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Interaction of Body Mass Index and Diabetes as Modifiers of Cardiovascular Mortality in a Cohort Study

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Objectives: Diabetes and obesity each increases mortality, but recent papers have shown that lean Asian persons were at greater risk for mortality than were obese persons. The objective of this study is to determine whether an interaction exists between body mass index (BMI) and diabetes, which can modify the risk of death by cardiovascular disease (CVD).

Methods: Subjects who were over 20 years of age, and who had information regarding BMI, past history of diabetes, and fasting blood glucose levels (n=16 048), were selected from the Korea Multi-center Cancer Cohort study participants. By 2008, a total of 1290 participants had died; 251 and 155 had died of CVD and stroke, respectively. The hazard for deaths was calculated with hazard ratio (HR) and 95% confidence interval (95% CI) by Cox proportional hazard model.

Results: Compared with the normal population, patients with diabetes were at higher risk for CVD and stroke deaths (HR, 1.84; 95% CI, 1.33 to 2.56; HR, 1.82; 95% CI, 1.20 to 2.76; respectively). Relative to subjects with no diabetes and normal BMI (21 to 22.9 kg/m^2), lean subjects with diabetes (BMI <21 kg/m^2) had a greater risk for CVD and stroke deaths (HR, 2.83; 95% CI, 1.57 to 5.09; HR, 3.27; 95% CI, 1.58 to 6.76; respectively), while obese subjects with diabetes (BMI ≥25 kg/m^2) had no increased death risk (p-interaction <0.05). This pattern was consistent in sub-populations with no incidence of hypertension.

Conclusions: This study suggests that diabetes in lean people is more critical to CVD deaths than it is in obese people.

Key words: Diabetes mellitus, Body mass index, Cardiovascular diseases, Mortality

INTRODUCTION

Diabetes is one of the most rapidly increasing public health issues. The prevalence rate of diabetes is expected to show a continual increase from 2.8% in 2000 to 4.4% in 2030, and the rate of increase will be higher in developing countries than in developed countries [1]. In South Korea, the prevalence rate in adults 30 years of age and older has rapidly increased from 1% to 4% in the 1970s to 9.5% in 2007 (the National Nutrition Survey [2]).

Obesity is an independent risk factor for diabetes [3]. Although insulin secretion is increased in obese persons, insulin action is decreased; these are the clinical conditions of type 2 diabetes [4,5].

Obesity is consistently associated with an increased risk in

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all causes of mortality, and particularly with cardiovascular disease (CVD), including ischemic heart diseases [6-9]. Diabetes is also associated with an increased risk for all-cause and CVD deaths [10]. Obesity is a risk factor for both diabetes and cardiovascular morbidity and mortality; therefore, the direct association between body mass index (BMI) and cardiovascular mortality observed in the general population might be expected. Persons with both disorders are expected to be at a higher risk for death relative to normal persons without both disorders because both factors are risk factors for CVD death. However, the combined effect of diabetes and obesity for CVD mortality may be more complicated and may generate results that are different from these simple expectations.

This study was designed to explore the combined effects of weight status and diabetes on cardiovascular mortality in prospective cohort study.

METHODS

Study Population and Data Collection

The study population was selected from the Korean Multicenter Cancer Cohort (KMCC), a community-based prospective cohort, and from participants recruited from urban and rural areas in Korea (Haman, Chungju, Uljin, and Youngil). The KMCC is described in more depth in a previous study [11].

We excluded 2361 of the KMCC participants whose enrollment age was under 20 years; 1527 who had no fasting blood glucose (FBG) levels, and 79 with no past medical history for diabetes. We ultimately analyzed 16 048 individuals in this study. By December 31, 2008, the total person-years were 147 296 person-years, and the median follow-up duration was 9.41 years.

