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Weight History and All-Cause and Cause-Specific Mortality in Three Prospective Cohort Studies

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Background: The relationship between body mass index (BMI) and mortality is controversial.

Objective: To investigate the relationship between maximum BMI over 16 years and subsequent mortality.

Design: 3 prospective cohort studies.

Setting: Nurses' Health Study I and II and Health Professionals Follow-Up Study.

Participants: 225 072 men and women with 32 571 deaths observed over a mean of 12.3 years of follow-up.

Measurements: Maximum BMI over 16 years of weight history and all-cause and cause-specific mortality.

Results: Maximum BMIs in the overweight (25.0 to 29.9 kg/m^2) (multivariate hazard ratio [HR], 1.06 [95% CI, 1.03 to 1.08]), obese I (30.0 to 34.9 kg/m^2) (HR, 1.24 [CI, 1.20 to 1.29]), and obese II (≥35.0 kg/m^2) (HR, 1.73 [CI, 1.66 to 1.80]) categories were associated with increases in risk for all-cause death. The pattern of excess risk with a maximum BMI above normal weight was maintained across strata defined by smoking status, sex, and age, but the excess was greatest among those younger than 70 years and never-smokers. In contrast, a significant inverse association between overweight and mortality (HR, 0.96 [CI, 0.94 to 0.99]) was observed when BMI was defined using a single baseline measurement. Maximum overweight was also associated with increased cause-specific mortality, including death from cardiovascular disease and coronary heart disease.

Limitation: Residual confounding and misclassification.

Conclusion: The paradoxical association between overweight and mortality is reversed in analyses incorporating weight history. Maximum BMI may be a useful metric to minimize reverse causation bias associated with a single baseline BMI assessment.

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Debate is ongoing about the optimal body mass index (BMI) in relation to all-cause mortality. A previous meta-analysis of 97 studies of BMI and mortality identified an inverse association for persons who were overweight (BMI of 25.0 to 29.9 kg/m^2) and a null association for those with grade I obesity (BMI of 30.0 to 34.9 kg/m^2) compared with normal-weight persons (BMI of 18.5 to 24.9 kg/m^2) (1). One explanation is that people often lose weight due to illness before death, leading to reverse causation bias (conditions leading to imminent death causing lower BMI rather than lower BMI causing death) and underestimation of the risks associated with overweight and obesity (2, 3). Confounding by smoking status may also attenuate risks above normal BMI because smokers tend to be leaner (4–6). Such techniques as the exclusion of persons with disease at baseline, exclusion of early follow-up (7), and restriction to never-smokers have been proposed (8–10), but these strategies reduce sample size, cannot account for participants with diseases with longer latency periods (up to a decade or more [11]) or with undiagnosed illnesses, and might reduce generalizability (12, 13).

Several prior studies have investigated risk for death by using maximum lifetime BMI, and the results suggested an increased risk with overweight (BMI of 25.0 to 29.9 kg/m^2) and a significant positive association with obesity (BMI ≥30.0 kg/m^2) (12, 14). This method is advantageous because it identifies persons who maintained a normal BMI over time as opposed to entering the normal category due to illness-induced weight loss. However, previous studies assessed maximum weight by recall and analyses were limited to never smokers. Furthermore, information on cause-specific mortality was not reported.

To address these limitations, we examined risks for all-cause and cause-specific death associated with overweight and obesity in 3 large cohorts of health professionals in the United States. Our aim was to generate estimates that minimized reverse causality without imposing the strict exclusion criteria applied in the prior literature. The availability of longitudinal data enabled us to define maximum BMI by using contemporaneous rather than recalled data on weight status. Furthermore, we included all participants in the analysis, regardless of smoking status, baseline illness, and other characteristics.

Methods

Study Population

The NHS (Nurses' Health Study) was initiated in 1976 with 121 700 female nurses aged 30 to 55 years. The NHS II (Nurses' Health Study II) began in 1989 with

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116 686 female registered nurses aged 25 to 42 years. The HPFS (Health Professionals Follow-Up Study) began in 1986 with 51 529 male health professionals aged 40 to 75 years. Questionnaires were administered biennially to update diet, lifestyle, and other health-related information.

