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ORIGINAL CONTRIBUTIONS

Fractures in Adults After Weight Loss from Bariatric Surgery and Weight Management Programs for Obesity: Systematic Review and Meta-analysis

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Abstract

Background Weight loss interventions for obesity, such as bariatric surgery, are associated with reductions in bone mineral density and may increase the risk of fractures. We undertook a systematic review and meta-analysis of bariatric surgery and lifestyle weight management programs (WMPs) with fracture outcomes.

Methods We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials from 1966 to 2018, and our trial registry of WMP randomized controlled trials (RCTs). We included RCTs, non-randomized trials, and observational studies of bariatric surgery, and RCTs of WMPs. Studies had follow-up ≥ 12 months, mean group body mass index ≥ 30 kg/m^2. The primary outcome measure was incidence of any type of fracture in participants, and the secondary outcome was weight change. We used random effects meta-analysis for trial data.

Results Fifteen studies were included. Three small trials provided short-term evidence of the association between bariatric surgery and participants with any fracture (365 participants; RR 0.82; 95% CI 0.29 to 2.35). Four out of six observational studies of bariatric surgery demonstrated significantly increased fracture risk. Six RCTs of WMPs with 6214 participants, the longest follow-up 11.3 years, showed no clear effect on any type of fracture (RR 1.04; 95% CI 0.91 to 1.18), although authors of the largest RCT reported an increased risk of frailty fracture by their definition (RR 1.40; 95% CI 1.04 to 1.90).

Conclusion Bariatric surgery appears to increase the risk of any fracture; however, longer-term trial data are needed. The effect of lifestyle WMPs on the risk of any fracture is currently unclear.

Keywords Fractures · Bariatric surgery · Obesity · Weight loss

Introduction

While bariatric surgery for adults with obesity is effective for weight loss and reduces many obesity-related diseases, reports on long-term complications beyond mortality are currently limited [1]. Risk of malnutrition and malabsorption of fat-soluble vitamins including vitamin D, as well as increased bone turnover and reduced bone mineral density (BMD) after surgery [2, 3], could increase the risk of fracture. Lifestyle weight management programs (WMPs), consisting of a variety of diets with or without exercise advice, are reported to be associated with a small reduction in total hip but not lumbar spine BMD measurements in observational data [4].

We undertook a systematic review of fracture outcome data from studies of bariatric surgery and lifestyle WMPs. Our aim was to examine whether weight loss increased the risk of participants sustaining any fracture, compared to adults with obesity who did not undergo bariatric surgery or undertake WMPs.

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Materials and Methods

We used a pre-specified protocol and followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) guidelines.

Selection Criteria

Bariatric Surgery Studies

There are presently few randomized controlled trials (RCTs) reporting fracture data post-bariatric surgery compared to no surgery; therefore, we included non-randomized controlled trials and observational studies in adults (≥ 18 years), with mean pre-surgery group body mass index (BMI) ≥ 30 kg/m^2. Studies had a minimum follow-up ≥ 1 year.

Lifestyle Weight Management Programs

We included RCTs of WMPs of reducing diets with or without physical activity advice and/or programs to attend, versus usual care/no intervention. Studies had minimum follow-up ≥ 1 year, mean baseline group BMI ≥ 30 kg/m^2, and mean group age ≥ 18 years.

Outcomes

Our primary outcome was participants with any fracture and our secondary outcome was weight change.

Search Strategy

We searched full texts of trial reports in our database of long-term RCTs of lifestyle WMPs for adults, compiled from MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials, from 1966 to 2016 [5, 6]. We performed an updated search from 2016 to July 2018 for WMP RCTs. Details of the search strategy (including for bariatric surgery) in MEDLINE can be found in Appendix A, which was adapted for other databases. We contacted the authors of eight WMP and bariatric surgery RCTs with bone mineral density data to request any additional unpublished fracture data.

Data Analysis

AA and ADA/BRB independently confirmed study eligibility. ADA extracted data, which were checked by AA. AA and ADA independently assessed quality of RCTs and non-randomized trials using the Cochrane risk of bias tool [7] and for observational studies using the Newcastle-Ottawa Quality Assessment Scale [8]. All differences were resolved by discussion.

Owing to limited data, we combined data from RCTs and non-randomized controlled trials of bariatric surgery in meta-analyses, using Review Manager Software version 5.3. Risk ratios (RR) and 95% confidence intervals (95% CI) were calculated for dichotomous outcomes. Heterogeneity was assessed using the I^2 test ($I^2 > 50\%$ was considered significant heterogeneity) in conjunction with the chi-squared test. Random effects meta-analysis was used to pool outcome data, due to known heterogeneity in weight loss interventions. We estimated mean differences (MD) and 95% CI for weight data, giving preference to follow-up data for all participants or data taking account of drop-outs (preferentially baseline observation carried forward) if these were provided. Missing standard deviations (SD) were derived using previously described methods [5].

Data from observational studies of bariatric surgery were not combined, but are discussed in a narrative review.

No external funding was provided. No ethical approval was required.

Results

We screened 1174 full-text trial reports and 4153 titles and abstracts, as outlined in Fig. 1.

Quality Assessment

Bariatric Surgery Trials

Appendix Table 3 provides our full risk of bias assessments for the three trials, two of which were RCTs. None were judged to be at low risk of bias for outcome assessment. We judged that there was a high risk of bias for incomplete outcome data due to high drop-out rates [9, 10], and the non-randomized controlled trial was potentially at a high risk of other bias due to the study being funded by industry [11].

All six observational studies of surgery (Appendix Table 4) were judged to be moderately representative of the average obese person in their communities. We judged the comparability of all of the studies in terms of controlling for factors associated with fractures to be acceptable; however, two of the studies failed to report numerical BMI data [12, 13].

