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Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? – A meta-analysis of cohort studies.

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Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? – A meta-analysis of cohort studies.

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Abstract

Objective: The aim of this study was to systematically review the literature to identify whether obesity or the regular practice of physical activity are predictors of clinical outcomes in patients undergoing elective hip and knee arthroplasty due to osteoarthritis searching the Medline, CINAHL, EMBASE, and Web of Science electronic databases.

Design: Systematic review and meta-analysis.

Eligibility criteria for selecting studies: Longitudinal cohort studies were included in the review. To be included, studies needed to assess the association between obesity or physical activity participation assessed at baseline and clinical outcomes (i.e. pain, disability, and adverse events) following hip or knee arthroplasty.

Data extraction: Two independent reviewers extracted data on pain, disability, quality of life, obesity, physical activity and any postsurgical complications.

Results: 63 full papers were included in this systematic review. From these, 31 were included in the meta-analyses. Our meta-analysis showed that non-obese participants tended to suffer less pain, less disability and report fewer postsurgical complications when compared to the obese participants.

Limitations of this review: We have dichotomized follow-up duration into short-term or long-term follow-up. There was large heterogeneity in duration of follow-ups within each category. Only four studies assessed the impact of physical activity participation on surgical outcomes and given their methodological discrepancies, no pooled analysis was conducted.

Conclusions: Pre-surgical obesity is associated with worse clinical outcomes of hip or knee arthroplasty in terms of pain, disability and complications in patients with osteoarthritis. No impact of physical activity participation has been observed.

Systematic review registration: PROSPERO registration CRD42016032711.

Keywords: Physical activity, obesity, arthroplasty, osteoarthritis, knee, hip, meta-analysis.

Strengths and limitations of this study

- The current review is the most comprehensive systematic review on the topic to date.

- The current review is the first review to use a quantitative approach to synthesize the results of pain, disability and surgical complications between non-obese and obese participants who underwent to hip or knee arthroplasty due to osteoarthritis.

- The methodological quality of the included studies was in general low.

- There was a substantial variability of follow-up duration across studies, ranging from 2 weeks to 11 years.

Introduction

Musculoskeletal pain, including knee and hip osteoarthritis, is the leading cause of physical disability in the world and responsible for an increasing burden to patient and society.(1) This problem aggravates with time, as the world population ages and physical disability resulting from declining health becomes increasingly prevalent.(2) The global health care expenditure for knee and hip osteoarthritis is substantial and most of these costs are incurred by surgical management and associated hospital care.(3) For instance, in the UK the direct costs of osteoarthritis were estimated at more than £1 billion in 2010, of which £850 million were spent just on surgical procedures.(4)

Although management of the early stages of this condition consists of a combination of nonpharmacological and pharmacological therapies (e.g. anti-inflammatory and analgesic drugs), surgery has become the most common treatment option for severe cases, especially when nonsurgical therapies fail to provide sufficient pain relief.(5) Osteotomy, mosaicplasty and arthroplasty are some of the existing types of surgery used to manage osteoarthritis of the hip and knee; with total or partial arthroplasty being the most commonly recommended.(6)

There are multiple risk factors for the development of knee OA, among which increased body weight and muscle weakness, resulting from a sedentary lifestyle, are particularly common.(7) Likewise, obesity and sedentary lifestyle behaviour have been associated with adverse health conditions including coronary heart disease, type 2 diabetes, breast, and colon cancers, and decreased life expectancy.(8) Although there is evidence for the role of obesity and physical inactivity in health conditions and quality of life in general,(9, 10) the actual impact of these factors, together or in isolation, on the outcomes of elective surgery of the knee and hip is still controversial.(11, 12) Although previous attempts to systematically review the literature have been made, these studies(13-15) have either failed to perform a quantitative summary of the evidence (i.e. meta-analysis), to include patients undergoing knee arthroplasty(16) or pain outcomes(13). No meta-analyses have been performed considering obesity and physical activity as predictors of surgical outcomes in terms of pain, disability, quality of life and complications after hip or knee arthroplasty for end stage osteoarthritis.

Identifying whether obesity and physical activity participation predict surgical outcomes in patients with knee and hip osteoarthritis will inform clinical practice in terms of prognosis and safety of an increasingly prevalent treatment approach. We have conducted a meta-analysis of cohort studies aiming to quantify the role of obesity and physical activity participation as predictors of clinical outcomes in terms of pain, disability, quality of life, and postsurgical complications. This review and meta-analysis focused on patients with knee and hip osteoarthritis undergoing hip or knee arthroplasty.

Methods

Data sources and searches

We conducted a systematic review following the PRISMA statement(17). This review was prospectively registered on PROSPERO, registration number CRD42016032711. A systematic electronic search was performed in the following databases from inception to January 2017: MEDLINE, EMBASE, CINAHL, and Web of Science. We used a combination of relevant keywords to construct the search strategy including: obesity, physical activity, knee osteoarthritis, hip osteoarthritis, arthroplasty, and elective surgery (Appendix Search Strategy). The first screening of potentially relevant records was conducted by one author (DP) based on titles and abstract, and two authors (DP and GM) independently performed the final selection of included trials based on full text evaluation. A third reviewer arbitrated in case of disagreement (MF). The reference list of included papers was checked for further possible studies. No restriction was applied on language.

Study selection

We included only longitudinal studies assessing the role of obesity or physical activity participation on the clinical outcomes following partial or total hip arthroplasty (THA) or partial or total knee arthroplasty (TKA) surgery. Clinical outcomes were defined in terms of pain, disability, quality of life, and complications post arthroplasty. To be eligible, studies had to be full reports, include participants who underwent elective arthroplasty of the hip or knee due to osteoarthritis, include data of pre-surgical and at least one post-surgical assessment of the clinical outcomes of interest, and assess the association between the predictors and outcomes of interest. Obesity and physical activity participation had to be

assessed at baseline. Studies on revision surgery were excluded. Studies were not excluded based on intensity or duration of symptoms.

