Postmenopausal weight change and incidence of fracture: post hoc findings from Women's Health Initiative Observational Study and Clinical Trials

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ABSTRACT

OBJECTIVES

To determine associations between postmenopausal change in body weight and incidence of fracture and associations between voluntary and involuntary weight loss and risk of fracture.

DESIGN

Post hoc analysis of data from the Women's Health Initiative Observational Study and Clinical Trials.

SETTING

40 clinical centers in the United States.

PARTICIPANTS

120 566 postmenopausal women, aged 50–79 at baseline (1993–98), followed through 2013 (mean fracture follow-up duration 11 years from baseline).

EXPOSURES

Annualized percentage change in measured body weight from baseline to year 3, classified as stable (<5% change), weight loss (≥5%), or weight gain (≥5%). Self assessment of whether weight loss was intentional or unintentional. Cox proportional hazards regression models were adjusted for age, race/ethnicity, baseline body mass index (BMI), smoking, alcohol intake, level of physical activity, energy expenditure, calcium and vitamin D intake, physical function score, oophorectomy, hysterectomy, previous fracture, comorbidity score, and drug use.

MAIN OUTCOMES

Incident self reported fractures of the upper limbs, lower limbs, and central body; hip fractures confirmed by medical records.

RESULTS

Mean participant age was 63.3. Mean annualized percent weight change was 0.30% (95% confidence

interval 0.28 to 0.32). Overall, 79 279 (65.6%) had stable weight; 18 266 (15.2%) lost weight; and 23 021 (19.0%) gained weight. Compared with stable weight, weight loss was associated with a 65% higher incidence rates of fracture in hip (adjusted hazard ratio 1.65, 95% confidence interval 1.49 to 1.82), upper limb (1.09, 1.03 to 1.16), and central body (1.30, 1.20 to 1.39); weight gain was associated with higher incidence rates of fracture in upper limb (1.10, 1.05 to 1.18) and lower limb (1.18, 1.12 to 1.25). Compared with stable weight, unintentional weight loss was associated with a 33% higher incidence rates of hip fracture (1.33, 1.19 to 1.47) and increased incidence rates of vertebral fracture (1.16, 1.06 to 1.26); intentional weight loss was associated with increased incidence rates of lower limb fracture (1.11, 1.05 to 1.17) and decreased incidence of hip fracture (0.85, 0.76 to 0.95).

CONCLUSIONS

Weight gain, weight loss, and intentional weight loss are associated with increased incidence of fracture, but associations differ by fracture location. Clinicians should be aware of fracture patterns after weight gain and weight loss.

Introduction

The influence of body weight on the risk of fracture is complex. Low body weight is considered a risk factor for osteoporotic fracture.¹ There is, however, increasing recognition that a high proportion of postmenopausal women with low trauma fractures are obese.² Moreover, beyond low body weight per se, change in body weight can have an important influence on risk of fracture. For example, longitudinal studies of postmenopausal white women in the United States have found that weight loss increases the risk of subsequent hip and other frailty fractures.^{3–6} Similar studies of postmenopausal non-white women are lacking, yet differences in body weight distributions⁷ and absolute risk of fracture⁸ across racial groups are striking.

There is also a paucity of information on whether the influence of weight change on subsequent risk of fracture varies by anatomical site. In longitudinal studies of white women aged ≥65, weight loss measured in various ways (over four years or since maximum weight or since age 50) was associated with an increased risk of hip fracture,^{4–6} whereas weight gain since age 25 was associated with a higher risk of ankle fracture.⁹ No longitudinal studies, however, have focused specifically on how weight change can differentially influence upper limb, lower limb, hip, and central body fractures among postmenopausal white or non-white women in the US. Also, few studies have considered the reason for underlying weight loss in the analysis of associations

WHAT IS ALREADY KNOWN ON THIS TOPIC

Low body weight is associated with increased risk of fracture

However, associations of weight loss and weight gain with subsequent fracture incidence, classified by anatomical region, in postmenopausal women are unclear.

How fracture patterns may differ after intentional and unintentional weight loss in postmenopausal women is also unknown

WHAT THIS STUDY ADDS

Weight gain, weight loss, and even intentional weight loss are associated with increased fracture incidence, but associations differ by anatomical fracture location.

Our findings challenge the traditional clinical model of weight gain being protective against fractures

Clinicians should be aware of fracture patterns both after weight gain and weight loss

between weight loss and fractures. This distinction might be important because serious illness could be an underlying cause of both involuntary weight loss and osteoporosis. In one study, associations between weight loss and increased risk of frailty fracture were significant only among women reporting involuntary, but not voluntary weight loss,³ whereas in another study, voluntary and involuntary weight loss among overweight women were each associated with similar (2.5-fold) increases in risk of hip fracture.⁴ Neither of those two studies adjusted for baseline weight or body mass index (BMI).