Lifestyle Intervention Studies

Three of the RCTs (see Appendix Table 3) were judged to be at low risk of bias for outcome assessment [14–16]. Three trials were also at low risk for both incomplete outcome data and selective reporting [15–17]. Two trials were judged to be potentially at high risk of bias due to premature termination [15] and industry sponsorship [18].

Study Characteristics

Bariatric Surgery Trials

Two RCTs (Table 1) were from the USA [9, 10] and one non-randomized controlled trial was from Norway [11],

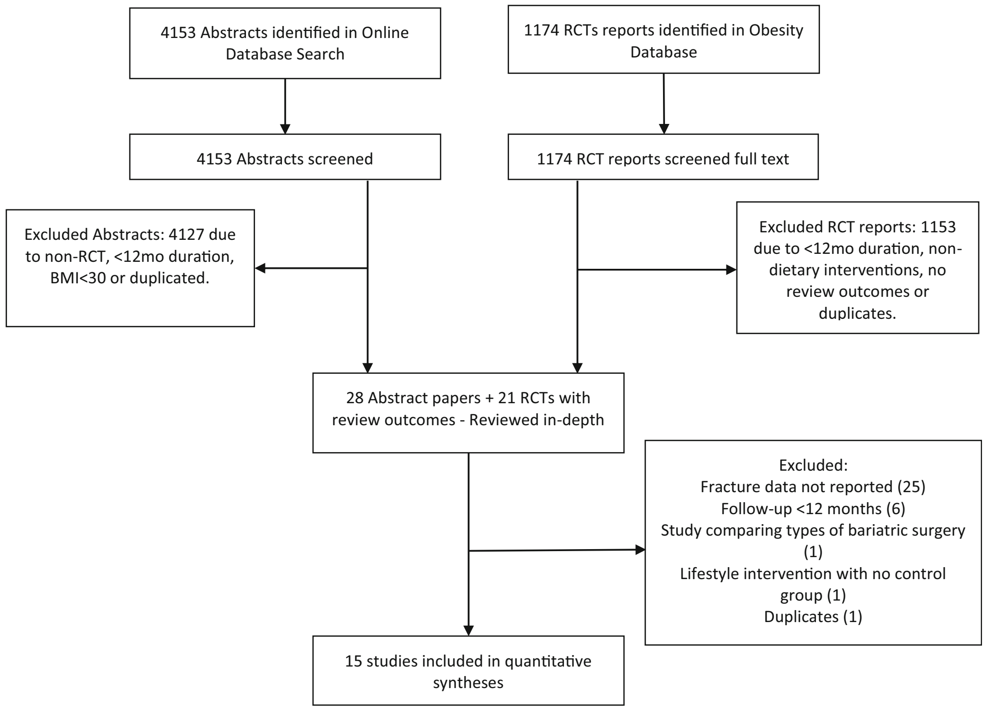

Fig. 1 Study selection

involving a total of 365 adults, mostly women (see Table 1). Roux-en-Y gastric bypass (RYGB) was used in all three trials, laparoscopic adjustable gastric banding (LAGB) in one [9] and laparoscopic sleeve gastrectomy (LSG) in one [10]. Both of the RCTs included participants with type 2 diabetes and associated comorbidities, and 27% of participants in the non-randomized trial had type 2 diabetes. At baseline, prior to bariatric surgical intervention, mean group ages ranged from 42.8–50.0 years and mean group BMI ranged from 35.3–46.7 kg/m^2. The maximum follow-up was only 2 years.

Bariatric Surgery Observational Studies

Table 2 provides details of the observational studies of bariatric surgery. There were 1872 fractures in 59,930 patients who underwent bariatric surgery versus 5408 fractures in 223,110 control patients, from the UK, Taiwan, and North America in one case-control study [13] and five cohort studies [7, 12, 20–23]. Each of the studies included patients undergoing a variety of restrictive and malabsorptive procedures, with the exception of one study of gastric bypass surgery only [20]. Trial participants had a wide range of comorbidities and were predominantly female. Where reported, group mean BMI was ≥ 40 kg/m^2 and group mean age < 50 years before surgery.

Lifestyle WMP RCTs

Table 1 provides details of the six WMP RCTs involving 6214 adult participants [14–19]. The Look AHEAD trial [15] was the largest study by far, with 5145 participants with type 2 diabetes followed for 11.3 years.

Five RCTs provided both diet and exercise advice (≥ 150 min of moderate physical activity per week) [14–17, 19] and one diet advice only [18]. Three trials [15–17] provided exercise programs for participants to attend. Two RCTs prescribed a calorie restriction of 1200–1800 kcal/day, which lasted between 27 and 115 months [15, 18]; two RCTs a calorie deficit of 500–1000 kcal/day [17, 19]; and two RCTs were unclear as to the calorie content prescribed [14, 16].

All six trials recruited participants with pre-existing comorbidities, with one trial enrolling participants with uncontrolled asthma where 32.1% of patients reported systemic corticosteroid use [19]. Five RCTs were conducted in the USA [14–17, 19] and one in Germany [18]. Two trials at baseline had group mean BMI ≤ 35 kg/m^2 [14, 18]. The studies recruited predominantly middle-aged adults, with the exception of Villareal and colleagues who recruited older adults (mean group age 69–70 years) [17]. Follow-up was usually ≤ 2 years, with the exception of the Look AHEAD trial with follow-up of 11.3 years [15]. The mean drop-out rate ranged from 3.4 to 38.0%, with the highest drop-out rate reported in the trial from Ditschuneit and colleagues [18].

