Body-Mass Index and Mortality among Adults with Incident Type 2 Diabetes

ORIGINAL ARTICLE

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ABSTRACT

BACKGROUND

The relation between body weight and mortality among persons with type 2 diabetes remains unresolved, with some studies suggesting decreased mortality among overweight or obese persons as compared with normal-weight persons (an "obesity paradox").

METHODS

We studied participants with incident diabetes from the Nurses' Health Study (8970 participants) and Health Professionals Follow-up Study (2457 participants) who were free of cardiovascular disease and cancer at the time of a diagnosis of diabetes. Body weight shortly before diagnosis and height were used to calculate the body-mass index (BMI, the weight in kilograms divided by the square of the height in meters). Multivariable Cox models were used to estimate the hazard ratios and 95% confidence intervals for mortality across BMI categories.

RESULTS

There were 3083 deaths during a mean period of 15.8 years of follow-up. A J-shaped association was observed across BMI categories (18.5 to 22.4, 22.5 to 24.9 [reference], 25.0 to 27.4, 27.5 to 29.9, 30.0 to 34.9, and ≥35.0) for all-cause mortality (hazard ratio, 1.29 [95% confidence interval {CI}, 1.05 to 1.59]; 1.00; 1.12 [95% CI, 0.98 to 1.29]; 1.09 [95% CI, 0.94 to 1.26]; 1.24 [95% CI, 1.08 to 1.42]; and 1.33 [95% CI, 1.14 to 1.55], respectively). This relationship was linear among participants who had never smoked (hazard ratios across BMI categories: 1.12, 1.00, 1.16, 1.21, 1.36, and 1.56, respectively) but was nonlinear among participants who had ever smoked (hazard ratios across BMI categories: 1.32, 1.00, 1.09, 1.04, 1.14, and 1.21) ($P=0.04$ for interaction). A direct linear trend was observed among participants younger than 65 years of age at the time of a diabetes diagnosis but not among those 65 years of age or older at the time of diagnosis ($P<0.001$ for interaction).

CONCLUSIONS

We observed a J-shaped association between BMI and mortality among all participants and among those who had ever smoked and a direct linear relationship among those who had never smoked. We found no evidence of lower mortality among patients with diabetes who were overweight or obese at diagnosis, as compared with their normal-weight counterparts, or of an obesity paradox. (Funded by the National Institutes of Health and the American Diabetes Association.)

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Excess adiposity is a well-established risk factor for premature death in the general population, including death due to cardiovascular disease or cancer.[1-4] However, a so-called obesity paradox (i.e., an association between obesity, as compared with normal weight, and reduced mortality) has been reported among patients with heart failure, end-stage renal disease, or hypertension, and, recently, among those with type 2 diabetes.[5-12] Most of these studies, however, have been limited by small samples and suboptimal control for smoking status and preexisting chronic conditions.

Smoking is a concern in analyses of body weight and mortality because it is associated with decreased body weight but an increased risk of death.[13] Statistical adjustment for smoking status (e.g., ever smoked vs. never smoked) is often insufficient to control for varying degrees of smoking duration and intensity. Thus, stratification according to smoking status can be an important way to examine the association between body weight and the risk of death; in addition, the subgroup analysis among persons who have never smoked can reduce residual bias related to smoking.[3,4,13-15] An additional concern is reverse causation, whereby underlying chronic disease or frailty both causes weight loss and elevates the risk of death. Exclusion of persons with known illnesses at baseline and censoring of data for patients who died early in the follow-up period are routinely performed to reduce this bias.[16]

To address the limitations of previous analyses, we conducted a detailed analysis of the association between body-mass index (BMI) and the risk of death among participants with incident diabetes from two large prospective cohort studies, the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).

Methods

Study Population

The NHS was initiated in 1976 with the enrollment of 121,700 female nurses 30 to 55 years of age. The HPFS began in 1986, enrolling 51,529 male health professionals between 40 and 75 years of age. Questionnaires are administered biennially to update medical, lifestyle, and other health-related information.[17,18] Cumulative follow-up exceeds 90% of potential person-time for both cohorts.

Our analyses included women and men reporting incident diabetes between baseline (1976 for the NHS and 1986 for the HPFS) and January 1, 2010 (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We excluded participants reporting a history of diabetes at baseline or reporting cardiovascular disease (stroke, coronary heart disease, or coronary-artery bypass graft surgery) or cancer before a diabetes diagnosis. Participants were excluded if they were underweight (BMI [the weight in kilograms divided by the square of height in meters] <18.5, because of limited statistical power for this group), had received a diagnosis of diabetes before 35 years of age (probably type 1 diabetes), or did not report body weight on the relevant questionnaire. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard School of Public Health, with participants' consent implied by the return of the questionnaires. The first, second, and last authors take complete responsibility for the integrity of the data and the accuracy of the data analysis.

Assessment of Type 2 Diabetes

Participants reporting a physician's diagnosis of diabetes on the biennial questionnaire were mailed a supplemental questionnaire. Confirmed cases were defined according to the National Diabetes Data Group classification,[19] updated in June 1998 to adopt a new threshold for a fasting plasma glucose level of at least 126 mg per deciliter (7.0 mmol per liter).[20] Validation studies with the use of medical records for 62 NHS participants[21] and 59 HPFS participants[22] showed very high accuracy of our classification (98% and 97%, respectively).

