Body mass index and short-term weight change in relation to mortality in Dutch women after age 50 y[1–3]

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ABSTRACT

Background: The question of whether weight loss increases a person's longevity is important given the high prevalence of obesity and the large number of people trying to lose weight in industrialized countries.

Objective: This study assessed the effect of body mass index (BMI) and weight change (within 1 y of baseline) on subsequent mortality.

Design: This prospective cohort study had a median follow-up of 17 y. Subjects were 8100 women aged 50–66 y who participated in a population-based breast cancer–screening project in the Netherlands between 1974 and 1977. Weight and height were measured during the first and second screening visits. All women were followed until 1996 for causes of death. Cox proportional hazard analyses were conducted for mortality from all causes ($n = 1269$), cardiovascular disease (CVD; $n = 402$), and cancer ($n = 492$).

Results: During follow-up we observed a statistically significant increased risk of mortality from all causes (hazard ratio: 1.4; 95% CI: 1.2, 1.6), cardiovascular disease, and cancer for women in the highest quartile of BMI (in kg/m^2), ≥27.77. Mortality from all causes, CVD, and cancer did not increase significantly in women with a weight gain of ≥15%. Weight loss was also not significantly related to mortality from all causes, CVD, and cancer.

Conclusions: Mortality was highest for women in the highest BMI quartile (≥27.77). Extreme weight gain or weight loss within 1 y was not statistically significantly associated with subsequent higher mortality. *Am J Clin Nutr* 2004;80:231–6.

KEY WORDS Body mass index, cancer mortality, cardiovascular mortality, cohort study, overall mortality, weight change

INTRODUCTION

Overall, there is agreement about the health risks of overweight and obesity. In fact, research has shown that excess body weight increases the risk of diabetes mellitus, ischemic heart disease, certain types of cancer, and premature mortality (1, 2). Obesity is a growing problem in industrialized countries. Several studies reported that the prevalence of obesity in adults is 10–25% in most countries of Western Europe and 20–25% in some states in the United States (3–5). The estimated annual number of deaths attributable to obesity (280 000) among US adults underlines the magnitude of this public health problem (6). Because the adverse effects of obesity are well known, weight loss efforts are being recommended and widely practiced. In 1996, 44% of adult US women reported that they were currently trying to lose weight (7). The long-term effects of weight loss, however, are not yet well known. Studies showed that successful weight loss improves several cardiovascular risk factors and diabetic control (8–10) but report little about the effects on mortality. Most observational cohort studies tend to show that higher mortality rates occur not only in adults who have gained excessive weight but also in adult who lose weight. The lowest mortality rates are generally associated with modest weight gains (11). Explanations for this finding were sought in the differential effects of weight change in healthy or diseased adults (12–17), young or older people (18, 19), intentional or unintentional weight loss (20), stable or fluctuations in weight loss (14, 21), and obese or nonobese people who were trying to lose weight (21–24).

The purpose of the present investigation was to study prospectively the long-term effects of body mass index (BMI) and weight change on all-cause and cause-specific mortality in a well-defined cohort of 8100 healthy Dutch women, aged 50–66 y at baseline, in whom 1269 deaths occurred in a median follow-up period of 17 y.

SUBJECTS AND METHODS

Study population

Between December 1974 and September 1977, 14 697 (72%) of the 20 555 women born between 1911 and 1925 and living in Utrecht, Netherlands, were enrolled in the DOM (Diagnostisch Onderzoek Mammacarcinoom, or Diagnostic Investigation into Breast Cancer) cohort as part of a population-based breast cancer–screening program (25). The screening examination was conducted by trained technicians, who measured, among other things, height and weight. The screening examination was repeated from 1 to 5 times, and some women dropped out of the study between screening rounds. Self-reported questionnaires were also used to gather information on smoking habits (never, past, and currently <10, 10–20, and >20 cigarettes/d) and on

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medication use during the previous 12 mo for the treatment of diabetes, hypertension, or heart disease. Of the 14 697 women enrolled, 2832 (19%) had at least one missing value for height, weight, or smoking habit at either the first or the second screening visit and were, therefore, excluded from the present study. An additional 3765 women were excluded because they reported using medication for hypertension, cardiovascular disease (CVD), or diabetes or for being on a restricted diet (salt-free, diabetic) at first or second examination. These exclusions resulted in a final study population of 8100 healthy women. The study was performed according to the responsible committee on human experimentation.

