	4188, 90.4	443, 9.6	
Men, %	78.2	73.8	0.04
Age, year	47.8 (7.1)	46.0 (6.8)	<0.001
Body mass index, kg/m ²	22.9 (2.8)	22.9 (3.0)	0.78
Smoking status, %			
Current	26.7	44.9	<0.001
Former	23.4	14.2	
Never	49.9	40.9	
Leisure-time physical activity, % ^d			
≥3 days/week	75.5	84.2	<0.001
<3 days/week	16.0	9.5	
Work-time physical activity, yes, %	5.3	7.7	<0.01
Family history of diabetes mellitus, yes, %	14.8	17.4	0.14
Fasting blood glucose, mg/dL ^e	92.3 (92.0–92.6)	92.5 (91.5–93.4)	0.74
Perceived stress, % ^d			
Very much	11.0	13.8	0.02
Much	40.1	39.7	
Ordinary	43.8	39.1	
Little	4.9	6.8	
Sleep duration, % ^d			
<7 hours/day	52.9	61.6	<0.001
≥7 hours/day	45.5	35.7	
Work schedule, % ^d			
Without shift work or night shifts	84.6	78.3	<0.001
With shift work but without night shifts	1.9	1.4	
Without shift work but with night shifts	6.8	7.9	
With shift work including night shifts	4.9	11.3	
Total energy intake, kcal/day	1942 (538)	1740 (553)	<0.001
Alcohol consumption, g/day	13.6 (19.2)	18.1 (26.4)	<0.001
Eating speed, % ^d			
Very fast	11.4	12.9	0.67
Relatively fast	35.8	37.9	
Medium	38.5	35.2	
Slow	12.6	12.4	
Satiation eater, %	61.2	59.1	0.24
Fruits and vegetables intake, g/1000 kcal/day	142.3 (67.0)	118.7 (61.2)	<0.001
Fish intake, g/1000 kcal/day	84.1 (41.9)	84.8 (39.4)	0.74
Frequency of whole-grain cereals intake, %			
Always	8.5	5.7	0.10
Sometimes	9.2	8.1	
Rarely	14.9	12.6	
No	67.4	73.6	
Frequency of coffee intake, % ^d			
≥4 cups/day	6.6	10.6	0.02
2–3 cups/day	39.0	39.1	
1 cup/day	24.3	23.7	
<1 cup/day	28.8	25.1	
Frequency of sugar-sweetened beverages intake, % ^d			
≥1 serving/day	5.5	9.3	<0.001
4–6 servings/week	5.3	7.0	
1–3 servings/week	29.9	36.3	
Never or rarely	57.6	45.1	
Snack intake, yes, %	95.3	94.8	0.61

Values are reported as mean (standard deviation) or percentage.

^aBreakfast eater was defined as those having breakfast eating frequency of 'every day or almost every day with occasional skips'.

^bBreakfast skipper was defined as those having breakfast eating frequency of '3–5 days/week, 1–2 days/week, or none'.

^cObtained from ANOVA and Chi-square test for continuous and categorical variables, respectively.

^dProportions in each category do not add up to 100% when there were missing data.

^eGeometric mean (95% confidence interval).

impaired fasting glycemic status at baseline (all interaction $P > 0.05$) (Table 3). Furthermore, similar associations were found in sensitivity analyses that excluded incident cases whose follow up periods in the cohort were less than 3 years

(model 3 HR 1.94; 95% CI, 1.24–2.98) and those who were night shift workers (model 3 HR 1.91; 95% CI, 1.30–2.80). Also, the association by the analysis that censored all the participants who reached 60 years did not materially differ

Table 2. Incidence rates and hazard ratios of type 2 diabetes mellitus according to breakfast consumption, Aichi, 2002–2011

