



## Body Mass Index and Incident Ischemic Heart Disease in South Korean Men and Women

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Asian populations have a higher body fat percentage for a given body mass index (BMI) than Caucasians. However, little information is available on the association of BMI with ischemic heart disease (IHD) incidence in Asians at low BMI levels. The authors prospectively evaluated the association of BMI (weight (kg)/height (m)<sup>2</sup>) with IHD incidence over 9 years of follow-up (1993–2001) among 133,740 South Korean adults (89,050 men, 44,690 women) who participated in the 1990 and 1992 examinations of the Korea Medical Insurance Corporation Study. Average BMI at baseline was 23.4 (standard deviation, 2.3) in men and 22.3 (standard deviation, 2.3) in women. After multivariate adjustment, there was a 14% (95% confidence interval: 12, 16) increased risk of incident IHD per unit of increase in BMI. This trend was also observed within the range considered normal by Western standards, and a BMI of 24–<25 was associated with an IHD hazard ratio of 2.01 (95% confidence interval: 1.32, 3.05) in comparison with a BMI of 18–<19. The association of BMI with IHD in this cohort of relatively young South Korean men and women was progressive over the range of BMI values, with no threshold of change in risk and no indication of a U-shaped relation at low BMI levels.

Asian continental ancestry group; body mass index; body weight; myocardial ischemia; obesity

Abbreviations: BMI, body mass index; CI, confidence interval; KMIC, Korea Medical Insurance Corporation.

Excess adiposity is associated with a variety of health risks, including an increased incidence of cardiovascular events (1–3). To facilitate clinical decision-making and public health interventions, standard body mass index (BMI; weight (kg)/height (m)<sup>2</sup>) thresholds have been established to define overweight (BMI 25–<30) and obesity (BMI ≥30) (1). However, these cutoffs were derived from studies performed in Western countries, primarily in Caucasian subjects, and they may not be appropriate for other racial/ethnic groups (4, 5). Specifically, several Asian populations have a higher body fat percentage for a given BMI than Caucasians (4, 6, 7). Furthermore, while the prevalence of obesity

and overweight in some Asian populations is low by Western criteria, diabetes, hypertension, and dyslipidemia occur at lower BMI levels in these populations than in Caucasians (7–12). Indeed, based on the association of increasing BMI with these risk factors, a World Health Organization Expert Consultation recently introduced 23 as a new BMI cutoff for public health action in Asian populations (6). Hence, the excess risk of ischemic heart disease associated with increased weight in Asian populations may occur well below a BMI of 25. However, previous studies of BMI and ischemic heart disease in Asian populations have not provided a detailed evaluation of the dose-response

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relation of body weight to disease endpoints or have been limited to mortality endpoints (6, 13–18).

The objective of this study was to evaluate the association between BMI and the incidence of ischemic heart disease events in a large cohort of South Korean men and women. We were particularly interested in the dose-response relation at BMI levels below conventional diagnostic thresholds used in Western populations.

## MATERIALS AND METHODS

### Study population

The Korea Medical Insurance Corporation (KMIC) Study is a prospective study of cardiovascular risk factors in South Korean men and women. Detailed descriptions of this cohort have been published previously (19–21). KMIC is a provider of health insurance to civil service workers, teachers, and their dependants in the Republic of Korea (South Korea). In 1990, KMIC insured 11 percent of the South Korean population. All insured workers are required to participate in biennial medical examinations performed by KMIC. In 1990 and 1992, 95 percent and 94 percent of workers completed the examinations, respectively. Among insured workers aged 35–59 years who attended both the 1990 and 1992 biennial examinations, we selected for inclusion in the KMIC cohort all female workers ( $n = 62,657$ ) and a 25 percent systematic random sample of male workers ( $n = 106,803$ ).

We excluded 183 participants who died before January 1, 1993; 6,288 participants with cardiovascular disease, liver disease, or cancer at or prior to the 1992 visit; 2,475 participants for whom the average of 1990 and 1992 liver enzyme (glutamic-oxaloacetic transaminase or glutamic pyruvic transaminase) levels was above 70 IU; 9,430 participants whose BMI changed by more than two units between the 1990 visit and the 1992 visit; and 1,834 participants for whom the average of the 1990 and 1992 BMI measurements was below 18. We also excluded 2,306 participants with missing BMI data in 1990 or 1992, as well as 13,204 subjects with missing data for any adjustment covariate. Thus, the final sample size for this study was 133,740 (89,050 men and 44,690 women).

