Surgical Endoscopy (2018) 32:2650–2655
https://doi.org/10.1007/s00464-017-5628-4

Bariatric surgery increases risk of bone fracture

Anna Z. Fashandi[1] · J. Hunter Mehaffey[1] · Robert B. Hawkins[1] · Bruce Schirmer[1] · Peter T. Hallowell[1]

Received: 9 April 2017 / Accepted: 26 May 2017 / Published online: 30 April 2018

Abstract

Introduction The purpose of this study was to determine the long-term incidence of bone fracture after bariatric surgery, identify specific risk factors for fracture, and compare these data to baseline risk in a comorbidity-matched morbidly obese population. We hypothesize that, despite prior studies with conflicting results, bariatric surgery increases a patient's long-term risk of fracture.

Methods All patients who underwent bariatric surgery at a single institution 1985–2015 were reviewed. Univariate analysis of patient demographic data including comorbidities, insurance payer status, procedure type, and BMI was performed. Multivariate logistic regression was used to identify independent predictors of fracture in this population. Finally, we identified a propensity-matched control group of morbidly obese patients from our institutional Clinical Data Repository in the same timeframe who did not undergo bariatric surgery to determine expected rate of fracture without bariatric surgery.

Results A total of 3439 patients underwent bariatric surgery, with 220 (6.4%) patients experiencing a bone fracture at mean follow-up of 7.6 years. On multivariate logistic regression, independent predictors of increased fracture included tobacco use and Roux-en-Y gastric bypass while private insurance and race were protective (table). Additionally, 1:1 matching on all comorbidity and demographic factors identified 3880 patients (1940 surgical patients) with equal propensity to undergo bariatric surgery. Between the propensity-matched cohorts, patients who had a history of bariatric surgery were more than twice as likely to experience a fracture as those who did not (6.4 vs. 2.7%, $p < 0.0001$).

Conclusions This study of bariatric surgery patients at our institution identified several independent predictors of post-operative fracture. Additionally, these long-term data demonstrate patients who had bariatric surgery are at a significantly increased risk of bone fracture compared to a propensity-matched control group. Future efforts need to focus on nutrient screening and risk modification to reduce the impact of this long-term complication.

Keywords Bariatric · Fracture · Bariatric surgery · Propensity match

Obesity remains a growing health concern and is associated with many comorbid medical conditions including hypertension, diabetes, dyslipidemia, coronary disease, stroke, and sleep apnea. In America, more than two-thirds (68.8%) of the adult population is considered overweight (BMI > 25 kg/m^2) and more than one-third (35.7%) is considered obese (BMI >30 kg/m^2) [1, 2]. Bariatric surgery is increasingly being used to combat the obesity epidemic and is currently used to treat patients with a BMI greater than 40 kg/m^2 or those with a BMI greater than 35 kg/m^2 who have obesity-related comorbid disease. Approximately 179,000 weight-loss surgeries were performed in 2013 in the US alone, most of which were Roux-en-Y gastric bypass (RYBG, 34.2%) or sleeve gastrectomy (SG, 42.1%) procedures, with fewer adjustable gastric banding (14%) and occasional biliopancreatic diversion (BPD) with duodenal switch (1%) procedures [3]. Bariatric surgery has been shown to have outstanding results with both durable weight loss and sustained reduction of obesity-related comorbid disease [4–6].

Presented at the SAGES 2017 Annual Meeting, March 22–25, 2017, Houston, Texas.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00464-017-5628-4) contains supplementary material, which is available to authorized users.

✉ Peter T. Hallowell
PTH2F@virginia.edu

[1] Department of Surgery, University of Virginia, Box 800709, Charlottesville, VA 22903, USA

Although bariatric surgery has many positive effects on patient health, there is some evidence of associated health risks, including an increased risk for bone disease. Several studies have shown that bariatric surgery leads to increased bone resorption markers [7, 8] and reduced bone mineral density [9]. These detrimental effects on bone health are multifactorial and likely involve nutritional deficiencies, changes in mechanical loading and alterations in various gastrointestinal and fat-associated hormonal factors [3, 8, 10–12]. Given these bone changes, several studies have been undertaken to assess the risk of bone fracture after bariatric surgery [13–16]. The results of these studies are conflicting; however, the true effect of bariatric surgery on skeletal fragility remains unknown.