	Frequency of eating breakfast				
	Every day	Almost every day with occasional skips	3–5 days/week	1–2 days/week	None
<i>n</i> of cases/ <i>N</i>	204/3648	35/540	15/121	17/197	14/125
Crude incidence rate ^a	7.4	8.4	16.6	11.4	15.4
Crude HR (95% CI)		1.13 (0.79–1.62)	2.25 (1.33–3.80)	1.54 (0.94–2.53)	2.08 (1.21–3.58)
Model 1 ^b HR (95% CI)	1 (reference)	1.11 (0.77–1.60)	1.93 (1.12–3.33)	1.51 (0.91–2.51)	1.96 (1.11–3.45)
Model 2 ^c HR (95% CI)		1.11 (0.77–1.60)	1.97 (1.14–3.39)	1.46 (0.87–2.44)	2.09 (1.18–3.68)
Model 3 ^d HR (95% CI)		1.06 (0.73–1.53)	2.07 (1.20–3.56)	1.37 (0.82–2.29)	2.12 (1.19–3.76)
	Breakfast eaters ^e		Breakfast skippers ^f		
<i>n</i> of cases/ <i>N</i>	239/4188		46/443		
Crude incidence rate	7.5		13.9		
Crude HR (95% CI)			1.85 (1.35–2.54)		
Model 1 ^b HR (95% CI)	1 (reference)		1.72 (1.23–2.40)		
Model 2 ^c HR (95% CI)			1.74 (1.24–2.43)		
Model 3 ^d HR (95% CI)			1.73 (1.24–2.42)		

CI, confidence interval; HR, hazard ratio; *n*, number; *N*, number of participants.

^aCrude incidence rate (per 1000 person-years).

^bModel 1: Adjusted for age, sex, total energy intake, smoking status, alcohol consumption, leisure-time physical activity, work-time physical activity, family history of diabetes mellitus, eating speed, perceived stress, sleep duration, work schedule, satiation eater, fruits and vegetables intake, fish intake, and intake frequencies of whole-grain cereals, coffee, sugar-sweetened beverages, and snacks.

^cModel 2: Model 1 + body mass index.

^dModel 3: Model 2 + fasting blood glucose (Log-transformed).

^eBreakfast eater was defined as those having breakfast eating frequency of 'every day or almost every day with occasional skips'.

^fBreakfast skipper was defined as those having breakfast eating frequency of '3–5 days/week, 1–2 days/week, or none'.

Table 3. Incidence rates and hazard ratios of type 2 diabetes mellitus according to breakfast consumption stratified by sex, body mass index, fasting blood glucose, and smoking status at baseline, Aichi, 2002–2011

Sex	Breakfast eaters ^a		Breakfast skippers ^b	
	Men		Women	
<i>n</i> of cases/ <i>N</i>	197/3273	34/327	42/915	12/116
Crude incidence rate ^c	7.8	13.8	6.4	14.4
Model 3 ^d HR (95% CI)	1 (reference)	1.54 (1.05–2.28)	1 (reference)	2.29 (1.05–5.02)
Smoking status	Current smoker		Never or former smoker	
<i>n</i> of cases/ <i>N</i>	85/1118	22/199	154/3070	24/244
Crude incidence rate	10.2	14.9	6.6	13.1
Model 3 ^d HR (95% CI)	1 (reference)	1.41 (0.85–2.33)	1 (reference)	2.17 (1.36–3.46)
Body mass index	<25 kg/m ²		≥25 kg/m ²	
<i>n</i> of cases/ <i>N</i>	148/3298	28/332	91/890	18/111
Crude incidence rate	5.9	11.0	13.6	23.6
Model 3 ^d HR (95% CI)	1 (reference)	1.67 (1.08–2.58)	1 (reference)	1.98 (1.13–3.47)
Fasting blood glucose	<110 mg/dL		≥110 mg/dL	
<i>n</i> of cases/ <i>N</i>	177/3943	36/414	62/245	10/29
Crude incidence rate	5.9	11.5	41.4	55.1
Model 3 ^d HR (95% CI)	1 (reference)	1.80 (1.23–2.64)	1 (reference)	1.62 (0.75–3.52)

CI, confidence interval; HR, hazard ratio; *n*, number; *N*, number of participants.

^aBreakfast eater was defined as those having breakfast eating frequency of 'every day or almost every day with occasional skips'.

^bBreakfast skipper was defined as those having breakfast eating frequency of '3–5 days/week, 1–2 days/week, or none'.

^cCrude incidence rate (per 1000 person-years).