Data Analyses

Appendix Table 5 provides details of the fractures reported and definitions of osteoporotic or frailty fractures, as defined by the investigators.

Table 1 Summary of bariatric surgery and weight loss trials

Author year location		Number	Intervention	Diet; calories kcal/day	Exercise minutes per/ week + intensity	% drop-out at the end of study	Follow-up months
Courcoulas et al. 2014 Pittsburgh, USA [9]	Control	23	Lifestyle weight loss intervention	1200–1800 Based on meal plans	300 min of moderate physical activity	26.1	12
	Intervention	46	Roux-en-Y gastric bypass surgery Laparoscopic adjustable gastric banding	NR	Exercise a min of 3–4 times per week and to focus on weight-bearing, aerobic activity	17.4	12
Daumit et al. 2013 Baltimore, USA [16]	Control	147	Group health classes quarterly with topics not related to weight	NR	–	3.4	18
	Intervention	144	Group and individual weight loss counseling and group physical activity classes	Moderate caloric restriction based on DASH diet	≥ 150 min/week of moderate physical activity	4.9	18
Ditschuneit et al. 1999 Ulm, Germany [18]	Control	50	Conventional foods	1200–1500 Balanced diet	–	38.0	27
	Intervention	50	2 meal replacements	1200–1500	–	36.0	27
Hofso et al. 2010 Tonsberg, Norway [11]	Control	66	Lifestyle modification	NR	–	4.5	12
	Intervention	80	Roux-en-Y gastric bypass surgery	788–908 3–6 weeks preceding surgery	–	5.0	12
Look AHEAD (Johnson et al. 2017) 16 clinical sites across the USA [15]	Control	2575	Diabetes support and education	NR	–	11.7	115
	Intervention	2570	Calorie restriction and exercise	1200–1800 Based on guidelines of the ADA and National Cholesterol Education program	≥ 175 min of moderate physical activity	10.1	115
Ma et al. 2013 California, USA [14]	Control	81	Usual care	NR	–	18.5	15
	Intervention	160	Coach lead exercise and self-directed exercise	Group Lifestyle Balance Program™ Lose 7% of weight through healthy eating	≥ 150 min of moderate physical activities	19.5	15
Ma et al. 2015 California, USA [19]	Control	165	Usual care	NR	–	10.9	12
	Intervention	165	Weight loss intervention	500–1000 kcal/d reductions, but daily total calories no less than 1200 kcal	≥ 150 min moderate physical activity	13.9	12
Maghrabi et al. 2015 Ohio, USA [10]	Control	50	Intensive medical therapy for diabetes	NR	–	15.0	24

Table 1 (continued)

	Intervention	100	RYGB plus intensive medical therapy and laparoscopic sleeve gastrectomy plus intensive medical therapy	NR	–	7.5	24
Villareal et al. 2011 St Louis, USA [17]	Control	53	Usual care and exercise	1500 mg/day calcium and 1000 ID/day of vitamin D	270 min 65% of their peak heart rate	15.1	12
	Intervention	54	Weight loss and weight loss with exercise	Supplements as per controls. Energy deficit of 500 to 750 kcal/day. 1 g of high-quality protein/kg weight	270 min 65% of their peak heart rate	11.1	12

Author year location	Comorbidities/ medications	Age (years) mean (SD)	% female	% ethnicity	BMI kg/m^2 mean (SD)	Weight change (kg) (SD)	Fractures
Courcoulas et al. 2014 Pittsburgh, USA [9]	Type 2 diabetes Hypertension	48.3 (4.7)	82.6	Black = 17.4	35.7 (3.3)	− 10.3 (11.8)	0
		46.8 (7.0)	80.5	Black = 23.5	35.5 (3.0)	− 22.2 (10.3)	1
Daumit et al. 2013 Baltimore, USA [16]	Schizophrenia Schizo-affective disorder	44.1 (11.0)	49.0	White = 81.0 Black = 59.0 Other = 7.0	36.5 (7.3)	− 0.2 (9.1)	4
	Bipolar disorder Major depression	46.6 (11.5)	51.4	White = 82.0 Black = 52.0 Other = 10.0	36.0 (7.2)	− 3.4 (7.8)	2
Ditschuneit et al. 1999 Ulm, Germany [18]	Absence of endocrine or psychiatric disease	46.6 (11.2)	82.0	–	33.8 (3.2)	− 5.9 (5)	1
		44.8 (9.7)	76.0	–	32.4 (4.2)	− 11.3 (6.8)	1
Hofso et al. 2010 Tonsberg, Norway [11]	Type 2 diabetes Hypertension Metabolic syndrome Albuminuria Left ventricular hypertrophy Coronary heart disease	47.0 (11.0)	66.7	White = 92.4	43.3 (5.0)	− 10.7 (12.0)	1
		42.8 (10.5)	66.3	White = 92.5	46.7 (5.7)	− 41.3 (13.1)	1
Look AHEAD (Johnson et al. 2017) 16 clinical sites across the USA [15]	Diabetes	58.9 (6.9)	59.7	Black = 15.7 White = 63.3 Hispanic = 13.2 Other = 7.8	36.0 (5.8)	− 4.8 (7.3)	358
		58.6 (6.8)	59.4	Black = 15.6 White = 63.1 Hispanic = 13.2 Other = 8.1	35.9 (6.0)	− 7.4 (8)	373
Ma et al. 2013		52.5 (10.9)	45.7	White = 77.8	32.4 (6.3)	− 2.4 (8.1)	0

Table 1 (continued)

