ORIGINAL ARTICLE

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Relationship of Weight, Height, and Body Mass Index With Fracture Risk at Different Sites in Postmenopausal Women: The Global Longitudinal Study of Osteoporosis in Women (GLOW)

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ABSTRACT

Low body mass index (BMI) is a well-established risk factor for fracture in postmenopausal women. Height and obesity have also been associated with increased fracture risk at some sites. We investigated the relationships of weight, BMI, and height with incident clinical fracture in a practice-based cohort of postmenopausal women participating in the Global Longitudinal study of Osteoporosis in Women (GLOW). Data were collected at baseline and at 1, 2, and 3 years. For hip, spine, wrist, pelvis, rib, upper arm/shoulder, clavicle, ankle, lower leg, and upper leg fractures, we modeled the time to incident self-reported fracture over a 3-year period using the Cox proportional hazards model and fitted the best linear or nonlinear models containing height, weight, and BMI. Of 52,939 women, 3628 (6.9%) reported an incident clinical fracture during the 3-year follow-up period. Linear BMI showed a significant inverse association with hip, clinical spine, and wrist fractures: adjusted hazard ratios (HRs) (95% confidence intervals [CIs]) per increase of 5 kg/m^2 were 0.80 (0.71–0.90), 0.83 (0.76–0.92), and 0.88 (0.83–0.94), respectively (all $p < 0.001$). For ankle fractures, linear weight showed a significant positive association: adjusted HR per 5-kg increase 1.05 (1.02–1.07) ($p < 0.001$). For upper arm/shoulder and clavicle fractures, only linear height was significantly associated: adjusted HRs per 10-cm increase were 0.85 (0.75–0.97) ($p = 0.02$) and 0.73 (0.57–0.92) ($p = 0.009$), respectively. For pelvic and rib fractures, the best models were for nonlinear BMI or weight ($p = 0.05$ and 0.03,

Received in original form May 14, 2013; revised form July 2, 2013; accepted July 18, 2013. Accepted manuscript online July 22, 2013.
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Journal of Bone and Mineral Research, Vol. 29, No. 2, February 2014, pp 487–493
DOI: 10.1002/jbmr.2051

respectively), with inverse associations at low BMI/body weight and positive associations at high values. These data demonstrate that the relationships between fracture and weight, BMI, and height are site-specific. The different associations may be mediated, at least in part, by effects on bone mineral density, bone structure and geometry, and patterns of falling. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: FRACTURES; OBESITY; POSTMENOPAUSAL WOMEN; BMI; OSTEOPOROSIS

Introduction

Low body mass index (BMI) is a well-established risk factor for fracture, particularly hip fracture. The relationship between BMI and fracture risk is nonlinear, the steepest gradient of risk being seen at BMI values $<20\,kg/m^2$ and only a small further decrease in risk being seen at levels $>25\,kg/m^2$.[1] Recent data indicate, however, that the association between BMI and fracture risk differs according to fracture site. Thus obesity (BMI $\geq 30\,kg/m^2$) has been associated, in some studies, with increased risk of ankle, upper leg, lower leg, and proximal humerus fracture in postmenopausal women,[2–7] whereas decreased risk of hip, pelvis, and wrist fractures has been reported in comparison with nonobese and underweight women.[2,4,7]

Although the classification of underweight, normal weight, overweight, and obese states is traditionally defined on the basis of BMI, BMI is influenced by both height and weight, each of which may independently contribute to the relationship between BMI and fracture risk. The aim of the present study was to investigate the relationships of weight, BMI, and height with incident clinical fracture in postmenopausal women. We hypothesized that the associations would be site-specific and would be differently influenced by weight/BMI and height.

Subjects and Methods

The Global Longitudinal study of Osteoporosis in Women (GLOW) is a prospective practice-based cohort study involving 723 physician practices at 17 sites in 10 countries (Australia, Belgium, Canada, France, Germany, Italy, Netherlands, Spain, UK, and USA). The study methods have been reported.[8] In brief, practices typical of each region were recruited through primary care networks organized for administrative, research, or educational purposes, or by identifying all physicians in a geographic area. Each site obtained local ethics committee approval to participate in the study. The practices provided the names of women aged ≥ 55 years who had been seen by their physician in the past 24 months. After appropriate exclusions, 60,393 women agreed to participate in the study.