### Baseline data collection

Baseline data were collected at the 1990 and 1992 biennial KMIC examinations, which were conducted in a standardized fashion by medical staff at 416 local hospitals throughout South Korea. Weight, height, blood pressure, and levels of total cholesterol, fasting glucose, and liver enzymes (glutamic-oxaloacetic transaminase and glutamic pyruvic transaminase) were measured at both the 1990 and 1992 medical examinations. BMI was calculated as weight in kilograms divided by height in meters squared. Systolic and diastolic blood pressure measurements were taken once at each examination in the seated position by a registered nurse or a blood pressure technician. A fasting serum specimen was drawn and analyzed for total cholesterol and glucose concentrations. Each participating hospital had in-

**TABLE 1. Baseline characteristics of the study population, Korea Medical Insurance Corporation Study, South Korea, 1990–1992**

Characteristic	Men ( $n = 89,050$ )	Women ( $n = 44,690$ )
Mean age (years)	44.8 (6.7)*	42.1 (6.0)
Mean body mass index†	23.4 (2.3)	22.3 (2.3)
Mean systolic blood pressure (mmHg)	125.0 (13.7)	115.8 (12.1)
Mean diastolic blood pressure (mmHg)	81.8 (9.4)	75.3 (8.7)
Mean total cholesterol level (mg/dl)	194.0 (32.6)	188.4 (32.1)
Mean fasting glucose level (mg/dl)	92.9 (20.8)	86.2 (12.9)
Smoking (%)		
Never smoker	21.2	99.3
Past smoker	20.9	0.4
Current smoker		
1–9 cigarettes/day	15.4	0.2
10–19 cigarettes/day	24.0	0.1
≥20 cigarettes/day	18.5	0.0
Frequency of alcohol drinking (%)		
Never	26.4	91.1
Occasionally	49.8	8.5
Often	23.8	0.4
Physical activity (%)	31.4	16.2
Hypertensive‡ (%)	26.7	9.4
Hypercholesterolemic‡ (%)	8.4	6.5
Diabetic‡ (%)	4.2	1.1

\* Numbers in parentheses, standard deviation.

† Weight (kg)/height (m)<sup>2</sup>.

‡ Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, hypercholesterolemia as total cholesterol ≥240 mg/dl, and diabetes as fasting glucose ≥126 mg/dl or previous diagnosis of diabetes.

ternal and external quality control procedures directed by the Korean Association of Laboratory Quality Control. In our analyses, values for baseline BMI, systolic and diastolic blood pressure, total cholesterol, and fasting glucose were the average of measurements taken in 1990 and 1992. Information on smoking history, frequency of alcohol drinking, physical activity, and previous comorbidity was obtained by questionnaire at the 1992 visit. Completed questionnaires were reviewed and edited by trained staff who followed the KMIC data collection procedures.

### Outcome definition and follow-up procedures

The study outcomes were hospitalization and mortality from acute myocardial infarction (*International Classification of Diseases*, Ninth Revision, code 410; *International Classification of Diseases*, Tenth Revision, codes I21–I22)

**TABLE 2. Hazard ratios for incident ischemic heart disease and acute myocardial infarction by body mass index category, Korea Medical Insurance Corporation Study, South Korea, 1993–2001**