The goal of this study was to determine the long-term incidence of bone fracture after bariatric surgery and to identify risk factors for fracture. We additionally aimed to compare the risk of fracture in a group of individuals who underwent bariatric surgery to that of a group of propensity-matched morbidly obese patients who did not undergo weight-loss surgery. We hypothesized that bariatric surgery would independently increase a patient's long-term risk of fracture.

Materials and methods

The University of Virginia Institutional Review Board approved this study (IRB Protocol #17132). All adults undergoing bariatric surgery at a single institution between 1985 and 2015 were reviewed from a previously validated institutional database [4]. This database included demographic data as well as preoperative comorbidities [diabetes mellitus, gastroesophageal reflux disease, obstructive sleep apnea (OSA), hypertension, osteoarthritis, pulmonary disease, and cardiac disease], operative details, and postoperative complications. Additionally, the institutional Clinical Data Repository (CDR) captures all patient visits recorded in our electronic medical record and was used to identify patients within our bariatric database who were evaluated or treated for a bone fracture. Patients were stratified by fracture status and univariate analyses characterized baseline and operative characteristics. The Mann–Whitney U test was used for independent continuous variables and the Wilcoxon signed-rank sum test for paired ordinal data. The χ^2 test was used for independent categorical variables. Multivariate logistic regression was utilized to identify predictors of long-term bone fracture. A priori, the decision was made to include all clinically reasonable preoperative variables and no selection methods were used.

To identify an appropriate control group, the CDR was used to find a matched cohort of morbidly obese patients not undergoing bariatric surgery. All baseline characteristics including demographics, comorbidities, obesity-related factors, and socioeconomic variables were collected at the time a control patient began accruing time in the database at first diagnosis of morbid obesity (BMI >35 kg/m^2). Patients were then matched on a 1:1 basis for the propensity to undergo bariatric surgery using propensity scores [17]. Balance was assessed by standardized mean difference (Supplemental Fig. 1) with adequacy considered as less than 20%. McNemar's test or Wilcoxon signed-rank test was used to compare the matched pairs including for fracture rates. Statistical significance was determined by two-sided α of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

A total of 3439 patients underwent bariatric surgery in the study period; the mean age at the time of surgery was 43 years and 2789 (81.1%) were women. Most (79.4%) of these patients underwent Roux-en-Y gastric bypass (RYGB) while 11.2% had gastric banding and 7.8% had SG procedures. "Other" procedures including BPD and vertical banded gastroplasty comprised only 1.7% of all surgical cases. Fractures occurred in 220 (6.4%) patients (Table 1) at a mean time of 7.6 $\pm$ 5.6 years after surgery; 50 (22.7%) of these patients experienced multiple different fracture events while 48 (21.8%) experienced one event resulting in multiple fractured bones. On univariate analysis, patients who experienced a fracture were more likely to have had RYGB or a history of chronic obstructive pulmonary disease, tobacco use, or congestive heart failure. Those who were Caucasian were less likely to experience a postoperative fracture. Most fractures occurred in the upper (39.1%) and lower (33.6%) extremities. Fractures of the hip accounted for 2.3% and facial/skull fractures accounted for 7.3% of all fractures. Fractures at "other" sites including pelvis, spine, ribs, and sternum comprised 17.3% of all recorded fractures.

Multivariate logistic regression identified Caucasian race [odds ratio (OR) 0.675; 95% confidence interval (CI) 0.458–0.996], and private insurance (OR 0.698; 95% CI 0.287–0.912) as patient factors that were protective against fractures (Table 2). Tobacco use (OR 3.124; 95% CI 1.633–5.977) and RYGB, when compared to SG (OR 2.175; 95% CI 1.046–4.525), were both independent predictors of fracture.

