Effect of Obesity on Incidence of Type 2 Diabetes Declines with Age Among Japanese Women

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Aims: **The present study sought to investigate whether the effect of obesity on the incidence of type 2 diabetes varies with age among Japanese.** ***Methods:*** **Employing two independent cohorts, one in Chiba City from 1994 to 2005 and the other in Kashiwa City from 2002 to 2006, the combined effect of body mass index (BMI) and age on the incidence of type 2 diabetes was evaluated by Cox regression analysis. A total of 37,564 and 26,959 subjects were enrolled in the cohorts and the follow-up rate was 94.7% and 93.3%, respectively.** ***Results:*** **In the Chiba cohort, the hazard ratio for incidence of type 2 diabetes was significantly higher in obese subjects (25.0 kg/m^2 $\leq$ BMI) than in normal weight subjects (18.5 kg/m^2 $\leq$ BMI $<$ 25.0 kg/m^2) across all age groups, with the highest hazard ratio observed in the youngest group aged 40–59 years. In the Kashiwa cohort, the hazard ratio was also significantly higher in obese subjects than in normal weight subjects in men aged 40–59 and 70–79 years and in women aged 40–59 years. Analysis for the interaction between age groups and obese subjects versus normal weight subjects revealed significant weakening of the effect of obesity in women in both cohorts in subjects aged 60–69 and 70–79 years compared to younger subjects aged 40–59 years. In men, however, a significant weakening of the effect was observed only in subjects aged 60–69 years in the Chiba cohort. The interaction between four BMI categories including an extremely obese group (30.0 kg/m^2 $\leq$ BMI) and age category was significant in women ($P < 0.001$) but not in men ($P = 0.113$) in the Chiba cohort.** ***Conclusion:*** **Based on data from the two independent cohorts, the effect of obesity on the incidence of type 2 diabetes was found to decline with age in Japanese women but not in men.** Exp Biol Med 234:750–757, 2009

Key words: incidence; type 2 diabetes; obesity; aging; cohort

Introduction

Recently, the prevalence of type 2 diabetes has been increasing rapidly. In 2000, the number of individuals with diabetes worldwide was estimated to stand at 151 million, with numbers expected to reach 221 million in 2010 and 300 million in 2025 (1). According to the National Health and Nutrition Survey in Japan published in 2008, the number of possible cases of diabetes in Japan has also been increasing; prevalence was estimated at 13.7 million in 1997, 16.2 million in 2002, and 18.7 million in 2006 (2). Diabetes and glucose intolerance are considered to correlate to mortality from all causes and cardiovascular disease (3, 4), and the prevention of diabetes is one of the most important health issues, both domestically and globally.

In 2008, the Japanese Ministry of Health, Labour and Welfare (MHLW) started a system of annual health examinations focusing specifically on metabolic syndrome (5). The guideline published by MHLW described that lifestyle change is more effective in reducing the incidence of dysglycemia in an age group of 40 to 65 years than in an older age group (5). This statement appears to agree with previous studies indicating that the relative risk of death associated with obesity declines with age in both American (6, 7) and Asian populations (8). However, whether the effect of obesity on the incidence of risk factors of type 2 diabetes varies with age is not yet clear. Many studies have reported that beta cell function declined with age independently of body mass index (BMI); however, insulin sensitivity was not affected by aging (9–12). Furthermore, it is suggested that diabetes in the elderly is metabolically distinct from that in both obese (13) and lean (14) middle-

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aged subjects. More specifically, type 2 diabetes in obese middle-aged subjects is characterized by impaired glucose-induced insulin release, altered regulation of hepatic glucose output, and resistance to insulin-mediated glucose disposal (13). In contrast, the primary defect in elderly obese patients with type 2 diabetes is resistance to insulin-mediated glucose disposal (13). In lean subjects, hepatic glucose production is elevated in middle-aged patients with type 2 diabetes compared with control subjects but not in elderly patients. Insulin responses to an oral and intravenous glucose challenge were shown to be reduced in both middle-aged and elderly lean patients with type 2 diabetes, and resistance to insulin-mediated glucose disposal is considered a manifestation of diabetes in both age groups (14). Given these previous studies, we hypothesize that the effect of obesity on the incidence of type 2 diabetes varies with age. The aim of this study is to evaluate the interaction between obesity and age on the incidence of type 2 diabetes employing data from two independent Japanese cohorts.