Body mass index*	No. of subjects	%	Ischemic heart disease					Acute myocardial infarction				
			No. of events	Model 1†		Model 2‡		No. of events	Model 1†		Model 2‡	
				HR§	95% CI§	HR	95% CI		HR	95% CI	HR	95% CI
18–<19	4,100	3.1	24	1.00¶		1.00¶		8	1.00¶		1.00¶	
19–<20	9,159	6.8	68	1.17	0.74, 1.87	1.13	0.71, 1.80	22	1.07	0.48, 2.41	1.01	0.45, 2.26
20–<21	15,127	11.3	123	1.20	0.77, 1.85	1.11	0.72, 1.72	42	1.12	0.53, 2.40	0.99	0.47, 2.12
21–<22	19,104	14.3	193	1.40	0.91, 2.24	1.26	0.82, 1.92	72	1.41	0.68, 2.92	1.19	0.57, 2.48
22–<23	21,114	15.8	238	1.47	0.97, 2.24	1.25	0.82, 1.90	74	1.23	0.59, 2.54	0.95	0.46, 1.98
23–<24	20,564	15.4	327	1.97	1.30, 2.99	1.62	1.07, 2.45	113	1.80	0.88, 3.70	1.34	0.65, 2.76
24–<25	17,633	13.2	298	2.01	1.32, 3.05	1.58	1.04, 2.40	111	1.96	0.95, 4.02	1.39	0.67, 2.85
25–<26	11,932	8.9	242	2.39	1.57, 3.64	1.82	1.20, 2.78	82	2.09	1.01, 4.32	1.43	0.69, 2.97
26–<27	7,349	5.5	163	2.61	1.70, 4.02	1.91	1.24, 2.95	57	2.37	1.13, 4.97	1.53	0.73, 3.22
27–<28	4,063	3.0	115	3.26	2.10, 5.07	2.30	1.47, 3.58	41	3.00	1.41, 6.42	1.84	0.86, 3.96
28–<29	1,982	1.5	56	3.29	2.04, 5.32	2.26	1.40, 3.66	24	3.68	1.65, 8.20	2.22	0.99, 4.96
29–<30	960	0.7	28	3.54	2.05, 6.11	2.36	1.36, 4.86	10	3.31	1.30, 8.39	1.91	0.75, 4.87
≥30	653	0.5	24	4.37	2.48, 7.69	2.75	1.55, 4.86	10	4.87	1.92, 12.34	2.60	1.02, 6.62
<i>p</i> for linear trend				<0.001		<0.001		<0.001		<0.001		

\* Weight (kg)/height (m)<sup>2</sup>.

† Hazard ratios were adjusted for age, sex, smoking (never smoker, past smoker, or current smoker of 1–9, 10–19, or ≥20 cigarettes/day), frequency of alcohol drinking (never, occasionally, or often), physical activity, and insurance premium (four categories).

‡ Hazard ratios were further adjusted for hypertension (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg), diabetes (fasting glucose ≥126 mg/dl or previous diagnosis of diabetes), and total cholesterol levels.

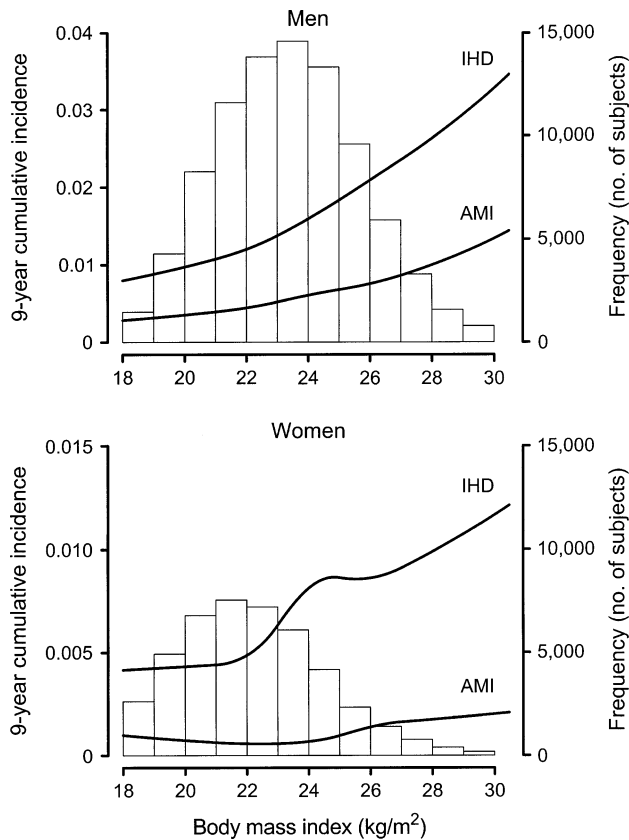
§ HR, hazard ratio; CI, confidence interval.

¶ Reference category.

