Table 2 Factors associated with OAB and non-OAB

	OAB, *n* (%)	Non-OAB, *n* (%)	Univariate analysis OR (95%CI)	*P*-value	Multivariate analysis OR (95%CI)	*P*-value
Sex				0.59		0.91
Male	73 (17.6)	341 (82.4)	1.10 (0.78–1.57)		1.03 (0.60–1.78)	
Female	80 (19.1)	339 (80.9)	1		1	
Age (years)				0.77		0.94
70–79	124 (18.2)	558 (81.8)	1		1	
80≤	29 (19.2)	122 (80.8)	1.08 (0.68–1.68)		1.02 (0.63–1.70)	
GDS				0.0001		<0.0001
<11	95 (15.3)	525 (84.7)	1		1	
≥11	58 (27.2)	155 (72.8)	2.07 (1.43–3.00)		2.37 (1.60–3.52)	
Alcohol intake				0.34		0.064
Never	62 (17.1)	301 (82.9)	1		1	
Ex-drinker	15 (15.2)	84 (84.8)	0.87 (0.45–1.60)		0.98 (0.50–1.91)	
Current drinker	76 (20.5)	295 (79.5)	1.25 (0.86–1.81)		1.65 (1.04–2.62)	
Smoking status				0.12		0.1
Never	90 (19.3)	377 (80.7)	1		1	
Ex-smoker	42 (15.1)	237 (84.9)	0.74 (0.50–1.11)		0.68 (0.39–1.19)	
Current smoker	21 (24.1)	66 (75.9)	1.33 (0.78–2.29)		1.27 (0.65–2.48)	
BMI				0.39		0.17
<18.5	9 (19.6)	37 (80.4)	1.25 (0.58–2.68)		1.23 (0.55–2.74)	
≥18.5 and <25	77 (16.3)	394 (83.7)	1		1	
≥25 and <30	59 (21.1)	220 (78.9)	1.37 (0.94–2.00)		1.51 (1.02–2.24)	
>30	8 (21.7)	29 (78.3)	1.41 (0.62–3.21)		1.74 (0.74–4.13)	
ABI				0.54		0.5
≤0.9	9 (22.0)	32 (78.0)	1.27 (0.59–2.71)		1.32 (0.59–2.99)	
>0.9	144 (18.2)	648 (81.8)	1		1	
baPWV (m/s)				0.77		0.7
<1.7	35 (19.6)	144 (80.4)	1		1	
≥1.7 and <1.9	34 (18.7)	148 (81.3)	0.95 (0.56–1.60)		0.91 (0.53–1.56)	
≥1.9 and <2.2	36 (16.1)	188 (83.9)	0.79 (0.47–1.32)		0.73 (0.43–1.26)	
≥2.2	48 (19.4)	200 (80.6)	0.99 (0.61–1.60)		0.92 (0.55–1.56)	
History/comorbidities						
Stroke				0.29		0.23
Yes	4 (11.4)	31 (88.6)	0.56 (0.20–1.62)		0.51 (0.17–1.55)	
No	149 (18.7)	649 (81.3)	1		1	
Hypertension				0.78		0.9
Yes	66 (18.8)	285 (81.2)	1.05 (0.74–1.50)		0.98 (0.66–1.44)	
No	87 (18.0)	395 (82.0)	1		1	
Myocardial infarction				0.13		0.16
Yes	22 (24.2)	69 (75.8)	1.49 (0.89–2.49)		1.48 (0.86–2.54)	
No	131 (17.7)	611 (82.3)	1		1	
Diabetes				0.54		0.61
Yes	25 (20.3)	98 (79.7)	1.16 (0.72–1.87)		1.14 (0.69–1.89)	
No	128 (18.0)	582 (82.0)	1		1	
Cancer				0.38		0.39
Yes	13 (14.9)	74 (85.1)	0.76 (0.41–1.41)		0.76 (0.40–1.43)	
No	140 (18.8)	606 (81.2)	1		1	
Kidney disease				0.8		0.92
Yes	11 (19.6)	45 (80.4)	1.09 (0.55–2.17)		1.04 (0.51–2.10)	
No	142 (18.3)	635 (81.7)	1		1	

ABI, ankle-brachial pressure index; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; GDS, Geriatric Depression Scale; OAB, overactive bladder; OR, odds ratio.

participants with depressive symptoms (OR = 2.37; 1.60–3.52, 95% confidence interval [CI]). Similarly, the risk of OAB was significantly higher in current drinkers (OR = 1.65; 1.04–2.62, 95%CI) and overweight participants (OR = 1.51; 1.02–2.24, 95%CI) (Table 2). While it did not reach statistical significance, obese participants also exhibited a higher OR for OAB (OR = 1.74; 0.74–4.12, 95%CI)

Discussion

In 2002, OAB was defined by the ICS as a syndrome of urgency and frequency of urination.[1] The ICS definition arose from a practical view of OAB, and the diagnostic standards of OAB were established based on subjective symptoms. These changes have allowed for more straightforward clinical judgment, diagnosis and evaluation of treatment effects. Since the ICS definition of OAB, epidemiological surveys have been performed in Europe, the USA, and in Asian countries.[2–5]These surveys have suggested a greater number of OAB patients than was anticipated from earlier studies.

Two large-scale studies on OAB prevalence have been reported. One was conducted in Europe,[2] and the other in the USA.[3] The former study was performed on 16 776 adults aged ≥40 years. The overall prevalence of OAB was 16.6%, with an increase to 22.1–41.9% in the elderly, aged 70 years or more. The other study in the USA reported that the overall prevalence was 16.0% in men, 16.9% in women, and more than 25% in the elderly ≥65 years. Regarding Japanese epidemiological investigations of OAB, there was one random sample study using a mail-in questionnaire in 2003.[5] In this study, participants were selected randomly in proportion to the numbers of households in Japan. The responses from 4570 subjects were collected and analyzed (collection rate, 45%). The overall prevalence of OAB was 12.4%, but it increased to 22.6% and 36.8%, in the elderly people, aged 70–79 years and over 80 years, respectively.

In our study, in which the participants were aged 70 years or older, the prevalence of OAB was 18.4%. One reason for the differences in the prevalence of OAB between the previous studies and ours may be in the environment and specific characteristics of the study population. There are several possible reasons for such differences. The first possibility is the difference in the subjects of the research. As our community-based study was a part of a health promotion program for the elderly, it may be that these participants tended more towards health-seeking behaviors compared with the general population. Those with health-seeking behaviors have a tendency to avoid risk factors for their own health, and may have a low prevalence of various disorders. Moreover, as all our subjects were asked to come to the public facility where we carried out the comprehensive assessment, it might be possible that those with severe disorders did not join in our research. For example, only 34 persons (4.2%) in the present study had previously suffered from stroke, and this selection bias could affect the result of analysis with OAB and the associated factors in this study.

The second is the difference in survey methods. Tikkinen *et al.* reported that the prevalence of OAB was 17.6% in men aged 70–79 years in the population-based study in Finland,[17] and this prevalence was similar to our outcome. They suggest that the prevalence of OAB has been overestimated in earlier studies by vague criteria. Both earlier studies were performed mainly by telephone interviews or postal questionnaires for a random sample of participants. Phone and postal surveys are less costly, and can collect information from a larger population than a face-to-face interview. However, phone interviews that are generally performed by multiple staff members may have problems in uniformity and reproducibility, in addition to deviations as a consequence of the relative responsiveness of the subjects. Postal surveys also have limitations similar to phone interviews, and generally achieve lower response rates, especially in the elderly population.[18] In contrast, the face-to-face interview used in our survey avoided these problems and can define strict criteria of urgency. Furthermore, several reports have described the differences between questionnaire and face-to-face interviews, all of which showed that the prevalence of disease based on face-to-face interview is lower than that obtained using a questionnaire.[18,19] To our knowledge, the present report is the first epidemiological study of definite OAB based on face-to-face interview data.

To date, there have been few surveys on OAB that included as large a sample size of older people as our study. In the National Overactive Bladder Evaluation study, among 5204 participants, 898 people (17.3%) were older than 65 years old.[3] However, this survey was performed by telephone interviews. Milsom *et al.* reported an international survey of OAB syndrome in Europe, but included few coexistence factors in the questionnaires.[2] In our survey, we performed a comprehensive geriatric assessment using many questionnaires and examinations of various types, and data obtained from 833 subjects aged 70 years old or older was analyzed in this report. To our knowledge, this study was the largest population survey of OAB in subjects aged 70 years or over, to date.

Comorbidities associated with OAB have been reported in some epidemiological studies, including age, sex, depression, menopause, parity, constipation, higher BMI, current smoker, diabetes, occupation, type of toilet, and place of residence.[3,20–23] We performed multivariate analysis on factors related to OAB, and found that OAB was significantly higher in participants with depressive symptoms, current drinkers and overweight subjects.

Some studies have reported that depressive symptoms often coexisted with urinary incontinence.[24] Increased frequency and urgency incontinence are frequently observed in

patients with psychological instability, and it is generally considered that the mental condition is the cause of the urgency incontinence, although there are different opinions on this issue.[25] A correlation between depression and nocturia has also been reported.[26] Stewart *et al.* first suggested an association between OAB and depression in the ICS definition of OAB,[3] but the cause of the correlation in the elderly population is not clear. One report describes that frontal cerebral blood flow is decreased in depressive disorder patients in late life using single photon emission computed tomography.[27] Furthermore, one of the bladder sensation centers in the cerebral cortex is found in the frontal lobe.[28] These findings suggest that some degree of idiopathic OAB and depression might have a common cause in elderly people.