Outcome ascertainment

Vital status of the DOM cohort members was obtained from the Utrecht Municipal Registry on a monthly basis until 1 January 1996. Causes of death were ascertained from the subjects' general practitioners and were coded according to the ninth revision of the International Classification of Diseases (ICD). The primary endpoint of the present study was total mortality (death from any cause). In addition, cause-specific mortality analyses were conducted for total CVD (ICD 390–459) and total cancer (ICD 140–208).

Predictors of mortality

Body mass index

Participants wore light indoor clothing and no shoes when weighed. BMI (in kg/m^2) quartiles were used in the analyses as follows: quartile 1 ($\leq$23.30), quartile 2 (23.31–25.41), quartile 3 (25.42–27.76), and quartile 4 ($\geq$27.77).

The normal range of BMI for adults (not age-specific) is 18.5–25, according to the World Health Organization Expert Committee on Physical Status, which corresponds to the first quartile and most of the second quartile in our study population (26). The World Health Organization defines overweight in adults to be BMI = 25.0–29.9 and obesity to be BMI $>$ 30.0. Of the 8100 women included in our study 939 (11.6%) had a BMI $>$ 30, accounting for 46% of the fourth quartile.

Weight change

Body weight was measured at baseline and at the second screening visit, on average 12 mo later (range: 6–41). Weight change was calculated as the difference between weights measured at the first (baseline) and the second visit. Weight change was categorized into 7 empirically based categories: $<$5% change (stable; reference), 5–9% gain (moderate), 10–14% gain (severe), $\geq$15% gain (extreme), 5–9% loss (moderate); 10–14% loss (severe), and $\geq$15% loss (extreme). No information was available on how weight loss was achieved (eg, diet, physical activity, stress, and morbidity) or whether the loss was intended.

Statistical analysis

To assess the effect on mortality, we used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% CIs for the BMI quartiles (reference: quartile 1) and for the weight-change categories (reference: stable with $<$5% weight change). Death from any cause was the endpoint. Losses to follow-up as a result of moving outside the study area and women alive at the end of follow-up (1 January 1996) were treated as censoring events. In the cause-specific mortality analyses (ie, cardiovascular), all other causes of death (ie, noncardiovascular) were treated as censoring events.

Adjustments were made for baseline information on age (continuous) and smoking (never, past, and currently $<$10, 10–20, and $>$20 cigarettes/d). We also evaluated confounding by number of children, age at first childbirth, hormonal replacement use, oral contraceptive use, and menopausal status. None of these variables meaningfully changed the β values, and they were, therefore, not included in the final models.

Tests for linear trends were performed for all-cause and cause-specific mortality. To control for type I error, we applied Bonferroni corrections to the level of significance (α).

To test the hypothesis that effects of weight loss might be beneficial only for overweight and obese women, we conducted a separate analysis for women above the normal range of baseline BMI (BMI $\geq$ 25). We also tested interaction between weight change and BMI (continuous) by including their product term as an interaction term in the models. All analyses were done with SPSS software package for WINDOWS, version 10.1. (SPSS Inc, Chicago).

RESULTS

Baseline characteristics of the study population are provided in **Table 1**. Moderate weight loss was more frequent in the women in the highest BMI quartile (9%, compared with 5–6% in women in the lowest 3 quartiles; $P = 0.001$ chi-square test). In contrast, moderate weight gain was more frequent in the leanest women (10%, compared with 6–7% in women in the upper 3 quartiles of BMI; $P = 0.001$ chi-square test). The percentage of current smokers decreased with increasing weight: 35% in the first, 29% in the second, 28% in the third, and 25% in the fourth BMI quartile ($P = 0.001$ chi-square test).

A total of 1201 (14.8%) women had moved outside the study area by the end of follow-up (1 January 1996). In addition, during 17 y of median follow-up (maximum: 21) or 140 468 women-years, 1269 deaths were ascertained (**Table 2**). Table 2 shows the crude mortality rates of total, CVD, and cancer mortality according to baseline BMI quartiles. After adjustment for age at baseline (continuous), smoking changes, and weight changes, mortality rates were highest in the fourth BMI quartile (Table 2). These women showed 40% higher overall mortality (HR: 1.4; 95% CI: 1.2, 1.6), with a greater number of deaths as a result of CVD (HR: 1.8; 95% CI: 1.3, 2.3) and cancer (HR: 1.5; 95% CI: 1.2, 2.0) than did women in the first quartile. Trend tests for total, CVD, and cancer mortality were all statistically significant.