Our primary analysis included participants who returned at least 2 questionnaires during the weight history periods for each cohort (1976 to 1992 for the NHS, 1989 to 2005 for the NHS II, and 1986 to 2002 for the HPFS). We excluded persons who were missing data on weight or age at baseline, died before baseline, or had a BMI less than 12.5 kg/m^2 or greater than 60.0 kg/m^2 at baseline. We did not exclude persons on the basis of smoking status or baseline illness. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health, with participants' consent implied by the return of the questionnaires.

Assessment of BMI

Height in inches and body weight in pounds were reported at cohort inception, and body weight was self-reported every 2 years thereafter. Self-reported weight has been validated against measured weight in the NHS and HPFS and is reported to be highly correlated (r = 0.97) (15). Body mass index was calculated as 703 × weight / height^2. Women who reported being pregnant were coded as missing BMI information for that questionnaire wave. Body mass index was categorized into 5 predefined categories for analysis: underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), obese I (30.0 to 34.9 kg/m^2), and obese II (≥35.0 kg/m^2) (16). Normal weight was used as the reference category for both baseline and maximum BMI.

Establishment of Weight History and Maximum BMI

We defined cohort inception as the year that each cohort was initiated (1976 for the NHS, 1989 for the NHS II, and 1986 for the HPFS) and baseline as an arbitrary year after cohort inception at which we began to count events and person-time. The weight history period was defined as the period between cohort inception and baseline (inclusive of both dates), during which events and person-time were not counted. The main exposure of interest, maximum BMI, was defined as the highest reported BMI from any questionnaire returned during the weight history period. For example, the maximum BMI for a participant in the NHS using a weight history of 16 years would be the highest reported BMI from questionnaires returned in 1976, 1978, 1980, 1982, 1984, 1986, 1988, 1990, and 1992. The exposure for the same participant using a weight history of 0 years would be the BMI reported in 1992 (equivalent to the baseline BMI). The purpose of establishing a weight history was to reduce reverse causation owing to participants losing weight due to illness before baseline.

To determine the optimal length of the weight history period, preliminary analyses were first conducted with varying lengths (0, 2, 4, 6, 8, 10, 12, 14, and 16 years) from the same baseline year (1992 for the NHS, 2005 for the NHS II, and 2002 for the HPFS), and a period was selected where the hazard ratios (HRs) for the overweight, obese I, and obese II categories seemed to stabilize. We also considered improvements in model fit according to the Akaike information criterion in our selection (**Table 1** of the **Supplement**, available at Annals.org) (17). For these analyses, we did not stratify by time since maximum BMI so that models would be comparable. We did not assess model performance for weight history periods exceeding 16 years in the full sample because this would have led to an excessively short follow-up in the NHS II. However, weight loss typically accelerates 9 to 10 years before death (11), so we expected that establishing a weight history length of 16 years would capture the maximum BMI of the vast majority of participants who had a negative weight trajectory later in life. We began counting events and person-time after the end of the weight history period until death or the end of follow-up (1992 to 2012 for the NHS, 2005 to 2013 for the NHS II, and 2002 to 2012 for the HPFS).

Ascertainment of Deaths

The primary outcome was death from any cause through the end of follow-up. Most deaths (>98%) were identified from reports by next of kin or postal authorities or from searches of the National Death Index. The cause of death was determined by physician review of medical records and death certificates. Diagnostic codes from the International Classification of Diseases, 8th Revision (ICD-8), were used to classify deaths as due to cardiovascular disease (CVD) (including heart failure, coronary heart disease, stroke, and any other vascular causes) (ICD-8 codes 390 to 459 and 795), coronary heart disease (mainly ischemic heart disease) (ICD-8 codes 410 to 414), stroke (ICD-8 codes 430 to 438), cancer (ICD-8 codes 140 to 239), respiratory diseases (ICD-8 codes 460 to 519), and other causes (such as Alzheimer disease, infectious diseases, and accidents).