California, USA [14]	Pre-diabetes mellitus or metabolic syndrome			Asian/Pacific Islander = 17.3 Latino/Hispanic = 4.9			
		53.2 (10.5)	46.9	White = 78.1 Asian/Pacific Islander = 16.9 Latino/Hispanic = 3.8	31.7 (4.9)	− 5.4 (8.1)	3
Ma et al. 2015 California, USA [19]	Asthma	47.7 (12.1)	70.9	White = 49.7 Black = 19.4 Asian/Pacific Islander = 8.5 Hispanic/Latino = 20.6	37.6 (5.7)	− 2.1 (10.3)	0
		47.5 (12.6)	70.3	White = 49.7 Black = 20.6 Asian/Pacific Islander = 7.9 Hispanic/Latino = 20.0	37.4 (6.0)	− 4.0 (10.3)	1
Maghrabi et al. 2015	Diabetes	50.0 (8.4)	47.1	Caucasian = 82.4	35.8 (3.0)	− 0.5 (4.1)	4
Ohio, USA [10]	Dyslipidemia Hypertension	47.7 (9.7)	64.3	Caucasian = 67.4	36.3 (2.9)	− 23.9 (9.54)	6
Villareal et al. 2011 St Louis, USA [17]	Chronic disease	69.5 (4.0)	64.5	White = 81 Black = 15 Other = 4	37.1 (5.0)	− 0.3 (3.52)	3
		70.0 (4.0)	61.0	White = 88.5 Black = 11.5 Other = 0	37.0 (4.9)	− 9.1 (4.6)	0

Table 2 Summary of bariatric surgery cohort and case-control studies by characteristics and fracture results

Author, year Location		Number	Intervention	Follow-up months	Comorbidities/ medications	Age (years) mean (SD)	% female	BMI (kg/m^2) mean (SD)	Fractures	Results (95% confidence interval)
Axelsson et al. 2018 Sweden [20]	Control	38,971	Usual Care	37.2 (median)	Comprehensive list of comorbidities, including the following: Diabetes Thyroid diseases Malnutrition Bone diseases Liver disease Renal diseases Bisphosphonates Hormone replacement	41.0 (11.2)	75.0	NA	774	Hazard ratio- Reference category
	Bariatric surgery	38,971	A variety of bariatric surgical interventions	37.2 (median)		40.9 (11.2)	76.4	42.4 (5.5)	1019	Adjusted hazard ratio for any fracture Patients with diabetes 1.26 (1.05–1.53) Patients without diabetes 1.32 (1.18–1.47) Adjusted for propensity score, age, sex, weight (only for patients with diabetes), height (only for patients with diabetes), rheumatoid arthritis, alcohol-related diseases, fracture-free time, any previous fracture, previous hip fracture, previous vertebral fracture, previous number of fractures, previous fall injury without fracture, previous osteoporosis, previous secondary osteoporosis, previous glucocorticoids (≥ 5 mg of prednisolone equivalents per day more than 3 months), previous calcium and vitamin D, Charlson comorbidity index
Douglas et al. 2015 UK [21]	Control	3882	Usual care	36 (median)	T2DM, hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, other atheroma, smoking status, alcohol consumption, and use of insulin, OADs, and statins	45 (11)	81.6	42.1 (6.5)	32	Hazard ratio- Reference category
	Bariatric surgery	3882	Gastric band, gastric bypass or sleeve gastrectomy	36 (median)		45 (11)	80.5	44.7 (8.8)	39	Hazard ratio Any fracture 1.26 (0.79–2.01) All patients in the bariatric surgery group were propensity matched with the non-surgery patients with the closest propensity score when considering the following factors: age (within 2.5 years), sex, general practice, and presence in the CPRD on the date bariatric surgery was recorded
Lalmohamed et al. 2012 UK [22]	Control	10,442	Usual care	28 (mean)	Rheumatoid arthritis Cerebrovascular disease Smoking	44.9 (11.2)	85.3	40.8 (6.4)	207	Relative risk- Reference category
	Bariatric surgery	2079	A variety of bariatric	26 (mean)		44.6 (11.1)	83.9	43.2 (7.2)	38	Adjusted relative risk for any fracture 0.89 (0.60–1.33)

Table 2 (continued)

Author, year Location		Number	Intervention	Follow-up months	Comorbidities/ medications	Age (years) mean (SD)	% female	BMI (kg/m^2) mean (SD)	Fractures	Results (95% confidence interval)
			surgical interventions							Adjusted for age, sex, and most recent record of body mass index before the index date; a history of fracture, inflammatory bowel disease, and cerebrovascular disease ever before; a history of falls in the previous 6–12 months; and use of glucocorticoids, calcium or vitamin D supplements, anti-obesity drugs, antihypertensive drugs, loop diuretics, organic nitrates, antidepressants, anxiolytics or hypnotics, bisphosphonates, opioids (tramadol or stronger), and proton pump inhibitors in the previous 6 months
Lu et al. 2015 Taiwan [12]	Control	5027	Usual care	59 (mean)	Diabetes Hypertension Hyperlipidemia	31.9 (9.9)	63.7	–	374	Adjusted hazard ratio-Reference category
	Bariatric surgery	2064	A variety of bariatric surgical interventions	57 (mean)		31.8 (9.2)	64.4	–	183	Adjusted hazard ratio for any fracture 1.21 (1.01–1.44) Adjusted for duration of follow-up, material and social deprivation, area of residence, history of fractures (analysis for period after index date only), and number of comorbidities in the previous 5 years
Nakamura et al. 2014	Control	–	–	–	–	–	–	–	–	Standardized Incidence Ratio-Reference category
Minnesota, USA [23]	Bariatric surgery	258	A variety of bariatric surgical interventions	107 (mean)		43.6 (9.9)	82.2	49.0 (8.4)	79	Standardized incidence ratio for any fracture 2.3 (1.8–2.8) Expected numbers were derived by applying age and sex-specific fracture incidence rates in the general population of this community to the age specific person-years of follow-up
Rousseau et al. 2016	Control	126,760	Non-obese	53 (mean)	Cardiovascular disease Hypertension	42.6 (11)	72.3	–	3008	Adjusted relative risk-Reference category

