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The association of body mass index with mortality in the California Teachers Study

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Abstract

Although underweight and obesity have been associated with increased risk of mortality, it remains unclear whether the associations differ by hormone therapy (HT) use and smoking. The authors examined the relationship between body mass index (BMI) and mortality within the California Teachers Study (CTS), specifically considering the impact of hormone therapy (HT) and smoking. The authors examined the associations of underweight and obesity with risks of all-cause and cause-specific mortality, among 115,433 women participating in the CTS, and specifically examined whether HT use or smoking modifies the effects of obesity. Multivariable Cox proportional hazards regression provided estimates of relative risks (RRs) and 95% confidence intervals (CIs). During follow up, 10,574 deaths occurred. All-cause mortality was increased for underweight (BMI < 18.5; adjusted relative risk [RR] = 1.33, 95% confidence interval [CI] =1.20–1.47) and obese participants (BMI ≥ 30: RR = 1.27, 95% CI = 1.19–1.37) relative to BMI of 18.5 – 24.9). Respiratory disease mortality was increased for underweight and obese participants. Death from any cancer, and breast cancer specifically, and cardiovascular disease was observed only for obese participants. The obesity and mortality association remained after stratification on HT and smoking. Obese participants remained at greater risk for mortality after stratification on menopausal hormone therapy and smoking. Obesity was associated with increased all-cause mortality, as well as death from any cancer (including breast), and cardiovascular and respiratory diseases. These findings help to identify groups at risk for BMI-related poor health outcomes.

Introduction

The prevalence of obesity has been rising in the United States and other western countries, as well as in developing nations [1–7]. Previous population-based research has linked high body mass index (BMI, kg/m^2), a measure of obesity, to all-cause mortality [8–14], as well as death from all cancers combined [10, 12, 15-18], and cardiovascular disease (CVD) [10, 12, 17, 19–21]. Low BMI has been associated with deaths due to respiratory disease, although this relationship is confounded by smoking-related morbidity [10]. BMI in adulthood

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and weight change throughout life have gender-specific effects on mortality [2, 6, 12-14, 18, 22, 23].

A recent collaborative cohort analysis of over 900,000 adults indicated that high BMI are associated with statistically significant changes in blood pressure, lipoprotein levels, and diabetes [10]. Weight loss lowers blood pressure, decreases serum lipids, cholesterol, and blood glucose [1], and the risk of vascular disease [24, 25]. Women with high BMI are at increased risk of coronary heart disease [19] and colon cancer [26], and tend to have more advanced stages of breast cancer at diagnosis [27]. Obesity is known to increase the risk of reproductive cancers in women [28] possibly due to greater concentrations of free estradiol and free testosterone in overweight and obese women [28]. However, postmenopausal women using menopausal hormone therapy (HT) have shown a reduction in all-cause mortality [29]. Therefore, it is important to explicitly consider history of HT use, as well as potential confounding factors when examining the association between BMI and mortality in women.

The aim of this paper is to investigate the relationship of BMI to all-cause and cause-specific (CVD, any cancer, breast cancer, and respiratory disease) mortality in the California Teachers Study (CTS). In addition we specifically looked at the impact of HT use and smoking on the obesity and mortality relationships.

Methods

The CTS is a prospective cohort study of 133,479 female California public school teachers and administrators who were enrolled in the California State Teachers Retirement System. A detailed account of the methods employed by the CTS has been published elsewhere [30]. Participants completed a baseline questionnaire and returned it by mail during 1995–1996 [30]. The baseline survey collected information on height, weight, history of oral contraceptive use, HT use, reproductive history, co-morbidities (including diabetes, heart attack, hypertension, stroke, and cancer) and family history of disease, as well as behavioral factors such as physical activity, caloric intake, alcohol consumption, and smoking. Institutional Review Board approval for the CTS was obtained from all participating institutions.

Study Sample

CTS participants were excluded sequentially in this analysis if they did not report their weight or height at baseline (n=6,235); if their BMI (kg/m^2) value was implausibly low or high (n=61); if they were older than 95 years at baseline (n=58); if they provided insufficient dietary information (n=11,623); and if they asked to be included only in breast cancer research (n=10). Participants who died within the first year of follow-up were also excluded (n=59), since weight loss and underweight may have resulted from pre-existing illness. After all exclusions, 115,433 participants remained eligible for this analysis.