Materials and Methods

We investigated the combined effects of age and body mass index (BMI) on the incidence of type 2 diabetes using data from two independent Japanese cohorts performed in Chiba City and Kashiwa City. We employed two independent cohorts of similar population structure in order to confirm the findings. Ratios of the juvenile population (under 15 years) and the elderly population (higher than 65 years) in 2005 were 13.8% and 16.5% in Chiba City and 13.4% and 16.4% in Kashiwa City, respectively, according to the National Census in 2005. We analyzed data obtained in the annual health examinations conducted in accordance with the Health and Medical Service Law for the Aged.

Subjects. *Chiba Cohort.* The subjects of the Chiba cohort were residents of Chiba City, Chiba prefecture, Japan. The data from annual health examinations were cumulated for 12 years from 1994 to 2005. The number of participants aged 40–79 years attending the annual health examination in 1994 was 53,891 (14,388 men and 39,503 women). We excluded 14,012 participants (5,134 men and 8,878 women) with missing information and 2,315 participants (1,092 men and 1,223 women) who had fasting blood glucose $\geq$126 mg/dl or non-fasting glucose $\geq$200 mg/dl and/or anamnesis for diabetes mellitus in 1994. After exclusion, the final number of subjects in this cohort was 37,564 (8,162 men and 29,402 women). Of these, 35,579 (7,523 men and 28,056 women) could be followed at least one time.

Kashiwa Cohort. The subjects of the Kashiwa cohort were residents of Kashiwa City, Chiba prefecture, Japan. The data from annual health examinations were cumulated for 5 years from 2002 to 2006. The number of participants aged 40–79 years attending the annual health examination in 2002 was 31,725 (8,782 men and 22,943 women). We excluded 56 participants (23 men and 33 women) with missing information and 1,889 participants (934 men and 955 women) who had fasting blood glucose (FBG) $\geq$126 mg/dl and/or HbA_{1c} level $\geq$6.5% in 2002. After exclusion, the final number of subjects in this cohort was 29,780 (7,825 men and 21,955 women). Of these, 27,760 (7,217 men and 20,543 women) could be followed at least one time.

Since the data from both cohorts were obtained from annual health examinations conducted in accordance with the Health and Medical Service Law for the Aged, consent was not obtained from the subjects. In order to convert the health examination data into anonymous data, personal information, such as name, date of birth, address and telephone number, were removed from the records at the responsible Health Centers before data analysis. Analysis of the cohort data was approved by Chiba University Institutional Review Board.

Baseline Examination. *Chiba Cohort.* We defined the annual health examination in 1994 as baseline. The examination was performed at the designated clinics or hospitals in Chiba where plasma glucose was measured. Data regarding fasting plasma glucose levels were available for 3,253 men and 10,620 women, and those for non-fasting plasma glucose levels were available for 4,270 men and 17,439 women. Here, 'fasting plasma glucose' is defined as the glucose level of plasma obtained from subjects who had gone without food and drink (except water) for at least eight hours before drawing blood, and 'non-fasting plasma glucose' refers to those who had eaten or drank fluids other than only water. On the basis of the fasting plasma glucose or non-fasting plasma glucose levels at baseline according to the guideline of the Japanese Diabetes Society (15), subjects were categorized into two groups: normal type (fasting plasma glucose $<$110 mg/dl or non-fasting plasma glucose $<$140 mg/dl) and borderline type (110 mg/dl $\leq$ fasting plasma glucose $<$ 126 mg/dl or 140 mg/dl $\leq$ non-fasting plasma glucose $<$ 200 mg/dl). We define the value determined for each patient as the baseline glucose type. A self-reported questionnaire completed by all subjects collected data on smoking habit (non-smoker or current smoker), family history of diabetes mellitus (negative or positive (first-degree relative, such as parents, brother and sister, has a history of diabetes)) and alcohol consumption (non-drinker or drinker (alcohol $\geq$22 g/day which is equivalent to sake $\geq$180 ml/day)).