We observed a positive correlation between OAB and current drinkers. With regard to the association between lower urinary tract symptoms (LUTS) and alcohol intake, inconsistent results have been reported in previous studies. Several studies found no significant association between drinking and LUTS.[29,30]Meanwhile, one study reported a significant negative association.[31] Because these previous studies did not include many elderly people, the association between drinking and LUTS might not be overt.

Many studies have shown that obesity or a higher BMI is one of the risk factors for stress urinary incontinence. Some reports have also revealed a positive correlation between obesity and OAB. However, the mechanism underlying this correlation has not been elucidated. Zhang *et al.* hypothesized that excess bodyweight might increase bladder pressure and urethral mobility, leading to OAB.[20] Dalloso *et al.* reported that while obesity was a risk factor for OAB onset in women, there was little evidence to indicate this in men.[31]

Recently, it has been assumed that pelvic arterial insufficiency and chronic ischemia of the bladder are associated with detrusor dysfunction. In experimental studies, Azadzoi *et al.* reported that moderate bladder ischemia was associated with detrusor overactivity in the rabbit bladder models.[32] Lower ABI suggest atherosclerosis in lower limbs or pelvic organs. In fact, bifurcation of the iliac arteries is often affected by atherosclerotic change. Although PWV is an indicator of arterial stiffness, we could not show significant associations between OAB and ABI, or PWV in the present study.

There are several limitations to the present study. First, there may be some selection bias, such as health-seeking behaviors and the relatively smaller participation rate in our community-based study. Second, our study design was a cross-sectional one. The inherent limitation of a cross-sectional study is that sampling takes place at only one time-point, so it can be difficult or impossible to infer cause and effect. Further studies are warranted to elucidate the cause of OAB.

Using a face-to-face interview method, we conducted a cross-sectional study on subjects aged 70 years or older in an urban community and assessed the prevalence of and risk factors for OAB in Japan. OAB was significantly associated with depressive symptoms, current drinkers, and BMI. These findings may help to prevent older people from developing OAB symptoms and to promote their health-related quality of life.

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ORIGINAL ARTICLE

Association between Body-Mass Index and Risk of Death in More Than 1 Million Asians

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ABSTRACT

BACKGROUND

Most studies that have evaluated the association between the body-mass index (BMI) and the risks of death from any cause and from specific causes have been conducted in populations of European origin.

METHODS

We performed pooled analyses to evaluate the association between BMI and the risk of death among more than 1.1 million persons recruited in 19 cohorts in Asia. The analyses included approximately 120,700 deaths that occurred during a mean follow-up period of 9.2 years. Cox regression models were used to adjust for confounding factors.

RESULTS

In the cohorts of East Asians, including Chinese, Japanese, and Koreans, the lowest risk of death was seen among persons with a BMI (the weight in kilograms divided by the square of the height in meters) in the range of 22.6 to 27.5. The risk was elevated among persons with BMI levels either higher or lower than that range — by a factor of up to 1.5 among those with a BMI of more than 35.0 and by a factor of 2.8 among those with a BMI of 15.0 or less. A similar U-shaped association was seen between BMI and the risks of death from cancer, from cardiovascular diseases, and from other causes. In the cohorts comprising Indians and Bangladeshis, the risks of death from any cause and from causes other than cancer or cardiovascular disease were increased among persons with a BMI of 20.0 or less, as compared with those with a BMI of 22.6 to 25.0, whereas there was no excess risk of either death from any cause or cause-specific death associated with a high BMI.

CONCLUSIONS

Underweight was associated with a substantially increased risk of death in all Asian populations. The excess risk of death associated with a high BMI, however, was seen among East Asians but not among Indians and Bangladeshis.

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Over the past few decades, there has been a dramatic increase in the prevalence of obesity in many countries. The World Health Organization (WHO) estimates that more than 1 billion adults worldwide are overweight; of these, at least 300 million are obese.[1] A large number of epidemiologic studies have evaluated the associations between body weight and, more often, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) and a wide range of health outcomes. Obesity is associated with multiple chronic diseases, including type 2 diabetes, hypertension, coronary heart disease, stroke, and several cancers.[2] Since most of the studies have been conducted in populations of European origin, however, the dose–response relationship between BMI and the overall risk of death among Asians, who account for more than 60% of the world population, remains unclear.

The definitions of overweight (BMI ≥25.0) and obesity (BMI ≥30.0) are based essentially on criteria derived from studies that involved populations of European origin. The validity of these criteria in Asian populations has yet to be determined. It has been suggested that the associations of BMI with body composition and health outcomes may differ between Asian and European populations.[3] Studies have shown that for a given BMI, Asians generally have a higher percentage of body fat than do Europeans.[3] Asian populations have also been shown to have an elevated risk of type 2 diabetes, hypertension, and hyperlipidemia at a relatively low level of BMI.[3] On the basis of these observations, it has been proposed that the BMI cutoff points for overweight and obesity should be lower for Asian populations than they are for European populations (suggested cutoff points for Asians, ≥23.0 for overweight and ≥27.5 for obesity).[3] However, a 2004 consensus statement from the WHO concluded that the available data were not sufficient to support Asian-specific cutoff points to define overweight and obesity.[3] The optimal weight range associated with a minimal risk of death in Asian populations remains controversial.

To address these unresolved issues, we evaluated the relationship between BMI and the risk of death using data from 19 cohorts, involving more than 1 million participants. Conducted as part of the Asia Cohort Consortium, this pooling project, with its large sample, provides the opportunity not only to address carefully the methodologic challenges that cannot be handled adequately in any single study but also to evaluate the associations according to major Asian ethnic groups.

METHODS

STUDY POPULATION

We identified cohorts that would be potentially eligible for inclusion in the Asia Cohort Consortium BMI Project through a systematic search of the literature in early 2008, followed by a survey that was sent to the investigators associated with each cohort to further determine eligibility for the study. A total of 19 cohorts were included in the pooling project. With the exception of the Taiwan Cardiovascular Disease Risk Factors Two-Township Study (CVDFACTS) cohort, all the cohorts had accrued at least 5 years of follow-up data and included a minimum of 10,000 participants with baseline data on BMI. All the participating cohorts were required to have available baseline data on BMI, age, sex, and cigarette-smoking status and follow-up data on deaths from any cause. Additional data were collected on selected baseline illnesses and cause-specific deaths. Individual data from participating cohorts were collected and harmonized for the statistical analysis. This study was approved by the ethics committee overseeing each of the participating studies and by the ethics committee at the Fred Hutchinson Cancer Research Center. Written or oral consent was obtained from all the subjects who participated in the study.

A total of 1,155,676 subjects were included in the 19 participating cohorts. We excluded from the analysis subjects with missing data on age (2 subjects), BMI (13,780), and vital status (7). In addition, we excluded subjects who were younger than 18 years of age (14 subjects), those who had a BMI of more than 50 (174), and those for whom data on survival were invalid or missing (105). After these exclusions, 1,141,609 subjects remained (535,199 men and 606,410 women).

STATISTICAL ANALYSIS

The association between BMI and the risk of death was analyzed with the use of Cox proportional-hazards regression models, with a categorical representation of BMI as the predictor variable. To define BMI groups for the analysis, we used the BMI cutoff points of more than 25.0 for overweight and more than 30.0 for obesity.

We then established 10 BMI levels that included the lowest BMI group (≤15.0) and the highest (>35.0) and 8 levels in between, each comprising 2.5 BMI units (i.e., ≤15.0, 15.1 to 17.5, 17.6 to 20.0 . . . 32.6 to 35.0, and >35.0). Using the BMI range of 22.6 to 25.0 as the reference, we estimated hazard ratios and 95% confidence intervals for the other BMI ranges, after adjusting for potential confounders, including baseline age, sex, educational level, urban or rural residence, and marital status. We performed additional analyses in which we also adjusted for the variables of cigarette-smoking status (former or current smoker vs. lifetime nonsmoker) and status with respect to known baseline conditions (cancer, coronary heart disease, stroke, diabetes, and hypertension). Analyses were performed separately on data from the Indian and Bangladeshi population and the East Asian population (Chinese, Japanese, and Koreans), since there is considerable heterogeneity between these two populations. Prespecified stratified analyses were performed according to smoking status and sex to evaluate the consistency of the associations. Some analyses were performed among lifetime nonsmokers to eliminate the potential confounding effect of cigarette smoking on the association between BMI and the risk of death. To minimize the influence of possible "reverse causation" (illnesses causing low BMI) owing to the presence of terminal diseases at baseline in some subjects, we excluded the first 3 years of follow-up and restricted some analyses to subjects who did not have a history of cardiovascular disease, stroke, or cancer at baseline and other analyses to lifetime nonsmokers without these conditions at baseline. The ages of the subjects when they entered and exited the cohort were used to define the time variable in the Cox models. The age at exit from the cohort was defined as the age at death or the age at the end of the follow-up period, whichever was earlier.