Outcomes

Participants contributed person-years of follow-up from the date of baseline questionnaire completion until the date of death or date of a censoring event (including date of a move outside of the United States, date of a death due to accident or suicide, or the end of follow-up on December 31, 2007). Deaths were identified via annual linkage with the State of California mortality files, the Social Security Administration Death Master File and the National Death Index. In this study we used cause of death information recorded on the death certificates as follows: deaths from any cancer (International Classification of Disease (ICD) codes: ICD-9 = 140–208, ICD-10 = C00-99.9, breast cancer (ICD-9=174, ICD-10=C50), or respiratory disease (ICD-9=460–519, ICD-10=J00-98). Cancer, CVD, and

respiratory illness were chosen because they are major groupings of possible causes of death. Breast cancer was also included in this analysis because it is a particular focus of the authors and the CTS in general.

For cause-specific mortality analyses, we excluded participants reporting a co-morbidity at baseline (i.e., prevalent cases) relating to the cause of death in the analysis, in order to limit survivor advantage of those cases. For CVD mortality, we excluded participants who reported a diagnosis of heart attack, stroke, and/or high blood pressure at baseline (n=1,511). For any cancer, we excluded participants reporting any cancer diagnosis at baseline (n=12,318), while for breast cancer mortality we excluded participants who reported a breast cancer diagnosis at baseline (n=5,500). For death due to respiratory illness, we did not exclude any additional participants at baseline beyond those excluded for the all-cause mortality analysis.

Independent variables

BMI at baseline was calculated from self-reported height and weight and was categorized based on the World Health Organization classification [2] as <18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25.0–29.9 kg/m^2 (overweight), and ≥30 kg/m^2 (obese). Weight change from age 18 to baseline was classified into four groups: decrease of more than 5 kg, no change (defined as +/− 5 kg), an increase of 5.1–10 kg, and >10 kg gain.

History of diabetes, hypertension, heart attack, and stroke, were obtained from self-report in the baseline questionnaire and supplemented by diagnoses listed in California Office of Statewide Health Planning and Development (OSHPD) hospital discharge records from 1991 until questionnaire completion [31]. Prevalent cancer diagnoses were obtained from self-report in the baseline questionnaire and supplemented by linkages with the California Cancer Registry, which receives reports of over 99% of cancer diagnoses occurring in California [32].

Detailed information on recreational physical activity was collected in the baseline questionnaire. Physical activity was reported as the average number of hours per week of strenuous or moderate exercise. Physical activity measures in the CTS have been further described elsewhere [33].

Average daily percentage of calories from fat was determined from the food-frequency portion of the baseline questionnaire [34], categorized into 4 groups: <25%, 25–29.9%, 30–34.9%, and ≥35%. Participants were classified as never smokers, former smokers, current smokers, or unknown smoking status. Alcohol use was based on the average number of alcoholic drinks consumed per day, and grouped into three categories: none, <20 grams/day, or ≥20 grams/day. Participants' self-reported race/ethnicity was categorized as non-Hispanic white, African American, Hispanic/Latina, Native American, Asian/Pacific-Islander, or other/unknown.

Participants were classified as either premenopausal or postmenopausal, with perimenopausal participants included in the postmenopausal group. Participants were classified as perimenopausal if they reported that their periods had stopped in the previous six months. Participants were classified as postmenopausal if they: reported natural menopause more than 6 months prior to baseline (n=34,147); had a bilateral oophorectomy (n=11,597); were 56 years or older and did not report being premenopausal (n=7,523); or if their periods had stopped due to other reasons including pituitary adenoma, medication, chemotherapy, radiation treatment, or another reason (n=4,902). The criterion for classifying women as menopausal at age 56 years or older, used in recent CTS analyses [35, 36], is based on previous work indicating that among women with natural menopause 97% were

postmenopausal by age 56 years [37]. Postmenopausal participants were grouped according to their HT use at baseline as never HT user, former user of any HT, current user of estrogen only, current user of estrogen and progestin, or unknown hormone therapy use [35].