The mortality HRs according to categories of weight change, adjusted for age, smoking habits, and BMI at entry are shown in **Table 3**. Total mortality and deaths from CVDs and cancer were all not statistically significantly increased in women with weight gain of $\geq$15%. Weight loss was also not statistically significantly related to overall mortality, CVD mortality, and cancer mortality.

Analyzing whether an effect of weight change could be observed in women with baseline BMI $\geq$ 25 did not essentially change the result (data not shown). The interaction between weight loss and BMI (continuous) at baseline was also tested. The *P* values for these terms for overall, CVD, and cancer mortality were 0.24, 0.15, and 0.61, respectively. This finding indicates that the absence of an effect of weight loss on mortality was

TABLE 1
Baseline characteristics of the study population according to BMI quartiles in 8100 healthy women aged 50–66 y in 1974–1977

	Quartile[1]				
	1 (n = 2023)	2 (n = 2028)	3 (n = 2025)	4 (n = 2024)	P[2]
BMI (kg/m^2)	21.6 ± 1.4[3]	24.4 ± 0.6	26.5 ± 0.7	30.5 ± 2.6	<0.001
Age (y)	56.4 ± 4.2	56.7 ± 4.3	56.9 ± 4.2	57.1 ± 4.2	<0.001
Height (cm)	163.1 ± 6.2	162.7 ± 6.0	162.1 ± 6.0	161.8 ± 6.2	<0.001
Weight (kg)	57.5 ± 5.8	64.6 ± 5.0	69.8 ± 5.4	80.0 ± 8.8	<0.001
Postmenopausal status [n (%)]	1692 (83.6)	1683 (83.0)	1705 (84.2)	1685 (83.3)	0.748
Smoking habit [n (%)]					
Never	1272 (62.9)	1405 (69.3)	1442 (71.2)	1501 (74.2)	<0.001
Past	37 (1.8)	34 (1.7)	27 (1.3)	28 (1.4)	—
Currently <10 cigarettes/d	254 (12.6)	235 (11.6)	224 (11.1)	220 (10.9)	—
Currently 10–20 cigarettes/d	346 (17.1)	272 (13.4)	266 (13.1)	211 (10.4)	—
Currently >20 cigarettes/d	114 (5.6)	82 (4.0)	66 (3.3)	64 (3.2)	—
Weight change [n (%)][4]					
Stable (<5% change)	1658 (82.0)	1743 (85.9)	1702 (84.0)	1606 (79.3)	<0.001
Moderate gain (5–9%)	197 (9.7)	132 (6.5)	150 (7.4)	132 (6.5)	—
Severe gain (10–14%)	37 (1.8)	16 (0.8)	13 (0.6)	15 (0.7)	—
Extreme gain (≥15%)	12 (0.6)	1 (0.0)	1 (0.0)	3 (0.1)	—
Moderate loss (5–9%)	108 (5.3)	120 (5.9)	124 (6.1)	179 (8.8)	—
Severe loss (10–14%)	7 (0.3)	13 (0.6)	31 (1.5)	57 (2.8)	—
Extreme loss (≥15%)	4 (0.2)	3 (0.1)	4 (0.2)	32 (1.6)	—

[1] BMI quartiles (in kg/m^2): 1 (BMI ≤ 23.30), 2 (BMI = 23.31–25.41), 3 (BMI = 25.42–27.76), and 4 (BMI ≥ 27.77).
[2] P for linear trend, except for smoking and weight change variables (chi-square test).
[3] $\bar{x}$ ± SD (all such values).
[4] Weight change status within 1 y of baseline.

observed in women with normal baseline weights as well as in women with weights above normal.

DISCUSSION

The present study showed statistically significant higher risks of all-cause, CVD, and cancer mortality for women who were in the highest BMI quartile at age 50–66 y. In this study these women had a BMI ≥ 27.77. Extreme weight gain (≥15%) did not show significantly higher risks of all-cause, cardiovascular, and cancer mortality. Weight loss, compared with stable weight, was also not associated with a significantly increased risk of dying of CVD or a decreased risk of dying of cancer.