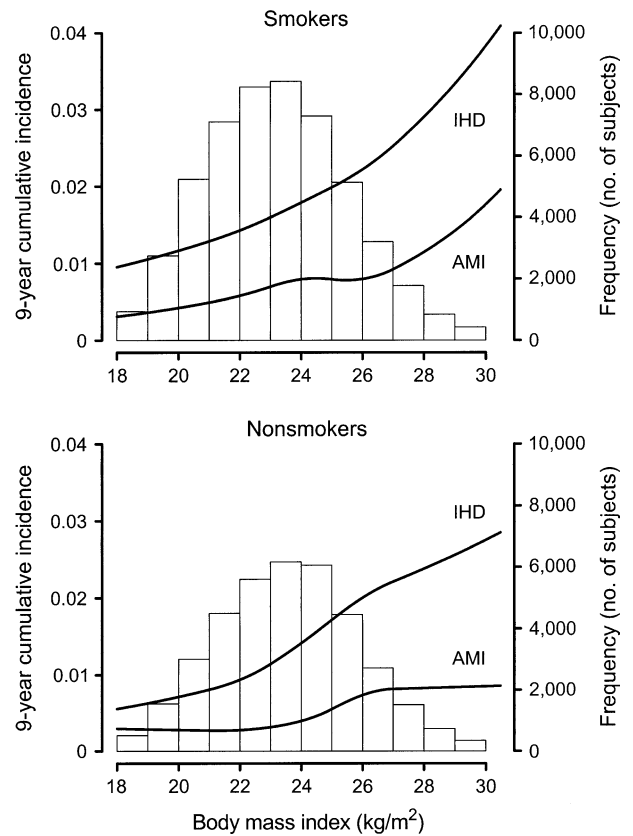
and ischemic heart disease (*International Classification of Diseases*, Ninth Revision, codes 410–414 and 429.2; *International Classification of Diseases*, Tenth Revision, codes I20–I25). Follow-up extended for 9 years (January 1, 1993–December 31, 2001). Hospitalization data were obtained from hospital discharge summaries, coded by professionally trained and certified medical chart recorders. Discharge charts were coded in a standardized fashion using World Health Organization criteria. Ascertainment of events requiring hospitalization among KMIC enrollees is considered nearly complete, since hospitals could not receive payment until the bill with the discharge diagnoses was submitted to KMIC. Mortality data were obtained from computerized searches of death certificates from the Korean National Statistical Office and are also likely to be nearly complete. Death certificates were completed by trained and certified recorders using information provided by physicians.

### Statistical analysis

Cox proportional hazards models were used to evaluate the association of baseline BMI with the incidence of ischemic heart disease events over the 9 years of follow-up (22). In the main analysis, we grouped BMI in one-unit categories to avoid the assumption of linear effects of BMI on disease endpoints. We performed subgroup analyses by sex and by smoking status in men (current smokers vs. those not currently smoking). For subgroup analyses and analyses of fatal events, we modeled BMI using restricted quadratic splines in Cox models because of the limited number of events for a fine categorization (23). The knots for the restricted quadratic splines were set at 21, 23, 25, and 27 BMI units (kg/m<sup>2</sup>). This parameterization of BMI requires only four parameters, and it can accommodate a wide variety of smooth dose-response curves. We conducted tests for linear trend by including in the regression model a variable



**FIGURE 1.** Nine-year cumulative incidence of ischemic heart disease (IHD) and acute myocardial infarction (AMI) by body mass index (weight (kg)/height (m)<sup>2</sup>) in men and women, Korea Medical Insurance Corporation Study, South Korea, 1993–2001. Risk trends were estimated from restricted quadratic spline Cox models adjusted for age, smoking, frequency of alcohol drinking, physical activity, and insurance premium. The bars represent the frequency distribution of body mass index among men and women.