Assessment of Body-Mass Index

Body weight was updated every 2 years by questionnaire. Weight at diagnosis was estimated from the most recent questionnaire before the diagnosis (mean time from questionnaire to diagnosis, 11 months). Self-reported weight was previously validated in a subgroup of 140 NHS participants and 123 HPFS participants (<1% of all participants) living in the Boston area, on the basis of the correlation between technician-measured and self-reported weight (Spearman correlation coefficient, 0.97 for both NHS and HPFS participants; mean difference [self-reported weight minus measured weight], –1.50 kg for NHS participants and –1.06 kg for HPFS participants).[23] A sensitivity

analysis assessed the potential effect of error in self-reported weight and height with the use of the sex-specific calibration equations proposed by Berrington de Gonzalez et al.[3] from the U.S. National Health and Nutrition Evaluation Survey sample ($BMI_{measured} = 0.63 + [1.01 \times BMI_{self\text{-}reported}] + [0.0006 \times \text{age in years}]$ for women and $0.29 + [0.98 \times BMI_{self\text{-}reported}] + [0.012 \times \text{age in years}]$ for men).

ASCERTAINMENT OF DEATHS

The primary outcome was death from any cause through January 1, 2012. Most deaths (>98%) were identified from reports by the next of kin or postal authorities or from searches of the National Death Index.[24,25] The cause of death was determined by physician review of medical records and death certificates. The diagnostic codes of the *International Classification of Diseases, 8th Revision* (ICD-8), were used to classify deaths as due to cardiovascular disease (ICD-8 codes 390 through 459 and 795), cancer (ICD-8 codes 140 through 207), or other causes.

ASSESSMENT OF COVARIABLES

Detailed information on cigarette smoking, physical activity, menopausal status (for NHS participants only), and several lifestyle factors and health outcomes were updated every 2 years. Marital status and status with respect to a family history of diabetes were assessed periodically. Dietary information was collected from validated food-frequency questionnaires approximately every 4 years. Diet quality was assessed with the use of the 2010 Alternate Healthy Eating Index (with scores ranging from 2.5 to 87.5 and higher scores indicating a healthier diet).[26] The covariables were derived from the most recent questionnaire before a diabetes diagnosis.

STATISTICAL ANALYSIS

Hazard ratios and 95% confidence intervals were estimated from Cox proportional-hazards models, with number of months since a diabetes diagnosis as the time scale. Person-time was calculated from the date of a diabetes diagnosis until death or the end of follow-up (January 1, 2012). BMI categories were defined as follows: 18.5 to 22.4, 22.5 to 24.9 (reference), 25.0 to 27.4, 27.5 to 29.9, 30.0 to 34.9, and 35.0 or higher. Multivariable models were adjusted for race or ethnic group (white, black, Asian American, Hispanic, or other), smoking status (never smoked; previously smoked; currently smokes 1 to 14, 15 to 24, or ≥25 cigarettes per day; or not reported), alcohol consumption (women: 0, 0.1 to 4.9, 5.0 to 14.9, or ≥15.0 g per day; men: 0, 0.1 to 4.9, 5.0 to 29.9, or ≥30.0 g per day), physical activity (<3.0, 3.0 to 8.9, 9.0 to 17.9, 18.0 to 26.9, or ≥27.0 hours of metabolic-equivalent tasks per week), marital status (married or unmarried), diet quality (in quintiles of Alternate Healthy Eating Index scores), family history of diabetes (yes or no), and menopausal status (for NHS participants only). The P values for linear trend were computed by modeling BMI as a continuous variable. Nonlinear trends were assessed with likelihood-ratio tests of restricted cubic splines.[27] A P value of less than 0.05 was considered to indicate a significant linear or nonlinear trend. The hazard-ratio estimates for the two cohorts were combined with the use of fixed-effect meta-analyses with inverse-variance weighting.

We repeated our analyses with stratification according to baseline smoking status and with early deaths (<4 years after diagnosis) excluded. Effect modification by smoking status (never smoked vs. ever smoked) and age at diagnosis (<65 years vs. ≥65 years) was estimated from the multiplicative interaction term between continuous BMI and the effect modifier added to the main effects model. The proportional-hazards assumption was evaluated with a likelihood-ratio test comparing the model with and without an interaction term between time period and BMI category. Data were analyzed with the use of SAS software, version 9.2 (SAS Institute), at a two-tailed alpha level of 0.05.

RESULTS

STUDY PARTICIPANTS

For the 11,427 participants included in our analysis, the mean age at diabetes diagnosis was 62 years (range, 35 to 86) among the 8970 NHS participants and 64 years (range, 41 to 91) among the 2457 HPFS participants. Baseline characteristics are presented in Table 1, stratified according to BMI categories. A higher BMI at diagnosis was inversely associated with age at diagnosis, physical activity, and Alternate Healthy Eating Index score. The lowest BMI category (18.5 to 22.4) had the highest prevalence of current smokers, and normal-weight participants (BMI, 18.5 to 24.9) were more likely to have lost weight before diagnosis than overweight participants (BMI, 25.0 to 29.9) and obese participants (BMI, ≥30).

ALL-CAUSE MORTALITY

A total of 3083 deaths from all causes were observed over a mean follow-up of 15.8 years, with a maximum follow-up of 36 years among women (mean, 16.2 years; 16.1 deaths per 1000 person-years) and 26 years among men (mean, 14.5 years; 21.8 deaths per 1000 person-years). The mean (±SD) age at death was 74.6±7.8 years for women and 78.7±8.7 years for men. In general, crude rates of death were higher among participants who had ever smoked than among those who had never smoked, across BMI categories (Table 2).