Kashiwa Cohort. We defined the annual health examination in 2002 as baseline. The examination was performed at the designated clinics or hospitals in Kashiwa City. Blood samples were taken from participants who fasted overnight and fasting blood glucose and hemoglobin A1C (HbA_{1c}) levels were measured. A self-reported questionnaire completed by subjects collected data on smoking habit (non-smoker or current smoker) and family history of diabetes mellitus (positive or negative).

Measurements Common to Both Cohorts. Height and weight were measured and BMI was calculated as weight divided by the square of the height (kg/m^2). On the

Table 1. Characteristics of Subjects at Baseline and Follow-Up in the Chiba and Kashiwa Cohorts[a]

Characteristics at baseline and follow-up	Men			Women		
	Chiba cohort (n = 7,523)	Kashiwa cohort (n = 7,217)	P value[b]	Chiba cohort (n = 28,056)	Kashiwa cohort (n = 20,543)	P value[b]
Age (years)	65 (53–69)	67 (63–72)	<0.001	54 (48–62)	60 (53–67)	<0.001
BMI (kg/m^2)	23.2 (21.3–24.9)	23.3 (21.5–24.9)	0.016	22.3 (20.5–24.3)	22.2 (20.5–24.2)	0.104
Follow-up period (years)	9.8 (5.1–10.8)	4.0 (3.1–4.0)	<0.001	10.3 (7.9–10.9)	4.0 (3.9–4.0)	<0.001
Fasting glucose[c]	94 (87–101)	95 (89–102)	—[f]	91 (85–97)	91 (86–97)	—[f]
Non-fasting glucose[d]	102 (91–118)	—[e]	—[f]	98 (89–111)	—[e]	—[f]
HbA_{1c} (%)	—[e]	5.1 (4.8–5.4)	—[f]	—[e]	5.1 (4.8–5.3)	—[f]
Baseline glucose type (%)						
Normal type	91.3	—[e]	—[f]	94.8	—[e]	—[f]
Borderline type	8.7	—[e]		5.2	—[e]	
Smoking habit (%)						
Non-smoker	62.4	70.9	<0.001	92.5	93.1	0.012
Current smoker	37.6	29.1		7.5	6.9	
Family history of diabetes (%)						
Negative	87.5	86.3	—[f]	83.4	76.8	—[f]
Positive	12.5	13.7		16.6	23.2	
Alcohol consumption (%)						
Non-drinker	40.8	—[e]	—[f]	93.3	—[e]	—[f]
Drinker	59.2	—[e]		6.7	—[e]	

[a] Data are shown as median (25 percentile–75 percentile).
[b] Distribution of age, BMI and follow-up period between the Chiba and Kashiwa cohorts were compared using the Mann-Whitney U test. The population with smoking habit was compared using Pearson's chi-square test.
[c] Number of subjects in the Chiba cohort is 3,253 men and 10,620 women.
[d] Number of subjects in the Chiba cohort is 4,270 men and 17,439 women.
[e] No data is available for the cohort.
[f] Comparison between the Chiba and Kashiwa cohorts could not be made because either the data were not available from one cohort or the categorization method or definition differed between the cohorts.

basis of BMI measured at baseline examinations, the subjects were categorized into three groups: underweight (BMI $<$ 18.5 kg/m^2), normal weight (18.5 $\leq$ BMI $<$ 25.0 kg/m^2; control group) and obese subjects (BMI $\geq$ 25.0 kg/m^2) according to the guideline of the Japan Society for the Study of Obesity (16). We combined the two groups of BMI $\geq$30.0 kg/m^2 and $\geq$25.0 kg/m^2 because of the small sample size of the BMI $\geq$30.0 kg/m^2 group. Subjects were also categorized into three age groups: 40–59, 60–69, and 70–79 years. The two age groups of 40–49 and 50–59 years were combined for the analysis because of the small sample size, especially in men.