In the models, the effect of BMI on the risk of death was assumed to be cohort-specific. For each cohort, we assumed that the log hazard ratio for BMI had a fixed-effect component that was common to all cohorts within each of the two major Asian populations (one comprising East Asians and the other compromising Indians and Bangladeshis) and a random effect that was cohort-specific. The random effects for the log hazard ratios were assumed to be normally distributed, with mean zero; that is, we assumed that $\hat{\beta}_{ij}$, the estimated log hazard ratio for the BMI level in a cohort, where j is the BMI level and i is the cohort, has the distribution $\hat{\beta}_{ij} \sim N(\beta_j, \hat{\sigma}_{ij}^2 + \hat{\tau}_j^2)$, where $\hat{\sigma}_{ij}^2$ is the within-study variance of $\hat{\beta}_{ij}$ and $\hat{\tau}_j^2$ is the between-cohort variance of $\hat{\beta}_{ij}$, as estimated from the Cox regression model.[4,5] The β_j parameters and their 95% confidence intervals were estimated in the meta-analysis. Cox model estimation for each cohort was performed with the use of the PHREG procedure in SAS, version 9.2. The meta-analysis estimation was performed with the use of the PROC MIXED procedure in SAS.

RESULTS

STUDY POPULATION

More than 1.14 million participants from 19 cohorts were included in the analysis (Table 1). Overall, the mean (±SD) BMI for the study population was 22.9±3.6 (range, 19.8 to 23.7). Nearly 34% of the study subjects were current or former smokers. Over a mean follow-up period of 9.2 years, approximately 120,700 cohort members died. Approximately two thirds of the deaths were due to cardiovascular diseases (35.7%) or cancer (29.9%), and the other third to other causes (34.3%). Considerable variation, however, existed across the cohorts.

ASSOCIATION BETWEEN BMI AND RISK OF DEATH FROM ANY CAUSE

In both Asian populations, the adjusted hazard ratios for death from any cause were elevated among groups with BMIs lower than the reference range of 22.6 to 25.0 (Table 2). Subjects in the lowest BMI group (≤15.0) had a risk that was increased by a factor of approximately 2.0 to 2.8. Among groups with BMIs higher than the reference range, the hazard ratios for death from any cause were elevated in the East Asian population but not in the Indian and Bangladeshi population. In general, the magnitude of the association was similar between subjects who were current or former smokers and those who were lifetime nonsmokers. The results for men and women were similar to the results of combined analyses of data from men and women (Tables 1 and 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

To evaluate the possible influence of reverse causation, we performed analyses that excluded subjects with a baseline diagnosis of coronary

Table 1. Characteristics of the Participating Cohorts.*

Cohort	No of Subjects	Dates of Enrollment	Mean Follow-up Period	Mean Age at Entry	BMI†	Female Sex	Current or Former Smoker	Deaths	Cause of Death‡		
									Cancer	CVD	Other
			yr			%		*no.*	%		
India											
Mumbai Cohort Study§	146,820	1991–1997	5.2	50.8	22.3±4.2¶	40.4	18.9	13,001	8.7	43.8	47.5
TOCS	129,097	1995–2002	7.5	49.5	21.8±4.1¶	61.6	23.5	10,680	11.8	37.4	50.8
Bangladesh: Health Effects of Arsenic Longitudinal Study	11,452	2000–2002	6.6	37.1	19.8±3.2¶	57.0	35.6	392	15.6	43.7	40.7
Mainland China											
CHEFS	154,737	1990–1992	7.2	55.4	22.6±3.7¶	51.1	37.9	17,687	22.5	46.4	31.0
SCS§	18,100	1986–1989	16.3	55.3	22.2±3.0	0.0	57.3	4,983	39.6	33.8	26.6
SMHS	61,379	2001–2006	3.1	54.9	23.7±3.1¶	0.0	69.6	946	45.2	31.1	23.7
SWHS	74,873	1996–2000	8.6	52.1	24.0±3.4¶	100.0	2.8	2,895	46.4	27.6	26.0
Taiwan											
CBCSP	23,763	1991–1992	15.2	47.3	24.0±3.4¶	49.7	28.9	2,758	36.6	20.1	43.3
CVDFACTS	5,129	1990–1993	14.9	47.0	23.7±3.5¶	55.9	24.8	829	26.7	26.3	47.0
Singapore: SCHS	63,242	1993–1999	11.5	56.5	23.1±3.2	55.8	30.6	10,689	36.4	34.7	28.9
Japan											
3 Pref Aichi§	32,210	1985	11.6	56.2	22.1±3.0	52.6	50.7	5,764	32.9	34.8	32.4
Ibaraki Prefectural Health Study	97,578	1993–1994	11.5	58.8	23.5±3.2¶	65.8	30.3	10,980	NA	NA	NA
JACC	86,671	1988–1990	12.7	57.6	22.8±3.0	58.2	38.6	12,888	36.8	31.0	32.2
JPHC1	42,771	1990–1992	14.4	49.6	23.6±3.0	52.2	40.3	3,394	43.6	26.1	30.3
JPHC2	55,712	1992–1995	11.5	54.2	23.5±3.1	52.6	40.1	5,357	44.5	24.9	30.7
3 Pref Miyagi	29,525	1984	11.6	56.9	23.2±3.3	55.0	43.1	5,880	30.2	40.5	29.3
Miyagi Cohort Study	44,867	1990	12.8	52.0	23.6±3.0	52.1	49.5	3,441	54.9	27.1	18.0
Ohsaki National Health Insurance Cohort Study	47,670	1995	9.9	60.1	23.5±3.1	51.8	48.6	6,892	35.9	32.9	31.2
Korea: KMCC§	16,013	1993–2004	6.5	55.6	23.7±3.3¶	60.3	36.4	1,302	29.6	25.4	45.0
Total	1,141,609	1984–2006	9.2	53.9	22.9±3.6	53.1	33.5	120,758	29.9	35.7	34.3

* Plus–minus values are means ±SD. CBCSP denotes Community-based Cancer Screening Project, CHEFS China National Hypertension Survey Epidemiology Follow-up Study, CVD cardiovascular disease, CVDFACTS Cardiovascular Disease Risk Factor Two-Township Study, JACC Japan Collaborative Cohort Study, JPHC Japan Public Health Center–based Prospective Study, KMCC Korea Multi-center Cancer Cohort, NA not available, SCHS Singapore Chinese Health Study, SCS Shanghai Cohort Study, SMHS Shanghai Men's Health Study, SWHS Shanghai Women's Health Study, 3 Pref Three Prefecture Cohort Study, and TOCS Trivandrum Oral Cancer Screening Trial.

† The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

‡ Deaths from unknown causes are not included.

§ Data on status with respect to diagnosed coronary heart disease at baseline were unavailable for these cohorts. Data for cohorts with and those without baseline data on coronary heart disease are available in Table 8 in the Supplementary Appendix.

¶ The BMI was calculated with the use of weight and height measured at enrollment. For the other studies, weight and height were self-reported.

Table 2. Association between Body-Mass Index and Risk of Death from Any Cause in Two Asian Populations, According to Smoking Status.*

Population	BMI at Baseline									
	≤15.0	15.1–17.5	17.6–20.0	20.1–22.5	22.6–25.0	25.1–27.5	27.6–30.0	30.1–32.5	32.6–35.0	35.1–50.0
All subjects										
East Asians										
No. of deaths	456	3795	13,547	21,200	21,391	11,009	4679	1623	484	283
Hazard ratio (95% CI)	2.76 (1.88–4.07)	1.84 (1.65–2.05)	1.35 (1.25–1.45)	1.09 (1.05–1.14)	Reference	0.98 (0.95–1.01)	1.07 (1.02–1.12)	1.20 (1.10–1.32)	1.50 (1.31–1.71)	1.49 (1.31–1.69)
Indians and Bangladeshis										
No. of deaths	755	2412	3340	3196	2349	1269	537	233	64	57
Hazard ratio (95% CI)	2.14 (1.78–2.57)	1.59 (1.40–1.81)	1.26 (1.12–1.41)	1.09 (0.97–1.23)	Reference	0.98 (0.84–1.13)	0.94 (0.77–1.16)	1.03 (0.77–1.39)	0.86 (0.50–1.49)	1.27 (0.71–2.26)
Current or former smokers										
East Asians										
No. of deaths	191	1990	7590	11,737	10,450	4733	1722	531	127	82
Hazard ratio (95% CI)	2.66 (1.62–4.37)	1.81 (1.61–2.04)	1.38 (1.28–1.49)	1.14 (1.09–1.18)	Reference	0.97 (0.93–1.00)	1.01 (0.95–1.07)	1.18 (1.07–1.30)	1.44 (1.13–1.84)	1.60 (1.26–2.03)
Indians and Bangladeshis										
No. of deaths	267	1055	1277	1067	678	318	116	41	9	5
Hazard ratio (95% CI)	1.97 (1.43–2.72)	1.59 (1.28–1.98)	1.24 (1.01–1.53)	1.13 (0.92–1.40)	Reference	0.99 (0.74–1.33)	0.99 (0.64–1.53)	1.16 (0.58–2.32)	NA	NA
Lifetime nonsmokers										
East Asians										
No. of deaths	247	1618	5280	8366	9925	5704	2713	1017	325	179
Hazard ratio (95% CI)	2.43 (2.06–2.87)	1.72 (1.52–1.94)	1.23 (1.12–1.35)	1.02 (0.97–1.07)	Reference	1.00 (0.95–1.06)	1.11 (1.04–1.20)	1.27 (1.12–1.43)	1.51 (1.30–1.76)	1.56 (1.31–1.86)
Indians and Bangladeshis										
No. of deaths	488	1357	2063	2128	1671	951	421	192	55	52
Hazard ratio (95% CI)	2.15 (1.71–2.69)	1.54 (1.31–1.81)	1.24 (1.07–1.43)	1.07 (0.93–1.23)	Reference	0.97 (0.82–1.16)	0.94 (0.74–1.19)	1.01 (0.73–1.41)	0.86 (0.48–1.55)	1.34 (0.73–2.46)