Table 2 (continued)

Author, year Location		Number	Intervention	Follow-up months	Comorbidities/ medications	Age (years) mean (SD)	% female	BMI (kg/m^2) mean (SD)	Fractures	Results (95% confidence interval)
Quebec, Canada [13]	Control	38,028	Obese without bariatric surgical intervention		Chronic pulmonary disease Diabetes Hypothyroidism Renal failure Depression Osteoporosis	42.7 (11)			1013	Adjusted relative risk- 1.04 (0.96 to 1.12) Adjusting for duration of follow-up, social deprivation, area of residence, history of fractures (analysis for period after index date only), and number of comorbidities in the previous 5 years, using multivariate conditional Poisson regression model
	Bariatric surgery group	12,676	A variety of bariatric surgical interventions			42.6 (11)			514	Adjusted relative risk- 1.44 (1.29 to 1.59)

NA not available

Bariatric Surgery RCTs

For our primary outcome, the results of our meta-analysis of trials revealed no significant association between bariatric surgery and participants developing any fracture ($n = 3$ trials; 13 events; RR 0.82; 95% CI 0.29 to 2.35; $I^2 = 0\%$) (Fig. 2). For our secondary outcome, bariatric surgery led to marked weight loss, with high heterogeneity between studies ($n = 3$ trials; MD −22.2 kg; 95% CI −31.6 to −12.8; $I^2 = 93\%$) (Fig. 3).

Bariatric Surgery Observational Studies

Four out of the six observational studies reported a statistically significant association between bariatric surgery and an increased likelihood of fracture (Table 2). The studies which reported an association between bariatric surgery and fracture incidence had longer periods of observation than the 3 years follow-up of the studies which reported no association. All studies adjusted for risk factors associated with fractures, such as fracture history, comorbidities, and age. However, Lalmohamed and colleagues, who observed no association between bariatric surgery and fracture, adjusted for a broader range of confounders, such as inflammatory bowel disease, glucocorticoids, proton pump inhibitors, and calcium and vitamin D supplementation [22].

Axelsson and colleagues [20] reported an increased risk of osteoporotic and hip fractures post-bariatric surgery. Lu and colleagues [12] had fewer events and did not find a statistically significant increase in osteoporotic or hip fractures. The increased risk post-surgery in the study by Rousseau and colleagues appeared to mainly relate to biliopancreatic diversion [13], which is rarely used today. Nakamura and colleagues reported an increased risk of fractures at traditional osteoporotic sites compared to community controls, matched for age and sex but not BMI [23].

Lifestyle WMP RCTs

In the lifestyle WMP RCTs, our meta-analysis showed no significant association between WMPs and participants developing any fracture ($n = 6$ trials; 746 events; RR 1.04; 95% CI 0.91 to 1.19; $I^2 = 0\%$) (Fig. 2). However, the largest trial, with follow-up of 5145 participants with diabetes, reported an increased risk of frailty fractures, a composite of hip, pelvis, upper arm, and shoulder fractures (hazard ratio 1.39; 95% CI 1.02 to 1.89). Weight loss at final follow-up showed high heterogeneity ($n = 6$ trials; MD −4.15; 95% CI −6.41 to −1.89; $I^2 = 92\%$).

Study or Subgroup	Weight loss Events	Weight loss Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Bariatric surgery						
Courcoulas 2014	1	46	0	23	0.2%	1.53 [0.06, 36.20]
Hofso 2010	1	80	1	66	0.2%	0.82 [0.05, 12.94]
Maghrabi 2015	6	100	4	50	1.2%	0.75 [0.22, 2.54]
Subtotal (95% CI)		**226**		**139**	**1.6%**	**0.82 [0.29, 2.35]**
Total events	8		5			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 2 (P = 0.92); I² = 0%						
Test for overall effect: Z = 0.36 (P = 0.72)						
1.1.2 Lifestyle Intervention						
Daumit 2013	2	144	4	147	0.6%	0.51 [0.09, 2.74]
Ditschuneit 1999	1	50	1	50	0.2%	1.00 [0.06, 15.55]
Look AHEAD	373	2570	358	2575	97.0%	1.04 [0.91, 1.19]
Ma 2013	3	160	0	81	0.2%	3.57 [0.19, 68.20]
Ma 2015	1	165	0	165	0.2%	3.00 [0.12, 73.11]
Villareal 2011	0	54	3	53	0.2%	0.14 [0.01, 2.65]
Subtotal (95% CI)		**3143**		**3071**	**98.4%**	**1.04 [0.91, 1.19]**
Total events	380		366			
Heterogeneity: Tau² = 0.00; Chi² = 3.57, df = 5 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Total (95% CI)		**3369**		**3210**	**100.0%**	**1.04 [0.91, 1.18]**
Total events	388		371			
Heterogeneity: Tau² = 0.00; Chi² = 3.93, df = 8 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.61)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.67), I² = 0%						