Assessment of Covariates

Baseline covariates included race (white or nonwhite), family history of CVD (yes or no), and family history of cancer (yes or no). Data on age, cigarette smoking (never; ever; or 1 to 14, 15 to 24, or >24 cigarettes per day currently), and alcohol consumption (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, or >14.9 g/d) were collected and updated from biennial survey data. For the NHS and NHS II cohorts, menopausal status (premenopausal, postmenopausal, or unsure or dubious), hormone therapy use (never, ever, current, or unsure or dubious), and parity (0, 1, 2, 3, or ≥4) were also recorded and updated biennially. In the NHS II, information on oral contraceptive use (never, ever, or current) was also recorded and updated biennially. Dietary information was collected from validated food-frequency questionnaires approximately every 4 years for all cohorts and was updated biennially (18). Covariates with missing values were assigned the last known reported

value since cohort inception. Otherwise, missing values were set to a separate missing data category for that particular covariate and were included as an indicator variable in the analysis.

Statistical Analysis

Hazard ratios and 95% CIs were estimated from Cox proportional hazards models, with age as the time scale and stratification by questionnaire cycle and years between maximum and baseline BMI. Likelihood ratio tests comparing a nested model with interaction terms for the maximum BMI and age categories and the full model without the interaction terms were not significant for any cohort, indicating that the proportional hazards assumption is reasonable for our data. Quintiles of calorie intake were calculated from food-frequency questionnaire data. Baseline and maximum BMI in the weight history period were used as the primary exposures and were not updated during follow-up in order to emulate extant studies and minimize reverse causality. The HR estimates for all cohorts were combined via fixed-effects meta-analysis (19). Sensitivity analyses were conducted with stratification by baseline disease exclusions, baseline physical activity, and different inclusion criteria for the number of surveys returned with BMI data during the weight history period. Data were analyzed using SAS, version 9.4 (SAS Institute), at a 2-tailed α level of 0.05.

Role of the Funding Source

The National Institutes of Health had no role in the study design, conduct, or reporting of results.

RESULTS

Study Participants in the Primary Analysis

Baseline characteristics of the 3 cohorts are presented in Table 1. The follow-up periods were 1992 to 2012 for the NHS, 2005 to 2013 for the NHS II, and 2002 to 2012 for the HPFS (Figure 1 of the Supplement). The proportions of participants who died before baseline or did not have valid weight data at baseline and were therefore excluded from the main analysis were 19.5% in the NHS, 29.0% in the NHS II, and 20.4% in the HPFS. A total of 225 072 participants were included in the primary analysis, representing 78.5% of the original study population at cohort inception. The mean ages at the start of follow-up were 58, 50, and 68 years in the NHS, NHS II, and HPFS, respectively. Compared with men, the distributions of maximum BMI for women were wider and contained a higher proportion who were underweight or obese at their heaviest. When maximum values were used, the percentage of overweight or obese participants at baseline was 59% in the NHS, 63% in the NHS II, and 74% in the HPFS. The corresponding values for baseline BMI were 52%, 57%, and 61%. Participants in the NHS tended to have higher parity and lower alcohol consumption than those in the NHS II.

Weight History

The distributions of years from baseline since maximum BMI are shown in Figures 2 to 4 of the Supplement. Most participants reached their maximum BMI during the weight history period at the most recent questionnaire (baseline). Results of the analysis for maximum BMI categories according to weight history length are provided in Table 1 of the Supplement. The HRs for the overweight and obese categories increased and the HRs for the underweight category decreased with longer weight history. Cohort-specific Akaike information criterion values also decreased with longer weight history, signifying better model fit. We used a weight history of 16 years in the primary analysis (1976 to 1992 in the NHS, 1989 to 2005 in the NHS II, and 1986 to 2002 in the HPFS) to minimize reverse causation bias while maximizing follow-up time. The weight history and follow-up periods are depicted in Figure 1 of the Supplement.

All-Cause Mortality

Among 35 369 men, a total of 7817 deaths were observed over 315 205 person-years of follow-up (mean follow-up, 8.9 years). We found significant associations between maximum BMI and mortality in the overweight (HR, 1.08 [95% CI, 1.03 to 1.14]), obese I (HR, 1.39 [CI, 1.29 to 1.50]), and obese II (HR, 1.88 [CI, 1.67 to 2.11]) categories (Table 2). Compared with adults older than 70 years, risks for death in the overweight and obese categories were higher in adults younger than 70 years.