Information on general lifestyle, anthropometric measurements, diet, cigarette smoking, alcohol consumption, reproductive factors, and other environmental factors were obtained using structured questionnaire interviews. Anthropometric indices (height, weight, etc.) were measured directly using standard methods during the baseline physical examination. Weight and height were measured to the nearest 0.5 kg and 0.5 cm, respectively. BMI was calculated as weight (kg), / height (m^2) and was categorized as <21, 21 to 22.9, 23 to 24.9, and ≥ 25 kg/m^2 [12]. Blood was collected after overnight fasting to determine FBG levels.

The study protocol for the KMCC was approved by the institutional review boards of Seoul National University and the National Cancer Center of Korea (H0110-084-002, C-1012-082-344).

Definition of Main Exposure and Outcome Variables

We used a combined definition that incorporated the past diagnosis of diabetes and the FBG levels at enrollment. Participants with diabetes were classified as patients having known diabetes mellitus (i.e., patients diagnosed as diabetic in a hospital or having undergone previous treatment for diabetes) or FBG ≥ 126 mg/dL. Participants with impaired glucose tolerance (IGT) were defined as having FBG levels of 100 to 125 mg/dL and no past history of diabetes. Those with 'No diabetes' was defined as having FBG levels of no more than 100 mg/dL and no past history of diabetes [13].

Overweight and obesity were defined by the World Health Organization (WHO) Asia-Pacific Guideline (overweight, $23 \leq$ BMI <25 kg/m^2; obesity, BMI >25 kg/m^2). Optimum BMI levels were defined as a BMI of 21 to 22.9 kg/m^2, based on a WHO expert consultation report [12] and BMI <21 kg/m^2 was defined as underweight in this study population.

We classified the cause of death according to the International Classification of Disease 10th revision (ICD-10). We used the national death certificate database and merged death certificate data until December 31, 2008. Deaths were divided into those resulting from CVD (ICD-10 codes I00-I99) [14], diseases of the heart (ICD-10 codes I00-I09, I11, I13, I20 -I51), and stroke (ICD-10 codes I60-I69) [15].

Statistical Analysis

Differences in means and proportions for baseline characteristics of the combined definition of past diagnosis of diabetes mellitus (DM) and FBG were tested using 1-way ANOVA and chi-square analyses, respectively. The Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for CVD mortality. Co-linearity between covariates was examined by calculating the mean and individual covariate variance inflation factors. None of the individual covariate variance inflation factors was greater than 1.5 and the mean variance inflation factor for all covariates included in the CVD models was 1.03. The assumption that each predictor affects mortality proportionally over the entire follow-up period was examined using graphical methods and was found to be reasonable for all the predictors considered here. The significance of the explanatory variables in-

cluded in the Cox models was computed by the likelihood-ratio test. Tests for trend were performed by using the ordered category as a continuous variable in the proportional hazard model.

We evaluated whether the association between diabetes and mortality was modified by obesity. The group with normal BMI (21 to 22.9) and no diabetes were chosen as a reference, to look into mortality according to the joint classification of BMI and the combined definition of past diagnosis of DM and FBG. We used the Cox regression model to test for an interaction the diabetes group and obesity group. To test an interaction, we performed the analysis including diabetes group, obesity group and multiplicative interaction terms of both. Statistical significance of interaction was assumed at a *p*-value of 0.05 or smaller.

Since cigarette smoking [16], alcohol consumption [17], and hypertension [18] are associated with higher risk for CVD deaths, we re-evaluated the combined effect between diabetes and BMI in the group without these three major risk factors. Analyses were done with SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Selected characteristics of the subjects are presented in Table 1. A total of 16 048 people were subjects of the analysis, with 60% females, and the total mean age was 55.7 years of age. At baseline (1993), subjects with diabetes were associated with greater age, higher levels of BMI, smoking status, and history of hypertension, but with a lower likelihood of being female, having a high education status, or alcohol drinking.