A J-shaped association between BMI and all-cause mortality was observed among all the participants (Table 2) ($P<0.001$ for nonlinearity among NHS participants; $P=0.59$ among HPFS participants). As compared with participants with a BMI of 22.5 to 24.9, those in the lowest BMI category, 18.5 to 22.4, had a significantly elevated all-cause mortality (hazard ratio, 1.29; 95% confidence interval [CI], 1.05 to 1.59), as did those in the highest BMI categories (BMI of 30.0 to 34.9: hazard ratio, 1.24; 95% CI, 1.08 to 1.42; BMI ≥35.0: hazard ratio, 1.33; 95% CI, 1.14 to 1.55).

Results indicated significant effect modification according to smoking status (Table 2) ($P=0.04$ for interaction), with divergent trends in the risk of death across BMI strata for participants who had ever smoked as compared with those who had never smoked. A significant linear trend was seen among participants who had never smoked ($P<0.001$), with no evidence of a nonlin-

Table 1. Baseline Characteristics of the Study Participants, According to Body-Mass Index (BMI) Categories.*

Characteristic	BMI Category					
	18.5–22.4	22.5–24.9	25.0–27.4	27.5–29.9	30.0–34.9	≥35.0
NHS cohort: women						
No. of participants	362	737	1465	1452	2740	2214
Age at the questionnaire return before diabetes diagnosis (yr)	63.2±11.0	62.8±10.2	62.7±9.2	62.4±8.8	60.7±8.6	58.3±8.4
Age at diabetes diagnosis (yr)	64.4±11.1	63.9±10.2	63.9±9.2	63.6±8.8	61.9±8.6	59.5±8.4
BMI	21.3±1.0	23.9±0.7	26.5±0.8	28.9±0.6	32.3±1.4	39.4±3.2
Physical activity (MET-hr/wk)	16.9±20.7	16.5±27.6	15.6±24.1	13.7±18.7	12.2±17.0	8.7±13.3
Alcohol intake (g/day)	5.7±10.7	5.3±9.5	4.0±8.5	3.6±7.9	2.8±6.7	2.1±6.5
Alternate Healthy Eating Index score†	53.0±11.7	52.9±10.9	51.9±10.7	51.8±11.0	50.4±10.6	48.9±10.5
Change in BMI during 2 yr before diabetes diagnosis	−0.1±2.6	0.4±3.1	0.8±3.7	1.4±4.4	1.7±5.4	2.9±7.1
Reduction in BMI of >1 unit during 2 yr before diabetes diagnosis (%)	21.9	18.9	19.8	16.5	18.2	16.7
White race (%)‡	93.9	94.6	95.2	94.8	96.0	96.3
One or more symptoms of diabetes at diagnosis (%)	35.4	34.7	37.9	40.6	39.6	44.2
Insulin use in first yr after diagnosis (%)	7.7	8.1	8.1	6.3	7.4	8.4
Postmenopausal (%)	77.9	78.0	78.8	79.7	76.2	69.3
Smoking status (%)						
Never smoked	43.4	43.8	45.7	43.9	44.6	45.5
Former smoker	34.3	38.3	37.8	41.0	41.6	43.2
Current smoker						
<15 cigarettes/day	14.4	13.6	12.8	10.6	9.9	8.0
≥15 cigarettes/day	7.5	4.3	3.3	4.5	3.7	3.0
Unknown	0.6	0.0	0.4	0.1	0.2	0.3
Married (%)	67.7	71.2	69.8	69.8	70.9	70.0
Family history of diabetes (%)	44.8	49.3	48.2	47.9	48.4	46.8
Hypercholesterolemia (%)	33.2	37.7	41.3	37.6	35.3	30.2
High blood pressure (%)	35.4	38.9	42.8	45.8	50.0	49.0

Table 1. (Continued.)

Characteristic	BMI Category					
	18.5–22.4	22.5–24.9	25.0–27.4	27.5–29.9	30.0–34.9	≥35.0
HPFS cohort: men						
No. of participants	64	337	630	558	620	248
Age at the questionnaire return before diabetes diagnosis (yr)	68.0±9.3	66.5±9.2	64.1±8.5	63.5±8.3	61.1±8.0	58.6±7.8
Age at diabetes diagnosis (yr)	69.2±9.3	67.6±9.2	65.2±8.5	64.6±8.2	62.3±8.1	59.7±7.7
BMI	21.4±1.0	23.9±0.6	26.2±0.8	28.7±0.7	32.0±1.4	38.5±3.6
Physical activity (MET-hours/wk)	34.0±39.0	32.0±33.4	28.2±31.4	27.0±35.8	24.9±36.0	17.8±25.1
Alcohol intake (g/day)	10.1±14.8	8.8±12.3	10.1±14.1	10.8±16.8	10.0±15.1	7.2±12.1
Alternate Healthy Eating Index score†	53.7±12.7	55.6±12.2	53.8±11.7	52.8±11.3	51.9±10.9	51.0±10.8
Change in BMI during 2 yr before diabetes diagnosis	–0.4±1.3	–0.3±1.0	–0.1±1.3	0.1±1.3	0.3±1.9	0.8±2.2
Reduction in BMI of >1 unit in 2 yr before diabetes diagnosis (%)	23.5	19.2	16.9	14.9	17.1	15.5
White race (%)‡	90.6	89.0	93.2	94.6	94.5	95.2
One or more symptoms of diabetes at diagnosis (%)	43.8	40.4	45.9	49.1	51.9	59.3
Insulin use in first yr after diagnosis (%)	4.7	1.2	2.4	2.3	2.1	2.4
Smoking status (%)						
Never smoked	40.6	40.7	37.9	38.4	42.3	45.6
Former smoker	40.6	47.5	51.3	52.0	47.6	46.8
Current smoker						
<15 cigarettes/day	12.5	8.0	5.4	3.6	5.2	1.6
≥15 cigarettes/day	3.1	1.5	2.2	2.0	2.3	2.4
Unknown	3.1	2.4	3.2	4.1	2.7	3.6
Married (%)	84.4	83.7	81.3	80.5	81.6	77.0
Family history of diabetes (%)	40.6	50.5	50.8	48.2	49.8	46.0
Hypercholesterolemia (%)	60.9	48.4	52.2	50.0	50.2	48.4
High blood pressure (%)	46.9	43.0	48.4	57.7	60.7	68.2