**FIGURE 2.** Nine-year cumulative incidence of ischemic heart disease (IHD) and acute myocardial infarction (AMI) by body mass index (weight (kg)/height (m)<sup>2</sup>) and smoking activity (current smokers vs. those not currently smoking) in men, Korea Medical Insurance Corporation Study, South Korea, 1993–2001. Risk trends were estimated from restricted quadratic spline Cox models adjusted for age, frequency of alcohol drinking, physical activity, and insurance premium. The bars represent the frequency distribution of body mass index by smoking category in men.

incorporating the median BMI of each category. The statistical significance of interactions was evaluated using likelihood ratio tests comparing models with and without the interaction terms. All models included adjustment for age, sex, smoking history, alcohol drinking frequency, physical activity, and insurance premium (a surrogate marker of socioeconomic status). In addition, we also fitted models with further adjustment for hypertension (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg), diabetes (fasting glucose level  $\geq 126$  mg/dl or previous diagnosis of diabetes mellitus), and total cholesterol levels to evaluate the effect of BMI that is not explained by traditional risk factors. Statistical analyses were performed using S-Plus (MathSoft, Inc., Seattle, Washington) (24).

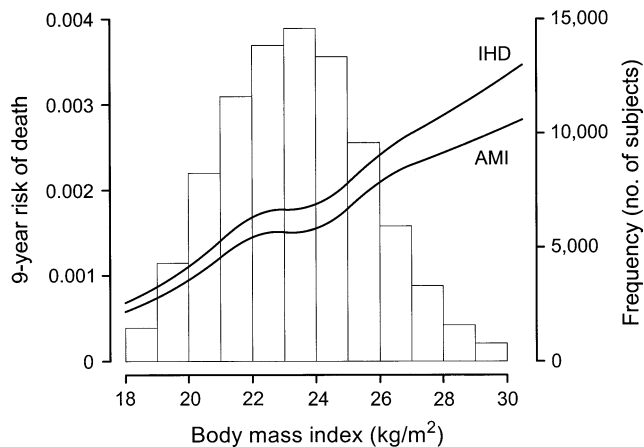
**RESULTS**

The average BMI of the study participants was 23.4 (standard deviation, 2.3) in men and 22.3 (standard deviation,

2.3) in women (table 1); 75.7 percent of men and 88.2 percent of women had a BMI below 25. Among men, the age-adjusted average BMI was 0.32 units (95 percent confidence interval (CI): 0.29, 0.35) lower in current smokers than in those not currently smoking. The age- and smoking-adjusted prevalences of hypertension, hypercholesterolemia, and diabetes increased progressively with BMI in both men and women ( $p < 0.001$  for all linear trends).

Over 9 years of follow-up, there were 1,899 incident cases of ischemic heart disease (1,586 in males, 313 in females), including 666 cases of acute myocardial infarction (621 in males, 45 in females). There were 209 deaths from ischemic heart disease (198 in males, 11 in females), including 181 deaths from acute myocardial infarction (172 in males, 9 in females).

As table 2 shows, there were strong, graded relations of increasing BMI with ischemic heart disease and myocardial infarction. On average, there was a 14 percent (95 percent CI: 12, 16) increased risk of incident ischemic heart disease



**FIGURE 3.** Nine-year risk of death from ischemic heart disease (IHD) and acute myocardial infarction (AMI) by body mass index (weight (kg)/height (m)<sup>2</sup>) in men, Korea Medical Insurance Corporation Study, South Korea, 1993–2001. Risk trends were estimated from restricted quadratic spline Cox models adjusted for age, smoking, frequency of alcohol drinking, physical activity, and insurance premium. The bars represent the frequency distribution of body mass index among men.

per unit of increase in BMI. This trend was also observed across the lower part of the BMI range, with a twofold rise (hazard ratio = 2.01, 95 percent CI: 1.32, 3.05) in the risk of ischemic heart disease events from the category 18–<19 to the category 24–<25. After adjustment for hypertension, diabetes, and total cholesterol levels (table 2), the relation of BMI with ischemic heart disease remained highly significant, albeit attenuated.

The direct and progressive associations of BMI with ischemic heart disease and myocardial infarction were observed in both men and women (figure 1), with no evidence of different risk trends by sex (*p* values for the effects of interaction between BMI and sex on the risks of ischemic heart disease and myocardial infarction were 0.77 and 0.84, respectively). Among men, the associations were also similar in current smokers and those not currently smoking (figure 2) (*p* values for the effects of interaction between BMI and smoking status on the risks of ischemic heart disease and myocardial infarction were 0.07 and 0.20, respectively).