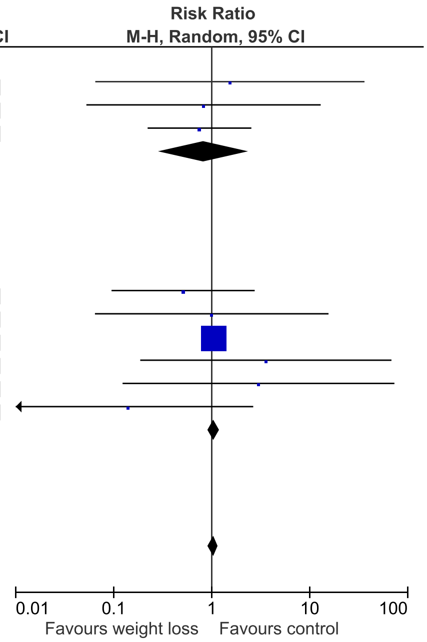

Fig. 2 Meta-analysis of weight loss intervention and incidence of fractures

Discussion

We found that bariatric surgery, predominantly malabsorptive in nature [12, 20], was associated with an increased risk of fracture compared to people of similar starting weight who did not undergo surgery. However, it is unclear whether the risk of fracture for adults post-bariatric surgery at their lower weight exceeds people of similar weight in the general population. Lifestyle WMPs were not associated with an increased risk of any fracture. However, there was some evidence from the Look AHEAD trial [15] to suggest that the risk of frailty fractures might be increased, but this trial did not report vertebral fractures and only around half of frailty fractures appeared to be related to low trauma. In the Look AHEAD trial, frailty fractures related to a composite of the first occurrence of a hip, upper arm, or shoulder fracture [15].

Weight loss programs, with or without bariatric surgery, are generally associated with advice to increase physical activity with or without exercise programs to attend. Thus, the effects of weight reduction on fracture risk cannot be separated in our studies from the possibility that a sudden increase in physical activity alone may have resulted in an increased propensity for injury.

There have been a number of systematic reviews and meta-analyses reporting on the association between bariatric surgery, particularly malabsorptive surgery, and significant

Study or Subgroup	Weight loss Mean	Weight loss SD	Weight loss Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Bariatric surgery								
Courcoulas 2014	-22.2	10.3	46	-10.3	11.79	23	32.0%	-11.90 [-17.56, -6.24]
Hofso 2010	-41.3	13.1	76	-10.7	12	63	33.7%	-30.60 [-34.78, -26.42]
Maghrabi 2015	-23.91	9.54	37	-0.5	4.09	17	34.3%	-23.41 [-27.05, -19.77]
Subtotal (95% CI)			**159**			**103**	**100.0%**	**-22.16 [-31.55, -12.77]**
Heterogeneity: Tau² = 63.45; Chi² = 27.18, df = 2 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 4.63 (P < 0.00001)								
1.2.2 Lifestyle intervention								
Daumit 2013	-3.4	7.8	119	-0.2	9.1	128	16.4%	-3.20 [-5.31, -1.09]
Ditschuneit 1999	-11.3	6.8	32	-5.9	5	31	14.5%	-5.40 [-8.34, -2.46]
Look AHEAD	-7.4	8	2481	-4.8	7.3	2476	19.0%	-2.60 [-3.03, -2.17]
Ma 2013	-5.39	8.1	160	-2.4	8.1	81	16.3%	-2.99 [-5.15, -0.83]
Ma 2015	-4	10.3	165	-2.1	10.3	165	16.2%	-1.90 [-4.12, 0.32]
Villareal 2011	-9.13	4.63	54	-0.3	3.52	53	17.6%	-8.83 [-10.39, -7.27]
Subtotal (95% CI)			**3011**			**2934**	**100.0%**	**-4.15 [-6.41, -1.89]**
Heterogeneity: Tau² = 6.96; Chi² = 60.75, df = 5 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.59 (P = 0.0003)								

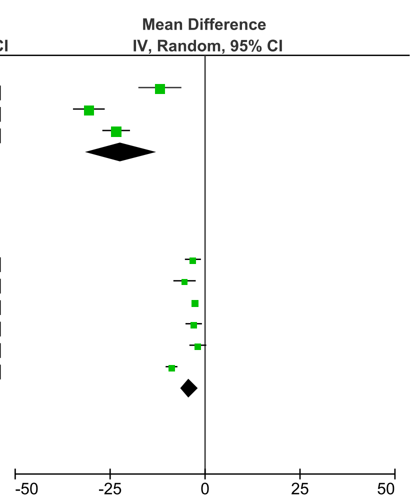

Fig. 3 Meta-analysis of weight loss intervention and sustained weight loss

BMD loss at the hip with less consistent results for the lumbar spine [2, 24–26]. However, the studies were sometimes without comparator groups and are difficult to interpret due to imaging limitations in severe obesity [27]. In a meta-analysis of five cohort studies and one RCT, Zhang and colleagues reported that bariatric surgery was associated with fractures at non-vertebral sites, especially upper limb fractures [28]. In contrast, in our meta-analysis of trials alone, the fractures reported were predominantly lower limb fractures such as tarsal and metatarsal fractures, but also included phalangeal fractures, suggesting short-term fractures secondary to physical activity [9–11]. Lu and colleagues in particular reported an increased risk of foot fractures, along with other sites not normally associated with osteoporosis [12].