Data collection

Questionnaires were designed to be self-administered and covered domains that included: demographic characteristics and risk factors; fracture history; current medication use; and other medical diagnoses. Data on height and weight were collected at baseline and BMI was calculated as weight (kg) divided by height squared (m^2).

Information was collected at baseline on previous self-reported fractures (ie, that had occurred since the age of 45 years), while incident fractures were reported on the 1-, 2-, and 3-year follow-up surveys. All surveys included details of fracture location, including hip, spine, wrist, and other nonvertebral sites (clavicle, upper arm/shoulder, rib, pelvis, ankle, upper leg, lower leg, foot, hand, knee, and elbow), and occurrence of single or multiple fractures. All fractures were self-reported and information on X-ray verification was not available. For the purpose of the present study, fractures of the elbow, feet, and hands were excluded from the analysis. Information was also obtained about comorbid conditions at baseline, including asthma, emphysema, osteoarthritis, rheumatoid arthritis, colitis, stroke, celiac disease, Parkinson's disease, multiple sclerosis, cancer, type 1 diabetes, hypertension, heart disease, and high cholesterol.

Statistical analysis

For each of 10 fracture sites (hip, spine, wrist, pelvis, rib, upper arm/shoulder, clavicle, ankle, lower leg, upper leg), we modeled the time to incident fracture over the 3-year period using the Cox proportional hazards model and adjusting for variables found to be associated with each specific fracture site, based on previous findings in the same cohort of women.[9] For each fracture site, we considered models containing BMI, height, or weight in three parametric forms: linear, restricted cubic splines, and the best fractional polynomial selected using the closed test procedure as described in Hosmer and colleagues.[10] For each fracture site, the best of the nine possible models was chosen as the model with the smallest Akaike information criterion (AIC). When the best model was based on restricted cubic splines, we plotted the log-hazard of fracture versus the covariate value to describe the nature of the nonlinear relationship between the covariate and the log-hazard of fracture. In the method of restricted cubic spines, three knots or join points were defined to be at the 10th, 50th, and 90th percentiles of the distribution of the variable. Between the minimum value and the 10th percentile, a straight line was used to model the log-hazard. Between the 10th and 50th percentiles and the 50th and 90th percentiles, cubic functions were used. In the last interval, between the 90th percentile and the maximum, a linear model was used. Each of the fits in the four intervals was constrained to join its neighboring fit(s) at the knot. The May and Hosmer goodness-of-fit test[11] was used to assess calibration of each of the fracture type models. All analysis was conducted using SAS software package (version 9.2; SAS Institute, Cary, NC, USA).

Results

Demographics of the study population are shown in Table 1. Of the study population of 52,629 women who had completed at least 1 year of follow-up, had weight and height measurements, and in whom data on incident fracture were available, 3628 (6.9%) sustained at least one incident clinical fracture during the 3-year follow-up period. The sites of fracture included in the analyses were as follows: hip ($n = 309$), spine ($n = 442$), wrist ($n = 923$), ankle ($n = 550$), upper arm/shoulder ($n = 484$), clavicle ($n = 133$), pelvis ($n = 162$), rib ($n = 536$), upper leg ($n = 174$), and lower leg ($n = 234$). Women with incident fracture were older and more likely to have a history of fracture (Table 1). Unintentional weight loss of $>5\,kg$ was more common in

Table 1. Demographics of the Study Population ($n = 52,629$)