We investigated associations between change in body weight (baseline to third annual visit) and subsequent incidence of fracture classified by anatomical region (for example, upper limb, lower limb, central body) among postmenopausal women and to what extent self reported voluntary and involuntary weight loss are associated with increased incidence of fracture. We hypothesized that associations between weight loss and increased fracture incidence would be more pronounced for hip fractures than for limb fractures because of the potential loss in soft tissue padding around the hip that could counteract traumatic forces. We also hypothesized that even voluntary weight loss would be associated with an increased incidence of hip fracture. We further postulated that weight gain would increase the incidence of limb fractures, as the upper and lower extremities have little overlying soft tissue to absorb the increased impact resulting from weight gain and because of poor neuromuscular conditioning.

Methods

Women's Health Initiative Study

We used data from the Women's Health Initiative Observational Study and the Women's Health Initiative Clinical Trials. At 40 clinical centers nationwide between 1993 and 1998, the Women's Health Initiative study enrolled postmenopausal women aged 50–79 at baseline who were free from serious cardiac, pulmonary, renal, and hepatic conditions and had at least three years' life expectancy.^{10–12} The three placebo controlled Women's Health Initiative clinical trials tested several interventions among postmenopausal women: a low fat eating pattern, menopausal hormone therapy, and calcium and vitamin D supplementation.¹² The Women's Health Initiative Observational Study examined the predictors and natural course of important causes of morbidity and mortality in postmenopausal women.¹¹ Recruitment details are available at <https://cleo.whi.org/about/SitePages/About%20WHI.aspx>. The com-

bined studies enrolled 161 808 participants (93 676 in the observational study and 68 132 in the clinical trial). Our analytic sample consisted of 120 566 participants from the two studies for whom information was available regarding weight change (from baseline to year three) and at least one year of follow-up (after the year three visit) regarding incident fractures (fig 1). Follow-up data were available for 31 March 1995 through 17 September 2013.

Participants were asked to complete baseline self assessment questionnaires. Weight and height were measured at baseline and at the third annual follow-up visit with standardized protocols. BMI was calculated as body weight in kilograms (kg) divided by the square of height in meters. Waist:hip ratio was calculated as the ratio of waist circumference (cm) to hip circumference (cm).

Outcomes

Our study outcome was incidence of fracture. Each year, participants were asked to report fracture events since the previous annual visit: "Has a doctor told you for the first time that you have a new broken, crushed, or fractured bone? Which bone did you break?" Questionnaire response choices included: hip, upper leg (not hip), pelvis, knee (patella), lower leg or ankle, foot (not toe), spine or back (vertebra), lower arm or wrist, hand (not finger), elbow, and upper arm or shoulder. We grouped each fracture into one of the following (mutually exclusive) categories: upper limb fracture (elbow, hand except fingers, lower arm/wrist, upper arm/humerus or shoulder), lower limb (foot except toes, knee/patella, upper leg except hip, lower leg/ankle), central body (hip, pelvis, and spine). All hip fractures were centrally adjudicated. Because our goal was to examine incidence of fracture subsequent to a change in weight between baseline and year three, we excluded fractures that were reported before the third annual follow-up visit.

Predictor variables

The main predictor of this study was change in body weight between baseline and year three (plus/minus 90 days), operationalized in two ways. First, based on percentage change in body weight (for instance, $((\text{weight}_{\text{visit 3}} - \text{weight}_{\text{baseline}}) / \text{weight}_{\text{baseline}}) \times 100$), we classified each participant's change in body weight into one of three categories: weight loss (decrease of 5% or more since the baseline examination), stable weight (change of less than 5% from baseline weight), and weight gain (increase of 5% or more since the baseline examination). We excluded data from participants who did not undergo measurement of body weight within 90 days of the year three visit. From the two Women's Health Initiative groups, we had information from 120 566 participants regarding weight change (from baseline to year three) and at least one year of follow-up (after the year three visit) regarding incident fractures. After exclusion of data from participants for whom we lacked data regarding covariates (10%), the sample size for analysis was 108 709.

Fig 1. | Weight change period in relation to fracture follow-up period. Mean follow-up duration was 11 years from baseline

Second, we examined unintentional and intentional weight loss as separate predictors of incident fracture. At the year three follow-up visit, participants were asked two yes/no questions: "In the past two years, did you lose five or more pounds [about ≥ 2.2 kg] not on purpose at any time?" (unintentional weight loss) and "In the past two years, did you lose five or more pounds on purpose at any time?" (intentional weight loss). We had responses from 81 652 participants regarding unintentional weight loss and 81 587 participants regarding intentional weight loss.

Other variables

On baseline self assessment questionnaires, participants were asked whether they had experienced previous fracture (response choices were hip, spine/back/vertebra, upper arm/humerus, lower arm/wrist, hand other than finger, lower leg/ankle, foot other than toe, or other). For this study, we collapsed responses to this question into a binary (yes/no) variable.