Criteria for Type 2 Diabetes Incidence During Follow-Up Period. *Chiba Cohort.* Participants were defined as having diabetes according to the following criteria: fasting plasma glucose $\geq$126 mg/dl or non-fasting plasma glucose $\geq$200 mg/dl and/or being newly diagnosed as having diabetes during follow-up.

Kashiwa Cohort. Participants were defined as having diabetes when their fasting blood glucose reached $\geq$126 mg/dl and/or HbA_{1c} reached $\geq$6.5% during follow-up.

Plasma glucose or HbA_{1c} was measured only one time in each cohort. Fasting plasma glucose or non-fasting plasma glucose in the Chiba cohort and fasting plasma glucose and HbA_{1c} in the Kashiwa cohort were measured. It is necessary to measure blood glucose twice for the clinical diagnosis of diabetes; however, 'diabetic type' hyperglycemia determined by a single test can be regarded as 'diabetes' for the purpose of an epidemiological study (15).

Statistical Analysis. Differences in the distribution of age and BMI at baseline and follow-up between the two cohorts were evaluated using the Mann-Whitney U test. A difference in the proportion of smoking habit between the cohorts was assessed using Pearson's chi-square test. However, due to the lack of available data in one of the cohorts or differences of categorization or definition, the distributions of fasting plasma glucose, non-fasting plasma glucose, and HbA_{1c} and the proportions of baseline glucose type, family history of diabetes, and alcohol consumption could not be compared between the cohorts. Hazard ratio (HR) was estimated by Cox regression analysis. The effects of BMI on the incidence of type 2 diabetes for each age group and of the interaction between the age groups and obese subjects versus normal weight subjects on the incidence of type 2 diabetes were evaluated after adjustment for current smoking habit, family history of diabetes mellitus, alcohol consumption, and baseline glucose type in the Chiba cohort and of current smoking habit, family history of diabetes mellitus, fasting plasma glucose at baseline (continuous variable), and HbA_{1c} at baseline (continuous variable) in the Kashiwa cohort. Four BMI categories ($<$18.5, $\geq$18.5 to $<$25.0, $\geq$25.0 to $<$30.0 and $\geq$30.0 kg/m^2) for analysis of interaction with age category could be assigned only in the Chiba cohort since this cohort

Table 2. Effects of BMI on the Incidence of Type 2 Diabetes for Each Age Group in the Chiba and Kashiwa Cohorts[a]

	Men					Women				
Age group and BMI group	*n*	Incidence	Person-years	HR (95% CI)	*P* value[b]	*n*	Incidence	Person-years	HR (95% CI)	*P* value[b]
Chiba cohort										
40—59 years										
BMI (kg/m^2)										
<18.5	48	2	402	0.44 (0.11–1.77)	0.248	1,125	39	9,901	0.80 (0.58–1.10)	0.166
18.5 ≤ BMI < 25.0	1,853	181	15,181	1.00 (reference)		14,901	675	134,764	1.00 (reference)	
25.0 ≤	737	160	5,866	2.11 (1.70–2.61)	<0.001	3,173	401	26,885	2.78 (2.46–3.15)	<0.001
60–69 years										
BMI (kg/m^2)										
<18.5	157	26	1219	1.14 (0.76–1.71)	0.513	370	25	3,219	0.98 (0.65–1.47)	0.919
18.5 ≤ BMI < 25.0	2,188	327	18,229	1.00 (reference)		4,375	340	39,934	1.00 (reference)	
25.0 ≤	753	160	5,943	1.44 (1.19–1.74)	<0.001	1,469	247	12,635	2.15 (1.83–2.54)	<0.001
70–79 years										
BMI (kg/m^2)										
<18.5	155	17	985	1.18 (0.71–1.95)	0.527	257	19	1940	0.75 (0.46–1.21)	0.233
18.5 ≤ BMI < 25.0	1,286	151	9,572	1.00 (reference)		1,746	165	13,796	1.00 (reference)	
25.0 ≤	346	68	2,514	1.79 (1.35–2.39)	<0.001	640	95	4,985	1.40 (1.08–1.80)	0.010
Kashiwa cohort										
40–59 years										
BMI (kg/m^2)										
<18.5	23	1	73	0.42 (0.06–3.11)	0.398	582	10	2,091	2.04 (1.06–3.92)	0.032
18.5 ≤ BMI < 25.0	789	46	2,697	1.00 (reference)		7,354	115	26,533	1.00 (reference)	
25.0 ≤	350	43	1,120	1.67 (1.09–2.55)	0.019	1,537	91	5,411	1.68 (1.26–2.23)	<0.001
60–69 years										
BMI (kg/m^2)										
<18.5	99	6	339	0.80 (0.35–1.80)	0.587	409	9	1,518	0.77 (0.39–1.50)	0.436
18.5 ≤ BMI < 25.0	2,353	192	8,424	1.00 (reference)		5,383	209	20,019	1.00 (reference)	
25.0 ≤	855	103	3,015	0.97 (0.76–1.23)	0.784	1,493	112	5,437	1.10 (0.87–1.38)	0.442
70–79 years										
BMI (kg/m^2)										
< 18.5	163	18	548	1.67 (1.02–2.71)	0.042	284	23	999	1.86 (1.20–2.89)	0.006
18.5 ≤ BMI < 25.0	1,990	181	6,982	1.00 (reference)		2,651	148	9,569	1.00 (reference)	
25.0 ≤	595	83	2,051	1.33 (1.03–1.73)	0.032	850	82	2,980	1.17 (0.89–1.53)	0.273