After 1:1 matching by propensity to undergo surgery, 3880 patients were found to be well matched with propensity score distributions shown in Supplemental Figs. 1 and 2. They were well balanced with all standardized mean differences $\leq$10% (Supplemental Fig. 3) and

Table 1 Preoperative characteristics between patients with and without fractures

Variables	Fracture	No fracture	p values
Patients	220	3219	–
Age (years)	43 ± 10	43 ± 10	0.933
Sex (female)	184 (83.6%)	2605 (80.9%)	0.321
Race (white)	183 (83.2%)	2851 (88.6%)	**0.017**
Body mass index (kg/m^2)	51.7 ± 9.7	50.6 ± 9.5	0.112
Private insurance	1932 (60.0%)	114 (51.8%)	0.311
Diabetes mellitus	64 (29.1%)	928 (28.8%)	0.934
Hypertension	115 (52.3%)	1645 (51.1%)	0.737
Obstructive sleep apnea	62 (28.2%)	883 (27.4%)	0.809
Degenerative joint disease	79 (35.9%)	1011 (31.4%)	0.165
Chronic obstructive pulmonary disease	15 (6.8%)	100 (3.1%)	**0.003**
Gastroesophageal reflux disease	56 (25.5%)	886 (27.5%)	0.506
Tobacco use	15 (6.82%)	51 (1.6%)	**<0.0001**
Congestive heart failure	18 (8.2%)	141 (4.4%)	**0.009**
RYGB	191 (86.8%)	2538 (78.8%)	**0.006**
Multiple fracture events	50 (22.7%)	–	
One event with multiple fractures	48 (21.8%)	–	
Time to fracture (years)	7.6 ± 5.6	–	

Bold values are statistically significant ($p < 0.05$)

Table 2 Logistic regression for fracture

Variables	Odds ratio	95% Confidence interval		p values
Sex (female)	1.271	0.857	1.887	0.233
Race (white)	0.675	0.458	0.996	**0.0477**
Private insurance	0.698	0.287	0.912	**0.0124**
Diabetes mellitus	1.021	0.73	1.428	0.9026
Hypertension	0.968	0.711	1.318	0.8349
Obstructive sleep apnea	0.925	0.659	1.298	0.6516
Degenerative joint disease	0.917	0.677	1.241	0.5738
Chronic obstructive pulmonary disease	0.665	0.36	1.228	0.1925
Gastroesophageal reflux disease	1.146	0.822	1.599	0.4209
Tobacco use	3.124	1.633	5.977	**0.0006**
Congestive heart failure	0.652	0.38	1.119	0.1207
Gastric band versus SG	1.342	0.556	3.24	0.5132
RYGB versus SG	2.175	1.046	4.525	**0.0376**
Age (years)	1.003	0.988	1.019	0.6808
Body mass index (kg/m^2)	1.002	0.987	1.018	0.7868

Bold values are statistically significant ($p < 0.05$)

similar at baseline except for OSA, which was statistically higher in the surgery group ($p = 0.011$; Table 3). When comparing the two groups for risk of fracture, the fracture rate was significantly higher in the surgical group than in the non-surgical group (6.4 vs 2.7%, respectively; $p < 0.0001$). These fractures occurred at an average of 8.2 ± 6.0 years after surgery.

Discussion

In this study of a single institution's bariatric surgery population of 3439 patients, RYGB and a history of tobacco use were both shown to be independent predictors of fracture. Importantly, we also demonstrated that obese patients undergoing surgery were more than twice as likely to experience a fracture as comorbidity- and BMI-matched patients who did not undergo weight-loss surgery.

Table 3 Characteristics between matched groups

Variables	Surgery	No surgery	*p* values
Age (years)	43 ± 10	43 ± 14	0.591
Sex (female)	1576 (81.2%)	1585 (81.7%)	0.703
Race (white)	1684 (86.8%)	1685 (86.9%)	0.962
Body mass index (kg/m^2)	48.2 ± 8.2	49.2 ± 11.5	0.158
Private insurance	1071 (55.2%)	1077 (55.5%)	0.382
Diabetes mellitus	436 (22.5%)	445 (22.9%)	0.722
Hypertension	776 (40.0%)	773 (39.9%)	0.917
Obstructive sleep apnea	198 (10.2%)	157 (8.1%)	**0.011**
Degenerative joint disease	360 (18.6%)	340 (17.5%)	0.386
Chronic obstructive pulmonary disease	44 (2.3%)	45 (2.3%)	0.916
Gastroesophageal reflux disease	337 (17.4%)	339 (17.5%)	0.930
Tobacco use	42 (2.2%)	42 (2.2%)	1.000
Congestive heart failure	94 (4.9%)	104 (5.4%)	0.461
Fracture	125 (6.4%)	53 (2.7%)	**<0.0001**
Time to fracture (years)	8.2 ± 6.0	9.0 ± 7.2	0.772