Statistical analyses

Characteristics of participants at baseline were compared across the subgroups defined by BMI at baseline (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2) using the chi-square statistic.

Multivariable Cox proportional hazards regression models were used to estimate the hazard rate ratio, a measurement of relative risk (RR), and 95% confidence intervals (CI) for the association of BMI with all-cause and cause-specific mortality. All models used age at cohort entry and age at death or censoring event as the time scale and were stratified by age at cohort entry. Four models were fit to examine the association between BMI and all-cause mortality. Model 1 was adjusted for race/ethnicity; Model 2 was additionally adjusted for HT use); Model 3 was further adjusted for physical activity; Model 4 was additionally adjusted for co-morbidities (including diabetes, hypertension, heart attack, stroke, and any cancer), smoking status, alcohol consumption, and percent of daily calories from fat; and Model 5 was further adjusted for weight change from age 18 to baseline. Finally, to examine the impact of smoking history and use of menopausal hormone therapy on the relationship between BMI and mortality (all-cause, and cause-specific) we stratified the analysis, using Model 5, by smoking history (never, ever), and HT history (never, ever).

Results

Cohort characteristics

The cohort consisted of 115,433 eligible women who were followed for 1,322,634 person-years. Overall, 10,594 women died during the follow-up time period. Causes of death for this study included any cancer (N=2,292); breast cancer (N=302); CVD (N=3,626); and respiratory disease (N=946). The average age at baseline was 53.1 years (standard deviation = 14.1 years).

Table 1 provides the age-adjusted distribution of several participant characteristics according to BMI at baseline. Approximately 60% of participants with normal BMI (18.5–24.9 kg/m^2) at age 18 still had normal BMI at cohort entry. Approximately 80% of participants who gained more than 10 kg since age 18 were overweight or obese at cohort entry. Higher BMI was observed among African-American women (and Native American women to a smaller extent), postmenopausal women (especially those who never used HT), women reporting fewer than 3 hours per week of strenuous or moderate physical activity, never drinkers of alcohol, never or former smokers, women with greater percentage of their daily calories from fat, and women with one or more co-morbidities.

BMI and all-cause mortality

Risk for all-cause mortality was statistically significantly increased for underweight participants (RR = 1.33, 95% CI = 1.20–1.47) and for obese participants (RR = 1.27, 95% CI = 1.19–1.37) compared to normal weight participants after adjustment for age, race/ethnicity, weight change from age 18 to baseline, physical activity, history of co-morbidities, smoking status, alcohol consumption, HT, and percent daily calories from fat (Model 5, Table 2). HT use (Table 2, Model 2 compared to Model 1) did not affect the association between BMI and all-cause mortality for any BMI category. Overweight participants did not significantly differ from normal weight participants with respect to all-cause mortality.

In a restricted model, we excluded participants who reported having had a defined co-morbidity at baseline (diabetes, hypertension, heart attack, stroke, and cancer). Among the 71,144 remaining participants, the mortality risk estimate for underweight and for obese participants (RR = 1.31, 95% CI = 1.09–1.58, and RR = 1.32, 95% CI = 1.15–1.53, respectively) were only slightly attenuated (data not shown).

BMI and cause-specific mortality

Compared to normal weight participants, underweight participants were at increased risk of death due to due to respiratory disease (RR = 1.79, 95% CI = 1.36–2.34) (Table 3). Obese participants, compared to participants of normal weight, were at an increased risk of death due to any cancer (RR =1.32, 95% CI = 1.14–1.53), breast cancer (RR =1.57, 95% CI = 1.07–2.31), CVD (RR =1.38, 95% CI = 1.22–1.55), and respiratory disease (RR =1.46, 95% CI = 1.15–1.85).