* The study included participants with incident type 2 diabetes from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). Plus–minus values are means ±SD. MET denotes metabolic-equivalent tasks.
† Scores on the Alternate Healthy Eating Index range from 2.5 to 87.5, with higher scores indicating a healthier diet.
‡ Race was self-reported.

ear trend (P=0.41 for NHS participants; P=0.22 for HPFS participants). Among participants who had ever smoked, however, there was a nonlinear J-shaped trend in the combined cohort of men and women and in the cohort of women (P<0.001 for NHS participants) but not in the cohort of men (P=0.72 for HPFS participants).

Significant effect modification according to age at diagnosis was observed (P<0.001 for interaction) (Table S1 in the Supplementary Appendix). Among adults younger than 65 years of age at diagnosis, there was a direct linear relationship between BMI and all-cause mortality (P<0.001 for linear trend among total participants, those who had never smoked, and those who had ever smoked). In contrast, a direct linear trend among participants 65 years of age or older at diagnosis was observed only among those who had never smoked (P=0.04), and among participants who had ever smoked, a significantly increased risk of death was observed only in the lowest BMI category (hazard ratio, 1.89; 95% CI, 1.32 to 2.71).

The results of the analyses that assessed residual confounding by smoking status and reverse causation are depicted in Figures 1A through 1F. Exclusion of participants who died in

Table 2. Cohort-Specific and Combined Hazard Ratios for All-Cause Mortality, According to BMI Shortly before Diagnosis of Type 2 Diabetes and Smoking Status.*

Variable	BMI Category					
	18.5–22.4	22.5–24.9	25.0–27.4	27.5–29.9	30.0–34.9	≥35.0
Combined NHS and HPFS cohorts†						
Total						
Age-adjusted hazard ratio	1.38 (1.12–1.69)	1.00	1.12 (0.97–1.28)	1.10 (0.95–1.27)	1.24 (1.08–1.41)	1.33 (1.15–1.55)
Multivariable-adjusted hazard ratio	1.29 (1.05–1.59)	1.00	1.12 (0.98–1.29)	1.09 (0.94–1.26)	1.24 (1.08–1.42)	1.33 (1.14–1.55)
Never smoked						
Age-adjusted hazard ratio	1.14 (0.78–1.66)	1.00	1.16 (0.92–1.47)	1.22 (0.96–1.55)	1.39 (1.11–1.73)	1.64 (1.30–2.08)
Multivariable-adjusted hazard ratio	1.12 (0.77–1.64)	1.00	1.16 (0.91–1.48)	1.21 (0.95–1.54)	1.36 (1.08–1.70)	1.56 (1.22–1.99)
Ever smoked						
Age-adjusted hazard ratio	1.46 (1.14–1.88)	1.00	1.08 (0.91–1.28)	1.03 (0.86–1.22)	1.13 (0.96–1.34)	1.19 (0.98–1.44)
Multivariable-adjusted hazard ratio	1.32 (1.02–1.71)	1.00	1.09 (0.92–1.30)	1.04 (0.86–1.24)	1.14 (0.96–1.36)	1.21 (0.99–1.47)
NHS cohort: women						
Total						
No. of deaths/person-yr	110/5632	184/11,997	388/23,287	341/23,097	726/44,466	592/36,615
Annual no. of deaths/1000 participants	19.5	15.3	16.7	14.8	16.3	16.2
Age-adjusted hazard ratio	1.39 (1.10–1.76)	1.00	1.14 (0.96–1.36)	1.01 (0.85–1.21)	1.24 (1.05–1.45)	1.40 (1.19–1.66)
Multivariable-adjusted hazard ratio	1.30 (1.03–1.65)	1.00	1.14 (0.95–1.36)	1.00 (0.83–1.19)	1.22 (1.04–1.44)	1.39 (1.17–1.65)
Never smoked						
No. of deaths/person-yr	29/2397	72/5414	154/10,677	139/10,192	285/20,344	251/17,061
Annual no. of deaths/1000 participants	12.1	13.3	14.4	13.6	14.0	14.7
Age-adjusted hazard ratio	1.01 (0.66–1.56)	1.00	1.18 (0.89–1.56)	1.10 (0.83–1.47)	1.26 (0.97–1.63)	1.55 (1.19–2.02)
Multivariable-adjusted hazard ratio	1.00 (0.65–1.54)	1.00	1.17 (0.88–1.55)	1.06 (0.79–1.42)	1.20 (0.92–1.57)	1.46 (1.11–1.92)
Ever smoked						
No. of deaths/person-yr	80/3215	112/6583	232/12,508	202/12,898	439/24,060	339/19,472
Annual no. of deaths/1000 participants	28.4	19.4	21.2	17.9	20.8	19.9
Age-adjusted hazard ratio	1.57 (1.18–2.10)	1.00	1.12 (0.89–1.40)	0.96 (0.76–1.20)	1.22 (0.99–1.50)	1.32 (1.06–1.64)
Multivariable-adjusted hazard ratio	1.45 (1.08–1.93)	1.00	1.11 (0.88–1.39)	0.95 (0.75–1.20)	1.22 (0.99–1.51)	1.33 (1.07–1.66)
HPFS cohort: men						
Total						
No. of deaths/person-yr	25/801	122/4806	196/8749	177/7519	165/8595	57/3518
Annual no. of deaths/1000 participants	31.2	25.4	22.4	23.5	19.2	16.2
Age-adjusted hazard ratio	1.33 (0.87–2.05)	1.00	1.08 (0.86–1.35)	1.27 (1.01–1.60)	1.24 (0.98–1.57)	1.14 (0.83–1.56)
Multivariable-adjusted hazard ratio	1.25 (0.81–1.94)	1.00	1.10 (0.88–1.39)	1.29 (1.01–1.63)	1.26 (0.99–1.61)	1.13 (0.81–1.57)