Table 1. General characteristics of the study population at the time of recruitment

	Normal population (n=11 791)	Subjects with IGT (n=2545)	Subjects with diabetes (n=1712)	*p*-value
Age	55.4 (12.1)	56.0 (12.4)	57.1 (11.8)	<0.001
Body mass index (kg/m^2)	23.5 (3.3)	23.6 (3.3)	24.3 (3.4)	<0.001
Duration of follow-up (y)	9.0 (3.4)	9.8 (4.1)	9.2 (4.0)	<0.001
Female	60.4	58.6	58.1	0.07
Educated	78.8	74.1	71.6	<0.001
Current smoker	27.4	28.4	28.5	0.03
Current drinker	38.0	37.3	35.6	0.006
History of hypertension	9.9	12.4	19.6	<0.001

Values are presented as mean (SD) or %.
IGT, impaired glucose tolerance.

Table 2 shows the HRs (95% CIs) of diabetes and IGT for CVD mortality, relative to the normal population without IGT and diabetes, in the KMCC cohort study subjects from 1993 to 2008. The hazard for CVD death was increased from that of the normal population by having diabetes or IGT ($p<0.001$). Compared to the normal population, subjects with diabetes had a 1.84-fold higher risk of CVD death (95% CI, 1.33 to 2.56). The hazard for heart disease and stroke also showed an increasing trend from the normal population to the IGT group to the diabetes groups (*p*-trend, 0.09 and 0.01, respectively). Diabetes was associated with a 1.84-fold and a 1.82-fold higher risk for

Table 2. HRs (95% CIs) of diabetes and IGT for cardiovascular disease mortality relative to normal population without IGT and diabetes in the KMCC cohort population from 1993 to 2008

	Person-year	No. of deaths	HR (95% CI)[1]	HR (95% CI)[2]
Cardiovascular disease mortality[3]				
Normal	106 657	161	1.00 (reference)	1.00 (reference)
IGT	24 849	41	1.09 (0.77, 1.54)	1.05 (0.74, 1.49)
Diabetes	15 788	49	1.92 (1.39, 2.64)	1.84 (1.33, 2.56)
p-trend			<0.001	<0.001
Heart disease mortality[4]				
Normal	106 657	50	1.00 (reference)	1.00 (reference)
IGT	24 849	13	1.06 (0.57, 1.94)	1.00 (0.54, 1.85)
Diabetes	15 788	15	1.93 (1.10, 3.38)	1.84 (1.04, 3.25)
p-trend			0.07	0.09
Stroke mortality[5]				
Normal	106 657	99	1.00 (reference)	1.00 (reference)
IGT	24 849	26	1.14 (0.74, 1.75)	1.09 (0.71, 1.69)
Diabetes	15 788	30	1.92 (1.27, .89)	1.82 (1.20, 2.76)
p-trend			0.008	0.01
Other cardiovascular disease mortality[6]				
Normal	106 657	10	1.00 (reference)	1.00 (reference)
IGT	24 849	2	0.86 (0.19, 3.92)	0.89 (0.19, 4.17)
Diabetes	15 788	3	1.85 (0.51, 6.71)	1.82 (0.49, 6.81)
p-trend			0.60	0.63

HR, hazard ratio; CI, confidence interval; IGT, impaired glucose tolerance; KMCC, Korean Multi-center Cancer Cohort; ICD-10, International Classification of Disease 10th revision.
[1]Adjusted for age (5-year categories).
[2]Adjusted for age (5-year categories), gender, educational attainment (high school graduate versus more, cigarette smoking (never, current, and past), alcohol consumption (never, current, and past), past history of hypertension (yes/no) and body mass index (<21, 21-22.9, 23-24.9, ≥25).
[3]ICD-10 codes of I00-I99.
[4]ICD-10 codes of I00-I09, I11, I13, I20-I51.
[5]ICD-10 codes of I60-I69.
[6]ICD-10 codes of I10 ,I12,I14-I19, I52-59, and I70-I99.