Bold values are statistically significant ($p < 0.05$)

Bariatric surgeries that involve a malabsorptive component result in greater weight loss and are more likely to cause protein and various nutritional deficiencies, including vitamin D and calcium deficiency, when compared to purely restrictive procedures [3, 10, 11]. Given the increased risk for these nutritional deficiencies which are known to affect bone health, it follows that patients undergoing malabsorptive procedures are likely at an increased risk for bone loss and fracture. On multivariate analysis of our entire bariatric surgery population, we found that RYGB, a mixed malabsorptive and restrictive procedure, indeed was associated with a higher risk for fracture when compared to SG, a purely restrictive surgery. Guidelines for malabsorptive bariatric surgery recommend postoperative supplementation with vitamin D and calcium and emphasize adequate protein intake in order to minimize these potential deficiencies. They also recommend that all bariatric patients incorporate strength training and daily aerobic activity into their postoperative fitness routines, which can help improve overall bone health [18]. Our analysis also identified tobacco use as an independent risk factor for postoperative fracture after bariatric surgery. Studies have shown that smoking causes decreased bone mineral density and up to one in eight hip fractures in women may be attributable to smoking, according to one meta-analysis [19]. Moreover, smoking is known to impair osteoblast production, causing any sustained fractures to heal at a slower rate [20].

Comparison with other studies of fracture risk

Four studies have been previously published addressing the risk of bone fracture after bariatric surgery. The first was a retrospective cohort study from the UK in which fracture risk was compared between 2079 bariatric surgery patients and 10,442 controls matched for BMI, age, and sex [13]. Lalmohamed et al. found no difference in overall fracture risk between the two groups, though the study only had 2.2 years of follow-up and relatively few observed fractures ($n = 39$). They also reported no difference in fracture risk between types of bariatric procedures. In their study, 60% of patients underwent gastric banding, a purely restrictive procedure, while only 29% underwent RYGB. It is therefore difficult to compare their results to ours given the difference in practice patterns, with RYGB being far more common in our surgical cohort. Given that restrictive procedures like gastric banding are not associated with alterations in vitamin D and calcium absorption, the majority of patients in the Lalmohamed study were likely at a lower risk for developing skeletal changes and, therefore, fractures.

Another retrospective study of 258 bariatric surgery patients (94% RYGB) in a single county in Minnesota between 1985 and 2004 showed that the fracture risk was two times higher in patients after RYGB compared to age- and sex-matched controls from the general population [14]. The patient population was similar to our cohort in age and gender, though they had a greater proportion of RYGB patients and no SG patients. This is reflective of surgical practice at the time, however, since SG was not yet popular by 2004. Despite this difference, their degree of increase in fracture risk is similar to our analysis and our study identified RYGB as an independent predictor of fracture risk. One weakness of the Nakamura study is that patients were not matched for many confounding factors including comorbid disease or BMI. This may lead to an overestimate of fracture risk in the surgical group, as these patients may have had increased fracture risk as a result of their baseline health and not from undergoing surgery, per se.

A retrospective study from Taiwan comparing fracture risk between 2064 bariatric surgery patients and 5027 propensity score-matched controls showed a 1.2-fold increase in fractures after surgery [15]. Lu et al. reported this increased risk was, as in our findings, limited to malabsorptive procedures; fracture risk was not elevated in patients undergoing purely restrictive bariatric surgery. The matching of patients in this study is similar to ours, except that their patients were not matched based on BMI. Additionally, the Taiwanese cohort was far younger (mean age of 31.8 years) than our bariatric patients, which also may contribute to an underestimated fracture risk.