Data extraction

Using a standardised form, data on study characteristics, predictors and outcome measures of interest were independently extracted from the included studies by two reviewers (DP and GM). A third author (MF) resolved any disagreement. Estimates of association between predictors and outcomes of interest were extracted as presented in each study, and included odds ratios, risk ratios, correlations, mean differences or regression coefficients. When studies reported more than one tool regarding the same topic (e.g. WOMAC, HOOS, OHS, KOOS, KSS) estimates were extracted from the group with the largest sample size.

We contacted the authors to provide further information when there were insufficient data reported in the manuscript. When authors were unavailable we estimated data using the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions.(18)

Outcome measures

Data on pain intensity was extracted as visual analogue scale (VAS) scores ranging from 0 to 10 and measured directly or as part of the following measurement tools: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Hip disability and Osteoarthritis Outcome Score (HOOS), the Knee disability and Osteoarthritis Outcome Score (KOOS) or the Harris Hip Score (HHS). If studies reported more than one measure for pain intensity or disability for the cohort, the most severe measure at baseline was included in the pooled analyses. Disability measures included the Oxford Hip Score (OHS), ranging from 12 to 60 being 12 the best result; Oxford Knee Score (OKS) ranging from 0 to 60 being 60 the best result; the Harris Hip Score (HHS) ranging from 0 to 100 being 100 the best result; Knee Society Score (KSS) ranging from 0 to 100 being 100 the best result; WOMAC total score ranging from 0 to 96 being 0 the best result; or WOMAC function subscale, ranging from 0 to 10 being 10 the best result; and were converted into a uniform 0-100 scale where 0 meant less disability. Extracted data on complications included any descriptive measure of the number of complications or number of patients with a complication reported during the study. Only two of the screened studies had reported specific raw data on quality of life among the participants after joint arthroplasty, but due to differences in follow-up length any meta-analysis made by merging this data would result in an unreliable measure.

Methodological Quality Assessment

The methodological quality of included studies was assessed using a standardized checklist based on recommendations for publishing a systematic review and the(19) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.(20) The checklist comprised six items:

A - Participants were selected as consecutive or random cases. We considered as non-representative samples those recruited from specific groups.

B – Full description of participant source and inclusion and exclusion criteria.

C –Outcome data were available for at least 85% of participants at 1 follow-up point.

D - Standardized and fully defined method to assess the predictor and outcome.

E - Raw data, percentages, risk estimators, and precision measure data reported at follow-up.

F - Multivariate analysis conducted with adjustment for potentially confounding factors.

Box 1: Criteria used to assess the methodological quality of screened

After the independent assessment of included studies by two authors (DP and GM) each study received an unweighted methodological quality score ranging from 0 to 100 expressing the percentage of fulfilled criteria (out of the total number of relevant criteria). A third reviewer (MF) resolved any disagreement. The quality scores for the studies were categorized as: good:>75%, medium: 50-75% and poor: <50% (21).

Data analysis

Data on baseline (i.e. pre-surgical scores) and postoperative outcome scores were weighed by the inverse study variance and used in fractional polynomial regression modelling to build graphs depicting the course of pain and disability over time. STATA14 was used for the analyses (Stata Corp LP, College Station, TX). (22)

Meta-analyses were performed to assess the differences in pain, disability and complications post-surgery, between predictor groups (i.e. obese and non-obese groups as defined by included studies), using a random effects model. When means and standard deviations of outcomes of interest were presented for multiple predictor groups (i.e. underweight (BMI<18), normal weight (BMI≥18<25), overweight (BMI≥25<30), and obese levels I (BMI≥30<35), II (BMI≥35<40) or III (BMI≥40)) these were combined into two groups (non-obese: BMI<30 and obese: BMI≥30) as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (18) before inclusion in the pooled analyses. Results were reported as standardized mean differences (SMD) and 95% confidence intervals (95%CI). Between-study heterogeneity was calculated using I^2 (I^2 <25%: small heterogeneity; 25% <I^2< 75%: moderate heterogeneity; I^2> 75%: large heterogeneity). All meta-analyses were conducted using Comprehensive Meta-Analysis software (Comprehensive Meta-Analysis, Englewood, NJ). For studies not reporting enough data to be included in the meta-analyses, the reported individual associations were tabulated and qualitatively presented in the supplementary material.

Results

Our search strategy identified 11,990 studies. Twenty-six additional studies were identified through other sources and were included for screening. After removing 381 duplicates, 11,220 studies were screened and excluded based on keywords, titles and abstracts. All the remaining 389 studies were written in English and were assessed by reading the full text, of which 327 were excluded, yielding 62 studies included in the systematic review.(23-84) From these, 31 presented enough data to be included in at least one of the meta-analyses (Figure 1).

Figure 1 – Flowchart of search strategy and screening steps.

Included Studies

Included studies reported data from 18 different countries: Australia,(39, 46, 71, 84) Canada,(37, 42, 77) China,(83) Denmark,(59) England,(26, 29) Finland,(48-51), France,(64, 72) Germany,(54, 74, 80) Italy,(27, 28) Japan,(82) Netherlands,(56, 75) Norway,(44) Scotland (24, 35), South Korea,(55) Spain,(40, 79) Switzerland,(60, 61, 68) United Kingdom(25, 34, 36, 45, 47, 52, 62, 66, 67, 70, 73) and USA.(23, 30-33, 38, 41, 43, 53, 57, 58, 63, 65, 69, 76, 78, 81) Demographic data from each study are presented in table 1.