Table 3. Hazard ratios[1] (95% confidence intervals) of each category of diabetes and BMI for cardiovascular disease mortality relative to normal population without IGT, diabetes, and with optimal BMI levels in the KMCC cohort population from 1993 to 2008

		Person-year	No. of deaths	Normal	No. of deaths	IGT	No. of deaths	Diabetes	*p*-interaction
Cardiovascular disease mortality[2]									
BMI	<21	30 012	34	0.88 (0.56, 1.40)	11	1.02 (0.52, 1.99)	16	2.83 (1.57, 5.09)	0.02
	21-22.9	32 823	39	1.00 (reference)	10	0.98 (0.49, 1.97)	12	2.10 (1.09, 4.02)	
	23-24.9	32 736	32	0.91 (0.57, 1.46)	6	0.67 (0.29, 1.59)	6	1.17 (0.49, 2.77)	
	≥25	42 004	49	1.09 (0.71, 1.68)	13	1.30 (0.69, 2.45)	12	1.15 (0.60, 2.21)	
Heart disease mortality[3]									
BMI	<21	30 012	12	0.91(0.41, 2.01)	4	1.07 (0.35, 3.31)	4	2.17 (0.70, 6.73)	0.71
	21-22.9	32 823	13	1.00 (reference)	5	1.44 (0.51, 4.08)	4	2.03 (0.66, 6.25)	
	23-24.9	32 736	9	0.77 (0.33, 1.79)	2	0.67 (0.15, 2.96)	2	1.28 (0.29, 5.71)	
	≥25	42 004	16	1.16 (0.56, 2.43)	2	0.62 (0.14, 2.75)	5	1.43 (0.51, 4.04)	
Stroke mortality[4]									
BMI	<21	30 012	20	0.89 (0.49, 1.63)	7	1.12 (0.48, 2.63)	11	3.27 (1.58, 6.76)	0.03
	21-22.9	32 823	23	1.00 (reference)	4	0.67 (0.23, 1.95)	8	2.43 (1.08, 5.44)	
	23-24.9	32 736	22	1.06 (0.59, 1.91)	4	0.77 (0.26, 2.21)	3	0.95 (0.28, 3.16)	
	≥25	42 004	29	1.12 (0.64, 1.94)	10	1.69 (0.79, 3.56)	6	0.98 (0.39, 2.42)	

BMI, body mass index; IGT, impaired glucose tolerance; KMCC, Korean Multi-center Cancer Cohort; ICD-10, International Classification of Disease 10th revision.
[1]Adjusted for age (5-year categories), gender, educational attainment (high school graduate versus more), cigarette smoking (never, current, and past), alcohol consumption (never, current, and past) and past history of hypertension (yes/no).
[2]ICD-10 codes of I00-I99.
[3]ICD-10 codes of I00-I09, I11, I13, I20-I51.
[4]ICD-10 codes of I60-I69.

heart disease and stroke deaths, respectively (95% CI, 1.04 to 3.24; 95% CI, 1.20 to 2.76).

Table 3 shows the HRs (95% CIs) for each category of diabetes and BMI for CVD mortality, relative to the normal population without IGT/diabetes and with optimal BMI levels, in the KMCC cohort study subjects from 1993 to 2008. Relative to diabetic subjects having optimal BMI levels and no IGT, the underweight diabetes group had a higher risk of CVD death (HR, 2.83; 95% CI, 1.57 to 5.09), whereas the obese diabetes group had a risk for CVD death similar to the reference group (HR, 1.15; 95% CI, 0.60 to 2.21). The risk for CVD death differed according to the presence of obesity and diabetes (*p*-for interaction, 0.019). Heart disease and stroke mortality also showed similar results. The hazard ratio of the underweight diabetes group was highest for heart disease and stroke (HR, 2.17; 95% CI, 0.70 to 6.73; HR, 3.27; 95% CI, 1.58 to 6.76; respectively). On the other hand, the obese diabetes group did not show any differences in heart disease and stroke mortality compared to the reference group (HR, 1.43; 95% CI, 0.51 to 4.04; HR, 0.98; 95% CI, 0.39 to 2.42; respectively). With respect to stroke mortality, the BMI and diabetes status showed a significant interaction (*p*-for interaction, 0.025); however, for heart disease mortality, no interaction was apparent (*p*-for interaction, 0.709).