After stratification by smoking status (Table 4), obese never smokers had increased risk of all cause mortality (RR=1.32, 95% CI=1.21–1.45), any cancer (RR=1.48, 95% CI= 1.21–1.82), and CVD (RR=1.50, 95% CI= 1.29–1.75) as compared to normal weight never smokers; but for obese ever smokers only risk of all-cause mortality was statistically significantly increased (RR= 1.13, 95% CI= 1.02–1.26) as compared to normal weight ever smokers. Never smokers who were underweight were at increased risk for all-cause mortality (RR =1.34, 95% CI = 1.17–1.54), and for CVD mortality (RR =1.34, 95% CI = 1.07–1.68), as compared to normal weight never smokers. For smokers, being underweight was associated with risk only for all-cause mortality (RR=1.41, 95% CI = 1.21–1.65) and respiratory disease mortality (RR = 2.22, 95% CI = 1.58–3.11). The analyses for underweight smokers and non-smokers for any cancer and breast cancer were based on small numbers.

After stratification by history of hormone therapy use (Table 5), obese never users of HT had increased risk of all cause mortality (RR=1.27, 95% CI=1.12–1.44), any cancer (RR=1.38, 95% CI= 1.03–1.84), and CVD (RR=1.41, 95% CI= 1.15–1.74) as compared to normal weight never users. Obese HT users had statistically significantly increased risk of all-cause mortality (RR= 1.19, 95% CI= 1.08–1.32), and any cancer mortality (RR=1.23, 95% CI=1.00, 1.50), as compared to normal weight ever users. Never users of HT who were underweight were at increased risk for all-cause mortality (RR =1.22, 95% CI = 1.02–1.47), and for respiratory disease (RR =1.97, 95% CI = 1.27–3.07), as compared to normal weight never users. For HT users, being underweight was associated with risk for all-cause mortality (RR=1.47, 95% CI = 1.27–1.69) and respiratory disease mortality (RR = 1.90, 95% CI = 1.28–2.82).

Further stratification on current smoking status (former and current) or type of HT use (estrogen-only and estrogen plus progestin) revealed similar associations, however the division into more strata resulted in small numbers of events in several categories of BMI (data not shown).

Discussion

Being underweight or obese was associated with an increased risk of all-cause mortality among participants in the CTS. A similar U-shaped association of BMI with all-cause mortality has been observed in other studies [8, 10, 22, 38, 39]. Control of HT use in our statistical models did not significantly alter the association between BMI and all-cause mortality overall or among postmenopausal women. When we included weight change from age 18 to baseline in our all-cause mortality analysis, the risk of death in obese participants slightly increased above the level of the HT-adjusted model, but was not as high as in the

unadjusted model. Obese participants also had an increased risk of death from any cancer (including breast cancer), CVD, and respiratory disease; over weight participants (those with BMI of 25–29.9) did not differ in mortality risk from normal weight participants; underweight participants had increased risk of death due to respiratory disease.

A variety of biological mechanisms may be responsible for linking obesity with mortality. A large prospective cohort study recently linked high BMI with high systolic blood pressure and high lipoprotein levels [10], and several other studies have linked high BMI to vascular disease [24, 25, 40]. Obesity has also been linked to increased risk of cancer [26, 41, 42]. Strategies to reduce obesity, such as through physical exercise, also have apparent anti-carcinogenic effects by decreasing fat deposits, changing sex-hormone levels, improving immune function, and/or reducing inflammation [43]. Obesity in postmenopausal women is associated with an increased risk of breast cancer [44, 45] perhaps because overweight and obese postmenopausal women have higher levels of circulating estrogens and androgens [46–48]. Cancers of the endometrium, large intestine, pancreas, and kidney, have also been associated with obesity, implicating a variety of biologic pathways in which body adiposity can impact apoptosis and cell proliferation in target cells [10, 48]. Beyond cancer risk, high BMI is a risk factor for cancer mortality [15]. On the other hand, low BMI and decreased adiposity has been implicated in increased mortality from respiratory illness (especially chronic obstructive pulmonary disease or COPD) [49].

We addressed smoking as a possible confounder by adjusting for smoking status in our multivariate models. The CTS is largely a non-smoking cohort (only about 5% of participants were current smokers at baseline and about 30% were former smokers), so the adjustment had little impact on risk estimates. However, we did look at the effect of BMI on mortality separately for smokers (current and former combined) and for never smokers. A similar U-shaped all cause mortality curve for never smokers and smokers was found, likely due to large number of former smokers in the smoking category. Moreover, we observed that history or type of HT use did not modify risk of mortality among post-menopausal women.