Methodological Quality

An overall assessment of the studies showed that methodological quality ranged from 33.3 to 100 points on a 0-100 scale (greater score indicate more quality), the mean methodological score for all included studies being 59.1 (SD 15). Only one study(79) fulfilled all six criteria assessed for methodological quality. Eight of the included studies(29, 41, 42, 48, 51, 54, 61, 63) reached the threshold of 75% proposed by Sorensen(21) to be considered as having good methodological quality. From the screened studies, 29 studies (47%) investigated a representative sample, only 19 studies (31%) provided sufficient definition of the sample, 49 studies (79%) had a follow-up rate >85%, all studies fully defined the method of assessment of the predictors and outcomes, 30 studies (48%) reported outcome data and 31 (50%) studies conducted adjustment for potentially confounding factors. The most frequent methodological flaws were not fully describing the inclusion and exclusion criteria of the subjects (n= 43 studies, 689) and not using a representative sample (n=33 studies, 53%).

Table 1 - Included studies and characteristics.

Author, year	Country	Sample Size	Predictor	Outcomes	Surgery	Follow-Up Duration	Quality Score
AbdelSalam et al, 2012	USA	210	Obesity	Complications	Total Hip and Knee Arthroplasty	9 years	33.3
Amin et al, 2006 A	United Kingdom	328	Obesity	Complications; Disability	Total Knee Replacement	6, 18, 36 and 60 months	66.7
Amin et al, 2006 B	Scotland	82	Obesity	Complications	Total Knee Replacement	38.5 months	66.7
Andrew et al, 2008	England	1,059	Obesity	Complications; Disability	Total Hip Arthroplasty	3, 12, 24, 36 and 60 months	33.3
Azodi et al, 2006	Italy	3,309	Obesity	Complications	Total Hip Replacement	6 to 9 years	50.0
Azodi et al, 2008	Italy	2,106	Obesity	Complications	Total Knee Arthroplasty	2 years	50.0
Baker et al, 2012	England	13,673	Obesity	Complications; Disability	Total Hip Arthroplasty	6 months	83.3
Belmont et al, 2014	USA	17,514	Obesity	Complications	Total Knee Arthroplasty	1 month	66.7
Belmont et al, 2014	USA	15,321	Obesity	Complications	Total Knee Arthroplasty	1 month	50.0
Bozic et al, 2012 A	USA	40,919	Obesity	Complications	Total Hip Arthroplasty	10 years	66.7
Bozic et al, 2012 B	USA	83,011	Obesity	Complications	Total Knee Arthroplasty	10 years	66.7
Chee et al, 2010	United Kingdom	106	Obesity	Complications; Disability	Total Hip Arthroplasty	6, 18, 36 and 60 months	66.7
Chesney et al, 2008	Scotland	1,278	Obesity	Complications	Total Knee Arthroplasty	6, 18 and 60 months	50.0
Collins et al, 2012	United Kingdom	385	Obesity	Complications; Disability	Total Knee Arthroplasty	6, 18 months, 3, 6, 9 years	66.7
Davis et al, 2011	Canada	931	Obesity	Pain	Total Hip and Knee Arthroplasty	2 weeks, 1, 3, 6, 12 months	66.7

Dewan et al, 2009	USA	220	Obesity	Complications; Disability	Total Knee Arthroplasty	5.4 years	50.0
Dowsey et al, 2008	Australia	1,207	Obesity	Complications	Hip Arthroplasty	1 year	50.0
Dowsey et al, 2010	Australia	471	Obesity	Complications; Pain; Disability	Total Hip Arthroplasty	1 year	66.7
Font-Vizcarra et al, 2011	Spain	402	Obesity	Complications	Total Hip Arthroplasty	3 months	66.7
Friedman et al, 2013	USA	12,355	Obesity	Complications	Hip and Knee Arthroplasty	2 months	83.3
Gandhi et al, 2010	Canada	1,224	Obesity	Pain; Disability	Total Hip Arthroplasty	1 year	83.3
Hamoui et al, 2006	USA	63	Obesity	Disability	Total Knee Arthroplasty	11.3 years	50.0
Heiberg et al, 2013	Norway	64	Obesity	Pain	Total Hip Arthroplasty	3 and 12 months	66.7
Ibrahim et al, 2005	United Kingdom	343	Obesity	Complications	Total Hip Arthroplasty	1 year	50.0
Jackson et al, 2009	Australia	100	Obesity	Complications; Pain; Disability	Total Knee Replacement	9.2 years	66.7
Jameson et al, 2014	United Kingdom	5,535	Obesity	Disability	Hip Arthroplasty	6 months	50.0
Jamsen et al, 2010	Finland	2,647	Obesity	Complications	Total Knee Arthroplasty	1 year	33.3
Jamsen et al, 2012	Finland	7,181	Obesity	Complications	Total Knee Arthroplasty	1 year	83.3
Jarvenpaa et al, 2010	Finland	100	Obesity	Complications; Pain	Total Knee Arthroplasty	3 months	50.0
Jarvenpaa et al, 2012	Finland	52	Obesity	Pain; Disability	Total Knee Arthroplasty	10.8 years	83.3
Judge et al, 2010	United Kingdom	908	Obesity	Disability	Hip Replacement	1 year	66.7