[a] HR, hazard ratio; CI, confidence interval; BMI, body mass index.
[b] Hazard ratio was calculated using Cox regression analysis and adjusted for smoking habit, family history of diabetes mellitus, alcohol consumption and baseline glucose type in the Chiba cohort and for current smoking habit, family history of diabetes mellitus, fasting blood glucose at baseline (continuous variable) and HbA_{1c} at baseline (continuous variable) in the Kashiwa cohort.

Table 3. Main Effects and Interaction Between Age Groups and Obese Subjects Versus Normal Weight Subjects on the Incidence of Type 2 Diabetes in the Chiba and Kashiwa Cohorts[a]

	Men		Women	
Main effect and interaction	HR (95% CI)	*P* value[b]	HR (95% CI)	*P* value[b]
Chiba cohort				
Number	7,163		26,304	
Age (years)				
40–59	1.00 (reference)		1.00 (reference)	
60–69	1.51 (1.26–1.81)	<0.001	1.67 (1.46–1.90)	<0.001
70–79	1.42 (1.14–1.76)	0.002	2.62 (2.21–3.11)	<0.001
BMI (kg/m^2)				
18.5 ≤ BMI < 25.0	1.00 (reference)		1.00 (reference)	
25.0 ≤	2.13 (1.72–2.64)	<0.001	2.78 (2.46–3.15)	<0.001
Age × BMI				
Age BMI				
60–69 × 25.0 ≤	0.67 (0.51–0.90)	0.007	0.78 (0.63–0.95)	0.016
70–79 × 25.0 ≤	0.85 (0.59–1.21)	0.354	0.52 (0.39–0.69)	<0.001
Kashiwa cohort				
Number	6,932		19,268	
Age (years)				
40–59	1.00 (reference)		1.00 (reference)	
60–69	1.10 (0.79–1.51)	0.597	1.66 (1.32–2.08)	<0.001
70–79	1.20 (0.86–1.66)	0.281	1.80 (1.40–2.30)	<0.001
BMI (kg/m^2)				
18.5 ≤ BMI < 25.0	1.00 (reference)		1.00 (reference)	
25.0 ≤	1.62 (1.07–2.46)	0.023	1.78 (1.35–2.35)	<0.001
Age × BMI				
Age BMI				
60–69 × 25.0 ≤	0.62 (0.38–1.00)	0.052	0.62 (0.43–0.89)	0.009
70–79 × 25.0 ≤	0.82 (0.50–1.35)	0.437	0.64 (0.43–0.94)	0.021