Limitations

Limitations of the present study include possible misclassification of exposures collected by self-report, including BMI at baseline and at age 18, smoking status, HT use, recreational physical activity, nutritional intake, and co-morbid conditions. However, any misclassification should be non-differential with respect to mortality outcomes because these data were collected before the patients who died were even diagnosed with the diseases of interest. A second limitation is that changes in BMI occurring after baseline, but before death or end of follow-up were not available and BMI at baseline may not reflect BMI at the time of diagnosis. Third, the CTS represents a sample of California women who are public school professionals and may not be fully representative of women across the United States. For example, the mean BMI in the CTS is slightly lower than that of a comparable age and race-matched California population (24.8 versus 25.7 kg/m^2, respectively) and fewer CTS participants were current smokers compared to this same population [30]. Fourth, our co-morbidity variables are based on self-report at baseline and diagnoses listed in California OSHPD hospital discharge records from 1991 through baseline. Using the OSHPD data to supplement reported co-morbidities may miss the diagnoses that did not require hospitalization. Fifth, cause of death may not be assigned in a consistent manner across the cohort. Finally, some of the stratified analyses were based on small numbers. Based on considerations of sample size in cohort studies by Breslow and Day [50], we can detect relative risks of around 1.30 with significance level at 5% and power at 80% in strata with about 200 events, indicating that all of our all-cause and cause-specific analyses, and most of the smoking- and HT- stratified analyses are sufficiently powered.

However, for less common outcomes such as breast cancer, some of the smoking- and HT-stratified analyses may be underpowered in BMI categories with few events, thus formal tests of interaction may also be underpowered. Nevertheless, the large and well-characterized CTS cohort provided a resource of women in which BMI could be assessed in relation to mortality after adjusting for potentially relevant confounding exposures including HT, diet, smoking and alcohol use.

Conclusions

This analysis confirms an increased risk of all-cause mortality for underweight and obese women in the CTS, that is independent of HT use and smoking history; further neither of exposures served to modify the main effects of BMI on risk of dying. Low BMI was associated with increased risk of death due to cancer and respiratory disease, while obesity was associated with increased risk of death from all cancers combined, breast cancer, CVD, respiratory disease, and diabetes. Further evaluation of modifiable risk factors contributing to women's BMI and risk of mortality from specific causes is warranted. This information may help inform groups who are at risk for CVD, cancer, respiratory disease and diabetes that may benefit from careful monitoring for these conditions as well as preventive interventions. With increasing obesity in the United States we may begin to see diminishing life expectancy in the future, further implicating obesity as a major contemporary public health problem.

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Table 1

Baseline characteristics of 115,433 participants from the California Teachers Study by body mass index (BMI, in kg/m^2) at baseline

	BMI at baseline, n (%[a])			
	<18.5	**18.5–24.9**	**25–29.9**	**≥30**
BMI at age 18, kg/m^2				
<18.5	757 (7.3)	6062 (69.9)	1541 (17.1)	493 (5.6)
18.5–24.9	2117 (2.1)	56349 (58.8)	24839 (26.3)	11524 (12.9)
25–29.9	163 (2.1)	3502 (41.1)	1929 (20.7)	3091 (36.2)
≥30	41 (1.3)	1240 (42.7)	594 (19.0)	1191 (36.9)
				p<.0001
Weight change from age 18 to baseline				
>5 kg loss	1351 (11.5)	8496 (77.0)	1066 (9.1)	291 (2.4)
No change: +/−5 kg	1675 (4.4)	32207 (89.1)	2150 (5.6)	344 (1.0)
5.1–10 kg gain	51 (0.2)	16906 (78.8)	4486 (19.3)	396 (1.7)
>10.0 kg gain	1 (<0.01)	9544 (21.0)	21201 (45.3)	15268 (33.7)
				p<.0001
Race/Ethnicity				
White	2667 (2.4)	59289 (58.4)	25207 (24.8)	13967 (14.4)
African American	23 (0.8)	1031 (37.9)	934 (34.1)	749 (28.3)
Hispanic/Latina	100 (2.0)	2486 (52.1)	1181 (27.2)	789 (18.7)
Native American	36 (3.2)	460 (47.0)	255 (27.9)	177 (21.9)
Asian/Pacific Islander	194 (4.4)	2678 (67.8)	783 (20.6)	266 (7.2)
Other/Unknown	58 (2.6)	1209 (54.2)	543 (25.5)	351 (17.7)
				p<.0001
Hormone therapy use				
None	444 (2.5)	8147 (50.2)	4618 (27.9)	2969 (19.5)
Past hormone therapy use	235 (2.1)	4977 (50.1)	2974 (30.0)	1578 (17.9)
Current estrogen use	360 (2.0)	9303 (53.3)	5051 (28.8)	2602 (15.9)
Current estrogen and progestin use	466 (2.3)	11917 (60.0)	5085 (25.2)	2399 (12.5)
Progestin only	24 (2.0)	537 (52.2)	254 (24.0)	236 (21.8)
Premenopausal	1397 (2.8)	28826 (62.7)	9081 (21.2)	5631 (13.3)
Unknown	152 (2.1)	3446 (54.8)	1840 (28.5)	884 (14.6)
				p<.0001
Smoking status				
Never	2167 (2.7)	44465 (58.2)	18432 (24.4)	10518 (14.7)
Former	685 (1.9)	18913 (56.9)	8803 (25.9)	4973 (15.3)
Current	202 (3.0)	3359 (57.3)	1520 (26.6)	729 (13.1)
Unknown	24 (3.6)	416 (62.0)	148 (21.3)	79 (13.1)
				p<.0001