^dModel 3 was adjusted for age, sex (if appropriate), total energy intake, smoking status (if appropriate), alcohol consumption, leisure-time physical activity, work-time physical activity, family history of diabetes mellitus, eating speed, perceived stress, sleep duration, work schedule, satiation eater, fruits and vegetables intake, fish intake, and intake frequencies of whole-grain cereals, coffee, sugar-sweetened beverages, and snacks, as well as body mass index (continuous) and fasting blood glucose (Log-transformed).

(model 3 HR 1.71; 95% CI, 1.21–1.49). The analysis updating breakfast skipping information also yielded similar results (model 3 HR 1.66; 95% CI, 1.19–2.32). In another ancillary analysis that used IFG or T2DM as the outcome among participants whose baseline FBG <110 mg/dL (3371 men and 986 women), skipping breakfast was also significantly associated with higher incidence of IFG or T2DM (n of incident cases: 707; model 3 HR 1.29; 95% CI, 1.02–1.63).

DISCUSSION

In the present study, we found that breakfast skipping was positively associated with T2DM incidence in middle-aged Japanese men and women, after adjustment for a number of potential confounding variables, including baseline BMI and FBG levels. We confirmed the associations in both men and women, and in individuals with or without overweight or IFG at baseline. Although the association in current smokers was not statistically significant, formal test of interaction did not suggest any statistically significant difference in the association between current and non-current smokers. The positive association between breakfast skipping and T2DM observed in our study is in line with previous studies conducted in the United States.^{9–11} We extended the finding to a Japanese sample and confirmed the associations in several subgroups.

The positive association between breakfast skipping and the risk of T2DM shown in our study is also roughly in line with a previous study in Japan,¹⁶ although the study only found the association in women, did not adjust for important lifestyle variables or perform detailed stratified analyses, and used IFG as the outcome. Our ancillary analysis that employed IFG or T2DM as the outcome found a weaker but similar association as the original analysis.

In the present study, we did not find a dose-response association between breakfast eating (skipping) frequency and T2DM incidence. This is not consistent with a finding from the CARDIA Study (average baseline age: 32 years), which reported a stepwise inverse association between breakfast eating frequency and T2DM incidence in white men and women and in black men but not black women. The reason for the discrepancy is not clear. Other studies conducted in the United States did not specifically address the issue of dose-response. Also, caution is required in interpreting results, since the definition of skipping breakfast differs by studies.^{10,11}

Since previous studies in Japan reported associations between breakfast skipping and higher BMI^{6,17} as well as regular smoking, we attempted to examine the association precisely by stratifying the analyses by these variables, and we found that the associations were similar across the strata. Nonetheless, the relatively stronger effect estimates observed among those in the higher baseline BMI categories may somehow corroborate the belief that BMI could influence

participants' dietary habits, including breakfast eating behavior, and hence may modify its association with T2DM.^{6,17} However, whether or not this was really due to the influence of participants' prior knowledge of their BMI and FBG needs further investigation.

We speculated a few mechanisms by which breakfast skipping could potentially cause T2DM. First, it has been reported that after-lunch postprandial glucose and insulin levels were significantly higher in participants who skipped breakfast than those who consumed breakfast.¹⁸ Similarly, omitting breakfast has been reported to impair postprandial insulin sensitivity.⁷ Since the level of 1,5-anhydroglucitol, an indicator for short-term hyperglycemia and glycemic excursions, was significantly associated with the development of diabetes independent of HbA1c levels, metabolic alterations induced by breakfast skipping may predispose individuals to diabetes.¹⁹ Second, skipping breakfast could mean having infrequent larger meals. Total energy intakes in the present study were 1942 and 1740 kcal/day in breakfast eaters and breakfast skippers, respectively. We could guess that breakfast skippers had more energy intake per serving, which means that they had larger serving sizes than breakfast eaters. This may also be associated with future diabetes incidence through greater postprandial glucose and insulin responses. The relationship between breakfast skipping and T2DM observed in our study could also be due to residual confounding of other lifestyles.¹⁷ Although we have adjusted for a number of lifestyles, breakfast skippers may have other lifestyle and behavior characteristics that may cause T2DM.