Kandil et al, 2015	USA	15,770	Obesity	Complications	Unicompartimental Knee Arthroplasty	3 months	50.0
Kessler et al, 2007	Germany	67	Obesity	Disability	Total Hip Replacement	10 days and 3 months	83.3
Kim et al, 2011	South Korea	227	Obesity	Complications	Total Knee Arthroplasty	6 months	66.7
Kort et al, 2007	Netherlands	46	Obesity	Complications	Unicompartimental Knee Replacement	2 years	50.0
Ledford et al, 2014	USA	316	Obesity	Complications	Total Hip and Knee Arthroplasty	2 months	33.3
Liabaud et al, 2013	USA	273	Obesity	Complications	Total Knee Arthroplasty	3 and 12 months	50.0
Liljensøe et al, 2013	Denmark	197	Obesity	Pain; Disability	Total Knee Arthroplasty	4 years	33.3
Luebbeke et al, 2007 A	Switzerland	2,495	Obesity	Complications; Disability	Total Hip Arthroplasty	5 years	83.3
Luebbeke et al, 2007 B	Switzerland	325	Obesity	Disability	Total Hip Arthroplasty	5 years	50.0
Mackie et al, 2015	United Kingdom	1,821	Obesity	Complications; Pain; Disability	Total Knee Arthroplasty	1 year	33.3
Madsen et al, 2014	USA	79	Obesity	Complications	Total Knee Arthroplasty	10 years	83.3
Maisongrosse et al, 2014	France	502	Obesity	Complications	Total Hip Arthroplasty	58 months	50.0
McLaughlin et al, 2006	USA	198	Obesity	Complications	Total Hip Replacement	14.5 years	50.0
Michalka et al, 2012	United Kingdom	191	Obesity	Complications; Pain; Disability	Hip Arthroplasty	6 weeks	66.7
Murray et al, 2013	United Kingdom	2,438	Obesity	Complications; Disability	Unicompartimental Knee Replacement	1 year	66.7
Naal et al, 2009	Switzerland	83	Obesity	Pain; Disability	Total Knee Arthroplasty	6 weeks, 3, 12 and 24 months	66.7
Namba et al, 2005	USA	1,813	Obesity	Complications	Total Hip and Knee Arthroplasty	1 year	50.0

Napier et al, 2014	United Kingdom	100	Obesity	Complications; Disability	Total Knee Arthroplasty	3 and 12 months	50.0
Naylor et al, 2008	Australia	99	Obesity	Pain	Total Hip and Knee Arthroplasty	2, 6, 12, 26 and 52 weeks	50.0
Ollivier et al, 2012	France	210	Physical Activity	Disability	Total Hip Arthroplasty	10 years	66.7
Patel et al, 2008	United Kingdom	527	Obesity	Complications	Total Knee Replacement	4 weeks, 6 weeks and 1 year	66.7
Pietschmann et al, 2013	Germany	171	Physical Activity	Disability	Unicompartimental Knee Arthroplasty	4.2 years	33.3
Poortinga et al, 2014	Netherlands	658	Physical Activity	Disability	Total Hip and Knee Arthroplasty	1 year	66.7
Pulido et al, 2008	USA	9,245	Obesity	Complications	Total Hip and Knee Arthroplasty	1 year	50.0
Rajgopal et al, 2008	Canada	760	Obesity	Complications; Disability	Total Knee Arthroplasty	1 year	66.7
Sechriest et al, 2007	USA	34	Physical Activity	Disability	Total Hip Arthroplasty	5 years	66.7
Villalobos et al, 2013	Spain	63	Obesity	Pain; Disability	Total Hip Arthroplasty	3 months	100.0
Vogl et al, 2014	Germany	281	Obesity	Disability	Total Hip Arthroplasty	6 months	33.3
Wang et al, 2010	USA	97	Obesity	Disability	Total Hip Arthroplasty	3 months, 1 and 2 years	50.0
Yasunaga et al, 2009	Japan	3,577	Obesity	Complications	Total Knee Arthroplasty	5 months	50.0
Zhang et al, 2012	China	714	Obesity	Complications; Disability	Total Hip Arthroplasty	5 years	66.7

The course of pain and disability over time

Figure 2 presents the course of disability over time for hip (A) and knee osteoarthritis (B) post-surgery; as well as pain for hip (C) and knee osteoarthritis (D). The central line represents the estimated pooled mean over time and the shaded area circumscribes its 95% confidence intervals. A total of eight studies with complete data (i.e., estimates of central tendency and variance) were included in the pain analysis and 17 studies were included in the disability analysis.

The fractional polynomial regression model resulted in a pooled mean disability score and standard deviation before hip arthroplasty of 59.42 (SD: 10.94; n=5,250). At 12 months post-surgery it had decreased to a mean of 31.31 (SD: 24.28; n= 3,017) and a further reduction was observed at 120 months, when the mean disability score after hip arthroplasty was 24.32 (SD: 19.53; n= 210). For knee osteoarthritis a pooled mean disability score of 56.88 (SD: 10.74; n= 17,225) was observed for patients undergoing arthroplasty. At 12 months after surgery this value decreased to 21.80 (SD: 13.51; n= 2,898) whilst at the 110-month follow-up, the mean disability score was 14.18 (SD: 0.77; n= 485). The pooled mean pain scores before hip arthroplasty was 54.86 (SD: 10.20; n= 2,517), decreasing to 13.76 (SD: 1.32; n= 1,058) 3 months after surgery, 10.8 (SD: 1.69; n= 1,212) at 6 months and slightly increasing to 13.45 (SD: 7.87; n= 2,173) at the 12 months follow-up. For patients undergoing knee arthroplasty, the pooled pain score at baseline was 57.78 (SD: 9.28; n= 2,211); which decreased to 25.67 (SD: 6.61; n= 1,222) at 6 months, and 14.18 (SD: 0.77; n= 1,820) at the 12-month follow-up.