	BMI at baseline, n (%[a])			
	<18.5	**18.5–24.9**	**25–29.9**	**≥30**
Strenuous or moderate physical activity				
0–0.509 hrs/week	448 (2.9)	7204 (50.8)	3860 (27.7)	2426 (19.1)
0.51–3.00 hrs/week	1398 (2.2)	32562 (56.6)	14779 (25.7)	8593 (15.5)
≥ 3.01 hrs/week	1214 (2.6)	27124 (61.6)	10127 (23.2)	5219 (12.6)
Unknown	18 (3.0)	263 (55.7)	137 (28.2)	61 (13.1)
				p<.0001
Average percent calories from fat				
< 25	641 (2.7)	14742 (65.1)	5294 (22.9)	2118 (9.4)
25–29.9	577 (2.1)	14845 (60.2)	6173 (25.4)	2903 (12.3)
30–34.9	743 (2.4)	16907 (57.9)	7323 (25.2)	4013 (14.5)
≥35	1117 (2.6)	20659 (52.1)	10113 (25.7)	7265 (19.7)
				p<.0001
Average alcohol consumption, g/day				
None	1182 (2.7)	20549 (52.2)	9951 (25.6)	7065 (19.5)
< 20	1643 (2.3)	40574 (60.3)	16388 (24.4)	8332 (13.0)
≥ 20	253 (2.5)	6030 (61.7)	2564 (26.3)	902 (9.5)
				p<.0001
History of diabetes				
No	3025 (2.5)	66155 (58.6)	27916 (24.9)	14994 (14.0)
Yes	53 (1.3)	998 (27.7)	987 (28.1)	1305 (42.9)
				p<.0001
Number of existing co-morbidities[b]				
None	2042 (2.6)	44143 (61.4)	16565 (23.6)	8394 (12.3)
1	849 (2.2)	19212 (53.3)	9644 (26.7)	5997 (17.8)
≥ 2	178 (1.8)	3614 (40.7)	2628 (31.1)	1878 (26.4)
Unknown	9 (2.8)	184 (60.3)	66 (25.4)	30 (11.5)
				p<.0001

[a] All percentages are standardized by 5-year age categories.