* Included in the analysis were all East Asian subjects (779,537) and Indian and Bangladeshi subjects (265,036), current and former smokers in the two populations (270,045 and 55,435 subjects, respectively), and lifetime nonsmokers in the two populations (479,492 and 209,596 subjects, respectively). The analyses for the calculation of hazard ratios were adjusted for age, sex, educational level, urban or rural residence, marital status, and status with respect to baseline illnesses; data from subjects with less than 3 years of follow-up were excluded. NA denotes not available.

heart disease, stroke, or cancer (Table 3). Excluding these subjects had only a minimal effect on the point estimate of hazard ratios for the association between BMI and the risk of death from any cause. Excluding 2 additional years of follow-up (i.e., excluding the first 5 years instead of the first 3 years) slightly attenuated the positive association of the risk of death with low BMI but had no effect on the results for high-BMI groups. In an analysis in which current or former smokers were excluded, the elevated risk associated with a lower BMI was attenuated, whereas the positive association with a higher BMI among East Asians was slightly strengthened. No positive association between death from any cause and a high BMI was seen in the Indian and Bangladeshi population in any of the analyses, regardless of the types of exclusions. These results indicate that any possible reverse causation was adequately addressed in the analyses that were performed on data from lifetime nonsmokers, after the exclusion of deaths that occurred within the first 3 years of follow-up — an approach that was used in all the main analyses in this study.

ASSOCIATION BETWEEN BMI AND RISK OF DEATH FROM SPECIFIC CAUSES

As with the findings for death from any cause, a U-shaped association was seen between BMI and the risk of death from cardiovascular disease, cancer, or other causes among East Asians but not among Indians and Bangladeshis (Fig. 1). In fact, no elevated risk of death from any of these three causes was seen in the high-BMI groups of Indians and Bangladeshis. The positive association between a low BMI and the risk of death was strongest for death from causes other than cardiovascular disease or cancer. The results of analyses stratified according to smoking status were, in general, consistent with the pattern shown in Figure 1, although point estimates for some BMI categories were not significant, owing to the small sample (Tables 3 and 4 in the Supplementary Appendix).

The strikingly positive association between low BMI and death from causes other than cardiovascular disease or cancer was primarily the result of deaths due to respiratory diseases (Fig. 2). After exclusion of deaths from respiratory diseases, the positive association with low BMI was substantially reduced. The association between BMI and death from respiratory diseases was similar in smokers and nonsmokers (Fig. 1 in the Supplementary Appendix). It is possible that the strong association observed between low BMI and death from respiratory diseases could be explained, in part, by reverse causation, since respiratory disease can lead to weight loss long before the clinical diagnosis is made.

DISCUSSION

In the pooled analysis of approximately 850,000 East Asians, both a low BMI and a high BMI were associated with an increased risk of death from any cause and of cause-specific death, resulting in an overall U-shaped association. Analyses of data from more than 287,000 Indians and Bangladeshis, however, showed an elevated risk of death only among those with a low BMI. This large pooled analysis not only provides reliable estimates of the overall effect of BMI on the risk of death from any cause and of cause-specific death among Asians, but also offers opportunities for a careful evaluation of the association between low BMI and the risk of death that could not be adequately investigated in most previous studies, which were conducted in populations of European origin.

A U-shaped association between BMI and the risk of death was also seen in a recent pooled analysis of data from the Prospective Studies Collaboration (PSC), involving 900,000 participants in 57 prospective studies, mostly in Western Europe and North America.[6] Only 8% of the PSC populations were Asians (Japanese). In our analysis of data from Indians and Bangladeshis, however, a virtually inverse association between BMI and death from any cause was seen. Even among East Asians, the shape of the curve for the association in our analysis was quite different from that in the PSC, as were the hazard ratios (which were higher at the low-BMI range among Asians than in the European population and higher at the high-BMI range in the European population than among Asians). Over the past 10 years, several large cohort studies have also evaluated the association between BMI and the risk of death, again mostly in populations of European origin.[6-10] Although the BMI groupings that were used varied among the studies, these studies, in general, have shown that the lowest risk of death is associated with a BMI in

Table 3. Association between Body-Mass Index and Risk of Death from Any Cause in Subgroup Analyses Designed to Address Reverse Causation.*

Subgroup Analysis	All Subjects				Lifetime Nonsmokers			
	Low BMI		High BMI		Low BMI		High BMI	
	no. of deaths	*hazard ratio (95% CI)*	*no. of deaths*	*hazard ratio (95% CI)*	*no. of deaths*	*hazard ratio (95% CI)*	*no. of deaths*	*hazard ratio (95% CI)*
East Asians								
All subjects	74,226	1.18 (1.14–1.22)	47,512	1.06 (1.04–1.08)	31,543	1.13 (1.09–1.18)	24,010	1.08 (1.05–1.10)
Excluding first 3 yr of follow-up	59,933	1.18 (1.14–1.22)	39,469	1.06 (1.04–1.08)	25,189	1.13 (1.09–1.18)	19,863	1.08 (1.05–1.10)
Including all subjects with baseline data on CHD†	49,807	1.18 (1.14–1.23)	34,666	1.05 (1.03–1.08)	21,895	1.14 (1.09–1.19)	17,999	1.08 (1.05–1.10)
Excluding subjects with CHD at baseline†	46,706	1.18 (1.14–1.23)	31,832	1.06 (1.03–1.08)	20,597	1.14 (1.09–1.19)	16,531	1.08 (1.05–1.11)
Excluding subjects with CHD, cancer, or stroke at baseline‡	44,115	1.18 (1.14–1.23)	29,964	1.06 (1.03–1.08)	19,425	1.13 (1.08–1.19)	15,529	1.08 (1.05–1.11)
Including only subjects with no CHD, cancer, or stroke at baseline§	27,367	1.19 (1.13–1.25)	20,162	1.06 (1.03–1.09)	11,012	1.13 (1.06–1.20)	9,775	1.08 (1.04–1.12)
Excluding first 5 yr of follow-up	48,187	1.16 (1.13–1.20)	32,353	1.06 (1.04–1.08)	20,078	1.12 (1.07–1.17)	16,124	1.08 (1.05–1.11)
Including all subjects with baseline data on CHD†	39,552	1.17 (1.12–1.22)	28,177	1.06 (1.03–1.09)	17,286	1.12 (1.07–1.17)	14,528	1.08 (1.04–1.11)
Excluding subjects with CHD at baseline†	37,137	1.17 (1.13–1.22)	25,916	1.06 (1.03–1.09)	16,280	1.12 (1.07–1.17)	13,362	1.08 (1.05–1.11)
Excluding subjects with CHD, cancer, or stroke at baseline‡	35,173	1.17 (1.13–1.21)	24,511	1.06 (1.03–1.09)	15,380	1.12 (1.06–1.17)	12,616	1.08 (1.05–1.12)
Including only subjects with no CHD, cancer, or stroke at baseline§	23,000	1.17 (1.12–1.23)	17,010	1.06 (1.02–1.10)	9,267	1.11 (1.04–1.18)	8,209	1.08 (1.03–1.13)
Indians and Bangladeshis								
All subjects	18,988	1.16 (1.12–1.21)	7,295	1.00 (0.93–1.06)	12,155	1.15 (1.09–1.21)	5,392	1.00 (0.93–1.07)
Excluding first 3 yr of follow-up	11,297	1.16 (1.12–1.21)	4,509	1.00 (0.93–1.06)	7,219	1.15 (1.09–1.21)	3,342	1.00 (0.93–1.07)
Including all subjects with baseline data on CHD†	5,876	1.17 (0.99–1.38)	1,962	0.99 (0.73–1.33)	3,410	1.17 (0.94–1.46)	1,437	0.99 (0.71–1.39)
Excluding subjects with CHD at baseline†	5,733	1.17 (0.99–1.39)	1,892	0.99 (0.73–1.34)	3,349	1.17 (0.94–1.47)	1,385	0.99 (0.71–1.39)
Excluding subjects with CHD, cancer, or stroke at baseline‡	5,694	1.17 (0.99–1.39)	1,871	0.99 (0.72–1.34)	3,322	1.17 (0.94–1.47)	1,369	0.99 (0.70–1.40)
Excluding first 5 yr of follow-up	5,459	1.14 (1.08–1.21)	2,154	0.98 (0.90–1.08)	3,398	1.12 (1.04–1.21)	1,599	1.00 (0.90–1.11)
Including all subjects with baseline data on CHD†	3,611	1.15 (0.93–1.43)	1,253	1.01 (0.70–1.47)	2,082	1.16 (0.87–1.54)	904	1.03 (0.68–1.55)
Excluding subjects with CHD at baseline†	3,529	1.15 (0.93–1.43)	1,216	1.01 (0.69–1.47)	2,045	1.16 (0.87–1.55)	875	1.02 (0.67–1.55)
Excluding subjects with CHD, cancer, or stroke at baseline‡	3,512	1.15 (0.93–1.43)	1,206	1.00 (0.68–1.47)	2,033	1.16 (0.87–1.55)	868	1.02 (0.67–1.55)

* The hazard ratios represent the incremental effect per category of BMI relative to the reference category (22.6 to 25.0). Low BMI refers to BMI levels below the reference level (i.e., 20.1 to 22.5, 17.6 to 20.0, and 15.1 to 17.5), and high BMI refers to BMI levels above the reference level (i.e., 25.1 to 27.5, 27.6 to 30.0, 30.1 to 32.5, 32.6 to 35.0, and 35.1 to 50.0). All the models were adjusted for age, sex, educational level, urban or rural residence, marital status, and status with respect to baseline coexisting conditions. Deaths among persons whose BMI was in the reference range were included in the proportional-hazards model for both low-BMI and high-BMI group analyses. CHD denotes coronary heart disease.