Finally, Rousseau et al. published a large retrospective, case–control study of 12,676 Canadian bariatric patients who were age and sex matched with 38,028 obese and 126,760 non-obese controls [16]. They showed that bariatric patients had a higher baseline fracture risk in addition to a higher postoperative fracture risk than both the obese [relative risk (RR) 1.38] and non-obese (RR 1.44) control patients, once adjustments were made for demographic data including comorbidities. When comparing fracture risk based on type of bariatric procedure, only patients undergoing BPD had an increased risk of fracture (adjusted RR 1.60). The RYGB group, who, like the BPD group, also underwent a mixed malabsorptive and restrictive procedure, did not have a significantly increased risk of fracture, though there was a trend in this direction. Rousseau et al. therefore reported their findings for RYGB as inconclusive as they had a relatively small number of RYGB cases. Their results may have fallen more closely in line with ours and shown an increased risk of fracture in this population if RYGB had not been underrepresented in their dataset. The Canadian study did not match patients based on BMI, allowing for the possibility that obese controls may have been less obese than the surgical group, which may have led to an exaggeratedly high fracture risk in the surgical cohort. Although obesity has long been thought to be protective against fracture owing to greater bone mineral density, recent studies have called this thought into question [3, 10]. One large meta-analysis showed that women with a higher BMI had an increased risk of fracture (hazard ratio per 1 unit increased in BMI 1.01; 95% CI 1.01–1.02), after adjusting for bone mineral density [21]. We controlled for this possibility by matching for both BMI and comorbidities, and still found the risk of fracture to be elevated after bariatric surgery.

Study strengths and limitations

There are several strengths of the current study including that it is a relatively large group of bariatric patients with a long average follow-up. Additionally, the propensity matching accounted for many variables between groups including BMI, which has only been done in one prior study of fracture risk. This allows a better indication of the fracture risk from surgery itself, and helps eliminate the chance that increased fracture risk is related only to morbid obesity. This study does, however, have several limitations including the risk of bias owing to its retrospective nature. The patient population is comprised only of those who received care at a single institution, and these results are therefore difficult to generalize to a national or international population. We did not have data on patients' osteopenia or osteoporosis, bone mineral density scans, prior fracture or fall history, baseline activity level or medication use, all of which may affect bone health. Additionally, we did not have information on the etiology of fractures including the level of trauma sustained by patients who experienced a fracture event. Another limitation of this study is that fractures were only recorded within our institution, so patients who were treated for fractures outside of this hospital system may not have been captured.

Conclusions

This study showed that bariatric surgery patients experienced over twice as many fractures as a propensity-matched cohort of morbidly obese patients who did not undergo surgery. Moreover, fracture risk is independently increased in tobacco users and greater in those who undergo mixed malabsorptive and restrictive bariatric procedures when compared to purely restrictive procedures. Bariatric surgery patients should be counseled regarding the increased risk of postoperative fracture, particularly in those who are planning on undergoing procedures with a malabsorptive component. Assistance with tobacco cessation should be provided in the preoperative setting to further decrease the deleterious effects of surgery on bone health. In order to mitigate the effects of bariatric surgery on bone health, physicians must emphasize the importance of patient adherence to guidelines regarding nutritional supplementation and physical activity after surgery.

Funding The National Institutes of Health under Award Number T32HL007849 supported research reported in this publication. The content is solely the responsibility of the authors and does not

necessarily represent the official views of the National Institutes of Health.

Compliance with ethical standards

Disclosures Drs. Fashandi, Mehaffey, Hawkins, Schirmer, and Hallowell have no conflicts of interest or financial ties to disclose.