Figure 2 - Fractional polynomial analysis of pain and disability over time

Association between obesity and post-surgical pain outcomes

Fourteen studies investigated the association between obesity and pain intensity in a total of 5,687 patients after hip or knee arthroplasty. Seven of the 14 studies presented enough data to be pooled in a meta-analysis. There was an overall significant difference in post-surgical pain between obese and non-obese patients post arthroplasty, with non-obese patients having better outcomes at short (SMD -0.43; 95%CI: -0.67 to -0.19; p=0.000), and long-term (SMD -0.36; 95%CI: -0.47 to -0.24; p=0.000). The pooled results for separate joints suggest non-obese participants have significantly less short-term (i.e. less than 6 months) post-surgical knee pain, compared to obese participants (SMD -0.54; 95%CI: -0.90 to -0.19; p=0.002) and post-surgical hip pain (SMD -0.34; 95%CI: -0.66 to -0.01; p=0.039). Obesity was defined as presenting BMI over 30 kg/m^2. At long term (i.e. equal or over 6 months), there was a significant difference between obese and non-obese groups in terms of knee pain (SMD -0.36; 95%CI: -0.47 to -0.24; p=0.000), however there was no difference between groups for hip pain (SMD -0.32; 95%CI: -0.84 to 0.19; p=0.222). The results of individual studies not included in the pooled analyses are presented in the table 2 below.

Figure 3 - Meta-Analysis of studies addressing pain

Obesity vs Pain			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Knee			
Davis 2011	NA	HOOS / KOOS	After adjusting for age, gender, joint and presence of back pain, an increased BMI was associated with worst pain outcomes (p<0.02) at long term after THA or TKA.
Jarvenpaa 2010	29.7 (NA)	VAS	Increased BMI correlate significantly to VAS pain scale (r=0.236; p=0.018) at short term after TKA.
Liljensøe 2013	30 (NA)	SF-36	BMI was **not** associated to SF-36 pain scale (OR= 0.96; p=0.1) at long term after TKA.
Mackie 2015	NA	WOMAC	Increased BMI was associated to less improvement in WOMAC pain scale (t= -2.64; p<0.001) at long term after TKA.
Hip			
Dowsey 2010	29.55 (5.64)*	Harris Hip Score	BMI was **not** associated with pain reduction (p=0.71) at long term after THA.
Heiberg 2013	27 (6.27)*	HOOS	BMI was **not** associated with HOOS pain scale (p>0.05) at short term after THA.

Table 2 – Results of individual studies on the association between post-surgical pain and baseline obesity.

BMI – Body Mass Index; SD – Standard deviation; THA – Total hip arthroplasty; TKA – Total knee arthroplasty; OR – Odds ratio; NA – Non available; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; HOOS - Hip dysfunction and Osteoarthritis Outcome Score; KOOS - Knee dysfunction and Osteoarthritis Outcome Score; VAS – Visual Analogue Scale; SF-36 – Short Form 36 Questionnaire; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between obesity and post-surgical disability outcomes

The impact of obesity on disability was investigated by 32 studies which compared post-surgery disability scores in 35,286 obese and non-obese participants. Of these, 19 studies presented complete data to be included in the pooled analysis. At short term no statistically significant difference in overall disability between obese and non-obese participants was observed (SMD -0.15, 95% CI -0.41 to 0.10, p=0.231) Likewise, no statistically significant difference was observed between obese and non-obese participants for post-surgical knee or hip disability (SMD -0.41, 95% CI -0.99 to 0.16, p=0.159 and SMD -0.09, 95% CI -0.38 to 0.19, p=0.527, respectively).

At long term follow-up however, there was an overall significant difference in post-surgical disability between obese and non-obese patients regardless of the joint (SMD -0.32; 95%CI: -0.36 to -0.28; p=0.000). That difference was still statistically significant when knee and hip joints were analyses separately (SMD -0.31, 95% CI -0.36 to -0.26, p=0.000 and SMD -0.34, 95% CI -0.44 to -0.25, p=0.000, respectively and favouring non-obese patients). The results of individual studies not included in the pooled analyses are presented in the table 3 below.

Figure 4 - Meta-Analysis of studies addressing disability

Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Knee			
Davis 2011	NA	WOMAC / KOOS	After adjusting for age, gender, joint and presence of back pain, an increased BMI was associated with worst outcomes (p<0.02) at long term after TKA or THA.
Dewan 2009	31 (0.5)	Knee Society Score	BMI was **not** associated with worst knee function (p>0.119) at long term after TKA.
Hamoui 2006	27.93 (7.1)*	Knee Society Score	N**o** significant association between BMI and KSS (p>0.05) were found at long term after TKA.
Kort 2007	NA	WOMAC	Obesity was **not** related to disability score (p>0.05) at long term after TKA.
Liljensøe 2013	30 (NA)	Knee Society Score	Increased BMI was associated with worst knee scores (OR 0.95, 95% CI 0.9 to 1.0, p=0.04) at long term after TKA. These results did not change significantly after adjusting for age, sex, primary