† The analysis was restricted to cohorts for which baseline data on prior diagnosis of CHD were collected.

‡ Baseline data on prior diagnosis of CHD were collected in all cohorts included in this analysis. Baseline data on cancer or stroke were not collected in some cohorts; subjects with missing data on prior diagnosis of cancer or stroke were included in the analysis.

§ The analysis was restricted to cohorts for which complete baseline data on prior diagnoses of CHD, cancer, and stroke were collected. This analysis was not performed in the case of the Indian and Bangladeshi subjects, since complete data on these diagnoses at baseline were not collected for any of the cohorts in this population.

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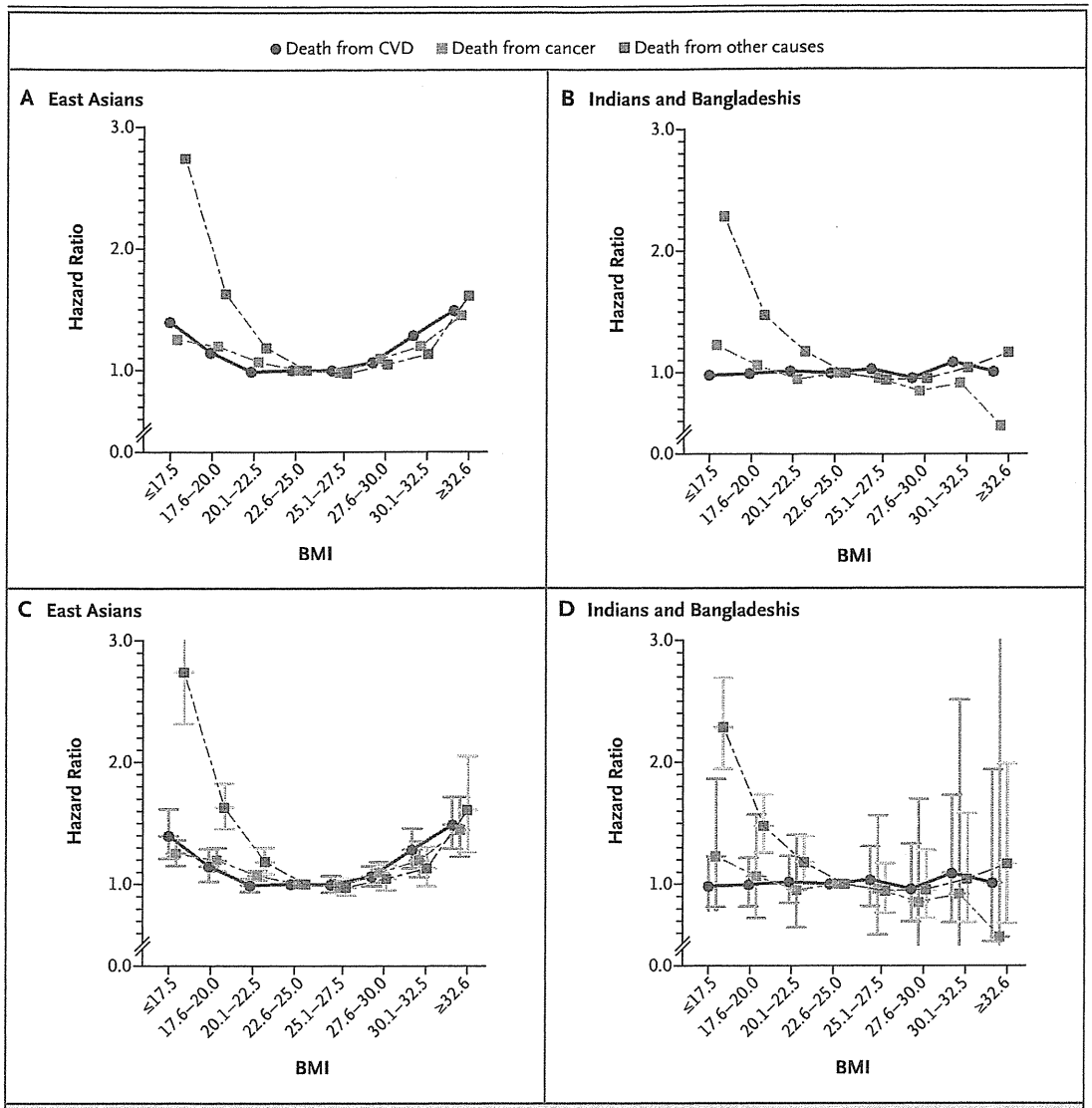

Figure 1. Association between Body-Mass Index and Risk of Cause-Specific Death in Two Asian Populations.

Hazard ratios are shown for the association between body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) and risk of death from cardiovascular disease (CVD), from cancer, and from other causes among East Asians (Chinese, Japanese, and Koreans) and Indians and Bangladeshis. Panels A and B show the hazard ratios without confidence intervals, and Panels C and D show the same data with 95% confidence intervals (I bars). The analyses were adjusted for age, sex, educational level, urban or rural residence, marital status, and status with respect to baseline illnesses; data from subjects with less than 3 years of follow-up were excluded.

the range of 23 to 27, regardless of the study population. The finding that the same optimal weight range is associated with the lowest risk of death both in the current study of East Asians and in previous studies involving populations of European origin argues strongly against the use of race- or ethnicity-specific BMI cutoff points to define overweight and obesity.

In a longitudinal analysis of approximately 1.2 million Koreans in the Korean Cancer Prevention Study (KCPS), Jee et al. reported a J-shaped association between BMI and the risk of death from any cause.[9] The BMI category associated with the lowest overall risk of death was 21.5 to 27.9 in the KCPS, which is similar to the findings among East Asians in our study (Tables 5, 6, and 7 in the Supplementary Appendix). However, for some of the analyses, the magnitude of

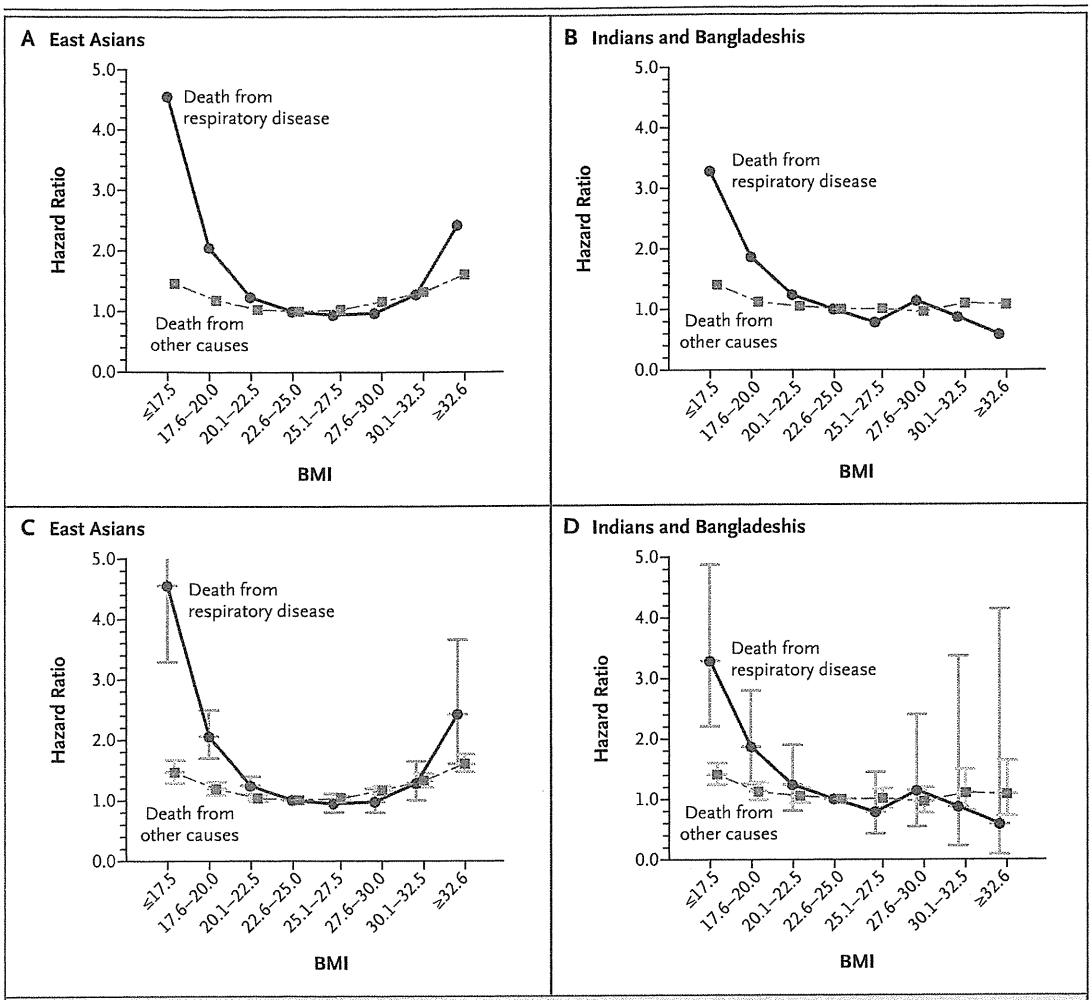

Figure 2. Association between the Body-Mass Index and the Risk of Death from Respiratory Diseases or Other Causes.