From the baseline self report questionnaires we gathered information on age, race/ethnicity, smoking, alcohol intake (non-drinker, past drinker, <1 drink/month, <1 drink/week, $1-7$ drinks/week, >7 drinks/week, where one drink corresponded to 12 ounces (240 ml) of beer, 6 ounces (170 ml) of wine, or 1.5 ounces (43 ml) of liquor), general health status ("in general, would you say your health is excellent, very good, good, fair, poor?"), number of falls to the ground during the past 12 months (none, once, twice, three times or more), oophorectomy or hysterectomy, recreational physical activity (total MET (metabolic equivalent) hours a week), energy expenditure from walking (MET hours a week), Rand 36-item health survey (SF-36) quality of life physical functioning score (range 0–100), comorbidity (modified Charlson index score¹³), previous diagnosis of cancer, average protein intake from foods and beverages (g/day),¹⁴ dietary¹⁴ and supplemental calcium intake (mg/day), and dietary¹⁴ and supplemental vitamin D intake (IU/day).

Information regarding current use of menopausal hormone therapy, daily oral corticosteroid use, baseline use of drugs for osteoporosis (bisphosphonates, selective estrogen receptor modulators, calcitonin, parathyroid hormone, denosumab), and use of oral or injectable drugs for the treatment of diabetes (thiazolidinediones, dipeptidyl peptidase-4 inhibitors, meglitinides, glucagon-like peptide-1 agonists, insulin injection, amylin analog, sulfonylureas, biguanides, and alpha-glucosidase inhibitors) was assessed at baseline by clinic staff who examined labels of drug containers.

Statistical analysis

We used Cox proportional hazards regression¹⁵ to determine the association between weight change between baseline and the third annual follow-up visit and time to first fracture after the third annual follow-up visit, using individual regression models for each anatomical fracture location: central body (hip, pelvis, spine), lower extremity (upper leg except hip, knee/patella, lower leg/ankle, foot except toe), and upper extremity

(upper arm/humerus, shoulder, lower arm/wrist, hand except finger, elbow). Fractures during the first three years of follow-up were excluded from this analysis. Among women who experienced fracture, duration of follow-up was defined as time to first fracture. Among women who did not experience fracture during follow-up, duration of follow-up was defined as time until last follow-up visit, or death, whichever came first. The main predictors (in separate regression models) were category of (measured) weight change (stable, weight loss, weight gain); self reported intentional weight loss of ≥ 2.2 kg in the two years preceding the year three follow-up visit (yes v no [reference]); and self reported unintentional weight loss (yes v no [reference]) of ≥ 2.2 kg in the two years before the year three follow-up visit.

Covariates included baseline height, baseline weight, age, race, smoking (current, never, past), alcohol intake, general health status, number of falls in the 12 months before baseline, oophorectomy, hysterectomy, recreational physical activity (MET hours/week), physical function score, comorbidity (Charlson index) score, baseline dietary and supplemental vitamin D intake, baseline dietary and supplemental calcium intake, use of menopausal hormone therapy at baseline, daily use of oral corticosteroids at baseline, use of oral or injectable diabetes drugs at baseline, study cohort (participation in the Women's Health Initiative Observational Study), previous fracture, and previous diagnosis of cancer (yes/no). To explore the influence of protein intake and walking on the associations of weight loss with risk of fracture, we added dietary protein intake (g/day) and energy expenditure from walking in kcal/week/kg (MET hours a week). Continuous predictors were handled as if linear, with the exception of vitamin D and calcium intake, which were categorized (<200 , $200-400$, $400-600$, and ≥ 600 IU/day for vitamin D and <800 , $800-1200$, or ≥ 1200 mg/day for calcium).

We tested the assumption that the hazard ratio of the primary predictor remained constant over time by introducing a cross product term for $\hat{t}$ weight $\times$ log(time) into the statistical model. The proportionality assumption was not violated.

We made the a priori decision to determine whether race/ethnicity, age category, and number of falls in the past 12 months (none, once, twice, three or more times) modified the associations between change in weight and incidence of fracture by including interaction terms in regression models. Race/ethnicity categories for interaction testing were white, black, Hispanic, Asian/Pacific Islander, and other. Age categories for interaction testing were $<50-59$, $60-69$, and ≥ 70 . We also examined whether associations between change in weight and fracture incidence varied by physical activity level (continuous, or binary above v below median), physical function level (continuous, or binary above v below median), and waist:hip ratio (≥ 0.9 v <0.9 ¹⁶).