			disease and surgical approach (OR 0.94, 95% CI 0.90 to 0.99, p=0.02).
Mackie 2015	NA	WOMAC	Increased BMI was associated with less improvement in disability scores (WOMAC t= -2.13; p=0.033) at long term after TKA.
Rajgopal 2008	32.3 (6.58)*	WOMAC	The morbidly obese group (BMI ≥40, n=69) does **not** present a statistically significant difference on improvement in WOMAC score (p=0.669) when compared to others BMI groups at long term after TKA.
Hip			
Heiberg 2013	27 (6.27)*	HHS	Increased BMI was associated with lower HHS (p<0.05) at short term after THA.
Jameson 2014	NA	OHS	Increased BMI was **not** associated with changes in OHS (p>0.05) at short term after THA.
Luebbeke 2007 B	26.4 (4.3)	HHS	Increased BMI was associated with lower hip score (r=-0.4, 95% CI -0.8 to -0.1) at long term after THA.
McLaughlin 2006	26 (NA)	HHS	The obese group (BMI ≥30; n=95) did **not** present any statistically significant difference from the non-obese group (BMI <30, n=103) with regards to clinical outcomes assessed by HHS (p>0.05) at long term after THA.
Vogl 2014	26.9 (4.9)	WOMAC	Obesity was associated with changes in WOMAC score (p<0.05) at short term after THA.
Wang 2010	29.14 (6.23)	WOMAC	Increased BMI was **not** associated with WOMAC score (p=0.114) at long term after THA.

Table 3 – Results of individual studies on the association between post-surgical disability and baseline obesity.

BMI – Body Mass Index; SD – Standard deviation; NA – Non available; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; KOOS - Knee disability and Osteoarthritis Outcome Score; TKA – Total knee arthroplasty; THA – Total hip arthroplasty; KSS – Knee Society Score; OR – Odds ratio; CI – Confidence interval; HHS – Harris Hip Score; OHS – Oxford Hip Score; r – coefficient of association; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between obesity and post-surgical complications

The association between obesity and complications after joint arthroplasty was assessed by 40 studies including a total of 245,433 patients who underwent knee or hip arthroplasty. Of these, 17 presented enough data and were included in the meta-analyses.

The pooled results suggest that at short term follow-up, non-obese participants are less likely to have post-surgical deep vein thrombosis (DVT) (OR 0.48; 95% CI 0.25 to 0.91; p=0.024) or infection (OR: 0.56; 95% CI: 0.43 to 0.72; p=0.000) when compared with obese ones. Likewise, 13 studies were pooled (n=22,782) showing non-obese patients are less likely to present any long-term (i.e. ≥ 6 months) dislocation (OR: 0.49; 95% CI: 0.31 to 0.79; p=0.003), DVT (OR: 0.61; 95% CI: 0.37 to 0.98; p=0.043) or infection (OR: 0.43; 95% CI: 0.25 to 0.72; p=0.001) post-surgery, compared to obese participants. Non-significant difference between groups was observed for long-term revision surgery between obese and non-obese participants (OR: 0.66; 95% CI: 0.34 to 1.27; p=0.217). The overall pooled analysis for incidence of complications suggests that non-obese participants are less likely to present any post-surgical complication at the short or long term follow-ups (OR: 0.54; 95% CI: 0.43 to 0.69; p=0.000 and OR: 0.53; 95% CI: 0.41 to 0.68; p=0.000, respectively). The results of individual studies not included in the pooled analyses are presented in the table 4 below.

Figure 5 - Meta-Analysis of studies addressing complications

Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Ollivier 20012	25.13 (3.14)*	HHS / HOOS	At long term high impact sports was associated with better HHS (p<0.001) after THA.
Pietschmann 2013	28.4 (4.62)*	OKS	At long term physical activities were **not** related to complications (p<0.01). Physically active patients had less pain and better OKS scores after UKA.
Poortinga 2014	28.7 (4.9)	WOMAC	At long term physical activity was **not** associated with WOMAC score (p>0.05) after THA or TKA.
Sechriest 2007	28.1 (8.3)	UCLA	At long term increased BMI was **not** correlated to UCLA physical activity score (R=-0.07; p=0.67) after TKA.

Table 4: Results of individual studies investigating the association between obesity and post-surgical complications.

BMI – Body Mass Index; SD – Standard deviation; HHS – Harris Hip Score; HOOS - Hip disability and Osteoarthritis Outcome Score; THA – Total hip arthroplasty; OKS – Oxford Knee Score; UKA - Unicompartimental knee arthroplasty; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; TKA – Total knee arthroplasty; UCLA - University of California, Los Angeles activity questionnaire; R –

Correlation coefficient; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between physical activity participation and disability

The association between physical activity and disability was investigated by four studies(72, 74, 75, 78) or 1,033 participants undergoing hip or knee arthroplasty. Included studies have not provided enough data to be pooled. The overall results from these 4 papers suggests that participants who practice more physical activity before the surgeries were more likely to experience less pain after either hip or knee surgery, however the evidence regarding disability scores is still unclear with studies presenting contradictory results. Table 5 below presents the results for the individual studies.

Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Ollivier 20012	25.13 (3.14)*	HHS / HOOS	At long term high impact sports were associated with better HHS (p<0.001) and HOOS (p<0.05) after THA.
Pietschmann 2013	28.4 (4.62)*	OKS / KSS / WOMAC	At long term physical activities were **not** related to complications. Physically active patients had less pain and better OKS, KSS and WOMAC scores (p<0.05) after UKA.
Poortinga 2014	28.7 (4.9)	WOMAC	At long term physical activity was **not** associated with WOMAC score (p>0.05) after THA or TKA.
Sechriest 2007	28.1 (8.3)	UCLA	At long term increased BMI was **not** correlated to UCLA physical activity score (R=-0.07; p=0.67) after TKA.

Table 5 – Individual results on the association between physical activity and pain or disability.