Table 4 shows the HRs (95% CIs) for each category of diabetes and BMI for CVD mortality, relative to the normal population without IGT or diabetes and with optimal BMI levels, among nonsmokers, nondrinkers, and subjects without hypertension history. Among nondrinkers and subjects without hypertension history, the risk for CVD and stroke mortality was significantly increased in the underweight diabetes group when compared to the reference group (for CVD: HR, 2.84; 95% CI, 1.26 to 6.38 and HR, 3.10; 95% CI, 1.72 to 5.61; for stroke: HR, 3.81; 95% CI, 1.44 to 10.99 and HR, 3.75; 95% CI, 1.79 to 7.84; respectively). Among nonsmokers, the risk elevation in the underweight diabetes group was maintained, although not statistically significant. In contrast, the risk for CVD and stroke was concurrently decreased in both the underweight non-diabetes and the non-IGT and obese diabetes groups without hypertension history (*p*-for interaction, 0.004 for CVD death; 0.012 for stroke death), although not statistically significant.

We shows that each of the three diabetes groups showed an increased hazard ratio as BMI decreased, when compared to the obese group (data are not shown). The normal and IGT groups showed no change in all mortality, while in the diabe-

Table 4. Hazard ratios (95% confidence intervals) of each category of diabetes and BMI for cardiovascular disease mortality among subjects without cigarette smoking, alcohol consumption, or hypertension in the KMCC cohort population from 1993 to 2008

		Person-year	No. of deaths	Normal	IGT	Diabetes	*p*-interaction
Cardiovascular disease mortality[1]							
Nonsmokers[2]							
BMI	<21	14 890	26	0.85 (0.47, 1.52)	0.35 (0.08, 1.48)	1.92 (0.74, 5.00)	0.44
	21-22.9	19 552	41	1.00 (reference)	0.93 (0.38, 2.26)	1.65 (0.72, 3.79)	
	23-24.9	21 291	29	0.71 (0.40, 1.26)	0.74 (0.29, 1.92)	0.89 (0.27, 2.92)	
	≥25	30 424	56	0.95 (0.58, 1.57)	1.21 (0.59, 2.50)	1.03 (0.49, 2.19)	
Nondrinkers[3]							
BMI	<21	16 167	34	1.05 (0.59, 1.88)	0.52 (0.16, 1.75)	2.84 (1.26, 6.38)	0.12
	21-22.9	18 115	37	1.00 (reference)	1.11 (0.45, 2.73)	1.95 (0.84, 4.56)	
	23-24.9	19 126	27	0.91 (0.49, 1.65)	0.74 (0.26, 2.15)	1.07 (0.32, 3.57)	
	≥25	26 012	52	1.19 (0.70, 2.04)	1.69 (0.83, 3.49)	1.02 (0.44, 2.38)	
Subjects without hypertension history[4]							
BMI	<21	28 470	55	0.68 (0.41, 1.12)	1.07 (0.54, 2.10)	3.10 (1.72, 5.61)	0.004
	21-22.9	30 423	57	1.00 (reference)	0.86 (0.39, 1.84)	2.04 (1.04, 4.01)	
	23-24.9	29 585	36	0.74 (0.44, 1.23)	0.74 (0.31, 1.76)	1.23 (0.49, 3.15)	
	≥25	35 518	55	0.97 (0.61, 1.54)	1.32 (0.67, 2.59)	0.82 (0.37, 1.84)	
Stroke mortality[5]							
Nonsmokers[2]							
BMI	<21	14 890	16	0.92 (0.42, 2.01)	0.33 (0.04, 2.51)	2.89 (0.96, 8.79)	0.42
	21-22.9	19 552	22	1.00 (reference)	0.87 (0.25, 3.01)	1.77 (0.59, 5.36)	
	23-24.9	21 291	21	1.07 (0.53, 2.16)	1.13 (0.38, 3.42)	0.54 (0.07, 4.07)	
	≥25	30 424	33	1.01 (0.52, 1.97)	1.78 (0.75, 4.22)	1.08 (0.39, 2.97)	
Nondrinkers[3]							
BMI	<21	16 167	20	1.05 (0.49, 2.28)	0.31 (0.04, 2.39)	3.81 (1.44, 10.09)	0.14
	21-22.9	18 115	18	1.00 (reference)	0.65 (0.15, 2.90)	1.49 (0.43, 5.26)	
	23-24.9	19 126	21	1.28 (0.62, 2.66)	0.98 (0.28, 3.47)	1.23 (0.28, 5.48)	
	≥25	26 012	31	1.28 (0.63, 2.57)	2.17 (0.89, 5.23)	0.77 (0.22, 2.71)	
Subjects without hypertension with diabetes[4]							
BMI	<21	28 470	34	0.74 (0.39, 1.42)	1.24 (0.53, 2.93)	3.75 (1.79, 7.84)	0.012
	21-22.9	30 423	31	1.00 (reference)	0.58 (0.17, 1.93)	2.37 (1.04, 5.58)	
	23-24.9	29 585	23	0.92 (0.49, 1.75)	0.89 (0.31, 2.59)	0.86 (0.20, 3.68)	
	≥25	35 518	34	1.03 (0.56, 1.88)	1.75 (0.77, 3.95)	1.07 (0.40, 2.84)	