References

1. Flegal KM, Carroll MD, Kit BK, Ogden CL (2012) Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 307:491–497
2. Ogden CL, Carroll MD, Kit BK, Flegal KM (2012) Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. JAMA 307:483–490
3. Gregory NS (2017) The effects of bariatric surgery on bone metabolism. Endocrinol Metab Clin N Am 46:105–116
4. Mehaffey JH, LaPar DJ, Clement KC, Turrentine FE, Miller MS, Hallowell PT, Schirmer BD (2015) 10-Year outcomes after Roux-en-Y gastric bypass. Ann Surg. https://doi.org/10.1097/SLA.0000000000001544
5. Mehaffey JH, Mullen MG, Mehaffey RL, Turrentine FE, Malin SK, Kirby JL, Schirmer B, Hallowell PT (2016) Type 2 diabetes remission following gastric bypass: does diarem stand the test of time? Surg Endosc. https://doi.org/10.1007/s00464-016-4964-0
6. Pories WJ, Mehaffey JH, Staton KM (2011) The surgical treatment of type two diabetes mellitus. Surg Clin N Am 91:821–836, viii
7. Bruno C, Fulford AD, Potts JR, McClintock R, Jones R, Cacucci BM, Gupta CE, Peacock M, Considine RV (2010) Serum markers of bone turnover are increased at six and 18 months after Roux-en-Y bariatric surgery: correlation with the reduction in leptin. J Clin Endocrinol Metab 95:159–166
8. Scibora LM, Ikramuddin S, Buchwald H, Petit MA (2012) Examining the link between bariatric surgery, bone loss, and osteoporosis: a review of bone density studies. Obes Surg 22:654–667
9. Yu EW, Bouxsein ML, Putman MS, Monis EL, Roy AE, Pratt JS, Butsch WS, Finkelstein JS (2015) Two-year changes in bone density after Roux-en-Y gastric bypass surgery. J Clin Endocrinol Metab 100:1452–1459
10. Stein EM, Silverberg SJ (2014) Bone loss after bariatric surgery: causes, consequences, and management. Lancet Diabetes Endocrinol 2:165–174
11. Hage MP, El-Hajj Fuleihan G (2014) Bone and mineral metabolism in patients undergoing Roux-en-Y gastric bypass. Osteoporos Int 25:423–439
12. Mehaffey JH, Mehaffey RL, Mullen MG, Turrentine FE, Malin SK, Schirmer B, Wolf AM, Hallowell PT (2017) Nutrient deficiency 10 years following Roux-en-Y gastric bypass: Who's responsible? Obes Surg. https://doi.org/10.1007/s11695-016-2364-0
13. Lalmohamed A, de Vries F, Bazelier MT, Cooper A, van Staa TP, Cooper C, Harvey NC (2012) Risk of fracture after bariatric surgery in the United Kingdom: population based, retrospective cohort study. BMJ 345:e5085
14. Nakamura KM, Haglind EG, Clowes JA, Achenbach SJ, Atkinson EJ, Melton LJ III, Kennel KA (2014) Fracture risk following bariatric surgery: a population-based study. Osteoporos Int 25:151–158
15. Lu CW, Chang YK, Chang HH, Kuo CS, Huang CT, Hsu CC, Huang KC (2015) Fracture risk after bariatric surgery: a 12-year nationwide cohort study. Medicine (Baltim) 94:e2087
16. Rousseau C, Jean S, Gamache P, Lebel S, Mac-Way F, Biertho L, Michou L, Gagnon C (2016) Change in fracture risk and fracture pattern after bariatric surgery: nested case–control study. BMJ 354:i3794
17. McMurry TL, Hu Y, Blackstone EH, Kozower BD (2015) Propensity scores: methods, considerations, and applications. J Thorac Cardiovasc Surg 150:14–19
18. Mechanick JI, Youdim A, Jones DB, Garvey WT, Hurley DL, McMahon MM, Heinberg LJ, Kushner R, Adams TD, Shikora S, Dixon JB, Brethauer S, American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery (2013) Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic and Bariatric Surgery. Obesity (Silver Spring) 21(Suppl 1):S1–27
19. Law MR, Hackshaw AK (1997) A meta-analysis of cigarette smoking, bone mineral density and risk of hip fracture: recognition of a major effect. BMJ 315:841–846
20. Ko CH, Chan RL, Siu WS, Shum WT, Leung PC, Zhang L, Cho CH (2015) Deteriorating effect on bone metabolism and microstructure by passive cigarette smoking through dual actions on osteoblast and osteoclast. Calcif Tissue Int 96:389–400
21. Johansson H, Kanis JA, Oden A, McCloskey E, Chapurlat RD, Christiansen C, Cummings SR, Diez-Perez A, Eisman JA, Fujiwara S, Gluer CC, Goltzman D, Hans D, Khaw KT, Krieg MA, Kroger H, LaCroix AZ, Lau E, Leslie WD, Mellstrom D, Melton LJ III, O'Neill TW, Pasco JA, Prior JC, Reid DM, Rivadeneira F, van Staa T, Yoshimura N, Zillikens MC (2014) A meta-analysis of the association of fracture risk and body mass index in women. J Bone Miner Res 29:223–233