[a] HR, hazard ratio; CI, confidence interval; BMI, body mass index.
[b] Hazard ratio was calculated using Cox regression analysis and adjusted for smoking habit, family history of diabetes mellitus, alcohol consumption and baseline glucose type in the Chiba cohort and current smoking habit, family history of diabetes mellitus, fasting blood glucose at baseline (continuous variable) and HbA_{1c} at baseline (continuous variable) in the Kashiwa cohort.

had a longer follow-up period and a larger number of subjects than the Kashiwa cohort. Results were considered statistically significant when two-tailed α was <0.05. All data were analyzed using the SPSS ver15.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Characteristics at baseline and during follow-up in the two cohorts are shown in Table 1. Subjects of both sexes were significantly older in the Kashiwa cohort than in the Chiba cohort. Men's BMI was higher in Kashiwa than in Chiba. The follow-up period was significantly longer in Chiba than in Kashiwa, and the proportion of current smokers of both sexes was significantly higher in Chiba than in Kashiwa.

The effect of BMI on the incidence of type 2 diabetes for each age group is shown in Table 2. The incidence of diabetes mellitus during follow-up was 1092 for men and 2006 for women in the Chiba cohort and 673 for men and 799 for women in the Kashiwa cohort. In Chiba, HR for the incidence of type 2 diabetes was significantly higher in obese subjects than in control subjects across all age groups in both sexes, while the highest HR was observed in subjects aged 40–59 years. In Kashiwa, HR for the incidence of type 2 diabetes was significantly higher in obese subjects than in control subjects in men aged 40–59 ($P = 0.019$) and 70–79 years ($P = 0.032$) and in women aged 40–59 years ($P < 0.001$). Moreover, in Kashiwa, HR for the incidence of type 2 diabetes was significantly higher in underweight subjects than in control subjects in men aged 70–79 years ($P = 0.042$) and in women aged 40–59 years ($P = 0.032$) and 70–79 years ($P = 0.006$).

The main effects and interaction between age groups and obese subjects versus control subjects are shown in Table 3. In women, the effects of obesity were weakened significantly in those aged 60–69 years (HR = 0.78, $P = 0.016$ in the Chiba cohort; HR = 0.62, $P = 0.009$ in the Kashiwa cohort) and 70–79 years (HR = 0.52, $P < 0.001$ in the Chiba cohort; HR = 0.64, $P = 0.021$ in the Kashiwa cohort) compared with those aged 40–59 years. In men, however, a significant weakening of the effect was observed only in those aged 60–69 years in the Chiba cohort (HR = 0.67, $P = 0.007$). Furthermore, the interaction between four BMI categories and age category was significant in women ($P < 0.001$) but not in men ($P = 0.113$), as shown in Figure 1.