We also examined the results stratified by category of baseline BMI (<24.9 , $25.0-29.9$, >29.9) because previous studies suggest that associations between weight

change and incident fracture could vary according to baseline BMI.^{5 6}

Because participants in the Women's Health Initiative Dietary Modification Trial could have had weight change patterns that were different from those of the remainder of the analytic sample, we performed a sensitivity analysis in which we restricted the analytic sample to participants in that trial (samples sizes of 34 050 for lower limb fracture, 34 089 for upper limb fracture, 34 657 for central body fracture, and 34 851 for hip fracture analyses). In another sensitivity analysis, we excluded data from participants who reported the use of drugs for osteoporosis at baseline. In the final sensitivity analysis, we used the following alternative categories of weight change: stable weight (<5% change, reference), weight gain 5%–<10%, weight gain ≥10%, weight loss 5%–<10%, and weight loss ≥10%.

Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

Results

The mean age of our study population was 63.3 (median 63, interquartile range 58–69) (table 1). Sixteen percent of participants were non-white (Table 2). At baseline, fewer than 10% of participants were current smokers (table 2) and about 30% had fallen at least once in the past 12 months (table 3). Among the weight change groups, the mean duration of follow-up for incident fractures ranged from 11.5–12.0 years from baseline.

figure 2 shows the distribution of annualized weight change. Mean annualized percentage change in measured body weight was 0.30%/year overall (–3.6 %/year in the weight loss group $n = 18\,266$, 0.09%/year in the stable weight group $n = 79\,279$, and 4.1%/year in the weight gain group $n = 23\,021$). Mean weight change (from baseline to year three) was –10.0 kg (SD 15.0 kg) in the weight loss group and 8.7 kg (SD 13.4 kg) in the weight gain group. Of the participants who responded to questions regarding unintentional ($n = 62\,185$) and intentional ($n = 62\,142$) weight loss (2.2 kg in the past two years), 27 530 (44%) reported intentional weight loss, and 14 653 (24%) of participants reported unintentional weight loss.

Characteristics of the analytic sample were similar to those of excluded participants except that, compared with the excluded participants, the participants in the analytic sample were more likely to be participants in the clinical trial (47% v 26%) and were more likely to be white (84% v 78%) (data not shown).

Adjusted associations between annualized percentage weight change and incidence of fracture

Associations between category of weight change (≥5% weight loss, ≥5% weight gain, stable weight) and incidence of fracture were adjusted for baseline age, race, baseline height, baseline weight, smoking, alcohol intake, total energy expended a week, baseline vitamin D intake, baseline calcium intake, physical function score, general health status, oophorectomy, hysterectomy, Charlson index score, use of menopausal hormone therapy, daily oral corticosteroid use, use of oral or injectable treatment for diabetes, study assignment (Women's Health Initiative Observational Study, Women's Health Initiative Clinical Trials), history of previous fracture, and previous diagnosis of cancer (Table 4). Compared with women who had stable weight between baseline and the third annual visit, women who lost weight had a 9% higher incidence of upper limb fracture (adjusted hazard ratio 1.09, 95% confidence interval 1.03 to 1.16), a 30% higher incidence of central body fracture (1.30, 1.22 to 1.39), and 65% higher incidence of hip fracture (1.65, 1.49 to 1.82). Compared with women who had stable weight, women who gained weight had a 10% higher incidence of upper limb fracture (1.10, 1.04 to 1.17) and an 18% higher incidence of lower limb fracture (1.18, 1.12 to 1.25). The addition of a covariate representing the number of falls in past 12 months did not notably alter the hazard ratios for the associations between weight change and fracture incidence. Similarly, further adjustment for weekly energy expenditure from walking, weekly energy expenditure from recreational activity, use of antidepressant drugs, and total protein intake did not notably alter the hazard ratios for the associations between weight change and incidence of fracture (data not shown).

When we restricted the analytic sample to participants in the Women's Health Initiative Dietary Modification Trial, results were similar to results in the overall analytic sample (data not shown).

Adjusted associations between intentional and unintentional weight loss and fracture incidence

We examined associations of self reported unintentional and intentional weight loss in the past two years with incidence of fracture (see table A in appendix). Compared with no unintentional weight loss, unintentional weight loss was associated with a 21% higher incidence of central body fracture (adjusted hazard ratio 1.21, 95% confidence interval 1.13 to 1.29), 33% higher incidence of hip fracture (1.33, 1.19 to 1.47), and 16% higher incidence of vertebral fracture (1.16, 1.06 to 1.26). Compared with stable weight, intentional weight loss was associated with increased incidence rates of lower limb fracture (1.11, 1.05 to 1.17) and decreased

Table 1 | Mean (SD) baseline characteristics of participants from Women's Health Initiative Observational Study and Women's Health Initiative Clinical Trials included in analytic sample* in study of effect of postmenopausal weight change on risk of fracture