Never smoked						
No. of deaths/person-yr	8/316	35/1923	51/3352	52/2914	67/3761	24/1596
Annual no. of deaths/1000 participants	25.3	18.2	15.2	17.9	17.8	15.0
Age-adjusted hazard ratio	1.66 (0.77–3.59)	1.00	1.12 (0.72–1.73)	1.57 (1.01–2.43)	1.81 (1.19–2.78)	2.10 (1.22–3.61)
Multivariable-adjusted hazard ratio	1.67 (0.75–3.70)	1.00	1.14 (0.72–1.80)	1.67 (1.06–2.63)	1.91 (1.22–2.98)	2.07 (1.18–3.62)
Ever smoked						
No. of deaths/person-yr	16/463	87/2757	140/5096	122/4304	92/4601	31/1805
Annual no. of deaths/1000 participants	34.6	31.6	27.5	28.3	20.0	17.2
Age-adjusted hazard ratio	1.14 (0.67–1.94)	1.00	1.03 (0.78–1.34)	1.14 (0.87–1.51)	0.98 (0.73–1.32)	0.83 (0.55–1.25)
Multivariable-adjusted hazard ratio	0.96 (0.56–1.65)	1.00	1.07 (0.81–1.40)	1.19 (0.89–1.59)	0.99 (0.73–1.35)	0.85 (0.55–1.31)

* The mean time from questionnaire return to date of diagnosis was 11 months. For the multivariable-adjusted hazard ratios, data were adjusted for age, race, marital status, menopausal status (for the NHS cohort only), presence or absence of a family history of diabetes, smoking status, alcohol intake, Alternate Healthy Eating Index score, and physical activity. For the analyses with stratification according to smoking status (never smoked vs. ever smoked), a total of 20 women (7 deaths) and 79 men (17 deaths) with missing data on smoking status were excluded.

† The results for the two cohorts were combined with the use of a fixed-effect meta-analysis.

the first 4 years of follow-up (a total of 227 participants: 78 who had never smoked and 149 who had ever smoked) (Fig. 1B, 1D, and 1F, respectively) resulted in a monotonic positive association between BMI and death among participants who had never smoked, and the results did not differ substantially from those of the primary analysis. Exclusion of participants with weight loss of more than 1 BMI unit before a diabetes diagnosis, adjustment for baseline hypertension or hypercholesterolemia, and adjustment for year of diabetes diagnosis produced similar results (data not shown). The tests for the proportional-hazards assumption did not indicate a violation in either cohort. Age-adjusted survival curves are depicted in Figures S2A through S2D in the Supplementary Appendix.

Using the traditional cutoff points for the BMI categories of normal weight, overweight, and obesity (Table S2 in the Supplementary Appendix) and correcting errors in self-reported weight and height (Table S3 in the Supplementary Appendix) did not significantly change the results.

CAUSE-SPECIFIC MORTALITY

We assessed the relationship between BMI just before a diabetes diagnosis and deaths due to cardiovascular disease (941 deaths), cancer (784 deaths), and other causes (e.g., respiratory diseases, renal disease, suicide, and accidents; 1358 deaths) (Fig. 2A, 2B, and 2C; and Table S4 in the Supplementary Appendix). There was a significant direct linear relationship between BMI and cardiovascular mortality among all participants ($P<0.001$ for linear trend) and among those who had never smoked ($P=0.004$), but the relationship appeared to be attenuated among those who had ever smoked ($P=0.02$). In the lowest BMI category (18.5 to 22.4), a significant increase in cancer mortality was seen among all participants (hazard ratio, 1.51; 95% CI, 1.00 to 2.28) and among those who had ever smoked (hazard ratio, 1.87; 95% CI, 1.15 to 3.04) but not among those who had never smoked (hazard ratio, 0.83; 95% CI, 0.34 to 2.05). The relationship between BMI and mortality from other causes appeared to be J-shaped for all participants.