Hazard ratios are shown for the association between BMI and risk of death from respiratory diseases and from causes other than respiratory diseases, cardiovascular causes, or cancer (other) among East Asians (Chinese, Japanese, and Koreans) and Indians and Bangladeshis. Panels A and B show the hazard ratios without confidence intervals, and Panels C and D show the same data with 95% confidence intervals (I bars). The analyses were adjusted for age, sex, educational level, urban or rural residence, marital status, and status with respect to baseline illnesses; data from subjects with less than 3 years of follow-up were excluded.

the associations differs between the KCPS and our study. Extensive exclusions were made in the KCPS; subjects with a baseline diagnosis of coronary heart disease, cancer, liver disease, diabetes, stroke, or respiratory disease were not included in that study. Most other cohort studies have not made such extensive exclusions from their analyses, nor did we in our study. Because only about 16,000 Koreans were included in our analysis, the East Asian group in our study consisted primarily of Chinese and Japanese subjects. Therefore, differences in characteristics across these populations could also contribute to inconsistencies between the findings of our study and those of the KCPS.

Although the risk of death is the most critical measure of the health consequences of excess adiposity, epidemiologic studies examining the relationship between body weight and the risk of death are fraught with methodologic challenges.[11,12] The most important of these is the problem of reverse causation, in which weight loss resulting from illness can distort the relationship between leanness and health. An additional

concern is confounding, mainly by smoking status, since smokers often have a lower body mass than do nonsmokers. To address these problems, investigators in multiple studies have performed analyses using data from nonsmokers only and from people who reported no serious underlying illness at the time of enrollment or have excluded from the analyses the early years of follow-up.[13-16] However, in our study, the PSC project, and the KCPS, as well as in some other large cohort studies,[6-10] a J-shaped or U-shaped relation between BMI and the risk of death persisted after major methodologic issues were addressed.

There is substantial evidence supporting the biologic plausibility of a positive association between excess adiposity and the risk of death. Obesity is a well-established risk factor for numerous chronic diseases.[2] Adipose tissue has been increasingly recognized as an active endocrine organ, capable of releasing a large number of cytokines and bioactive mediators that play important roles in the pathogenesis of many obesity-related diseases.[17] In contrast, the increased risk of death associated with a low BMI, observed in our study and in other studies, remains to be fully explained. Inadequate or incomplete control for confounding or reverse-causation bias could in part explain the increased risk.[18] A residual influence of reverse causation may remain in our study, particularly since we did not have information on the presence of infections and on diagnoses of chronic lung disease at baseline; therefore, data from subjects with those conditions could not be excluded from our analysis. A low BMI can be an indicator of certain other chronic medical conditions that were not adequately controlled in the study or an indicator of poor health or a low standard of living, which may contribute to such conditions as undernutrition and may increase the risk of premature death.[19] Several cohort studies have shown that, even among persons with a low BMI, an elevated waist-to-hip ratio or waist circumference (each of which is a measure of abdominal adiposity) was associated with a significantly increased risk of death[10,20]; this suggests that the observed excess risk of death among subjects with a low BMI may be due, in part, to abdominal adiposity, which cannot be assessed adequately on the basis of the BMI.[21]

We did not assess the risk of death in relation to abdominal obesity, which may be a particularly important factor in Asian populations. In the case of several cohorts participating in this consortium, the interval between the assessment of BMI and the ascertainment of the outcome of death was relatively short, raising concern about the effects of subclinical or undiagnosed chronic diseases on the results. Data from subjects with self-reported height and weight measurements were included in our analysis, although the pattern of association between BMI and death from any cause was similar regardless of the method for assessing height and weight (Table 9 in the Supplementary Appendix). Socioeconomic status could confound the association between BMI and the risk of death, since in less well-developed countries, people with a high BMI are more likely to have a high socioeconomic status (and thus better access to health care) than are those with a lower BMI. Although we adjusted for several indicators of socioeconomic status, such as educational level, which is a major measure of socioeconomic status, it is possible that residual confounding effects of socioeconomic status remain that could attenuate the positive association between high BMI and the risk of death.

In conclusion, this large pooled analysis revealed a U-shaped association between BMI and the risk of death in East Asians, with a pattern broadly similar to that seen in previous studies involving mostly North American and European populations. In Indians and Bangladeshis, however, no elevated risk of either death from any cause or cause-specific death was seen in high-BMI groups. Overall, the risk of death among Asians, as compared with Europeans, seems to be more strongly affected by a low BMI than by a high BMI. Given the limitations of the current study, in which the risk of death was used as the outcome, additional studies are needed to quantify the association between BMI and the incidence of disease, in order to better define BMI criteria for overweight and obesity in Asians.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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Relationship Between Serum Adiponectin Levels and Disability-Free Survival Among Community-Dwelling Elderly Individuals: The Tsurugaya Project

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Background. Mortality risk tends to be higher among elderly individuals with higher serum adiponectin levels. The objective of this study was to clarify whether the relationship between adiponectin and a higher risk of disability or death can be explained by physical function, bone mineral density, depression, and malnutrition.

Methods. We analyzed 505 individuals who underwent comprehensive geriatric assessment and who agreed to provide information on long-term care insurance. The endpoint was the composite outcome of death and incident disability defined as a first certification for any level of care need. Relationships between adiponectin and incident disability or death were estimated using the Cox proportional hazards model.

Results. During 6 years of follow-up, 179 incident disabilities or deaths occurred. Among them, 20 and 23 died with and without disability, respectively. The risk of incident disability or death was significantly higher among participants with adiponectin greater than or equal to 22.4 (90%) than 8.0 or less (25%) mg/L (Hazard ratio: 95% confidence interval, 1.92: 1.01–3.64) in the model adjusted for age, sex, and metabolic risk factors. Adjustment for N-terminal pro-B–type natriuretic peptide and nutritional status did not substantially alter this risk estimate, although the association ceased to be statistically significant. Adjustment for physical function did attenuate the relationship, however, which ceased to be apparent upon exclusion of disability or death occurring within 3 years of follow-up.

Conclusion. The relationship between adiponectin and the composite outcome of incident disability and death was at least partly explained by reduced physical function and wasting in participants with higher adiponectin levels.

Key Words: Adiponectin—Disability—Mortality—Physical function—Prospective studies.

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ALTHOUGH adiponectin is a protein that is derived predominantly from adipose tissue (1,2), levels are paradoxically inversely associated with obesity. Laboratory studies have shown that adiponectin is antiatherogenic (3). Whereas the findings of several studies have associated higher adiponectin levels with a lower risk of cardiovascular disease (CVD) and mortality (4,5,6), the results of a meta-analysis suggest that the relationship between adiponectin and CVD is not as close as was previously thought (7). Furthermore, studies that have focused on elderly individuals have also generated contradictory findings (8,9,10), having consistently demonstrated a positive association between adiponectin and CVD or all-cause mortality.

Physical function (11), bone mineral density (12), depression (13), and malnutrition (14) are associated with premature death or disability among elderly individuals. Adiponectin levels that are inversely associated with obesity might be associated with these risk factors. In addition, an experimental study of transgenic mice suggested that circulating adiponectin plays a negative role in the acquisition of bone during growth (15). Therefore, these factors must be taken into consideration when investigating relationships between adiponectin and health outcomes among elderly individuals. Recent studies also suggest that higher mortality rates in individuals with higher adiponectin levels can be explained by the contribution of N-terminal pro-B–type natriuretic peptide (NT-pro-BNP; 2,16). Natriuretic peptide is a marker of cardiac dysfunction that enhances adiponectin production by human adipocytes in vitro, and adiponectin levels are in fact increased in patients with chronic heart

failure and cardiac dysfunction (17). This also suggests that NT-pro-BNP plays an important role in the relationship between adiponectin and mortality or death.

The Tsurugaya Project estimated not only the CVD risk profile but also the physical function, depressive symptoms, nutritional status, and NT-pro-BNP levels. This study aimed to determine whether physical function, bone mineral density, depression, malnutrition, and a higher NT-pro-BNP level can explain the relationship between adiponectin and increased risk of disability or death.

Methods

Study Participants

The Tsurugaya Project was a comprehensive geriatric assessment (CGA) implemented in 2002 and 2003 that included medical status as well as physical and cognitive functions (18,19,20,21). The present study is based on the data from 2002 because stored blood samples from that time period were available (21).