[b] Self-reported co-morbidities include diabetes, hypertension, heart attack, stroke, and any cancer

Table 2

Multivariable adjusted* relative risks (RR) and 95% confidence intervals (CI) or all-cause mortality associated with body mass index (BMI) at baseline

	Person-years N (deaths)		Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]		Model 5[e]	
			RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
BMI at baseline, kg/m^2												
< 18.5 (under weight)	34032	427	1.56	1.41, 1.72	1.55	1.40, 1.71	1.54	1.39, 1.69	1.46	1.32, 1.61	1.33	1.20, 1.47
18.5–24.9 (normal weight)	771411	5618	1.0		1.0		1.0		1.0		1.0	
25–29.9 (over weight)	330721	2906	0.99	0.95, 1.04	0.98	0.94, 1.02	0.98	0.93, 1.02	0.94	0.89, 0.98	1.04	0.98, 1.10
≥30 (obese)	186470	1623	1.32	1.25, 1.40	1.28	1.21, 1.36	1.28	1.21, 1.35	1.12	1.06, 1.19	1.27	1.19, 1.37

[a] Stratified by age (in years) at baseline and adjusted for race/ethnicity.

[b] Additionally adjusted for hormone therapy

[c] Additionally adjusted for physical activity.

[d] Additionally adjusted for diabetes, co-morbidities (incl. hypertension, heart attack, stroke, and any cancer), smoking status, alcohol consumption, and percent daily calories from fat.

[e] Further additionally adjusted for weight change (in Kg) from age 18 to baseline.

Table 3

Multivariable adjusted* relative risks (RR) and 95% confidence intervals (CI) for cause-specific mortality associated with body mass index (BMI) at baseline[a]

	Any Cancer	Breast Cancer	Cardiovascular Disease	Respiratory Disease
Total Deaths	2291	302	3626	946
BMI at baseline, Kg/m^2 <18.5 (under weight)				
Deaths	64	7	139	65
Person-years	31026	32956	33632	34032
RR	1.05	1.28	1.15	1.79
95% CI	0.81, 1.36	0.58, 2.79	0.96, 1.38	1.36, 2.34
18.5–24.9 (normal weight)				
Deaths	1178	141	1939	545
Person-years	698848	739182	763980	771411
RR	1.0	1.0	1.0	1.0
25–29.9 (over weight)				
Deaths	665	89	1005	191
Person-years	295044	314483	326320	330721
RR	1.11	1.14	1.06	0.79
95% CI	0.99, 1.25	0.82, 1.58	0.96, 1.16	0.65, 0.96
≥30 (obese)				
Deaths	384	65	543	145
Person-years	167779	178572	184067	186470
RR	1.32	1.57	1.38	1.46
95% CI	1.14, 1.53	1.07, 2.31	1.22, 1.55	1.15, 1.85

[a]Stratified by age (in years) at baseline and adjusted for hormone therapy, weight change (in Kg) from age 18 to baseline, physical activity, co-morbidities (incl. diabetes, hypertension, heart attack, stroke, and any cancer), smoking status, alcohol consumption, and percent daily calories from fat.

Table 4

Multivariable adjusted [a] relative risk (RR) and 95% confidence interval (CI) for all-cause, any cancer-specific, breast cancer-specific, cardiovascular-specific, and respiratory-specific mortality according to body mass index (BMI) at baseline, stratified by self-reported smoking history at baseline[b]

	Smoking Status	All-Cause		Any Cancer		Breast Cancer		Cardiovascular Disease		Respiratory Disease	
		Never	Ever	Never	Ever	Never	Ever	Never	Ever	Never	Ever
	Total Deaths	5962	4548	1174	1103	165	134	2199	1407	391	548
BMI at baseline, Kg/m^2											
< 18.5 (under weight)	Deaths	240	183	30	34	3	4	89	49	21	43
	Person-yrs	24332	9444	22534	8272	23696	9016	24141	9247	24332	9444
	RR	1.35	1.39	1.00	1.21	0.93	1.91	1.37	1.02	1.39	2.20
	95% CI	1.18, 1.55	1.19, 1.63	0.68, 1.46	0.85, 1.73	0.29, 3.04	0.67, 5.50	1.09, 1.72	0.76, 1.38	0.87, 2.24	1.58, 3.11
18.5–24.9 (normal weight)	Deaths	3121	2460	585	583	81	58	1161	767	226	317
	Person-yrs	513960	252695	471001	223820	495365	239280	509411	249872	513960	252695
	RR	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25–29.9 (over weight)	Deaths	1675	1217	346	316	43	46	621	378	81	108
	Person-yrs	211710	117334	190722	102857	202129	110777	209018	115625	211710	117334
	RR	1.07	1.00	1.18	1.04	0.93	1.44	1.12	0.99	0.75	0.80
	95% CI	1.00 1.15	0.92, 1.09	1.00, 1.39	0.88, 1.23	0.59, 1.48	0.90, 2.31	1.00, 1.26	0.85, 1.15	0.56, 1.02	0.62, 1.04
≥30 (obese)	Deaths	926	688	212	170	38	26	328	213	63	80
	Person-yrs	120932	64645	109933	57037	116420	61296	119548	63644	120932	64645
	RR	1.34	1.17	1.49	1.11	1.52	1.53	1.50	1.21	1.43	1.37
	95% CI	1.22, 1.47	1.05, 1.31	1.22, 1.83	0.89, 1.37	0.91, 2.55	0.85, 2.76	1.29, 1.75	0.99, 1.46	1.00, 2.05	0.99, 1.88