DISCUSSION

Our analyses of data from two large, long-term, prospective cohort studies indicate a J-shaped as-

sociation between BMI immediately before a diagnosis of type 2 diabetes and all-cause mortality. This relationship was linear among participants who had never smoked but was nonlinear among those who had ever smoked. We did not observe a benefit of excess adiposity with regard to the risk of death; thus, our findings support the current recommendation that patients with diabetes achieve or maintain a normal weight.[28]

Although our findings are largely consistent with the results of previous analyses in the general population,[1-4] they contradict the results of several studies of BMI and mortality among participants with diabetes. Prior studies largely suggest inverse,[10] J- or U-shaped,[11,29,30] or flat or null associations[9,31]; however, notable limitations include a short follow-up duration,[9,11,30] a small number of deaths,[10,29,31,32] and a lack of analyses assessing biases from smoking or undiagnosed chronic diseases.[9-11,29-32] The majority of these studies involved patients who already had diabetes, with BMI assessed up to several decades after the diagnosis; these factors substantially increase susceptibility to reverse-causation bias.[9,29-32]

Recently, Carnethon et al.[10] analyzed pooled data from five large U.S. cohorts and concluded that adults who were of normal weight at the time of a diabetes diagnosis had a risk of death that was twice as high as that among their overweight or obese counterparts (hazard ratio, 2.01; 95% CI, 1.44 to 2.81); however, several of the limitations outlined above apply to this study. Relatively low statistical power (449 total deaths) limited their BMI classification to two broad and heterogeneous exposure groups (participants with a BMI of 18.5 to 24.9 and those with a BMI ≥25.0). Subgroup analyses were also underpowered, such that conclusions could not be drawn. In addition, BMI was measured after the diabetes diagnosis for many participants, allowing additional bias from the initiation of diabetes treatment or the progression of other underlying illnesses.[10]

The attenuated relationship between BMI and mortality among smokers has frequently been observed in the general population.[3,4,14,15] It is unclear whether this effect modification represents biologic differences between smokers and nonsmokers or is largely due to bias.[13] Additional studies are needed to answer this question.

In our study, effect modification according to age at diagnosis indicated a direct linear trend among participants younger than 65 years of age but a null or weakened linear association among participants 65 years of age or older. These findings, which are consistent with the results of previous studies involving participants with type 2 diabetes[32] and the general population,[1,33] may reflect well-known limitations in analyses of mortality among older persons, including an increased prevalence of coexisting chronic diseases, which increases the potential for reverse-causation bias; an increased prevalence of competing risk factors, which reduces the proportional effect of a single factor; and decreased validity of BMI as a measure of adiposity owing to age-related declines in muscle mass and wasting.[34] It has also been suggested that excess adiposity may confer a metabolic advantage and improved survival among the elderly. Therefore, caution should be taken in interpreting the results among the older participants.

Our findings with respect to the relationship between BMI and mortality due to specific causes are consistent with those of prior studies conducted in the general population.[2-4,14,15] Among participants who had never smoked, the relationship of BMI to both cardiovascular mortality and cancer mortality appeared to be monotonic and linear. No significant association was observed between any BMI category and the risk of death from cardiovascular disease among participants who had ever smoked; however, participants in the lowest BMI category who had ever smoked had a significantly elevated risk of death from cancer.

Proposed biologic mechanisms of the alleged obesity paradox include an increased genetic influence and more severe diabetes among normal-weight persons with diabetes or the effect of a "metabolically obese normal weight" phenotype.[35,36] However, normal-weight participants in our cohort were no more likely to report diabetes symptoms or coexisting chronic diseases or to require insulin than were overweight or obese participants. In contrast, normal-weight participants were more likely to be smokers and to have lost weight before a diagnosis of diabetes. Comparisons with this heterogeneous normal-weight group may therefore underestimate the risk of death among the overweight and obese.

Strengths of our study include the large sample (3083 deaths among 11,427 adults with incident diabetes), permitting detailed exami-