BMI, body mass index; KMCC, Korean Multi-center Cancer Cohort; IGT, impaired glucose tolerance; ICD-10, International Classification of Disease 10th revision.
[1]ICD-10 codes of I00-I99.
[2]Adjusted for age (5-year categories), gender, educational attainment (high school graduate versus more), alcohol consumption (never, current, and past) and past history of hypertension (yes/no).
[3]Adjusted for age (5-year categories), gender, educational attainment (high school graduate versus more), cigarette smoking (never, current, and past) and past history of hypertension (yes/no).
[4]Adjusted for age (5-year categories), gender, educational attainment (high school graduate versus more), cigarette smoking (never, current, and past) and alcohol consumption (never, current, and past).
[5]ICD-10 codes of I60-I69.

tes group, CVD and stroke mortality increased in the underweight group (HR, 2.34; 95% CI, 1.06 to 5.19; HR, 2.99; 95% CI, 1.01 to 8.58; respectively).

DISCUSSION

In this prospective cohort study, we found that lean persons (BMI <21 kg/m^2) with diabetes had at an elevated risk for CVD death, whereas obese persons (BMI ≥25 kg/m^2) with diabetes

had no elevated risk for death. These results are consistent in a hypertension-free population; a similar pattern is found in nonsmokers and nondrinkers, despite a lack of statistical significance due to the small sample size.

Some recent studies match the conclusion of our study [19]. However, BMI and CVD mortality with respect to diabetes currently show a variety of results, including positive [20,21], inverse [22], and null [23] associations. For example, the study by Batty et al. [20], which targeted only Caucasian males, indicated that the diabetes group shows an increased CVD mortality as BMI increases. However, a different study that compared BMI and CVD mortality in White and African-American males showed different results [24]. A study by Khalangot et al. [21], which targeted patients with diabetes, indicated an increased mortality in the underweight group, no increased mortality in class I obesity (BMI, 30 to 34.9), similar to our results, however a severely obese group (BMI $\geq$35) showed increased mortality. However, these findings have low comparability with our study since the study was focused on Ukrainian people.