[a] Stratified by age (in years) at baseline and adjusted for race/ethnicity, weight change (in Kg) from age 18 to baseline, physical activity, co-morbidities (incl. diabetes, hypertension, heart attack, stroke, and any cancer), alcohol consumption, hormone therapy, and percent daily calories from fat and stratified by age

[b] Table 4 does not include participants with missing smoking status (n=667).

Table 5

Multivariable adjusted [a]relative risk (RR) and 95% confidence interval (CI) for all-cause, any cancer-specific, breast cancer-specific, cardiovascular-specific, and respiratory-specific mortality according to body mass index (BMI) at baseline, stratified by history of menopausal hormone therapy (HT) use[b]

		All-Cause		Any Cancer		Breast Cancer		Cardiovascular Disease		Respiratory Disease	
	HT Use	**Never**	**Ever**	**Never**	**Ever**	**Never**	**Ever**	**Never**	**Ever**	**Never**	**Ever**
	Total Deaths	**3156**	**5588**	**564**	**1293**	**63**	**159**	**1182**	**1849**	**315**	**492**
BMI at baseline, Kg/m^2											
< 18.5 (under weight)	Deaths	134	222	15	37	2	4	52	60	25	31
	Person-yrs	4386	11350	3686	9774	3995	10855	4272	11168	4386	11350
	RR	1.20	1.40	0.78	1.18	1.89	1.30	1.20	1.02	1.85	1.62
	95% CI	1.00, 1.44	1.21, 1.62	0.45, 1.33	0.84, 1.66	0.42, 8.60	0.46, 3.64	0.89, 1.61	0.77, 1.34	1.19, 2.88	1.09, 2.41
18.5–24.9 (normal weight)	Deaths	1586	3069	264	694	22	83	606	1017	182	291
	Person-yrs	88303	297187	70850	261345	77155	282864	87076	293318	88303	297187
	RR	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
25–29.9 (over weight)	Deaths	883	1529	171	372	22	41	320	535	60	100
	Person-yrs	50592	149359	41225	131205	44342	142556	49749	146899	50592	149359
	RR	1.04	1.02	1.17	1.04	1.74	0.86	1.01	1.08	0.72	0.78
	95% CI	0.94, 1.15	0.95, 1.10	0.92, 1.48	0.89, 1.22	0.85, 3.57	0.54, 1.37	0.85, 1.18	0.95, 1.23	0.51, 1.01	0.59, 1.03
≥30 (obese)	Deaths	553	768	114	190	17	31	204	237	48	70
	Person-yrs	32692	74883	26940	65719	29189	71824	32128	73601	32692	74883
	RR	1.28	1.21	1.38	1.22	2.27	1.27	1.42	1.21	1.22	1.38
	95% CI	1.13, 1.46	1.10, 1.34	1.04, 1.85	1.00, 1.49	0.97, 5.29	0.75, 2.17	1.16, 1.75	1.01, 1.44	0.80, 1.86	0.99, 1.93

[a]Stratified by age (in years) at baseline and adjusted for race/ethnicity, weight change (in Kg) from age 18 to baseline, physical activity, co-morbidities (incl. diabetes, hypertension, heart attack, stroke, and any cancer), smoking status, alcohol consumption, and percent daily calories from fat and stratified by age.

[b]Table 5 does not include premenopausal women or women with missing HT status (n=52308).