This study has some strong methodologic points, ie, a prospective design with a long follow-up period (17 y) for a large group (8100) of healthy women. For all women 2 anthropometric measurements were available taken by medical technicians with an interval of approximately 1 y. Although the range of the interval varied from 6 to 41 mo, 90% of all women were measured for the second time within a period of 10–14 mo and 97% within 16 mo. Furthermore, results were adjusted for smoking, an important determinant of mortality. We did not take into account changes in smoking habits between first and second measurement, because only 67 women reported to have stopped smoking in between the 2 examinations. No one reported taking up smoking.

Frequently in cohort studies, deaths occurring in the first years of follow-up are excluded from analyses as an approach to adjust for confounding by occult disease present at baseline. It was shown that this is not necessarily an effective strategy for dealing with this type of confounding (27); therefore, we did not exclude any deaths. An analysis excluding deaths that occurred within the first 4 y of follow-up did not change the results.

We had no information on the stability of the observed weight change over a longer period of time. It was reported that most people who intentionally lose weight eventually regain it (28, 29). Moreover, some of the women who lost (or gained) weight could belong to the group of women whose weight fluctuates. Several studies showed that individuals with a large fluctuation in body weight are at higher risk of hypertension and of overall and CVD mortality (30–33). There are, however, populations that do not show this association (34, 35). Another study showed that the incidence of, and mortality from, CVDs is not higher with fluctuating body weight but that glucose tolerance is decreased (36).

We had no information on how weight loss was achieved. It could be unintentional as a consequence of underlying illnesses, although we tried to prevent this possibility by excluding women on medication. Unintentional weight changes also could be caused by (random) fluctuations in the sizes of fat mass and fat-free mass (37). If weight loss was intentional, it could have been achieved by a restricted diet or by increased physical activity. A study by Wood et al (38) showed beneficial effects on plasma lipoproteins from losing weight either by diet or by increased physical activity. Other studies reported that exercise is associated with unique favorable effects on CVD, cancer, and diabetes, independent of weight loss (39, 40). We were not able to study this effect, because no data on diet or physical activity were available for our population. A lack of fitness could be as important as (or even more important than) fatness, because lean physical unfit men show higher overall and CVD mortality than obese men who are fit (41–43).

TABLE 2
Follow-up results and incidence density rates of cause-specific mortality, according to BMI quartiles

	Quartile[1]				*P* for linear trend
	1 (n = 2023)	2 (n = 2028)	3 (n = 2025)	4 (n = 2024)	
Follow-up period					
(mo)	208.4 ± 54.8[2]	208.5 ± 55.0	208.2 ± 55.2	207.4 ± 55.4	—
(y)	17.4 ± 4.6	17.4 ± 4.6	17.4 ± 4.6	17.3 ± 4.6	—
Person-years (n)	35 200	35 287	35 235	35 015	—
All-cause mortality					
Death (n)	294	272	309	394	—
Mortality rate per 1000 person-years	8.4	7.7	8.8	11.3	—
Mortality hazard ratio[3]	Reference	0.9 (0.8, 1.1)	1.1 (0.9, 1.2)	1.4 (1.2, 1.6)	0.001
Cardiovascular disease mortality					
Death (n)	79	88	96	139	—
Mortality rate per 1000 person-years	2.2	2.5	2.7	4.0	—
Mortality hazard ratio[3]	Reference	1.1 (0.8, 1.5)	1.2 (0.9, 1.7)	1.8 (1.3, 2.3)	0.001
Total cancer mortality (all sites combined)					
Death (n)	106	106	124	156	—
Mortality rate per 1000 person-years	3.0	3.0	3.5	4.5	—
Mortality hazard ratio[3]	Reference	1.0 (0.8, 1.3)	1.2 (0.9, 1.5)	1.5 (1.2, 2.0)	0.001
Death from other/unknown cause (n)	109	78	89	99	—

[1] BMI quartiles (in kg/m^2): 1 (BMI ≤ 23.30), 2 (BMI = 23.31–25.41), 3 (BMI = 25.42–27.76), and 4 (BMI ≥ 27.77).
[2] $\bar{x}$ ± SD (all such values).
[3] Adjusted for age (continuous), smoking habits (never; past; and currently <10, 10–20, and >20 cigarettes/d), and weight change status within a year [stable (<5%), moderate gain (5–9.99%), severe gain (10–14.99%), extreme gain (≥15%), moderate loss (5–9.99%), severe loss (10–14.99%), extreme loss (≥15% loss)]; 95% CI in parentheses.