Among 189 703 women, a total of 24 754 deaths were observed over 2.4 million person-years of follow-up (mean follow-up, 12.9 years). We observed a J-shaped relationship for maximum BMI and mortality in the underweight (HR, 1.49 [CI, 1.26 to 1.76]), overweight (HR, 1.05 [CI, 1.01 to 1.08]), obese I (HR, 1.21 [CI, 1.16 to 1.26]), and obese II (HR, 1.71 [CI, 1.64 to 1.78]) categories (Table 2). Hazard ratios for all categories were stronger in adults younger than 60 years. The HRs for mortality among never-smokers were generally higher and also followed a J-shaped curve, with normal BMI conferring the lowest risk (Table 2). Analyses with fine BMI categories revealed that the 22.5 to 24.9 kg/m^2 and 20.0 to 24.9 kg/m^2 categories contained the nadir for risk for all-cause death among all participants and never-smokers, respectively (Tables 2 and 8 of the Supplement).

Participants who lost a significant amount of weight after attaining their maximum BMI had the highest risk for death compared with those who were currently at their maximum BMI (Table 6 of the Supplement). Those who had a BMI less than 25.0 kg/m^2 at baseline but once had a BMI of at least 35.0 kg/m^2 during the weight history period had an HR of 2.60 (CI, 2.00 to 3.40). Participants who had a BMI less than 25.0 kg/m^2 at baseline but were overweight (25.0 to 29.9 kg/m^2) at their maximum BMI also had elevated risks for death (HR, 1.24 [CI, 1.19 to 1.29]).

The risks associated with a maximum BMI in the overweight and obese categories remained elevated in

Table 1. Baseline Characteristics of All Persons Studied in the NHS (1992), NHS II (2005), and HPFS (2002)*

Characteristic	NHS (*n* = 97 158)	NHS II (*n* = 92 545)	HPFS (*n* = 35 369)
Mean age (SD), *y*	58.4 (7.2)	50.4 (4.6)	68.3 (8.9)
Smoking status			
Never	43.7	64.9	46.5
Ever	40.9	27.0	45.8
Current	14.4	7.9	3.1
Maximum BMI			
Underweight (<18.5 kg/m^2)	0.4	0.3	0.1
Normal weight (18.5–24.9 kg/m^2)	40.8	36.1	27.4
Overweight (25.0–29.9 kg/m^2)	35.0	30.5	53.5
Obese I (30.0–34.9 kg/m^2)	15.3	16.9	15.2
Obese II (≥35.0 kg/m^2)	8.5	16.0	3.8
Baseline BMI			
Underweight (<18.5 kg/m^2)	1.4	1.1	0.5
Normal weight (18.5–24.9 kg/m^2)	46.7	42.3	38.6
Overweight (25.0–29.9 kg/m^2)	32.5	29.0	47.1
Obese I (30.0–34.9 kg/m^2)	13.1	15.3	11.2
Obese II (≥35.0 kg/m^2)	6.3	12.3	2.5
White race	93.7	96.1	91.4
Family history of cardiovascular disease	15.8	21.8	33.1
Family history of cancer	14.8	9.9	16.6
Menopausal status			
Premenopausal	15.5	45.0	–
Postmenopausal	75.7	46.3	–
Unsure/dubious	8.7	7.2	–
Oral contraceptive use			
Never	–	11.0	–
Ever	–	83.1	–
Current	–	4.4	–
Hormone replacement therapy			
Never	39.8	38.0	–
Ever	28.2	31.0	–
Current	16.2	16.9	–
Unsure/dubious	9.4	14.1	–
Parity			
Nulliparous	5.6	16.0	–
1	7.1	12.7	–
2	27.7	36.6	–
3	27.3	19.4	–
≥4	30.3	7.1	–
Alcohol consumption at baseline			
Never (0 g/d)	45.5	42.0	15.3
Very light (0.1–4.9 g/d)	29.8	33.8	28.2
Light (5.0–9.9 g/d)	9.6	11.5	17.2
Moderate (10.0–14.9 g/d)	6.4	6.6	13.0
Heavy (>14.9 g/d)	8.8	6.2	26.4
Mean total energy intake at baseline (SD), *kcal/d*	1758 (491)	1832 (534)	1986 (538)

BMI = body mass index; HPFS = Health Professionals Follow-Up Study; NHS = Nurses' Health Study.
* Data are percentages unless otherwise indicated. Percentages may not sum to 100 due to missing data. Participants with missing data were classified into a separate missing data category.

sensitivity analyses with exclusions for baseline illness (Table 13 of the Supplement), exclusions for missing BMI data during weight history (Table 14 of the Supplement), physical activity levels (Table 15 of the Supplement), and missing covariate data (Table 16 of the Supplement).