Variable	No incident fracture ($n = 49,001$)	Incident fracture ($n = 3628$)	p
Age, years	68.0 ± 8.5	70.8 ± 9.3	<0.001
BMI, kg/m^2	26.9 ± 5.7	26.6 ± 5.8	<0.001
Weight, kg	70.1 ± 15.4	69.0 ± 15.7	<0.001
Height, cm	161.4 ± 6.8	160.9 ± 7.1	0.002
Prior fracture	21.9	41.7	<0.001
Lost >5 kg	8.9	12.7	<0.001
General health			<0.001
Excellent	9.3	6.7	
Very good	29.6	25.1	
Good	40.2	38.6	
Fair	18.5	24.8	
Poor	2.4	4.8	
Physical activity			<0.001
Very active	31.3	28.0	
Somewhat active	46.6	44.5	
A little active	17.9	21.3	
Not at all active	4.2	6.2	
Falls			<0.001
None	63.5	50.1	
One	22.5	25.5	
Two or more	14.0	24.3	
Asthma	11.1	13.8	<0.001
Cancer	14.0	16.9	<0.001
Emphysema	8.3	12.3	<0.001
High cholesterol	50.3	50.5	0.83
Osteoarthritis	39.4	48.4	<0.001
Ulcerative colitis	1.9	2.9	<0.001

Values are given as mean ± SD or %.
BMI = body mass index.

women with incident fracture and self-reported general health was poorer. Self-reported asthma and ulcerative colitis and a history of falls were also more common in women with incident fracture.

Fracture sites for which linear BMI or weight showed the strongest associations are shown in Table 2. BMI was inversely associated with hip, clinical spine, and wrist fractures, whereas for ankle fractures, the association with weight was positive. The adjusted hazard ratios (HRs) were lower for hip, spine, and wrist fractures for every 5-kg/m^2 increase in BMI and higher for ankle fracture for every 5-kg increase in weight (Table 2). Linear weight showed similar, but slightly weaker, associations with hip, spine, and wrist fractures, and linear BMI for ankle fracture. No association was found between height and hip, wrist, or ankle fracture, but the risk of spine fracture was positively related to linear height with an adjusted HR of 1.6 (95% confidence interval [CI], 1.1–2.3) per 10-cm increase.

For upper arm/shoulder and clavicle fractures, the best model was for linear height, with an inverse correlation and a reduction in adjusted HR per 10-cm increase in height (Table 3). Neither weight nor BMI were significantly associated with fracture at these sites.

Table 4 shows the results for pelvic and rib fractures. Nonlinear models were best for both sites. For pelvic fractures, BMI was marginally superior to weight; whereas for rib fractures, weight showed the strongest association. Figure 1 shows that the log-hazard for pelvic fracture decreases sharply from the minimum BMI value of about 13 kg/m^2 to the minimum log-hazard at about 30 kg/m^2 and then rises gradually. A similar pattern was seen for the log-hazard of rib fracture as a function of weight, the log-hazard decreasing to its minimum at a weight of around 80 kg and increasing thereafter. As for pelvic fracture, the curve describing the log-hazard was asymmetric about the minimum value, dropping rapidly and then rising gradually.

For lower and upper leg fractures, no association was found with weight, BMI, or height using any of the three models.

We assessed the goodness-of-fit of all eight models. For three fractures—hip, rib, and spine—the p value of the test was <0.05. Further examination of the calibration tables used to compute the test revealed good agreement between the observed and the model-based estimated expected number of fractures in 80% of the groups. As a result, the departure from fit was not deemed sufficiently broad to reject any of the three models. Thus inferences, for all fractures, are based on the described best models.

Discussion

This study provides novel information on the relationships between BMI, weight, and height and fracture risk at multiple fracture sites and demonstrates that site-specific associations are seen for both BMI/weight and height. For most fracture sites, the relationships were linear, but for rib and pelvic fracture, a nonlinear relationship was seen, with increased fracture risk at both extremes of BMI and weight, although risk was much greater at lower BMIs.