BMI – Body Mass Index; SD – Standard deviation; HHS – Harris Hip Score; HOOS - Hip disability and Osteoarthritis Outcome Score; THA – Total hip arthroplasty; OKS – Oxford Knee Score; KSS – Knee Society Score; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; UKA - Unicompartimental knee arthroplasty; TKA – Total knee arthroplasty; UCLA - University of California, Los Angeles activity questionnaire; R – Correlation coefficient; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Discussion

Statement of principal findings

Our results suggest that non-obese patients experience further reductions in both pain and disability post knee and hip arthroplasty, when compared to obese patients, where obesity has been defined as having a BMI of 30 kg/m^2 or over. These differences seemed to be more accentuated for knee pain outcomes following arthroplasty, than for hip pain or disability outcomes. They also experience significantly less post-surgical complications, including dislocation, DVT and infection especially following hip arthroplasty. Our analyses also demonstrate that obesity is a reliable predictor of complications after total hip arthroplasty and total knee arthroplasty, not only short term after the procedure, but also at longer follow-ups. The evidence on physical activity remains unclear due to conflicting results of included studies, especially in terms of disability. The four included cohort studies, however, suggest that physical activity participation is associated with better pain outcomes following surgery.

Our results have also shown that patients experience a favorable course of pain and disability post-surgery, with decreases in symptoms from baseline of approximately 70% at 6 months and 75% at 12 months for pain and 55% at 12 months and 67% at 120 months for disability. The interpretation of the results on the post-surgical course of pain and disability, however, needs to be taken in the context of the inclusion criteria we have used in our review, given we have only included data from cohort studies that have assessed the role of obesity or physical activity participation on surgical outcomes.

Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

Our meta-analysis results regarding the association between obesity and post-surgical complications found that obese patients present higher complication rates than non-obese patients. These results are consistent with the findings of previous systematic reviews of Hofstede,(14) Samson(15) and Liu(16). Our meta-analysis results regarding the association between obesity and post-surgery disability also agreed with the findings of Buirs *et al*(13) and Samson *et al*(15) which found that obesity (defined as having BMI over 30 kg/m^2), was associated with worst postsurgical functional score. Only one of the existing reviews(16) conducted a meta-analysis of the findings. The study, however, has only focussed on hip arthroplasty in terms of complications and functional score. Moreover, the authors have included 15 studies in their analysis, 18 less than our review.(16) Hofstede *et al*(14) have also conducted a systematic review of the literature on pre-operative predictors of surgical outcomes after hip replacement in patients with osteoarthritis. Although the authors have included 35 studies, only 5 investigated the role of obesity on post-surgical pain, disability and quality of life.(14) No meta-analysis has been performed.

Implications for clinicians or policymakers

Our results have a direct impact on clinical practice as patients need to be made aware of the risk of complications and worse prognosis in terms of pain and disability reduction, associated with pre-surgical obesity. These results also allude to the importance of identifying and implementing effective pre-surgical rehabilitation and weight loss approaches to optimise post-surgical outcomes and minimize harm to the patient. The importance of weight loss has been highlighted in international clinical guidelines on non-surgical management of knee osteoarthritis for instance, given the pain and disability reductions observed following weight loss regimes.(85) Past research also suggests there is a dose-response relationship between weight loss and clinical outcome improvement. A recent completer-type analysis of 1,383 participants with knee osteoarthritis showed that a weight loss of 7.7% of body weight or more is associated with clinically important changes in pain and disability, as measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS).(86) This evidence reinforces the importance of pre-surgical weight loss programs and strategies in order to optimize post-surgical recovery.

Strengths and weaknesses of the study

The current review has included 62 cohort studies and a total of 256,481 participants and is the most comprehensive systematic review on the topic to date. It is also the first review to use a quantitative approach to synthesize the results of pain, disability and surgical complications between non-obese and obese participants and consider the physical activity level of participants who underwent to hip or knee arthroplasty due to osteoarthritis.

Our review has some limitations. The methodological quality of the included studies was in general low. The most common methodological flaw among included cohorts was not fully describing the sample (n= 43 studies, 69%), followed by not using a representative sample (n=33 studies, 53%). Moreover, we have observed a substantial variability of follow-up duration across studies, ranging from 2 weeks to 11 years. We have used a cut-off of 6 months to define short (i.e. < 6 months) or long-term (i.e. ≥ 6 months) follow-ups. We, however, acknowledge that within each follow-up category there was substantial variation in the duration of follow-up across studies.

There was also great variability in definitions of obesity categories across studies. Although obesity was assessed using BMI scores in all studies, we defined obesity as a BMI score of 30 kg/m^2 or more, different categories have been used to classify participants. For instance, whereas some studies have used only two obesity groups (i.e. obese or non-obese), others use several categories including underweight, normal or overweight, obese and morbidly obese. These needed to be combined for our pooled analyses. We also acknowledge that the mean physical activity load reported by the included studies varied substantially, ranging from low to high frequency of participation in low and high impact activities and this between-study heterogeneity needs to be taken into consideration when interpreting the results.

Conclusion

Our results have shown that obese patients undergoing hip or knee arthroplasty due to osteoarthritis have worse outcomes in terms of pain and complications when compared to non-obese patients, with differences more accentuated for patients with knee osteoarthritis. Likewise, obese patients will have worse surgical outcomes in terms of disability, but only at long-term follow-ups. It is still unclear whether pre-surgical physical activity participation has an impact on surgical outcomes. However, we acknowledge that the health benefits of physical activity participation for patients with knee and hip osteoarthritis are multiple and reach beyond those considered in this review.