Variable	Stable weight ($n=79\,279$)	Weight loss ($n=18\,266$)	Weight gain ($n=23\,021$)
Age (years)	63.5 (7.1)	64.2 (7.3)	61.5 (7.0)
Weight (kg)	72.1 (15.2)	78.9 (21.8)	71.6 (14.9)
Height (m)	161.8 (6.5)	161.4 (7.2)	162.0 (6.7)
Years since menopause	15.2 (9.1)	16.0 (9.4)	13.6 (9.0)
Waist (cm)	85.5 (13.4)	89.1 (14.2)	85.1 (13.2)
Waist/hip ratio	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
Physical activity (MET hours/week)	12.9 (13.8)	11.1 (12.8)	12.5 (13.8)
Physical functioning	82.8 (18.4)	78.2 (21.1)	82.4 (19.3)
Comorbidity	0.99 (1.1)	1.11 (1.1)	0.98 (1.1)
Age (years) at menopause	48.3 (6.3)	48.1 (6.5)	47.9 (6.4)
Mean (95% CI) annualized percent weight change	0.09 (0.27 to 0.31)	–3.67 (–3.71 to –3.62)	4.1 (4.07 to 4.25)

*All $P < 0.001$ for difference between weight groups. Overall mean annualized percent weight change (95% CI) in the entire sample was 0.30 (0.28 to 0.32).

Table 2 | Baseline sociodemographic characteristics of participants from Women's Health Initiative Observational Study and Women's Health Initiative Clinical Trials included in analytic sample* in study of effect of postmenopausal weight change on risk of fracture. Figures are numbers (percentage) of participants

Variable	Stable weight (n=79 279)	Weight loss (n=18 266)	Weight gain (n=23 021)	Total
Participant in Women's Health Initiative Clinical Trial:				
Yes	42 528 (54)	8758 (48)	12 147 (53)	63433 (53)
No	36 751 (46)	9508 (52)	10 874 (47)	57133 (47)
Total	79 279	18 66	23 021	120 566
Age (years) at screening:				
<50–59†	24 221 (31)	5119 (28)	9670 (42)	39 010 (32)
60–69	37 063 (47)	8279 (45)	9898 (43)	55 240 (46)
≥70	17 995 (23)	4868 (27)	3453 (15)	26 316 (22)
Total	79 279	18 266	23 021	120 566
Race/ethnicity (missing = 280):				
White	66 915 (85)	15 534 (85)	19 124 (83)	101 573 (84)
Black	6045 (8)	1494 (8)	2000 (9)	9539 (8)
Hispanic	2639 (3)	554 (3)	865 (4)	4058 (3)
Asian/Pacific Islander	2390 (3)	382 (2)	603 (3)	3375 (3)
Other	1095 (1)	264 (1)	382 (2)	1741 (2)
Total	79 084	18 228	22 974	120 286
Smoking (missing = 1377):				
Never smoked	41 695 (53)	9272 (51)	11 193 (49)	62 160 (52)
Past smoker	32 517 (41)	7509 (42)	9512 (42)	49 538 (42)
Current smoker	4194 (5)	1248 (7)	2053 (9)	7495 (6)
Total	78 406	18 029	22 758	119 193
Alcohol intake (missing = 381):				
Non-drinker	8402 (11)	2105 (12)	2348 (10)	12 855 (11)
Past drinker	13 259 (17)	3571 (20)	4478 (20)	21 308 (18)
<1 drink/month	9521 (12)	2298 (13)	3083 (13)	14 902 (12)
<1 drink/week	16 243 (21)	3586 (20)	4901 (21)	24 730 (21)
1–<7 drinks/week	21 465 (27)	4387 (24)	5716 (25)	31 568 (26)
≥7 drinks/week	9887 (13)	2171 (12)	2359 (10)	14 417 (12)
Total	79 048	18 186	22 951	120 185
BMI (missing = 220):				
Underweight (<18.5)	626 (1)	97 (1)	298 (1)	1021 (1)
Normal (18.5–24.9)	29 207 (37)	4506 (25)	8550 (37)	42 263 (35)
Overweight (25.0–29.9)	27 544 (35)	6312 (35)	8243 (36)	42 099 (35)
Obesity I (30.0–34.9)	14 093 (18)	4010 (22)	3889 (17)	21 992 (18)
Obesity II (35.0–39.9)	5461 (7)	1817 (10)	1397 (6)	8675 (7)
Extreme obesity III (≥40)	2478 (3)	1165 (7)	653 (3)	4296 (4)
Total	79 409	17 907	23 030	120 346

*All $P < 0.001$ for difference between weight groups.

†Five participants were aged 49 at enrollment in Women's Health Initiative.

incidence of central body fracture (0.93, 0.88 to 0.99) and hip fractures (0.85, 0.76 to 0.95).