The potential mechanisms underlying reductions in bone density and strength from weight loss which may precipitate bone fracture include mechanical, hormonal changes, and malabsorptive factors [27]. The reduction in force placed upon bones due to weight loss leads to higher levels of sclerostin, which inhibits osteoblastic activity and bone formation [27], while markers of bone turnover are considerably increased [4, 27]. Furthermore, estrogen and androgen status may decline particularly in postmenopausal women after bariatric surgery [29]. Bariatric procedures such as Roux-en-Y may lead to malabsorption of micronutrients required to maintain BMD [30]. Malabsorption of micronutrients including vitamin D, protein, and calcium, particularly after certain bypass procedures, may therefore require supplementation, e.g., vitamin D supplementation, to prevent secondary hyperparathyroidism [31]. Despite recommendations for patients post-bariatric surgery to take additional nutrient supplementation [31, 32], adherence is poor, e.g., vitamin D supplementation has been reported to be as low as 33% at 1 year [33], with factors such as male sex and working full-time associated with poor concordance [34]. BMD loss due to these factors, when additionally compounded by a sudden rise in physical activity in a previously sedentary adult, may place the bone under increased stress while also increasing the opportunities for the bone to fracture.

We attempted to identify all studies of WMPs and surgical RCTs which reported fractures, including contacting authors who had published BMD data to seek additional fracture data. However, the fracture data in the trials were often only reported as adverse events, and it is likely that fracture outcome data in other trials are unreported in the literature. Trials were often underpowered with short follow-up periods, such that it would be unlikely for changes in BMD to manifest as fractures.

In order for trials to meaningfully assess the long-term risk of fractures in bariatric patients, results from observational studies suggest that it is imperative that follow-up periods are sufficiently long [12, 13, 23], for example, Nakamura and colleagues reported that the median time to first fracture was 13 years [23]. It is important to acknowledge the difficulty maintaining prolonged follow-up in this patient group, but routine data collection through health records would allow evaluation. In a nationwide cohort study of 16,620 patients, Thereaux and colleagues observed that follow-up rates at 1 year and 5 years decreased from 87.1 to 29.6% [33]. Factors such as male sex and younger age were predictors of poor 5-year follow-up [33].

There is growing evidence to suggest that very large weight losses produced by bariatric surgery are associated with an increased risk of fracture. High rates of loss to follow-up in this patient group may hinder accurate evaluation; nevertheless, there remains a concerning lack of reporting on this adverse outcome. We suggest that bariatric surgery studies habitually report the presence (or absence) of fractures during long-term follow-up, including information on patient characteristics and types of fractures.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Appendix A. Search Strategy in MEDLINE

1. exp Obesity/
2. weight loss/ or overweight/
3. obes$.tw.
4. (weight adj1 (los$ or reduc$ or maint$ or control)).tw.
5. 1 or 2 or 3 or 4
6. diet therapy/ or caloric restriction/ or diet, carbohydrate-restricted/ or diet, fat-restricted/ or diet, reducing/
7. diet$.tw.
8. ((calori$ or fat or carbohydrate) adj3 (reduc$ or restrict$ or limit$)).tw.
9. surger$.ti
10. 6 or 7 or 8 or 9
11. Bone Density/
12. exp Fractures, Bone/
13. Osteoporosis/
14. (bone adj3 (density or loss or reduc$)).tw.
15. Osteopor$.tw.
16. Postoperative Complications/
17. 11 or 12 or 13 or 14 or 15 or 16
18. 5 and 10 and 17

Table 3 Cochrane risk of bias

	Villareal ***et al.*****, 2011** [17]	**Maghrabi** ***et al.*****, 2015** [10]	**Ma** ***et al.*****, 2015** [23]	**Ma** ***et al.*****, 2013** [14]	**Look AHEAD (Johnson** ***et al.*****, 2017)** [15]	**Hofso** ***et al.*****, 2010** [11]	**Ditschuneit** ***et al.*****, 1999** [18]	**Daumit** ***et al.*****, 2013** [16]	**Courcoulas** ***et al.*****, 2014** [9]
Random sequence generation (Selection bias)	🟢	🟢	🟢	🟢	🟢	🔴	🟢	🟡	🟢
Allocation concealment (Selection bias)	🟡	🟢	🟢	🟡	🟢	🔴	🟡	🟢	🟡
Blinding of participants and personnel (Performance bias)	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴	🔴
Blinding of outcome assessment (Detection bias)	🟡	🟡	🟡	🟢	🟢	🔴	🟡	🟢	🟡
Incomplete outcome data (Attrition bias)	🟢	🔴	🟢	🟡	🟢	🟢	🔴	🟢	🔴
Selective reporting (Reporting bias)	🟢	🟡	🟡	🟡	🟢	🟡	🟡	🟢	🟢
Other bias	🟢	🟡	🟢	🟢	🔴	🔴	🔴	🟢	🟢

🟢 = low risk of bias, 🟡 = unclear risk of bias, 🔴 = high risk of bias

Table 4 Newcastle-Ottawa Scale assessment for included case-control and cohort studies

Study	Selection[a]				Comparability[b]	Outcomes[a]			Total
	Representative of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at the start of the study		Assessment of outcomes	Length of follow-up	Adequacy of follow-up	
Axelsson et al. 2018 [20]	*	*	*		**		*	*	7
Douglas et al. 2015 [21]	*	*	*	*	**		*	*	8
Lalmohmed et al. 2012 [22]	*	*	*		**			*	6
Lu et al. 2015 [12]	*	*	*	*	*		*	*	7
Nakamura et al. 2014 [23]	*		*	*	**		*	*	7
Rousseau et al. 2016 [13]	*	*	*		*		*	*	6

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories

[b] A maximum of two stars can be given for comparability

Table 5 Summary of bariatric surgery and weight loss study description of fracture type and osteoporotic/fragility fracture definition