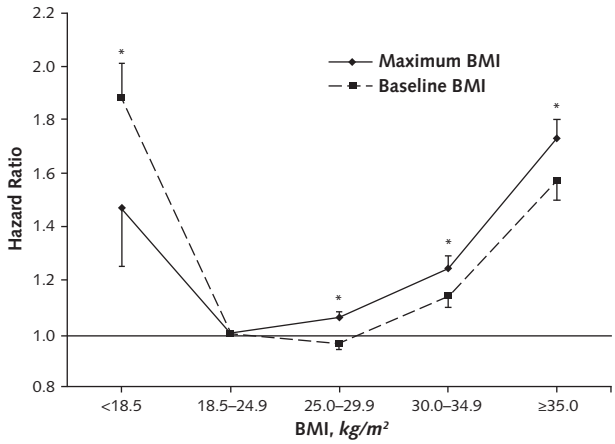
Compared with the results for maximum BMI in the overweight (HR, 1.06 [CI, 1.03 to 1.08]) and obese I (HR, 1.24 [CI, 1.20 to 1.29]) categories, the results for baseline BMI were weaker in the overall sample (HRs, 0.96 [CI, 0.94 to 0.99] and 1.14 [CI, 1.10 to 1.18], respectively) (Figure 1). When considering only never-

Table 2. HRs for All-Cause Mortality in the NHS, NHS II, and HPFS for Maximum BMI With 16 Years of Weight History, Stratified by Smoking Status, Baseline Age, and Sex*