Among 2,730 inhabitants aged 70 years or more living in the Tsurugaya area of Sendai, Japan, 1,177 provided written informed consent to participate in the study. Because we did not obtain agreement to review information regarding long-term care insurance (LTCI) in 2002, we requested agreement to do so from participants who underwent CGA in 2003. Of the 1,177 participants who underwent CGA in 2002, 671 underwent another CGA in 2003 and 657 agreed to a review of their LTCI information. Among these 657 participants, we excluded those who had already been certified as having a disability determined by LTCI certification by 2003 ($n = 55$), did not agree to their blood samples being analyzed or stored ($n = 6$), or whose serum samples were of insufficient volume to measure adiponectin ($n = 91$). Thus, the present study analyzed data from 505 participants.

A comparison of the 657 individuals who agreed to a review of their LTCI information and 520 who did not participate in the 2003 survey or who did not agree to a review of their LTCI information showed that the mean age of the former group was lower (75.6 vs 76.8 years; $p < .01$) and the proportion of women was lower (54.9% vs 63.1%; $p < .01$).

The Ethics Committee of Tohoku University Graduate School of Medicine approved the study protocol.

Serum Adiponectin and NT-pro-BNP

Blood samples collected under nonfasting conditions were immediately cooled at 4°C, centrifuged within 4 hours at 3,000*g* at 4°C for 10 minutes, and stored at −80°C. Levels of adiponectin were measured using an enzyme-linked immunosorbent assay or a latex particle-enhanced turbidimetric immunoassay. The values of adiponectin determined by enzyme-linked immunosorbent assay and by latex particle-enhanced turbidimetric immunoassay are closely correlated ($r = .98$). Others have reported a similarly close correlation (22). Levels of NT-pro-BNP were measured using an electrochemiluminescence immunoassay kit (MODULAR ANALYTICS E10; Roche Diagnostics, Penzberg, Germany; 21). All the above assays proceeded at a clinical testing laboratory (SRL, Tokyo, Japan).

Other Measurements

Information about smoking status, alcohol consumption, history of disease, and physical activity was surveyed using a questionnaire, and drug information was confirmed by an experienced pharmacist. Symptoms of depression were assessed based on the Japanese version of the 30-item geriatric depression scale (19). Functional reach, which measures how far an individual can reach forward beyond arm's length while standing without losing balance, was measured as a parameter of physical function (20). We measured quantitative ultrasound parameters, such as the speed of sound (meters/second), broadband ultrasound attenuation (decibels/megahertz), and the stiffness index (Stiffness), which was derived from the speed of sound and broadband ultrasound attenuation. These parameters were measured in the right calcaneus using an Achilles Ultrasound Bone Densitometer (A-1000; GE-Lunar Corporation, Madison, WI; 23). Self-measured blood pressure at home was measured using an automated device (HEM747IC; Omron Life Science Co. Ltd, Tokyo, Japan; 18). The participants were classified into groups based on those with home hypertension, home borderline hypertension, and home normotension according to the guidelines for home blood pressure (24). Participants prescribed with antihypertensive medication were classified into the home hypertension group. Serum albumin, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and glucose levels were also measured. Glomerular filtration ratios were estimated using a modified equation for Japanese individuals based on the abbreviated Modification of Diet in Renal Disease study (25).

LTCI Certification

We defined incident disability as assessed by the LTCI certification system that was launched as the national insurance scheme during April 2000 (26,27,28) and followed up those with certified incident disability for 6 years.

Individuals living in Japan aged 40–64 years who are diagnosed with aging-related diseases (eg, Alzheimer's disease and stroke) and those aged 65 years or more who are certified as requiring care are eligible for benefits based on the level of care under the LTCI certification (29). To receive LTCI services, elderly individuals or their caregivers (family or professional) must contact the municipal government to have their care needs officially certified (27). A trained local government official visits their homes to evaluate nursing care needs using a questionnaire that assesses their current physical and mental status and use of medical procedures (26). Standardized scores for physical

and mental functions and the estimated amount of time required for care for nine categories (grooming/bathing, eating, using the toilet, transferring, eating, assistance with instrumental activities of daily living, behavioral problems, rehabilitation, and medical services) are then calculated using software. Based on national values, a decision is reached as to whether applicants should be certified to receive LTCI services, and the system assigns a care needs level determined by a certification board comprising physician nurses and other experts in health and social services appointed by the local mayor.

Care needs are assessed in seven levels that closely correlate with the Barthel Index (Spearman's coefficient: −.86) and the Mini-Mental State Examination (Spearman's coefficient: −.42; 29,30). The definition can be considered as a comprehensive measure of disability among elderly individuals (30).

Sendai City Municipal Authority provided annual information about LTCI certification including care level, date of certification, moving, and death for the 6 years between June 30, 2003, and June 30, 2009. We defined incident disability as certification at any level of care need and the first date of certification as the date of incident disability occurrence. Only six individuals were lost due to moving during follow-up. We used a composite outcome of disability and death, which can be considered as an indicator of disability-free survival.

Statistical Analysis

We classified the study participants into five groups based on an adiponectin distribution of 8, 11, 16, and 22.4 mg/L using 25%, 50%, 75%, and 90%, respectively, as cutoff points. To distinguish the characteristics of a group with higher adiponectin levels, we added a 90% cutoff in addition to the traditional quartiles because serum adiponectin levels were skewed. This approach has been applied in several epidemiological studies in which values were skewed (31).

Baseline characteristics were compared using the χ^2 test and analysis of variance as appropriate. We assessed the proportionality assumption by examining changes in risk factor effects with time and by examining the possibility that risk factor effects could be different risk factor strata. The results of these analyses indicated that the proportionality assumption was appropriate. The Hazard ratio and 95% confidence interval for the relationship between adiponectin and the composite outcome of incident disability or mortality were calculated using the following Cox proportional hazards models. Model 1 was adjusted for age, sex, smoking, alcohol consumption (<23, 23–45.9, and ≥46 g of ethanol/day), and factors related to metabolic syndrome, namely, blood pressure category (home hypertension, home borderline hypertension, and home normotension), blood glucose category (diabetes: nonfasting blood glucose ≥200 mg/dL [11.1 mmol/L] or taking antidiabetic drugs; impaired blood glucose as nonfasting blood glucose 140–199 mg/dL [7.7–11.0 mmol/L]), triglycerides, high-density lipoprotein cholesterol, quintiles of body mass index, and a history of CVD. Model 2 was adjusted for Model 1 plus NT-pro-BNP using 49, 81, 137, and 250 pg/mL as cutoffs (25th, 50th, 75th, and 90th percentiles). Participants without NT-pro-BNP data were categorized into a "missing data" category ($N = 44$). Model 3 was adjusted for Model 1 plus malnutrition as albumin less than or equal to 3.8 g/dL and total cholesterol (continuous) and depression. Model 4 was adjusted for Model 1 plus estimated glomerular filtration ratios. Model 5 was adjusted for Model 1 plus physical function (sex-specific quartile of functional reach) and bone mineral density (sex-specific quartile of stiffness assessed by quantitative ultrasound). Model 6 excluded participants who died or who were certified as having a disability within 3 years of follow-up. Model 7 was fully adjusted and included participants who died or who were certified as having a disability within 3 years of follow-up. Model 8 was fully adjusted and excluded participants who died or who were certified as having a disability within 3 years of follow-up. The median adiponectin value in each adiponectin category served as the representative value in the category to calculate p values for linear trends.

We also analyzed the relationship between serum adiponectin and the composite outcome of incident disability or mortality excluding participants with a history of CVD using Model 1.

The level of statistical significance was set at $p < .05$. All data were statistically analyzed using SAS software, version 9.1 (SAS Institute, Cary, NC).

Results

Table 1 shows the baseline characteristics according to adiponectin categories. Mean age was higher in the categories with higher adiponectin values. Higher adiponectin values were associated with larger proportions of women and those who had never smoked, were underweight, and had a lower functional reach, depressive symptoms, less stiffness, and higher NT-pro-BNP values. Conversely, lower values for factors related to metabolic syndrome (hypertension, diabetes, triglycerides, high-density lipoprotein cholesterol, and obesity) and fewer participants with a history of CVD were associated with higher adiponectin values.

Of 179 individuals who developed incident disability or died during the 6 years of follow-up, 20 and 23 died with and without LTCI certification, respectively, and 136 (76%) were certificated as LTCI only. The rate of incident disability or deaths was lower and higher in the categories with decreased and elevated adiponectin values, respectively (<25th and ≥90th percentiles: 45.4/1,000 and 138.0/1,000 person-years, respectively; Table 2). This relationship was also evident in the model adjusted for age, sex, smoking, and factors related to metabolic syndrome (Model 1). This positive relationship persisted when participants with a history of CVD were excluded (data not shown). The Hazard ratio for the comparison of the highest and lowest

Table 1. Baseline Characteristics of the Participants According to the Serum Adiponectin Level, the Tsurugaya Project, 2002