Recent studies comparing fracture incidence in obese and nonobese individuals have demonstrated that obesity, defined on the basis of BMI, is associated with increased risk of fracture at some sites but is protective at others. Reduced risk of hip fracture

Table 2. Fracture Types For Which the Fitted Model Linear BMI or Linear Weight Had the Most Significant Association

Fracture site	Best form of BMI/weight/height	Adjusted HR (95% CI)	χ^2	p	Next best model with different covariate	χ^2	p
Hip[a] ($n = 309$)	Linear BMI (per 5 kg/m^2)	0.80 (0.71–0.90)	14.3	<0.001	Linear weight	12.9	<0.001
Spine[b] ($n = 442$)	Linear BMI (per 5 kg/m^2)	0.83 (0.76–0.92)	14.5	0.0001	Linear weight	6.9	<0.01
Wrist[c] ($n = 923$)	Linear BMI (per 5 kg/m^2)	0.88 (0.83–0.94)	16.3	<0.0001	Linear weight	13.4	<0.001
Ankle[d] ($n = 550$)	Linear weight (per 5 kg)	1.05 (1.02–1.07)	13.9	<0.001	Linear BMI	11.4	<0.001

BMI = body mass index; HR = hazard ratio; CI = confidence interval.
[a]Adjusted for age, prior hip fracture, falls, unintentional weight loss of >5 kg, and physical activity.
[b]Adjusted for age, prior spine fracture, prior fracture of another bone, unintentional weight loss of >5 kg, asthma, general health, and physical activity.
[c]Adjusted for age, prior wrist fracture, prior fracture of another bone, falls, and osteoarthritis.
[d]Adjusted for age, prior ankle fracture, prior fracture of another bone, falls, emphysema, and cancer.

Table 3. Fracture Types For Which the Fitted Model Linear in Height Had the Most Significant Association

Fracture site	Best form of BMI/weight/height	Adjusted HR (95% CI)	χ^2	p	Comments
Upper arm/shoulder[a] ($n = 484$)	Linear height (per 10 cm)	0.85 (0.75–0.97)	5.71	0.02	Neither weight nor BMI were significant in predicting upper arm/shoulder fracture
Clavicle[b] ($n = 133$)	Linear height (per 10 cm)	0.73 (0.57–0.92)	6.91	0.009	Neither weight nor BMI were significant in predicting clavicle fracture

BMI = body mass index; HR = hazard ratio; CI = confidence interval.
[a]Adjusted for age, prior arm fracture, prior fracture of another bone, falls, and general health.
[b]Adjusted for age, prior clavicle fracture, falls, unintentional weight loss >5 kg, and ulcerative colitis.

Table 4. Fracture Types For Which the Fitted Model Nonlinear BMI or Nonlinear Weight Had the Most Significant Association

Fracture site	Best form of BMI/weight/height	χ^2	p	Next best model with different covariate	Comments
Pelvis[a] ($n = 162$)	BMI modeled using restricted cubic splines with 3 knots[b]	3.87	0.05	Weight splines	Weight and BMI were similar at predicting pelvis fracture
Rib[c] ($n = 536$)	Weight modeled using restricted cubic splines with 3 knots[b]	4.57	0.03	BMI splines	Weight and BMI were similar at predicting rib fracture

BMI = body mass index.
[a]Adjusted for age, prior pelvis fracture, falls, and high cholesterol.
[b]Knots at the 10th, 50th, and 90th percentiles of the distribution.
[c]Adjusted for age, prior rib fracture, prior fracture of another bone, falls, asthma, and general health.

in obese postmenopausal women compared with nonobese women has been a consistent finding,[2,4,7] and a lower incidence of wrist fracture in obese compared with nonobese women has also been reported.[4] Conversely, obesity has been associated with an increased risk of ankle and other leg fractures (excluding hip)[3,4,6] and an increased risk of proximal humerus fracture.[5,7] The results of such studies are influenced to some extent by the distribution of BMI in the population studied; eg, in cohorts with a low prevalence of obesity, a predilection for certain fracture sites in obese individuals becomes difficult to detect, whereas in populations with a high prevalence of obesity, previously unreported associations may emerge. Additionally, the design of such studies does not enable examination of the nature of the relationship between fracture and BMI, weight, or height over the whole range of values.