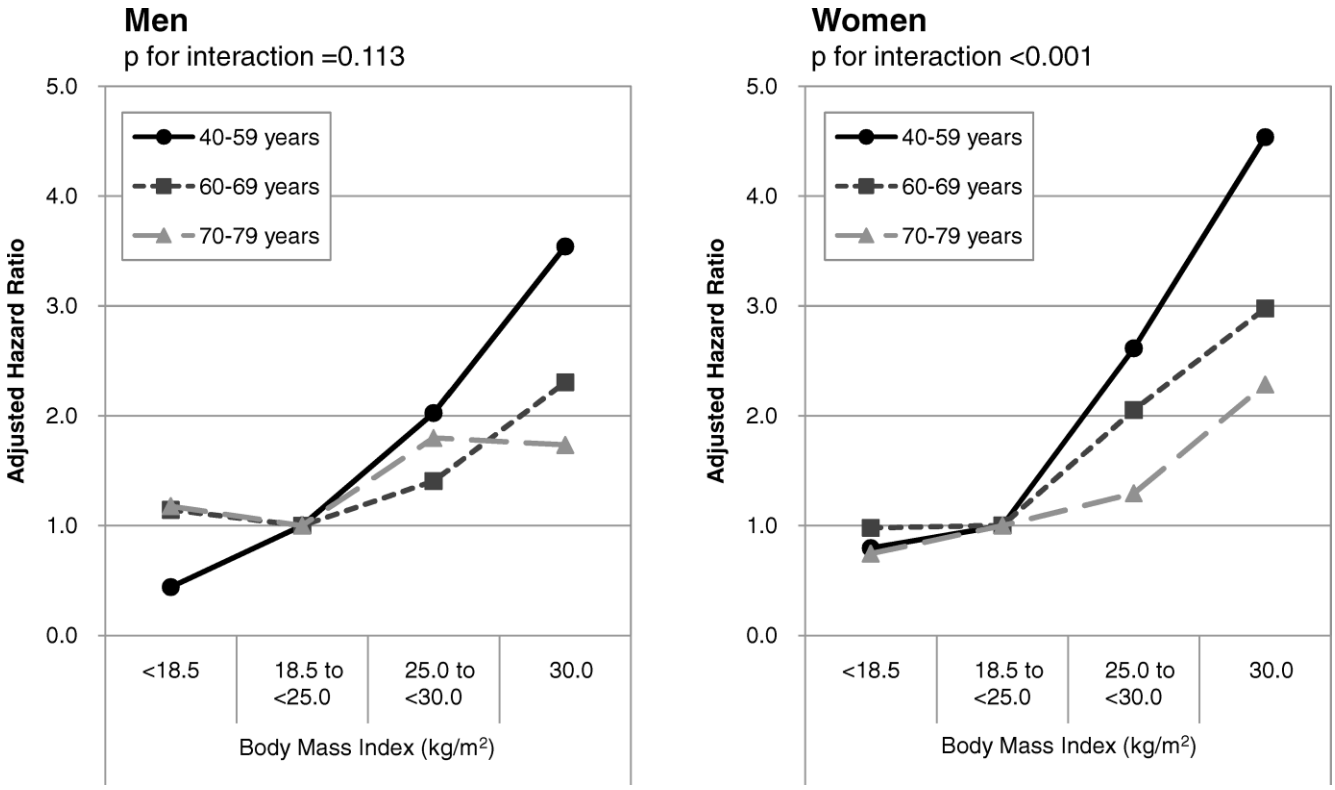

Figure 1. Adjusted hazard ratios (HRs) for four BMI categories among each age group in the Chiba cohort. HRs were adjusted for current smoking habit, family history of diabetes mellitus, alcohol consumption, and baseline glucose type.

Discussion

According to the National Institutes of Health-American Association of Retired Persons Diet and Health Study, the elevated risk of death from all causes in an extremely obese population decreases slightly with age in both U.S. men and women (6). The Cancer Prevention Study I conducted by the American Cancer Society revealed that the relative risk of death from all causes and cardiovascular disease associated with greater BMI declines with age (7). A similar result was also observed in an Asian population; the Korean Cancer Prevention Study showed that the highest relative risks associated with high BMI were observed among subjects below 50 years of age, and an increase in BMI to >25.0 kg/m^2 was not associated with an increased risk of death from any cause among men and women aged 65 years or older (8). These studies support the hypothesis that the relative risk of death associated with excess adiposity is lower in the elderly than in younger adults. However, the combined effects of obesity and age on the incidence of type 2 diabetes have not yet been thoroughly confirmed. In the present study, we showed that the effect of obesity on the incidence of type 2 diabetes was much weakened in senior Japanese women in the two independent cohorts. The risk of diabetes is significantly higher in Asian women than in Caucasian women regardless of the difference in the BMI profile (17). In addition, despite the lower BMI of all age groups in the Japanese population than in the European population, the prevalence of diabetes among Japanese is similar to that among Europeans in both men and women (18). These results indicate that the Japanese population tends to develop type 2 diabetes more easily. The prevalence rate of extremely obese subjects (BMI $\geq$ 30 kg/m^2) was only 1.7% and 1.8% each in the Chiba and Kashiwa cohorts, the rate being similar to a previous Japanese study (19). Thus, we combined the two groups of BMI $\geq$30.0 kg/m^2 and $\geq$25.0 kg/m^2. The interaction between extreme obesity and age on mortality was previously reported (6–8). Although most of our subjects were moderately obese, a significant interaction between obesity and age on the incidence of type 2 diabetes was observed in women in our two independent cohorts. Such an interaction may have been revealed despite the lack of an extreme obese group due the ethnic characteristic of higher susceptibility of type 2 diabetes among Japanese. Furthermore, in the Chiba cohort, a significant interaction between four BMI categories including an extreme obese group (BMI $\geq$ 30 kg/m^2) and age category was again significant only in women (Fig. 1).