Interaction tests: associations between weight change and fracture incidence according to baseline BMI, frequency of falls, age, race/ethnicity, diabetes, physical activity, physical function, and waist:hip ratio Associations of intentional and unintentional weight loss did not vary by age group, with one exception: associations between intentional weight loss and lower limb fracture were more pronounced in younger than in older women ($P = 0.008$ for interaction). Among women aged 50–59, those with intentional weight loss had a 25% higher risk of lower limb fracture than women without intentional weight loss (see table B in appendix).

Associations between weight change and incidence of fracture did not significantly differ by baseline BMI category, number of falls in the past 12 months, race/

ethnicity, presence or absence of diabetes mellitus at baseline, physical activity levels, and physical function levels (for upper limb, lower limb, and central body fractures all $P > 0.05$ for interaction).

Among women who gained weight, associations between weight gain and fracture did not differ by waist:hip ratio (>0.9 v ≤ 0.9).

Sensitivity analyses

We performed a sensitivity analysis in which we added extra categories of weight change. We used the following categories: stable weight (<5% change, reference), weight gain 5%–<10%, weight gain $\geq 10\%$, weight loss 5%–<10%, and weight loss $\geq 10\%$. The pattern of results was similar to those of the primary analyses (Table 5).

For all analyses, results were similar when we excluded data from participants who reported the use of drugs for osteoporosis at baseline (data not shown).

Discussion

Principal findings

In this large cohort of postmenopausal women, compared with women with stable weight over three years, women who had lost 5% or more of their body weight had about 65% higher incidence rates of hip fracture, 30% higher rates of central body fracture, and 9% higher rates of upper limb fracture over about 11 years of follow-up. Also, compared with women who had stable weight, women who had weight gain of 5% or more had 10% higher incidence rates of upper and 18% higher rates of lower limb fractures but no difference in central body fractures. These associations were not explained by baseline frequency of falls or diagnosis of cancer before the third year of follow-up. Compared with stable weight, unintentional weight loss was associated with an increased risk of hip and spine fractures, whereas intentional weight loss was associated with a decreased risk of hip fractures and increased risk of lower limb fractures.

Comparison with other studies

As far as we are aware, this study is the first longitudinal study to focus specifically on how weight change can differentially influence upper limb, lower limb, and central body fractures among postmenopausal women in the US. The associations that we found between weight loss and increased rates of hip fracture, however, agree with those of previous studies. In a previous study of white women aged ≥ 65 , weight loss over four years of follow-up was associated with an increased risk of hip fracture.⁴ Similarly, self reported weight loss of $\geq 10\%$ of body weight since age 50 among white women aged 67 and older⁵ and self reported weight loss of $\geq 10\%$ from maximum weight among white women aged 50–74⁶ were each associated with an increased risk of hip fracture. Our results were also consistent with those of a previous study in which weight gain since age 25 was associated with a higher risk of ankle fracture among white women aged ≥ 65 .⁹ Finally, our results are consistent with results of studies from other countries—for example, Norwegian cohort

Table 3 | Baseline clinical and health related characteristics of participants from Women's Health Initiative Observational Study and Women's Health Initiative Clinical Trials included in analytic sample* in study of effect of postmenopausal weight change on risk of fracture. Figures are numbers (percentage) of participants

Variable	Stable weight (n = 79 279)	Weight loss (n = 18 266)	Weight gain (n = 23 021)	Total
Daily oral corticosteroid use:				
No	77 889 (98)	17 743 (97)	22 531 (98)	118 163 (98)
Yes	1390 (2)	523 (3)	490 (2)	2403 (2)
Total	79 279	18 266	23 021	120 566
Dietary + supplemental calcium (mg/day):				
<800	26 648 (34)	6359 (35)	8123 (35)	41 130 (34)
800-<1200	19 670 (25)	4535 (25)	5516 (24)	29 721 (25)
≥1200	32 961 (42)	7372 (40)	9382 (41)	49 715 (41)
Total	79 279	18 266	23 021	120 566
Dietary + supplemental vitamin D (IU/day):				
<200	29 223 (37)	6879 (38)	8735 (38)	44 837 (37)
200-<400	14 906 (19)	3459 (19)	3994 (17)	22 359 (19)
400-<600	19 563 (25)	4486 (25)	5873 (26)	29 922 (25)
≥600	15 587 (20)	3442 (19)	4419 (19)	23 448 (20)
Total	79 279	18 266	23 021	120 566
Arthritis:				
Rheumatoid arthritis	3504 (4)	972 (5)	1053 (5)	115 037 (95)
Other/don't know	75 775 (96)	17 294 (95)	21 968 (95)	5529 (5)
Total	79 279	18 266	23 021	120 566
Diabetes treatment (oral or injectable) (missing = 95):				
No	76 457 (97)	17 266 (95)	22 109 (96)	115 832 (96)
Yes	2756 (3)	987 (5)	896 (4)	4639 (4)
Total	79 213	18 253	23 005	120 471
Bilateral oophorectomy (missing = 2594):				
No	62 361 (80)	14 240 (80)	18 170 (81)	94 771 (80)
Yes	15 264 (20)	3583 (20)	4354 (19)	23 201 (20)
Total	77 625	17 823	22 524	117 972
Hysterectomy (missing = 52):				
No	46 539 (59)	10 678 (58)	13 483 (59)	70 700 (59)
Yes	32 699 (41)	7583 (42)	9532 (41)	49 814 (41)
Total	79 238	18 261	23 015	120 514
Menopausal hormone therapy use (missing = 88):				
Never used	33 992 (43)	8420 (46)	9451 (41)	51 863 (43)
Past user	12 757 (16)	2995 (16)	3644 (16)	19 396 (16)
Current user	32 472 (41)	6838 (37)	9909 (43)	49 219 (41)
Total	79 221	18 253	23 004	120 478
Self rated general health status (missing = 663):				
Excellent	14 639 (19)	2618 (14)	4109 (18)	21 366 (18)
Very good	34 123 (43)	7272 (40)	9570 (42)	50 965 (42)
Good	24 667 (31)	6470 (36)	7310 (32)	38 447 (32)
Fair	5104 (6)	1629 (9)	1746 (8)	8479 (7)
Poor	323 (0)	159 (1)	164 (1)	646 (1)
Total	78 856	18 148	22 899	119 903
No of falls in past 12 months (missing = 5271):				
None	51 686 (68)	11 334 (65)	14 753 (67)	77 773 (67)
1	15 255 (20)	3608 (21)	4448 (20)	23 311 (21)
2	6046 (8)	1567 (9)	1886 (9)	9499 (8)
≥3	2886 (4)	827 (5)	999 (5)	4712 (4)
Total	75 873	17 336	22 086	115 295