A study by Weiss et al. [22] indicated a decreased mortality in patients with diabetes as their weight increased. It is difficult to apply the findings of this study to our study, or to generalize the results, since the study was focused on an elderly, hospitalized population. A study by Nilsson et al. [19], which targeted the general population group, indicated that the cause of mortality as an outcome was a combined effect of diabetes and BMI, similar to the findings of our study, but no analysis of CVD mortality was possible because the targeted number of patients was only 432 people. Generalization to the entire population was also difficult since this study was focused on a population group consisting of people over 75 years old.

The findings of the present study show interaction of BMI and diabetes to modify cardiovascular mortality in sub-populations without cigarette smoking, alcohol drinking or hypertension. Our results also indicated that subjects without hypertension history were consistent. However, nonsmokers and non-drinker groups tended to be consistent but the results were not statistically different from the main results of the present study. In the case of smoking and drinking, Nonsmokers and non-drinker groups had more deaths resulting from causes other than CVD and stroke mortality. The obesity paradox implies paradoxically decreased mortality in association with increasing BMI up to and including obesity and has been reported among patients with hypertension [25]. To our results, a combined effect of BMI and diabetes could modify CVD and stroke mortality without the obesity paradox effect of hypertension.

In the general population, obesity is a risk factor for both diabetes and CVD mortality [26,27]. A positive association between obesity and CVD mortality has also been identified in individuals with coronary heart disease at baseline [28] . Therefore, the lack of an association between increasing BMI and CVD mortality observed in the present study seemed counter-intuitive.

We suggest several explanations for the protective effect of elevated BMI on mortality in subjects with diabetes. For example, overweight may reflect the protective effects of increased energy stores. In end-stage renal disease patients, protein-energy wasting and inflammation contribute to elevated mortality and underpin the direct association observed between BMI and survival [29,30]. The increased energy stores in subjects with diabetes who also have elevated BMI may therefore protect them from similar energy wasting and inflammation. Indeed, adipose tissue acts as a buffer against malnutrition and may represent an evolutionary survival advantage [31].

Our study has some limitations. For example, BMI was measured on only a single occasion. As such, the potential impact of weight change over time cannot be assessed. Therefore, obese or overweight people who lost weight may have altered their survival. A second possibility is that the lowest BMI values in the present study may possibly have resulted from a catabolic process and did not reflect long-term thinness. Subjects with less than one year of follow up were omitted from the analysis, to minimize the impact of this possibility. Another limitation is that the use of self-reported information prevented us from distinguishing between the two types of the disease. The possibility of weight loss after diagnosis of diabetes (mainly of type 1) would result in an underestimate of the role of BMI in determining the risk of the disease. However, the prevalence of type 1 diabetes is substantially lower than that of type 2 diabetes in this region [32,33] and type 1 diabetes also increases CVD mortality [34] so that an inability to distinguish between types of diabetes probably does not substantially affect the interpretation of the results. The use of self-reported diabetes may also represent some measurement error; however, studies conducted in community-based populations have found self-reported diabetes to be moderately to highly accurate in determining disease status [35].

Nonetheless, the present study has the following merits. First, it can clearly identify the timing of the findings according to a

population based prospective cohort and it indicates a decreased possibility of bias resulting in potential confounding variables due to memory, according to the survey data. In addition, the median length of follow-up was 9.4 years (25 to 75 percentile; 5.8 to 11.6 years), which provided relatively good statistical power.

The present investigation demonstrates that lean people with diabetes constitute a high-risk group for CVD mortality. No similar effect on CVD mortality is seen in overweight or obese people, either with or without diabetes. These observations can have important clinical implications because they indicate that in lean people with diabetes might have a worse prognostic significance than in normal and obese people with diabetes or without diabetes.

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CONFLICT OF INTEREST

The authors have no conflicts of interest with the material presented in this paper.

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