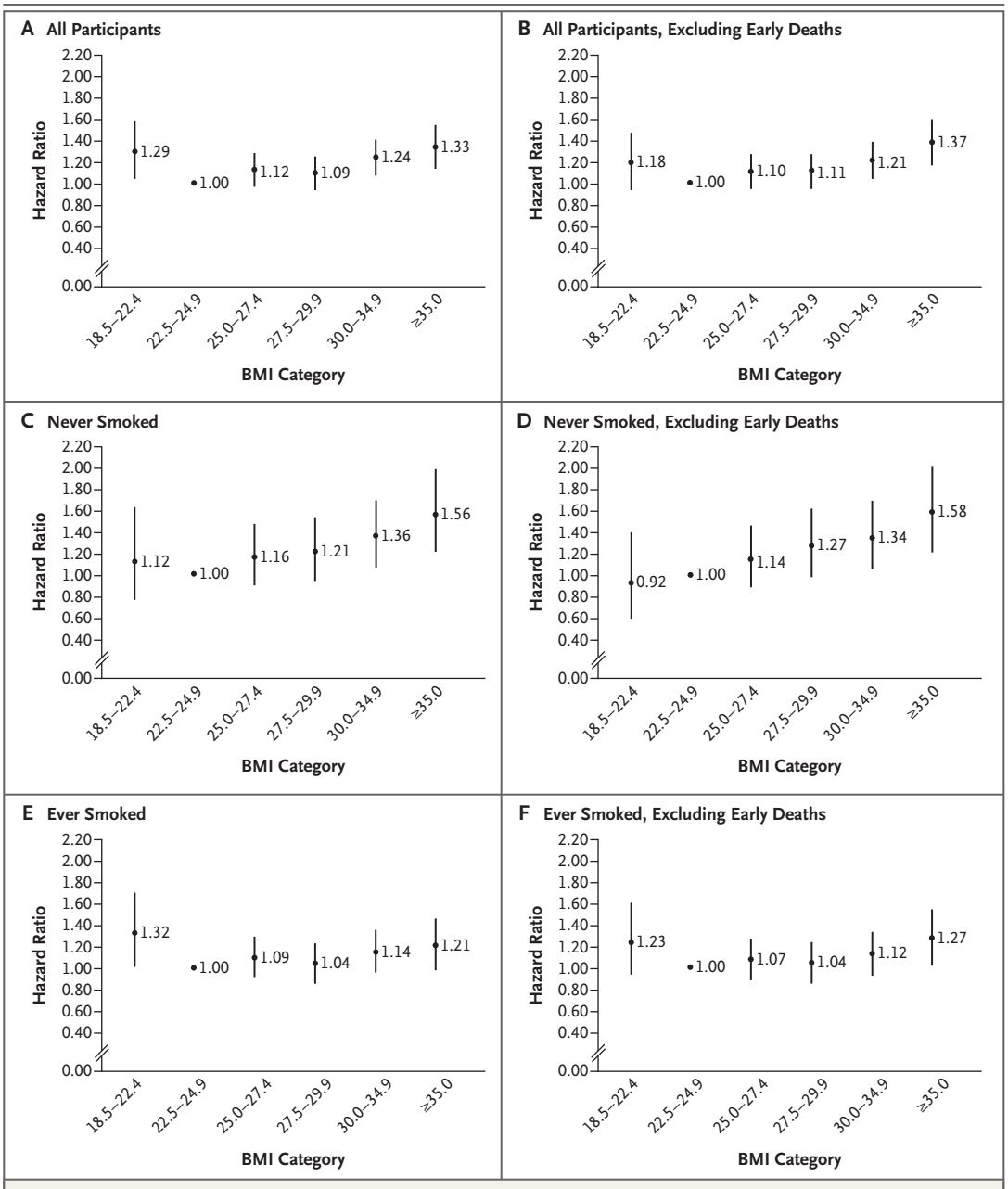

Figure 1. Hazard Ratios for All-Cause Mortality among Participants with Incident Type 2 Diabetes, According to Body-Mass Index (BMI) Shortly before Diagnosis of Type 2 Diabetes.

The results from the two cohorts (Nurses' Health Study [NHS] and Health Professionals Follow-up Study) were combined with the use of a fixed-effect meta-analysis. Panel A shows the results for the total study population (3083 deaths; 179,081 person-years). Panel B shows the results of the analysis that excluded deaths occurring in the first 4 years of follow-up (2856 deaths; 177,906 person-years). Panel C shows the results for participants who had never smoked (1167 deaths; 79,946 person-years). Panel D shows the results for participants who had never smoked, with the exclusion of deaths occurring in the first 4 years of follow-up (1089 deaths; 79,546 person-years). Panel E shows the results for participants who had ever smoked (1892 deaths; 97,762 person-years). Panel F shows the results for participants who had ever smoked, with the exclusion of deaths occurring in the first 4 years of follow-up (1743 deaths; 96,999 person-years). All estimates have been adjusted for age, race, marital status, menopausal status (for the NHS cohort only), presence or absence of a family history of diabetes, smoking status (in Panels A, B, E, and F), alcohol intake, Alternate Healthy Eating Index score, and physical activity. A total of 20 women (7 deaths) and 79 men (17 deaths) with missing data on smoking status were excluded from the stratified analyses. The bars represent 95% confidence intervals.