The absence of information on whether or not weight change was intentional might be important (44), because unintentional weight loss is usually caused by illness. In a population-based study of American women aged 55–69 y, 69% reported having at least one period in adulthood in which they had intentional weight loss, whereas 29% experienced an unintentional weight loss (45). A study also showed that intentional weight loss resulted in no effects on cardiovascular mortality, whereas unintentional weight loss was related to higher mortality (46, 47).

Although mortality from CVD with weight loss was not statistically significantly increased in our population, weight loss and subsequent higher mortality were reported in several populations (12, 14, 15, 18, 20, 48–55). Some of those studies seem to indicate that the effect of weight loss is differential with regard to baseline health characteristics. People who are obese and suffer from obesity-related health problems (ie, hypertension, diabetes) and, thus, have a high risk of dying of CVDs (or other obesity-related diseases) could benefit from weight loss. Clinical trials showed that intentional weight loss by obese individuals results in reduced blood pressure, reduced total serum cholesterol, and improved glucose tolerance (8, 9). Other studies also showed that weight loss greatly improves glycemic control in obese type 2 diabetic subjects (10, 56) and that such improvements can last for 1–3 y even if some weight is regained (38). However, we were not able to show beneficial effects of weight loss in women who were overweight at baseline.

The relation of weight loss and mortality can be influenced also by age (57, 58). Weight gain during (early) adulthood is detrimental, whereas overweight, although associated with mortality in all age classes (59), can be less of a problem for the elderly (19, 60, 61). Some older women can benefit from a slight overweight. The reason can be found in the association between leanness (or weight loss) and mortality from causes other than CVD (62). Of the 12 000 women participating in the Adventist Health Study, weight loss substantially related to higher risk of fatal respiratory disease (63–65). BMI was positively associated

TABLE 3
Mortality hazard ratio (and 95% CI) of death in 8100 women with regard to 1-y weight change[1]

	Extreme loss (n = 43)	Severe loss (n = 108)	Moderate loss (n = 531)	Stable (n = 6709)	Moderate gain (n = 611)	Severe gain (n = 81)	Extreme gain (n = 17)	*P* for linear trend[2]	
								Weight loss	Weight gain
All-cause mortality	0.8 (0.4, 1.8)	0.9 (0.5, 1.4)	1.4 (1.1, 1.6)	1.00	1.0 (0.8, 1.2)	1.1 (0.6, 1.9)	2.9 (1.2, 6.9)	NS	NS
Cardiovascular disease mortality	1.6 (0.6, 4.3)	1.4 (0.7, 2.8)	1.5 (1.1, 2.1)	1.00	0.9 (0.6, 1.3)	1.1 (0.4, 2.9)	4.1 (1.0, 16.7)	0.02	NS
Total cancer mortality	0.3 (0.01, 2.3)	0.4 (0.1, 1.2)	1.2 (0.8, 1.6)	1.00	1.0 (0.7, 1.5)	1.1 (0.4, 2.6)	1.4 (0.2, 9.8)	NS	NS

[1] Adjusted for age (continuous), smoking habits (never, past, and current), and BMI (continuous). Weight change status is listed in footnote 2 of Table 2.
[2] Compared with stable-weight women after Bonferroni correction. NS = $P > 0.20$.

with overall mortality, although mortality was also higher in lean older women not on hormonal replacement treatment (65). Those researchers hypothesized that lean older women can experience a higher mortality risk because they have lower levels of adipose tissue–derived estrogen (65). In our population, only 720 women (8.9%) reported the use of hormonal treatment therapy, and adjustment did not change the results.

In conclusion, we observed that women who were classified in the upper quartile of BMI aged between 50 and 70 y showed highest risks of dying during subsequent years. Weight gain of ≥15% within 1 y was not statistically significantly associated with increased risk of mortality. Weight loss was also not significantly associated with CVD or cancer deaths.

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