Because of the small number of fatal events in women, the analyses of fatal endpoints were restricted to men. For fatal cases, the dose-response relation increased gradually throughout the entire range of BMI values (figure 3), with an 11 percent (95 percent CI: 5, 18) increased risk of death from ischemic heart disease per unit of increase in BMI.

## DISCUSSION

In our large cohort of South Korean men and women, BMI was strongly related to the incidence of ischemic heart disease, including acute myocardial infarction, throughout its entire range. A BMI of 24–<25, considered normal by

Western standards, was still associated with double the risk of ischemic heart disease in comparison with a BMI of 18–<19. The excess risk associated with increased BMI persisted after adjustment for hypertension, hypercholesterolemia, and diabetes.

In a meta-analysis of the predictive ability of BMI to estimate percent body fat across different ethnic groups, Deurenberg et al. (4) estimated that for the same percentage of body fat, subjects from different East Asian countries would have BMIs 1.9–3.2 units lower than those of Caucasians. While the precise reasons for these differences are not completely understood (6), Asians tend to have a more slender body build than Caucasians, and slimmer subjects tend to have less muscle mass and connective tissue than stockier subjects (25). The shorter relative leg length in Asians compared with Caucasians has also been suggested as a possible explanation for these differences (4). In addition, Asian populations may have a different fat distribution pattern than Western populations and may be more prone to central obesity, even at low BMI levels (6, 9). Such considerations raise the possibility that the risks associated with adiposity at lower levels of BMI are higher in Asian populations and that BMI thresholds derived from Caucasian populations do not apply to Southeast Asian populations.

On the basis of these considerations, a recent World Health Organization Expert Consultation introduced a new BMI cutoff of 23 for public health action in Asian populations (6). While the expert committee recognized the continuum of increased risk with increasing BMI, its decision is controversial because it was not directly supported by mortality data (26, 27). Our results indicate a continuous, strong, and graded relation between BMI and ischemic heart disease incidence throughout the entire BMI range, without specific thresholds of abrupt change in risk and without a U-shaped relation at low BMI levels. Our findings are consistent with those of available studies containing detailed information on the relation between BMI and ischemic heart disease mortality (13, 18). This information should be incorporated into decision analytic models to evaluate the cost-effectiveness of alternative BMI cutoffs for public health action in different populations. It further indicates that traditional risk factors provide only a partial image of the risks associated with increases in BMI below conventional thresholds.

The findings of our study may also be relevant to Western populations. Because of the obesity epidemic, the BMI distribution in Western populations has shifted towards higher values (1). The average BMIs of US adult men and women aged ≥40 years in the 1999–2002 National Health and Nutrition Examination Survey were 28.4 and 28.6, respectively, with only 8.1 percent of men and 14.4 percent of women having a BMI below 22 (28, 29). It is thus difficult to identify large numbers of Western subjects with low BMI, even in large cohorts, and we speculate that the low BMI group in most Western studies overrepresents subjects with preexisting conditions who are at increased risk of mortality. As a consequence, the association between BMI and disease risk at low BMI levels may be underestimated in Western populations (30, 31).

The strengths of our study include a large sample size, the use of two biennial examinations to establish a more stable baseline, and the attempt to control for conditions that may affect BMI and mortality simultaneously (30, 31), including liver disease and nonintentional weight loss. In addition, exclusion of participants with more than two units of difference in BMI between 1990 and 1992 is likely to have reduced random variability, since highly disparate measures may also be the consequence of measurement error. However, some limitations must be considered in the interpretation of our findings. We lacked information on measures of abdominal adiposity, such as waist circumference, and we could not determine whether the increased risk associated with increased BMI depended on overall adiposity or on specific adipose tissue distribution patterns. We also lacked information on treatment of hypertension and hypercholesterolemia, and thus control for these two conditions was imperfect. In addition, outcome ascertainment was based on administrative claims data and death certificate information. These sources of error, however, are most likely non-differential and will tend to reduce the estimated effect of increased BMI. Finally, the association of BMI with cardiovascular disease is stronger in younger subjects than in elderly subjects (32). Thus, our findings may not be generalizable to older Asian populations.

In conclusion, our data provide strong evidence that the association between BMI and ischemic heart disease is graded throughout the entire BMI range, with no apparent thresholds even at low BMI levels and no indication of a U-shaped relation at low BMI levels.

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