Risk Factors	<25 Percentile (*N* = 116)	25–49 Percentile (*N* = 126)	50–74 Percentile (*N* = 134)	75–89 Percentile (*N* = 78)	≥90 Percentile (*N* = 51)
Adiponectin, mg/L, range	2.0–7.9	8.0–10.9	11.0–15.9	16.0–22.3	22.4-
Age at baseline, year, mean ± *SD*	74.4 ± 3.5	74.8 ± 4.3	75.2 ± 4.4	77.2 ± 4.3	77.4 ± 4.8
Sex					
Women, %	33	47	57	67	82
Smoking					
Current, %	13	17	10	9	4
Past, %	47	34	27	21	20
Never, %	38	48	62	65	75
Alcohol drinking					
Nondrinker, %	51	69	67	78	82
<23 g of ethanol/day, %	26	19	21	8	18
23–46 g of ethanol/day, %	11	5	4	9	0
≥46 g of ethanol/day, %	12	7	8	5	0
BP category					
Home HT, %	71	71	66	63	53
Home BHT, %	14	10	13	10	12
Home NT, %	14	16	20	18	18
Did not measure home BP, %	2	3	1	9	18
Glucose category					
Diabetes, %	13	9	7	4	0
Impaired blood glucose, %	10	8	7	5	10
Triglyceride, mg/dL, median, interquartile range	166.5 (140.0–217.5)	152.0 (115.0–197.0)	143.0 (88.0–184.0)	98.5 (74.0–149.0)	91.0 (69.0–121.0)
High-density lipoprotein cholesterol, mg/dL, mean ± *SD*	48.8 ± 12.7	52.8 ± 12.0	57.2 ± 14.8	60.2 ± 12.3	68.0 ± 15.0
Functional reach					
Could not measure, %	1	2	1	0	0
Men 0–30.4 cm, women 0–26.3 cm, %	21	19	27	36	43
Men 30.5–33.3 cm, women 26.4–29.9 cm, %	23	24	25	29	25
Men 33.4–36.4 cm, women 30–33.4 cm, %	27	21	22	21	24
Men 36.5 cm-, women 33.5 cm-, %	28	35	25	14	8
Depression, %	20	29	23	32	33
Overweight/obesity, %	45	44	35	23	14
Underweight, %	1	1	4	8	20
Albumin, g/dL, mean ± *SD*	4.4 ± 0.2	4.4 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3
Total cholesterol, mg/dL, mean ± *SD*	203.3 ± 32.8	201.7 ± 32.0	203.7 ± 34.3	203.0 ± 30.7	211.4 ± 32.2
Stiffness					
Men 0%–59.9%, women 0%–49.9%	14	20	25	35	41
Men 60%–73.4%, women 50%–58.4%	16	28	21	35	37
Men 73.5%–81.4%, women 58.5%–65.9%	33	29	19	22	14
Men 81.5%-, women 66.0%-	37	24	34	9	8
Chronic kidney disease, %	20	31	31	31	29
History of CVD, %	19	14	11	14	8
N-terminal pro-B–type natriuretic peptide, pg/mL, median, interquartile range	56.0 (32.0–113.0)	70.0 (45.0–123.0)	90.0 (48.0–135.0)	96.5 (65.0–137.0)	148.0 (80.0–234.0)

Notes: Cutoff of adiponectin value was defined as 25%, 50%, 75%, and 90%; home HT = home systolic BP ≥135 mm Hg and/or home diastolic BP ≥85 mm Hg and/or user of antihypertensive medication; home BHT = not satisfied with home HT criteria and home systolic BP ≥125 mm Hg and/or home diastolic BP ≥80 mm Hg; home NT = home systolic BP <125 mm Hg and home diastolic BP <80 mm Hg without antihypertensive medication; diabetes= user of antidiabetic drug or nonfasting blood glucose ≥200 mg/dL (11.1 mmol/L); impaired blood glucose = nonfasting blood glucose 140–199 mg/dL (7.7–11.0 mmol/L); overweight/obesity = body mass index ≥25 kg/m^2; underweight = body mass index <18.5 kg/m^2; low albumin = albumin ≤3.8 g/dL; depression = user of antidepressant or geriatric depression scale ≥11 points; chronic kidney disease= glomerular filtration ratio ≤ 60 mL/min/1.73 m^2; BHT = borderline hypertensive; BP = blood pressure; CVD = cardiovascular diseases; HT = hypertensive; NT = normotensive.

adiponectin categories did not materially change after adjustment for NT-pro-BNP, malnutrition and depressive symptoms, or estimated glomerular filtration rate (Models 2–4). In contrast, adjustment for physical function and bone mineral density attenuated the positive relationship between adiponectin and the composite outcome of disability. In turn, the positive relationship disappeared when participants who moved (N = 4), died, or were certified as having incident disability (N = 88) within 3 years of follow-up were excluded. Model 6 comprised 413 participants and 91 died or were certified as having a disability by the end of follow-up. The fully adjusted model that included participants who moved, died, or were certified as having a disability within 3 years of follow-up (Model 7) revealed the same modest association as Model 5. In the fully adjusted model that excluded participants who died or were certified as having a disability within 3 years of follow-up (Model 8), the positive relationship between serum adiponectin and the composite outcome of disability and death disappeared altogether.

Table 2. The Relationship Between Baseline Adiponectin Level and Incident Disability or Death, the Tsurugaya Project 2003–2009

Adiponectin Value (mg/L)	Person-Years	Disability or Death	Rate/1,000 Person-Years	HR (95% CI)							
				Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
2.0–7.9	617	28	45.4	1	1	1		1	1	1	1
8.0–10.9	624	42	67.4	1.42 (0.86–2.35)	1.42 (0.85–2.35)	1.36 (0.82–2.25)	1.41 (0.85–2.34)	1.41 (0.84–2.37)	0.95 (0.48–1.86)	1.33 (0.78–2.25)	0.86 (0.42–1.76)
11.0–15.9	663	44	66.3	1.40 (0.84–2.32)	1.37 (0.82–2.28)	1.25 (0.75–2.08)	1.38 (0.83–2.30)	1.24 (0.74–2.07)	0.87 (0.43–1.75)	1.09 (0.64–1.87)	0.79 (0.37–1.66)
16.0–22.3	387	36	93.1	1.40 (0.79–2.50)	1.37 (0.76–2.47)	1.36 (0.76–2.44)	1.39 (0.77–2.48)	1.20 (0.67–2.17)	1.43 (0.68–3.04)	1.14 (0.61–2.11)	1.44 (0.64–3.23)
22.4–	210	29	138.0	1.92 (1.01–3.64)	1.80 (0.93–3.49)	1.86 (0.98–3.53)	1.89 (0.99–3.61)	1.49 (0.76–2.93)	0.95 (0.37–2.44)	1.41 (0.69–2.86)	0.86 (0.30–2.45)
p For trend				.11	.17	.11	.12	.51	.67	.63	.71

Notes: Model 1 = adjusted for age, sex, smoking, alcohol drinking, history of cardiovascular diseases, and metabolic syndrome–related factors, quintiles of body mass index, hypertension, diabetes, triglyceride, and high-density lipoprotein cholesterol; Model 2 = Model 1 + N-terminal pro-B–type natriuretic peptide (missing, <48, 49–80, 81–137, 137–249, ≥250 pg/mL); Model 3 = Model 1 + factors related to malnutrition (low albumin and total cholesterol) and depression; Model 4 = Model 1 + estimated glomerular filtration rate; Model 5 = Model 1 + factors related to physical function (functional reach test) and bone mineral density; Model 6 = Model 1 + excluding 92 participants who were censored due to moving, death, and certificated as disability within 3 years of follow-up; Model 7 = Model 1 + all aforementioned factors used in Model 2–Model 5; Model 8 = Model 7 + excluding 92 participants who were censored due to moving, death, and certificated as disability within 3 years of follow-up; CI = confidence interval; HR = Hazard ratio.

Discussion

The present study clarified that the positive relationship between adiponectin and the composite outcome of disability and death was attenuated by adjusting for physical function or excluding early events. Therefore, assessing physical function and subclinical wasting might be required to assess participants with higher adiponectin levels.

The advantages of the present study are as follows. We assessed comprehensive geriatric parameters including physical function and depressive symptoms. Furthermore, whether the contribution of high BNP could help to explain the relationship between serum adiponectin and disability-free survival in this population was determined based on NT-pro-BNP values. The LTCI certification is based upon strictly established, uniform rules throughout Japan (26,27), and the included information enabled a very high follow-up rate in the present study (98.8%). Nevertheless, this system is not perfect because elderly individuals or caregivers must initiate contact with the municipal government to receive LTCI services, and thus, some elderly individuals with a disability might not be certified. Another issue is the date of incident disability. Although we used the date for LTCI certification as date of incident disability, the actual date would normally be earlier than that date certified as LTCI. Other methodological limitations are also associated with the study. Because we did not obtain the agreement of participants to review their LTCI information in 2002, we analyzed 60% of those who had a CGA at 2002. Participants who agreed to such review were younger than those who did not participate in the 2003 survey or who refused to permit disclosure of their LTCI information. We also excluded those who already had a disability according to LTCI certification at 2003. Therefore, the prevalence of a higher serum adiponectin value in this study might not accurately represent the prevalence in this area. Nevertheless, we considered that the relationship between adiponectin and incident disability and mortality was clarified. Another limitation was that the lack of information about the causes of disability, which obstructed clarification as to whether the frequency of incident disability due to stroke, mobility restriction, or other reasons was higher in the group with higher serum adiponectin values. Finally, we did not obtain fasting blood samples, and thus, the accuracy of diabetes-related assessments or of total cholesterol might be limited in this study.

Several mechanisms could explain the positive relationship between adiponectin and disability or death. The present study showed that adjustment for physical function and bone mineral density largely attenuated the relationship. A recent study found an inverse association between adiponectin and muscular fitness (32), and our cross-sectional findings revealed an inverse association between physical function and adiponectin. Furthermore, the Cardiovascular Health Study All Stars Study showed that adiponectin was associated with a greater physical decline (33). Thus, older participants with higher adiponectin