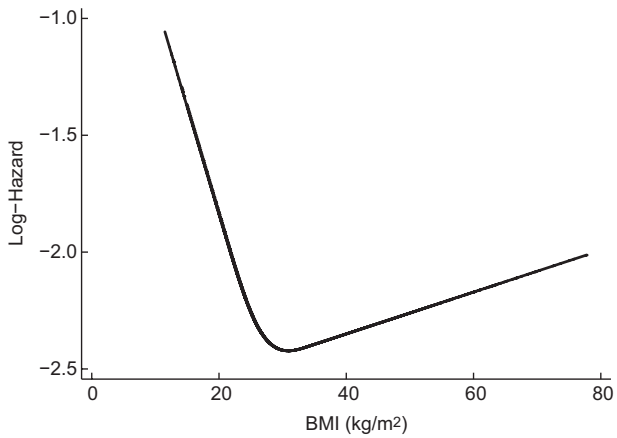

Fig. 1. Log-hazard plot for pelvis fracture by BMI, modeled using restricted cubic spines with three knots at the 10th, 50th, and 90th percentiles of the distribution.

Studies of the relationship between spine fractures and BMI/weight have produced conflicting data. In two cross-sectional studies, a positive association between BMI and prevalent morphometric vertebral fractures has been reported in postmenopausal women,[12,13] whereas in the present study, BMI and weight were inversely related to clinical incident vertebral fractures. Prieto-Alhambra and colleagues[7] did not observe differences in clinical spine fracture incidence between obese and nonobese postmenopausal women, although in men, obesity was associated with a significantly reduced risk of clinical spine fracture. The reasons for these contrasting findings are unclear, but may reflect the differences in BMI distribution in the populations, as discussed in the previous paragraph, as well as variations in the criteria for diagnosis of vertebral fracture.

A number of mechanisms whereby BMI/weight may influence fracture risk have been proposed.[14] These include effects on bone mineral density; muscle strength; the frequency, direction, and impact of falls, with greater biomechanical forces resulting from higher body weight; the protective response to falling; and the presence or absence of soft tissue padding. In addition, increased cytokine production by visceral fat, altered insulin homeostasis, and higher prevalence of vitamin D insufficiency in obese individuals may be implicated.[15–27]

Greater body height has been reported by several groups to be a risk factor for hip and wrist fracture in postmenopausal women,[28–36] and in one study, height at the age of 25 years was also positively correlated with vertebral fracture prevalence.[31] In the present study, we found a positive association between

height and spine fracture, but not hip or wrist fracture, whereas an inverse relationship was observed between height and clavicular and upper arm/shoulder fractures. Mechanisms by which greater height may increase fracture risk include greater impact of falling, greater cortical porosity,[29] and, for hip fracture, greater hip axis length. The reason why smaller height is associated with clavicle and upper arm fractures is unclear. Greater risk might be expected in taller people because of a greater impact of falling; in addition, there is evidence that cortical thickness relative to bone size is reduced in taller people and that cortical porosity is increased.[29] However, the wider bones in taller people may offset the potentially adverse effects of these changes in cortical structure, and the narrower bones in smaller people might thus be more prone to fracture.

Previous studies investigating the relationship between BMI/weight and fracture have not specifically examined the relationship between BMI and weight and pelvic and rib fractures and our study is the first to demonstrate that this relationship is nonlinear for these fractures. Lower risk of pelvis fractures has been reported in obese compared with nonobese postmenopausal women[4]; however, our data indicate that increased risk is seen at both extremes of BMI and weight. Associations between BMI and rib fractures have not been reported in postmenopausal women, although in a recent study, a significantly higher risk of multiple rib fractures was reported in obese men when compared with normal or underweight men.[37]

Strengths and limitations

Our study has several strengths, including the large sample size, prospective design, and international scope. There are also, however, some limitations. GLOW is a practice-based rather than a population-based study and is therefore subject to bias both in the selection of physicians and in the sampling and recruitment of patients. All data were collected by patient self-report and may be limited by recall bias and measurement error with regard to reported height and weight. Studies that have examined the validity of self-reported fractures have shown reasonable accuracy,[38,39] although this may be less true for rib fractures, which are seldom verified radiologically. However, there is no reason why accuracy of reporting of any fractures should differ according to BMI. We therefore believe that the generalizability of our findings to clinical practice in the general population is likely to be good, but cannot exclude possible effects of sampling bias and inaccuracies resulting from self-report of fractures. Finally, only women were included in the study, and relationships between fracture and BMI, weight, and height may be different in men.