Stratum	Underweight (<18.5 kg/m²)	Normal Weight (18.5–24.9 kg/m²)	Overweight (25.0–29.9 kg/m²)	Obese I (30.0–34.9 kg/m²)	Obese II (≥35.0 kg/m²)
All participants					
Men (HPFS)					
All ages					
Events, *n/1000 person-years*	5/0.2	2229/86.0	4103/169.2	1150/48.0	330/11.8
Age-adjusted HR (95% CI)	1.03 (0.42–2.49)	1.00 (reference)	1.11 (1.05–1.17)	1.45 (1.34–1.56)	1.96 (1.74–2.20)
Multivariate HR (95% CI)	1.10 (0.45–2.67)	1.00 (reference)	1.08 (1.03–1.14)	1.39 (1.29–1.50)	1.88 (1.67–2.11)
Age <70 y					
Events, *n/1000 person-years*	1/0.1	290/48.7	720/101.3	319/32.0	133/8.3
Multivariate HR (95% CI)	1.63 (0.23–11.80)	1.00 (reference)	1.17 (1.02–1.35)	1.64 (1.40–1.93)	2.62 (2.12–3.23)
Age 70–79 y					
Events, *n/1000 person-years*	2/0.1	825/25.9	1738/50.9	518/13.2	150/3.0
Multivariate HR (95% CI)	0.77 (0.19–3.11)	1.00 (reference)	1.10 (1.01–1.19)	1.38 (1.23–1.55)	1.77 (1.48–2.11)
Age ≥80 y					
Events, *n/1000 person-years*	2/0.01	1114/11.3	1645/17.0	313/2.9	47/0.5
Multivariate HR (95% CI)	1.30 (0.31–5.40)	1.00 (reference)	1.05 (0.97–1.14)	1.28 (1.12–1.46)	1.24 (0.92–1.67)
Women (NHS and NHS II)					
All ages					
Events, *n/1000 person-years*	143/9.5	8954/974.9	8417/825.9	4212/381.8	3028/251.9
Age-adjusted HR (95% CI)	1.57 (1.33–1.85)	1.00 (reference)	1.07 (1.04–1.10)	1.26 (1.22–1.31)	1.86 (1.79–1.94)
Multivariate HR (95% CI)	1.49 (1.26–1.76)	1.00 (reference)	1.05 (1.01–1.08)	1.21 (1.16–1.26)	1.71 (1.64–1.78)
Age <60 y					
Events, *n/1000 person-years*	42/6.6	2481/683.8	2152/550.1	1208/264.9	1193/199.3
Multivariate HR (95% CI)	1.67 (1.22–2.27)	1.00 (reference)	1.04 (0.98–1.10)	1.24 (1.16–1.33)	1.74 (1.62–1.87)
Age 60–64 y					
Events, *n/1000 person-years*	25/1.2	1952/131.8	1821/123.0	977/54.8	723/27.2
Multivariate HR (95% CI)	1.66 (1.11–2.47)	1.00 (reference)	1.01 (0.95–1.08)	1.22 (1.13–1.32)	1.72 (1.57–1.88)
Age ≥65 y					
Events, *n/1000 person-years*	76/1.7	4521/159.2	4444/152.8	2027/62.1	1112/25.4
Multivariate HR (95% CI)	1.39 (1.11–1.75)	1.00 (reference)	1.06 (1.02–1.10)	1.18 (1.12–1.25)	1.65 (1.54–1.76)
Never-smokers only					
Men (HPFS)					
All ages					
Events, *n/1000 person-years*	3/0.1	1015/49.7	1544/83.6	412/22.0	121/5.2
Age-adjusted HR (95% CI)	0.94 (0.30–2.99)	1.00 (reference)	1.09 (1.00–1.18)	1.50 (1.33–1.69)	2.21 (1.82–2.69)
Multivariate HR (95% CI)	0.92 (0.29–2.93)	1.00 (reference)	1.09 (1.00–1.18)	1.48 (1.31–1.67)	2.20 (1.80–2.67)
Age <70 y					
Events, *n/1000 person-years*	1/0.1	132/30.3	289/53.5	122/15.5	52/3.9
Multivariate HR (95% CI)	2.89 (0.39–21.34)	1.00 (reference)	1.27 (1.03–1.57)	1.78 (1.39–2.29)	3.19 (2.29–4.44)
Age 70–79 y					
Events, *n/1000 person-years*	1/0.05	339/13.4	604/22.4	170/5.3	47/1.1
Multivariate HR (95% CI)	0.66 (0.09–4.84)	1.00 (reference)	1.12 (0.97–1.28)	1.45 (1.20–1.75)	1.95 (1.42–2.66)
Age ≥80 y					
Events, *n/1000 person-years*	1/0.01	544/6.0	651/7.7	120/1.2	22/0.2
Multivariate HR (95% CI)	0.70 (0.09–5.32)	1.00 (reference)	1.02 (0.90–1.15)	1.41 (1.14–1.75)	1.66 (1.06–2.60)
Women (NHS and NHS II)					
All ages					
Events, *n/1000 person-years*	52/4.9	3165/493.6	3257/413.6	1773/198.9	1424/140.3
Age-adjusted HR (95% CI)	1.55 (1.18–2.05)	1.00 (reference)	1.15 (1.09–1.21)	1.43 (1.35–1.51)	2.26 (2.12–2.40)
Multivariate HR (95% CI)	1.50 (1.14–1.98)	1.00 (reference)	1.10 (1.05–1.16)	1.30 (1.23–1.38)	1.96 (1.83–2.09)
Age <60 y					
Events, *n/1000 person-years*	17/3.6	829/363.1	764/285.1	477/142.6	553/113.5
Multivariate HR (95% CI)	1.90 (1.16–3.09)	1.00 (reference)	1.09 (0.99–1.20)	1.36 (1.21–1.53)	2.13 (1.90–2.39)
Age 60–64 y					
Events, *n/1000 person-years*	6/0.4	619/55.3	615/54.2	380/24.9	311/12.9
Multivariate HR (95% CI)	1.72 (0.76–3.90)	1.00 (reference)	1.01 (0.90–1.13)	1.29 (1.13–1.47)	1.92 (1.67–2.22)
Age ≥65 y					
Events, *n/1000 person-years*	29/0.8	1717/75.2	1878/74.4	916/31.4	560/13.8
Multivariate HR (95% CI)	1.31 (0.90–1.90)	1.00 (reference)	1.13 (1.06–1.21)	1.27 (1.17–1.38)	1.85 (1.67–2.04)