Our study has several other limitations. First, although the BDHQ had fair reproducibility over 9 months as well as 5 years, breakfast consumption was self-reported and subject to a subjective interpretation of what constitutes a breakfast and duration of fasting before the meal. However, the possible information bias as a result would be non-differential and is not expected to influence our findings. Indeed, no material difference in our finding was seen after excluding night shift workers who may have the habit of taking early morning snacks.^{20,21} Second, there was no information on the nutrient composition of the breakfast consumed, and we could not assess the effect of quality of breakfast on the association between breakfast consumption and T2DM. Since breakfast cereal intake was inversely associated with T2DM incidence,²² the association might have been different if we had the information. Third, we ascertained T2DM incidence by a single identification of diabetic FBG level. Although this definition is commonly employed in epidemiologic studies, additional measurement of HbA1c or oral glucose tolerance test results should ideally be used. We also utilized self-reports for T2DM ascertainment, which would have high specificity but relatively low sensitivity.²³ Finally, the observational nature of the present study would prevent any definitive statement about causality. Although our study participants

were relatively homogeneous middle-aged Japanese civil servants with similar demographic, socioeconomic, and environmental backgrounds, there may still be unknown or uncontrolled confounding. While a long-term randomized controlled trial would be difficult to conduct, well-designed cohort studies in other settings may be useful, since findings on the issue are still scarce and have not always been consistent.

In summary, our findings indicate that skipping breakfast increased the risk of T2DM in middle-aged Japanese workers, and the association was independent of several dietary and lifestyle factors, as well as baseline levels of BMI and FBG. Public health messages promoting the benefits of eating breakfast could be distributed in civil service institutions in Japan and the public at large.

ONLINE ONLY MATERIAL

Abstract in Japanese.

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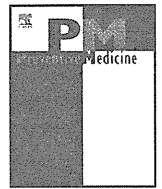
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Association between parental history of diabetes and the incidence of type 2 diabetes mellitus differs according to the sex of the parent and offspring's body weight: A finding from a Japanese worksite-based cohort study

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ABSTRACT

Objective. To investigate differences in the association of parental history of diabetes with the risk of type 2 diabetes mellitus (T2DM) in the offspring according to the sex of the parent and the offspring's body weight.

Methods. A prospective cohort study of 4446 middle-aged non-diabetic Japanese men and women were followed in Aichi Prefecture, central Japan, from 2002 to 2011. Subjects were categorized by their self-reported parental history of diabetes ("no parental history," "father only," "mother only," and "both"). The association of parental history of diabetes and incidence in the offspring was examined according to overweight status adjusted for age, sex, birth weight, smoking, alcohol consumption, physical activity, total energy intake, body mass index, and number of metabolic syndrome components.

Results. During follow-up (median 8.9 years), 277 subjects developed T2DM. Parental history of diabetes was positively associated with T2DM incidence. However, stratified analysis by overweight status revealed that only maternal history was associated with increased T2DM incidence in non-overweight subjects (hazard ratio = 2.35, 95% confidence interval: 1.41–3.91). While in overweight subjects, paternal history was significantly associated with higher T2DM incidence (hazard ratio = 1.98, 95% confidence interval: 1.19–3.28).

Conclusions. Our results suggest that parental history of diabetes mellitus is associated with the incidence of T2DM in offspring differently according to the sex of the affected parent and the offspring's body weight.

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Introduction

Obesity is a well-known risk factor for type 2 diabetes mellitus (T2DM) development (Ardissone Korat et al., 2014). However, some non-obese individuals develop T2DM, suggesting the existence of a familial influence (Paolo, 2007; Vaag and Lund, 2007). Indeed, family history was more strongly associated with diabetes prevalence in non-overweight individuals than in the overweight or obese in US blacks

and Hispanics, but not in whites (Suchindran et al., 2009). Although the finding indicated existence of higher genetic influence in lean non-white populations, the issue has not been explored in other ethnicities, particularly in prospective studies. In addition, some previous studies have indicated a stronger maternal-offspring association with T2DM compared with the paternal-offspring association (Alcolado et al., 2002; Lin et al., 1994; Sakurai et al., 2013; Thorand et al., 2001). Therefore, it would be relevant to examine the association of a parental history of diabetes with T2DM risk in the offspring according to the sex of the parent and the offspring's body weight.

Furthermore, it is well known that one's weight could decrease or fluctuate due to his/her worsened glycemic control. Alternatively, it is also possible for the weight to increase during the follow-up before

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