In conclusion, our results in this large cohort of postmenopausal women demonstrate that associations between fracture risk and height, weight, and BMI differ according to fracture site. Inverse linear associations between BMI or weight and hip, spine, and wrist fracture were observed, whereas a positive linear association was seen with ankle fracture. A positive association was also seen between height and spine fracture. Upper arm/shoulder and clavicle fractures were not associated with BMI or weight, but were inversely associated with height, and nonlinear associations with BMI and weight were seen for pelvis and rib fractures. No significant associations were seen between height, weight, or BMI and lower or upper leg fractures. In view of the rapidly rising incidence of obesity in many parts of the world,[40–43] our results have implications for the epidemiology of fractures in elderly populations and suggest that, in the future, changes may emerge in the distribution of fractures at different skeletal sites.

Disclosures

JEC has previously consulted for Servier, Shire, Nycomed, Novartis, Amgen, Procter & Gamble, Wyeth, Pfizer, The Alliance for Better Bone Health, Roche, and GlaxoSmithKline; has received lecture fees, travel, and accommodation from Servier, Procter & Gamble, and Lilly; and has received grant support from Nycomed (2009–2012) and Acuitas (2009–2011). JF, DH, and JWN state that they have no conflicts of interest. NBW has received honoraria for lectures during the past year from Amgen, Lilly, Novartis, and Warner Chilcott; consulting fees during the past year from Abbott, Amgen, Bristol-Myers Squibb, Endo, Imagepace, Johnson & Johnson, Lilly, Medpace, Merck, Nitto Denko, Noven, Novo Nordisk, Pfizer/Wyeth, and Quark; research support (through his Health System) from Merck and NPS; and cofounded, has stock options in and is a director of OsteoDynamics. ESS has previously consulted for Amgen, Lilly, Novartis, Merck, and Pfizer; and has served on Speakers' Bureaus for Amgen and Lilly. SS has received grant support from Wyeth, Lilly, Novartis, and Alliance; has served on Speakers' Bureaus for Lilly, Novartis, Pfizer, and Procter & Gamble; has received honoraria from Procter & Gamble; and has previously consulted/acted as an Advisory Board member for Lilly, Argen, Wyeth, Merck, Roche, and Novartis. KGS has consulted for or received other remuneration from Merck, Amgen, and Eli Lilly; has received research grants from Merck; and has held non-remunerative positions of influence on the NOF Board of Trustees and as ACR Chair on the Quality of Care Committee. CR has received honoraria from and consults/acts as an advisory board member for Alliance, Amgen, Lilly, Merck, Novartis, Nycomed, Roche, GlaxoSmithKline, Servier, and Wyeth. MR is on the Speakers' Bureau for Roche. JP has received grant support from Amgen, Kyphon, Novartis, and Roche; has received grant support for equipment from GE Lunar; has served on Speakers' Bureaus for Amgen, sanofi-aventis, GlaxoSmithKline, Roche, Lilly Deutschland, Orion Pharma, Merck, Merckle, Nycomed, and Procter & Gamble; and has acted as an Advisory Board member for Novartis, Roche, Procter & Gamble, and Teva. JCN has previously consulted for Roche Diagnostics, Daiichi-Sankyo, Proctor & Gamble, and Nycomed; has received lecture fees, travel and accommodation from E. Lilly, Amgen, Novartis, and Will Farma and has received grant support from The Alliance for Better Bone Health and Amgen. LM has acted as an Advisory Board member for Servier and received speakers' bureau fees and support to travel to scientific meetings from Servier, Merck, and Pfizer. AZL has received funding from The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott) and is an Advisory Board member for Amgen. FHH, SHG, and FAA have received funding from Pfizer. SLG has previously consulted/been an Advisory Board member for Amgen, Lilly, and Merck; and has received grant support from The Alliance for Better Bone Health (sanofi-aventis and Proctor & Gamble) and Lilly. AD-P has received consulting fees and lectured for Eli Lilly, Amgen, Procter & Gamble, Servier, and Daiichi-Sankyo; has been an expert witness for Merck; consults for/is an Advisory Board member for Novartis, Eli Lilly, Amgen, and Procter & Gamble; has received honoraria from Novartis, Lilly, Amgen, Procter & Gamble, and Roche; has previously been an expert witness for Merck; and has previously consulted/acted as an Advisory Board member for Novartis, Lilly, Amgen, and Procter & Gamble. CC has previously