BMI = body mass index; HPFS = Health Professionals Follow-Up Study; HR = hazard ratio; NHS = Nurses' Health Study.
* Multivariate HRs were adjusted for race (white or nonwhite), family history of cardiovascular disease (yes or no), family history of cancer (yes or no), alcohol consumption (0, 0.1 to 4.9, 5.0 to 9.9, 10.0 to 14.9, or >14.9 g/d), and total daily energy intake (quintiles). HRs for participants in the NHS and NHS II were also adjusted for menopausal status (premenopausal, postmenopausal, or unsure/dubious), postmenopausal hormone use (current, ever, never, or unsure/dubious), and parity (nulliparous, 1, 2, 3, or ≥4). HRs for participants in the NHS II were also adjusted for oral contraceptive use (ever, never, or current). Follow-up periods were 1992 to 2012 for the NHS, 2005 to 2013 for the NHS II, and 2002 to 2012 for the HPFS.

Figure 1. Hazard ratios for maximum BMI with 16 y of weight history and baseline BMI among all participants.



Error bars represent 95% CIs. BMI = body mass index.
* $P < 0.05$ for difference.

smoking participants, estimates for all categories were strengthened (Figure 2). Risk for death in the underweight group decreased but was still significantly elevated when maximum BMI (HR, 1.47 [CI, 1.25 to 1.74]) was considered instead of baseline BMI (HR, 1.88 [CI, 1.75 to 2.01]).

Cause-Specific Mortality

We examined the relationship between maximum BMI and mortality due to CVD (8017 events), coronary heart disease (3410 events), stroke (1998 events), cancer (11 135 events), respiratory disease (2607 events), and other causes (10 790 events) (Table 2 of the Supplement). The NHS II was excluded from analyses for respiratory disease, stroke, and coronary heart disease due to the low number of events. The strongest association was observed for CVD mortality (overweight HR, 1.21 [CI, 1.15 to 1.28]; obese I HR, 1.63 [CI, 1.52 to 1.74]; obese II HR, 2.74 [CI, 2.53 to 2.97]), particularly death due to coronary heart disease (overweight HR, 1.32 [CI, 1.21 to 1.44]; obese I HR, 1.97 [CI, 1.78 to 2.19]; obese II HR, 3.34 [CI, 2.95 to 3.79]). The association between maximum overweight and death from other causes (excluding CVD, cancer, or respiratory diseases) was also significantly elevated (HR, 1.07 [CI, 1.02 to 1.12]). Compared with all participants, the HRs among never-smokers were generally stronger (Table 8 of the Supplement).

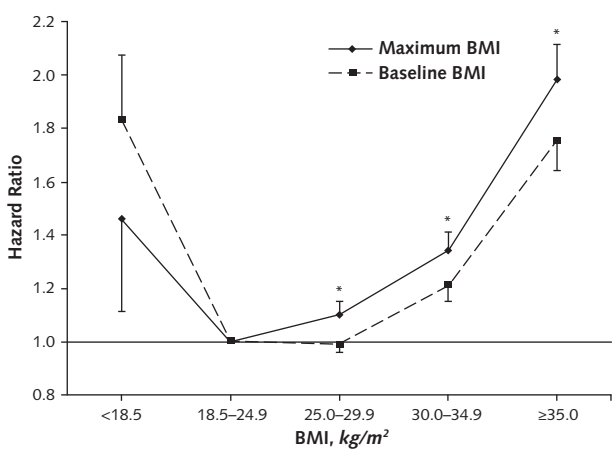
DISCUSSION

In our primary analysis of 3 large cohorts of health professionals, using a 16-year weight history, we found that compared with participants with a maximum BMI of 18.5 to 24.9 kg/m^2, those with a maximum BMI in the overweight or obese categories were at elevated risk for all-cause death; CVD death; and death due to non-CVD causes, cancer, or respiratory disease. Our findings corroborate previous pooled analyses by the Global BMI Mortality Collaboration (7), the Prospective Studies Collaboration (20), and Berrington de Gonzalez and colleagues (6), as well as a recent dose-response meta-analysis (21) suggesting an optimal BMI range of 18.5 to 24.9 kg/m^2 for never-smokers and for all persons.