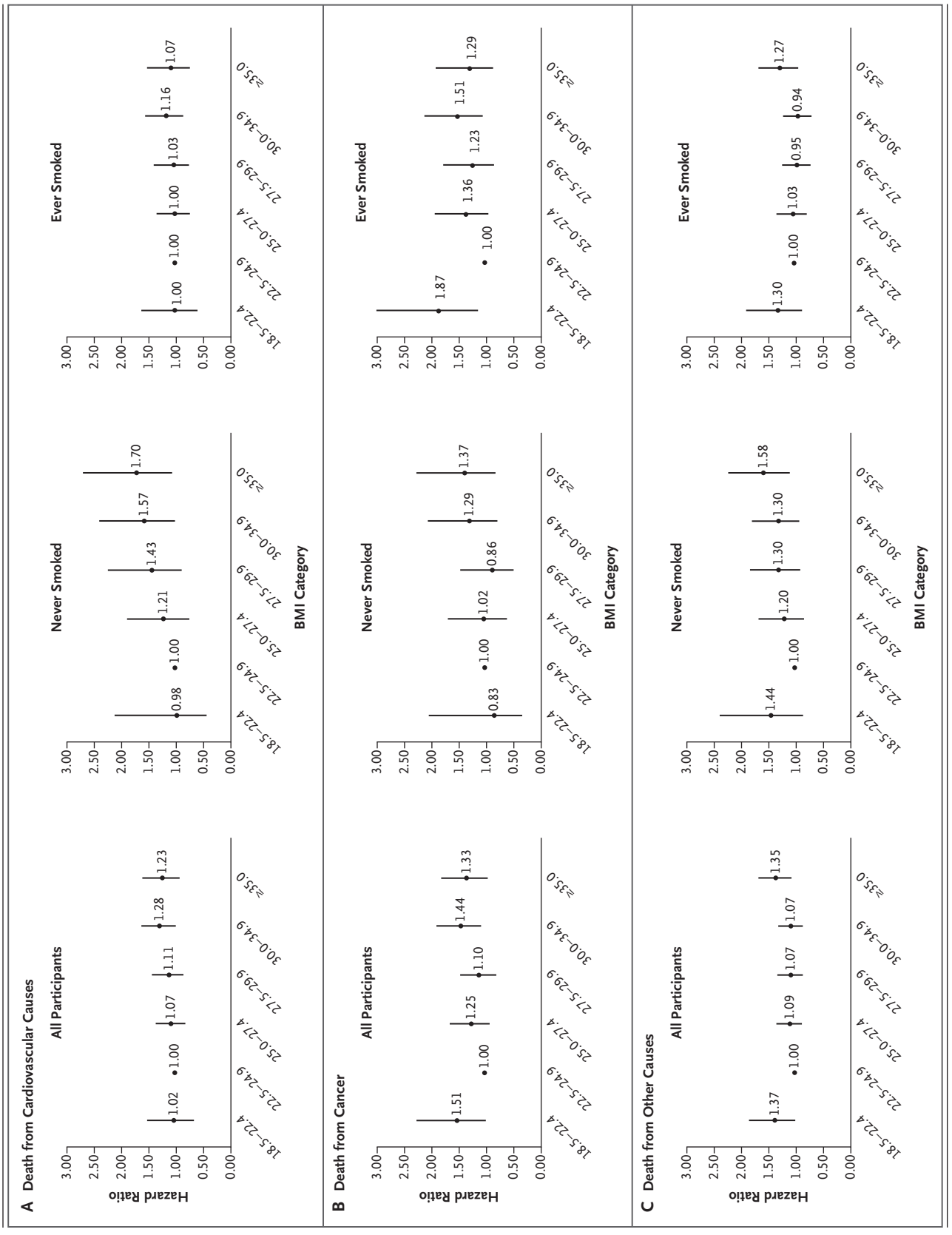

Figure 2 (facing page). Hazard Ratios for Cause-Specific Mortality among Participants with Incident Type 2 Diabetes, According to BMI Shortly before Diagnosis of Type 2 Diabetes.

The results from the two cohorts (NHS and Health Professionals Follow-up Study) were combined with the use of a fixed-effect meta-analysis. The numbers of person-years were 179,081 for all participants, 79,546 for those who had never smoked, and 97,762 for those who had ever smoked. Panel A shows cardiovascular mortality in the total study population (941 deaths), among participants who had never smoked (340 deaths), and among those who had ever smoked (592 deaths). Panel B shows cancer mortality in the total study population (784 deaths), among participants who had never smoked (266 deaths), and among those who had ever smoked (514 deaths). Panel G shows mortality from other causes in the total study population (1358 deaths), among participants who had never smoked (561 deaths), and among those who had ever smoked (786 deaths). All estimates have been adjusted for age, race, marital status, menopausal status (for the NHS cohort only), presence or absence of a family history of diabetes, smoking status (among all participants and those who had ever smoked), alcohol intake, and Alternate Healthy Eating Index score. A total of 20 women and 79 men with missing data on smoking status were excluded from the stratified analyses (24 total deaths, including 9 from cardiovascular causes, 4 from cancer, and 11 from other causes). The bars represent 95% confidence intervals.

nation across multiple BMI categories and key analyses to address potential biases. Prospectively measured body weight, documented just before or at the time of a diabetes diagnosis, prevents misclassification from weight change due to early pharmacologic treatments or lifestyle changes shortly after diagnosis. Enrollment of health professionals has proved beneficial with respect to the reliability and validity of self-reported health-related exposures and outcomes, and it reduces confounding by educational and socioeconomic factors.

Limitations of the study include the reliance on self-reported weight measures, although erroneous reporting was shown to be very minimal in validation studies, and corrections of errors in BMI measurement produced similar findings. Information on weight was obtained an average of 11 months before diagnosis as a proxy for the weight at diagnosis, but this is unlikely to have resulted in appreciable error. Finally, the relative homogeneity of the NHS and HPFS cohorts may limit the generalizability of our findings to other racial and ethnic groups.

In conclusion, our results indicate a J-shaped relationship between BMI at the time of a diabetes diagnosis and the risk of death from all causes, with the lowest risk observed among normal-weight participants with a BMI of 22.5 to 24.9. Among participants who had never smoked, there was a direct linear relationship between BMI and mortality, whereas a nonlinear relationship was observed among those who had ever smoked. There was no evidence of a protective effect of overweight or obesity on mortality. In addition, given the relationship of overweight and obesity to other critical public health end points (e.g., cardiovascular disease and cancer), the maintenance of a healthy body weight should remain the cornerstone of diabetes management, irrespective of smoking status. Further evidence is needed to corroborate our findings in other populations.

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