Author, year Location		Intervention	Number of all fractures reported	Fracture type	Number of osteoporotic fractures reported as defined by authors	Description of osteoporotic/fragility fracture
Axelsson et al. 2018 Sweden [20]	Control	Usual care	774	Hip, upper limb, lower leg, hip/vertebra/wrist/surgical neck of humerus fractures	193	Major osteoporotic fracture defined as hip, vertebra, wrist, or surgical neck of the humerus fracture
	Intervention	A variety of bariatric surgical interventions	1019	Hip, upper limb, lower leg, hip/vertebra/wrist/surgical neck of humerus fractures	333	
Courcoulas et al. 2014 Pittsburgh, USA [9]	Control	Lifestyle weight loss intervention	–	–	–	–
	Intervention	Roux-en-Y gastric bypass surgery Laparoscopic adjustable gastric banding	1	Traumatic foot fracture due to a kick injury	–	
Daumit et al. 2013 Baltimore, USA [16]	Control	Group health classes quarterly with topics not related to weight	4	No description available, author contacted with no response	–	–
	Intervention	Group and individual weight loss counseling and group physical activity classes	2	No description available, author contacted with no response	–	
Ditschuneit et al. 1999 Ulm, Germany [18]	Control	Conventional foods	1	Malleolar fracture due to falling while downhill skiing	–	–
	Intervention	2 meal replacements	1	Partial rib fracture due to falling while wrestling	–	
Douglas et al. 2015	Control	Usual care	32	Any, hip, wrist, spine fractures.	–	–

Table 5 (continued)

Author, year Location		Intervention	Number of all fractures reported	Fracture type	Number of osteoporotic fractures reported as defined by authors	Description of osteoporotic/fragility fracture
UK	Intervention	Gastric band, gastric bypass or sleeve gastrectomy	39	Any, hip, wrist, spine fractures	–	
Hofso et al. 2010 Tonsberg, Norway [11]	Control	Lifestyle modification	–	–	–	–
	Intervention	Roux-en-Y gastric bypass surgery	1	Fifth right proximal phalange fracture	–	
Look AHEAD (Johnson et al. 2017) [15]	Control	Diabetes support and education	358	Hand (not fingers), lower arm or wrist, elbow, upper arm (humerus), shoulder, or clavicle, vertebrae (thoracic or lumbar), tailbone, pelvis, hip, upper leg (not hip), knee (patella), lower leg or ankle, foot (not toes) fractures	70	Frailty fracture was classified as a composite of hip, pelvis, or upper arm/shoulder fracture
	Intervention	Calorie restriction and exercise	373	Hand (not fingers), lower arm or wrist, elbow, upper arm (humerus), shoulder, or clavicle, vertebrae (thoracic or lumbar), tailbone, pelvis, hip, upper leg (not hip), knee (patella), lower leg or ankle, foot (not toes) fractures	98	
Lalmohamed et al. 2012 UK [22]	Control	Usual care	207	A breakdown of the fracture types was not provided.	Did not report	Osteoporotic fractures defined as spine, hip, forearm, or humerus
	Intervention	A variety of bariatric surgical interventions	38	A breakdown of the fracture types was not provided	13	
Lu et al. 2015 Taiwan [12]	Control	Usual care	374	Skull/face, hands/fingers, distal forearm, proximal humerus, clavicle/scapula/sternum, ribs, thoracic lumbar vertebrae, cervical vertebrae, pelvis, proximal, other leg, feet/toe fractures	Did not report	Osteoporotic fractures defined as fractures of the vertebral column, humerus, radius/ulnar, carpal bones, neck of femur
	Intervention	Bariatric surgery	183	Skull/face, hands/fingers, distal forearm, proximal humerus, clavicle/scapula/sternum, ribs, thoracic lumbar vertebrae, cervical vertebrae, pelvis, proximal, other leg, feet/toe fractures	Did not report	
Ma et al. 2013 California, USA [14]	Control	Usual care	0	–	–	–
	Intervention	Coach lead exercise and self-directed exercise	3	No description available, author contacted with no response	–	
Ma et al. 2015 California, USA [19]	Control	Usual care	0	–	–	–
	Intervention	Weight loss intervention	1	Wrist fracture due to a fall while walking	–	
	Control		4		–	–

Table 5 (continued)

Author, year Location		Intervention	Number of all fractures reported	Fracture type	Number of osteoporotic fractures reported as defined by authors	Description of osteoporotic/fragility fracture
Maghrabi et al. 2015 Ohio,		Intensive medical therapy for diabetes		Tarsal/metatarsal, arm, ankle fractures		
USA [10]	Intervention	RYGB plus intensive medical therapy and laparoscopic sleeve gastrectomy plus intensive medical therapy	6	Tarsal/metatarsal fractures	–	
Nakamura et al. 2014 Minnesota, USA [23]	Control	–	–	–	–	–
	Intervention	A variety of bariatric surgical interventions	79	Skull/face, hands/fingers, distal forearm, proximal humerus, other arm, clavicle/scapula/sternum, ribs, thoracic/lumbar vertebrae, pelvis, proximal femur, other leg, feet/toe fractures	–	
Rousseau et al. 2016 Quebec, Canada [13]	Control	Non-obese	3008	Distal lower limb (knee, foot, ankle, and tibia/fibula), clinical spine, pelvis, hip, femur, upper limb (shoulder, humerus, elbow, forearm, and wrist) fractures	–	–
	Control	Obese without bariatric surgical intervention	1013			
	Intervention	A variety of bariatric surgical interventions	514	Distal lower limb (knee, foot, ankle, and tibia/fibula), clinical spine, pelvis, hip, femur, upper limb (shoulder, humerus, elbow, forearm, and wrist) fractures	–	
Villareal et al. 2011 St Louis, USA [17]	Control	Usual care and exercise	3	Humeral fracture due to fall while traveling abroad, ankle fracture due to fall during physical function test and wrist fracture due to falling on the ice	–	–
	Intervention	Weight loss and weight loss with exercise	0		–	

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