Compared with using BMI data from 1 baseline questionnaire, use of extended weight histories revealed stronger associations with risk for death and reversed the paradoxical association between overweight and mortality that previous analyses have reported (1). Although the magnitude of association for a maximum BMI in the overweight category was relatively small, this association was robust in sensitivity analyses. The reversal of the HR associated with being overweight from significantly protective to significantly harmful is also noteworthy and suggests that reverse causation plays a vital role in creating the purported obesity paradox. Furthermore, use of fine BMI categories revealed significant increases in risk for participants in the range of 25.0 to 27.4 kg/m^2 and those in the range of 27.5 to 29.9 kg/m^2 when 22.5 to 24.9 kg/m^2 was used as the reference. These significant elevations in risk are important from a public health perspective because about one third of adults in the United States and more than one quarter of the world population is overweight (22, 23).

Analyses stratified by both maximum and baseline BMI revealed that the highest risk for death occurred among participants who had substantial decreases in weight, which most likely reflects unintentional weight loss caused by apparent or preclinical disease. Consistent with our findings, weight loss without regard to intent has been identified as a significant predictor of death (24–27) because most permanent weight loss tends to be unintentional (28–30). However, successful intentional weight loss has been associated with decreased risk for early death (24, 30, 31). By using max-

Figure 2. Hazard ratios for maximum BMI with 16 y of weight history and baseline BMI among never-smokers.



Error bars represent 95% CIs. BMI = body mass index.
* $P < 0.05$ for difference.

imum BMI with an extended weight history, we were able to address the problem of reverse causation associated with illness-induced weight loss (12, 14). Because weight loss can initiate a decade or more before death (11), use of an extended weight history is important to minimize bias in studies of BMI and mortality. We chose a 16-year weight history to strike a tradeoff between minimal reverse causation and maximum follow-up time, but we note that in an extended analysis in the NHS only, estimates did not completely stabilize even after 24 years of weight history (**Tables 17** and **18** of the **Supplement**). Thus, our HRs are likely overestimated for underweight maximum BMI and underestimated for overweight and obese maximum BMI.

Our study has several strengths. We analyzed 3 large cohorts of men and women of various ages with long follow-up periods. Enrollment of health professionals allowed for high response rates, increased validity of exposure and outcome data, and minimization of confounding due to educational and socioeconomic homogeneity. In contrast to using retrospective data (12), the prospective nature of our cohorts reduced recall bias and selection bias. The establishment of an extended weight history period also diminished reverse causation by capturing BMI data before disease development, even if the disease had not been diagnosed, allowing us to retain the vast majority of participants in our study (11). Our analyses that included only never-smokers showed a similar J-shaped association, with greater magnitude of excess risk in all BMI categories above the normal-weight category, enhancing the generalizability of our results.

Limitations include the use of data from predominantly white participants, most of whom had high socioeconomic status. Future research may benefit from incorporation of maximum BMI with weight history to study mortality in other diverse cohorts. We also cannot rule out residual confounding and confounding by unmeasured variables. Although the use of BMI as a measure for adiposity is imperfect because it does not differentiate between fat and lean body mass, most population variance in adiposity is explained by BMI (2, 32). Because BMI was self-reported, systematic underestimation of true BMI may have occurred, although the correlation between self-reported and measured weight was generally high in the NHS (r = 0.97) (15). Recalled maximum BMI should also be validated against longitudinal data because such a measure would capture lifetime maximum BMI. A prior study investigating the validity of recalled maximum BMI found a strong correlation with contemporaneous data; however, the gold standard was based on self-reported data, and validity was evaluated only over a 12-year period (33). Finally, a substantial number of participants had missing BMI values from at least 1 survey cycle, which may have introduced bias if the participant's maximum weight was more likely to have occurred during survey cycles with missing data.

Our findings suggest that the lowest risk for death occurs among persons with a maximum BMI of 18.5 to 24.9 kg/m^2 at all ages, regardless of sex and smoking status. Maximum BMIs in the overweight and obese categories were associated with elevated risks for all-cause death and death due to CVD, cancer, and other causes. In contrast to baseline BMI, use of maximum BMI with an extended weight history period may minimize reverse causation due to illness-induced weight loss.

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