*All P < 0.001 for differences between weight groups.

studies that found associations between weight loss and an increased risk of distal forearm fractures¹⁷ and non-vertebral fractures¹⁸ in women.

Although our study focused on change in body weight and incidence of fracture, a previous Women's Health Initiative study examined the differential effects

Fig 2. | Histogram of distribution of annualized weight change

of baseline weight on fractures at various anatomical locations.¹⁹ In that study, higher baseline BMI was associated with a decreased incidence of hip fractures and central body fractures, whereas the risk of upper extremity fracture was independent of baseline BMI. The authors of that study postulated that the greater soft tissue padding of the hip and central body could counteract the higher traumatic forces that accompany higher body weight. The results of our study possibly support that hypothesis, in that weight gain was not associated with an increased risk of hip fracture but was associated with an increased incidence of upper and lower limb fractures, anatomical sites that have less soft tissue padding.

Serious illness can be an underlying cause of both involuntary weight loss and osteoporosis. The associations that we found between weight loss and incidence of fracture persisted after adjustment for a diagnosis of cancer and other comorbidities. Also, in the current study, only unintentional, not intentional, weight loss was associated with an increased risk of hip fracture. Previous studies regarding voluntary weight loss and risk of fracture have focused on non-vertebral or overall frailty fractures rather than fractures according to specific anatomical regions.^{3 20} In one study, however, voluntary and involuntary weight loss among overweight women were each associated with similar (2.5-fold) increases in risk of hip fracture.⁴ Compared with the participants of the previous study, participants of the Women's Health Initiative were younger at baseline and probably generally healthier.

Strengths and limitations

Strengths of our study include its long duration of follow-up, detailed information regarding risk factors for fracture, objective measurement of body weight (as opposed to self reported body weight), and large sample size including more than 18 000 non-white women (9539 black women) and nearly 40 000 younger postmenopausal women (aged 50–59 at baseline) who were not the focus of previous studies.^{3 4}

Our study has potential limitations. Although we used adjudicated information regarding hip fractures, information regarding other fractures was self reported. The validity of self report of fractures varies by anatomical site in Women's Health Initiative, being higher for hip (78%) and forearm/wrist (81%) fractures than for

Table 4 | Association between postmenopausal change in body weight (third annual follow-up visit minus baseline) and incidence of fracture in Women's Health Initiative Observational Study and Women's Health Initiative Clinical Trials according to fracture site, before and after adjustment for falls*. Figures are adjusted hazard ratios† (95% confidence interval)

Fracture site and weight change category	Model 1	Model 1 + No of falls past 12 months
Upper limb‡		
Stable weight (reference)	1.00	1.00
Weight loss	1.09 (1.03 to 1.16)	1.08 (1.02 to 1.15)
Weight gain	1.10 (1.04 to 1.17)	1.09 (1.04 to 1.16)
Lower limb§		
Stable weight (reference)	1.00	1.00
Weight loss	0.98 (0.92 to 1.05)	0.98 (0.92 to 1.04)
Weight gain	1.18 (1.12 to 1.25)	1.18 (1.11 to 1.24)
Central body¶		
Stable weight (reference)	1.00	1.00
Weight loss	1.30 (1.22 to 1.39)	1.30 (1.21 to 1.38)
Weight gain	0.96 (0.90 to 1.03)	0.96 (0.90 to 1.03)
Hip		
Stable weight (reference)	1.00	1.00
Weight loss	1.65 (1.49 to 1.82)	1.64 (1.49 to 1.82)
Weight gain	0.96 (0.86 to 1.08)	0.96 (0.86 to 1.08)