The interaction between obesity and age on the incidence of type 2 diabetes may be useful for detecting a high-risk subpopulation of type 2 diabetes. The results of our study indicate that middle-aged obese females constituted a high-risk group for type 2 diabetes. The MHLW described that a change in lifestyle is more effective in reducing the incidence of dysglycemia in an age group of 40

to 65 years than in an older age group according to the guideline concerning annual health examinations (5). Our results are concordant with this description only in women, and not in men. The effect of sex difference according to the interaction between BMI and age on the incidence of type 2 diabetes may be due to the power of the test employed since the number of subjects and the incidence of type 2 diabetes in men were smaller than those in women in both cohorts. Our finding should be confirmed in future studies.

Recently, low BMI was found to be associated with risk of type 2 diabetes among elderly Japanese (20). The present study found that being underweight was a significant predictor for the incidence of type 2 diabetes in those aged 70–79 years in both men and women in the Kashiwa cohort, but not in the Chiba cohort. There are some methodical differences among the Chiba and Kashiwa cohorts. In the Chiba cohort, diabetes is diagnosed based on fasting plasma glucose or non-fasting plasma glucose, whereas in the Kashiwa cohort, diabetes is diagnosed based on fasting blood glucose and/or HbA_{1c}. HbA_{1c}, an established marker for the mean blood glucose level of recent one or two months, is useful for diabetic care in an out-patient clinic (5). A feature using criterion based on $HbA_{1c} \geq 6.5\%$ is high specificity with relatively low sensitivity for diagnosis (15). Thus, subjects with $HbA_{1c} \geq 6.5\%$ are unlikely to be classified as "normal type" or "borderline type" by oral glucose tolerance test (OGTT). On the other hand, patients with $HbA_{1c} < 6.5\%$ cannot be diagnosed as normal. In fact, a significant portion of subjects of "diabetic type" classified by OGTT have HbA_{1c} lower than 6.5% (15). Considering this, the criteria based on HbA_{1c} appears to be stricter than the criteria based on non-fasting blood glucose. In accordance with this assumption, the incidence of type 2 diabetes in the Kashiwa cohort (9.3% for men and 3.9% for women), whose criteria are based on HbA_{1c} and fasting blood glucose, was lower than that in the Chiba cohort (14.5 for men and 7.1% for women), whose criteria are based on fasting or non-fasting blood glucose. Not only the method of diagnosis of diabetes, but also adjusted confounding factors, number of subjects and follow-up periods differed between the Chiba and Kashiwa cohorts. These differences may be one of the reasons for the discrepancy in the results between the two cohorts. Further studies are needed to confirm the increased risk of type 2 diabetes in underweight subjects.

It is well documented in many prospective cohort studies that being overweight and obese are powerful independent predictors of the incidence of type 2 diabetes (21–23). In most of these studies, type 2 diabetes was diagnosed only by administering a self-reported questionnaire, which could make the survey results unreliable because people usually do not recognize themselves as having type 2 diabetes during the symptom-free early stage of the disease (5). In the present study, we measured fasting plasma glucose or non-fasting plasma glucose in the Chiba cohort and fasting plasma glucose and HbA_{1c} in the Kashiwa cohort in order to accurately ascertain the incidence of type 2 diabetes. In addition, heavier persons are known to underreport their weight than leaner persons (24) and one of the advantages of our study could be the ascertainment of type 2 diabetes from accurately measured fasting plasma glucose, non-fasting plasma glucose or HbA_{1c}, and BMI according to accurately measured height and weight rather than from self-reported heights and weights that almost all previous large cohort studies have employed (6, 7).

In conclusion, through analysis of two independent Japanese cohorts, we found for the first time that the effect of obesity on the incidence of type 2 diabetes is weakened in senior subjects compared with middle-aged subjects in women but not in men.

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