consulted for/received lecture fees from Amgen, The Alliance for Better Bone Health (sanofi-aventis and Warner Chilcott), Lilly, Merck, Servier, Novartis, and Roche-GSK. RDC has received funding from the French Ministry of Health, Merck, Servier, Lilly, and Procter & Gamble; has received honoraria from Amgen, Servier, Novartis, Lilly, Roche, and sanofi-aventis; and has previously consulted/acted as an Advisory Board member for Amgen, Merck, Servier, Nycomed, and Novartis. SB has received grant support from Amgen, Lilly, Novartis, Pfizer, Procter & Gamble, sanofi-aventis, Roche, and GlaxoSmithKline; and has received honoraria from, served on Speakers' Bureaus for and previously consulted/acted as an Advisory Board member for Amgen, Lilly, Merck, Novartis, Procter & Gamble, sanofi-aventis, and Servier. SA has received honoraria for boards and speeches from Merck, Eli-Lilly, and Amgen. JDA has received consulting fees or other remuneration from Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott; has received research grants from Amgen, Eli Lilly, Merck, and Novartis; has held a non-remunerative position of influence on the IOF Board of Directors, Osteoporosis Canada; and has been on speakers bureaus for Amgen, Eli Lilly, Merck, Novartis, and Warner Chilcott.

Acknowledgments

Financial support for the GLOW study is provided by Warner Chilcott Company, LLC, and sanofi-aventis to the Center for Outcomes Research, University of Massachusetts Medical School. JEC acknowledges support from the Cambridge Biomedical Research Centre and the National Institute for Health Research (NIHR). Sophie Rushton-Smith, PhD, coordinated revisions and provided editorial assistance, including editing, checking content and language, formatting, and referencing.

Authors' roles: Study design: JEC, NBW, ESS, SS, KGS, CR, JP, JWN, JCN, LM, AZL, FHH, SLG, SHG, ADP, CC, RDC, SB, FAA, SA, and JDA. Study conduct: JEC, NBW, ESS, SS, KGS, CR, MR, JP, JWN, JCN, LM, AZL, FHH, SLG, SHG, ADP, CC, RDC, SB, FAA, SA, and JDA. Data collection: NBW, SS, KGS, CR, MR, JP, JWN, JCN, LM, AZL, SHG, ADP, CC, RDC, SB, SA, and JDA. Data analysis: JF and DWH. Data interpretation: JEC. Drafting manuscript: JEC. Revising manuscript content: JEC, JF, DWH, NBW, ESS, SS, KGS, CR, MR, JP, JWN, JCN, LM, AZL, FHH, SLG, SHG, ADP, CC, RDC, SB, FAA, SA, and JDA. Approving final version of manuscript: JEC, JF, DWH, NBW, ESS, SS, KGS, CR, MR, JP, JWN, JCN, LM, AZL, FHH, SLG, SHG, ADP, CC, RDC, SB, FAA, SA, and JDA. JEC, JF, and DWH take responsibility for the integrity of the data analysis.

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