*Sample sizes with complete covariate information according to fracture site were: 106 113 for lower limb fracture, 106 286 for upper limb fracture, 108 003 for central body fracture, and 108 709 for hip fracture analyses. Over follow-up period, 8531 upper limb fractures, 8529 lower limb fractures, 6791 central body fractures, and 2436 hip fractures occurred in analytic sample.

†Adjusted for baseline age, race, height, baseline weight, smoking, alcohol intake, total energy expended per week, dietary and supplemental vitamin D intake, dietary and supplemental calcium intake, physical function score, general health status, oophorectomy, hysterectomy, Charlson index score, use of menopausal hormone therapy, daily oral corticosteroid use, use of oral or injectable diabetes medication, study group (Women's Health Initiative Observational Study, Women's Health Initiative Clinical Trials group assignment), previous diagnosis of cancer, and previous fracture.

‡Includes fractures of upper arm/humerus, shoulder, lower arm/wrist, hand (except finger), and elbow.

§Includes fractures of upper leg (except hip), knee/patella, lower leg/ankle, and foot (except toe).

¶Includes fractures of hip, pelvis, and spine.

Table 5 | Sensitivity analysis: associations between body weight change (third annual follow-up visit minus baseline) and incidence of fracture by site in Women's Health Initiative Observational Study and Women's Health Initiative Clinical Trials according to anatomical location, with additional weight change categories.*

Weight change category	Upper limb	Lower limb	Central body	Hip
Stable weight (reference)	1.00	1.00	1.00	1.00
Weight loss 5%–≤10%	1.07 (1.00 to 1.15)	0.96 (0.89 to 1.03)	1.27 (1.18 to 1.37)	1.53 (1.36 to 1.72)
Weight loss >10%	1.13 (1.03 to 1.25)	1.03 (0.93 to 1.14)	1.35 (1.22 to 1.50)	1.87 (1.61 to 2.17)
Weight gain 5%–≤10%	1.11 (1.05 to 1.19)	1.18 (1.11 to 1.25)	0.96 (0.89 to 1.04)	0.93 (0.81 to 1.06)
Weight gain ≥10%	1.08 (0.98 to 1.18)	1.18 (1.08 to 1.29)	0.98 (0.87 to 1.09)	1.08 (0.90 to 1.31)

*Adjusted for baseline age, race, height, baseline weight, smoking, alcohol intake, total energy expended per week, dietary and supplemental vitamin D intake, dietary and supplemental calcium intake, physical function score, general health status, oophorectomy, hysterectomy, Charlson index score, use of menopausal hormone therapy, daily oral corticosteroid use, use of oral or injectable diabetes medication, study group (Women's Health Initiative Observational Study, Women's Health Initiative Clinical Trials), previous diagnosis of cancer, and previous fracture. Includes fractures of upper arm/humerus, shoulder, lower arm/wrist, hand (except finger), and elbow. Includes fractures of upper leg (except hip), knee/patella, lower leg/ankle, and foot (except toe). Includes fractures of hip, pelvis, and spine.

clinical spine fractures (51%).²¹ We did not have information regarding circumstances of the fracture (such as specific activities that immediately preceded fractures). To examine associations between weight change and subsequent incident fractures, we examined associations between change in weight from baseline to the third annual follow-up visit in relation to incident fractures subsequent to the third annual follow-up visit.

Participants might, however, have experienced weight change during the fracture follow-up period. Finally, we did not adjust for multiple statistical comparisons, so the probability that at least one of the reported confidence intervals will exclude unity under an overall null hypothesis is greater than 0.05.

Conclusions and policy implications

In conclusion, our finding that weight gain (≥5% of body weight over three years) is associated with increased incidence rates of upper and lower limb fractures is a novel finding. We found that weight loss (≥5% of body weight over three years) is associated with a markedly increased rate of hip fracture, as well as increased rates of central body and upper limb fractures, compared with stable weight. These findings have clinical and research implications and challenge the traditional clinical paradigm of weight gain protecting against fractures. Clinicians should be aware that even intentional weight loss is associated with increased rates of lower limb fractures. Weight loss intervention trials should consider potential effects on the incidence of fracture.

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Data sharing: Women's Health Initiative Study data are available via the BioLINCC website of the National Heart, Lung, and Blood Institute at <https://biolincc.nhlbi.nih.gov/home/>

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