Contributors: DP, GCM, PHF, FB and MF were involved in the conception and design of the review. DP, GCM and MF developed the search strategy and performed study selection. DP and GCM extracted data from included studies. DP and MLF were involved in the data analysis. DP, GCM, PHF, FB and MF were involved in the interpretation and discussion of results. DP drafted the manuscript, and GCM, PHF, FB and MF contributed to the drafting of the review. GCM, PHF, FB and MF revised it critically for important intellectual content. All authors approved the final version of the article. All authors had access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 6 - MEDLINE search strategy terms used:

1	obesity.mp. or exp Obesity/ or exp Obesity, Abdominal/	197.941
2	Physical Activity.mp. or exp Motor Activity/	231.947
3	sedentar$.mp.	19.058
4	(time adj5 sitting).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	688
5	**1 or 2 or 3 or 4**	**414.967**
6	exp Postoperative Complications/ or exp Hip Prosthesis/ or exp Arthroplasty, Replacement, Hip/ or hip arthroplasty.mp. or exp Osteoarthritis, Hip/ or exp Hip Joint/	469.282
7	knee arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/	17.365
8	exp Elective Surgical Procedures/ or elective surgery.mp.	14.058
9	osteoarthritis.mp. or exp Osteoarthritis, Hip/ or exp Osteoarthritis/ or exp Osteoarthritis, Knee/	55.493
10	exp Osteonecrosis/ or Osteonecrosis.mp.	13.961
11	arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty, Replacement/ or exp Arthroplasty/ or exp Arthroplasty, Replacement, Hip/	53.979
12	**6 or 7 or 8 or 9 or 10 or 11**	**546.616**
13	exp Cohort Studies/ or cohort.mp.	1.526.984
14	incidence.mp. or exp Incidence/	587.274
15	exp Follow-Up Studies/ or follow-up.mp.	912.064
16	prognosis.mp. or exp Prognosis/	1.273.869
17	exp Prognosis/ or predictors.mp.	1.258.014
18	exp Time Factors/ or course.mp.	1.403.404
19	exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ or survival.mp.	843.771
20	logistic.mp.	198.801
21	cox.mp.	84.820
22	life table.mp. or exp Life Tables/	18.098
23	log rank.mp. or exp Follow-Up Studies/	533.280
24	**13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23**	**4.460.132**
25	Animals/	5.495.334
26	exp Editorial/ or editorial.mp.	376.114
27	case report.mp. or exp Case Reports/	1.754.352
28	letter.mp. or exp Letter/	895.420
29	25 or 26 or 27 or 28	8.184.015
30	**5 and 12 and 24**	**7.601**
31	**30 not 29**	**6.869**

Fig 2 – Data for hip (A) and knee (B) disability scores and hip (C) and knee (D) pain scores over time.

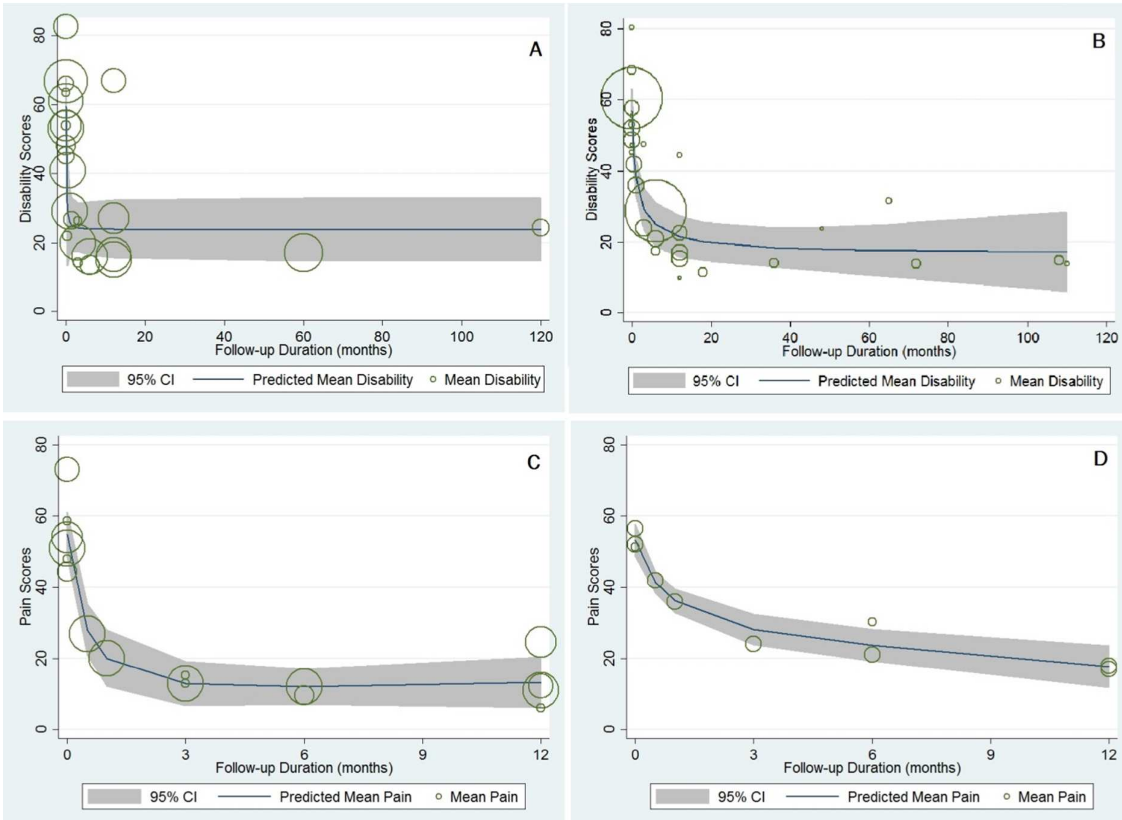


Fig 3 – Pooled standardised mean difference in pain at short and long term post-surgery between obese and non-obese patients.

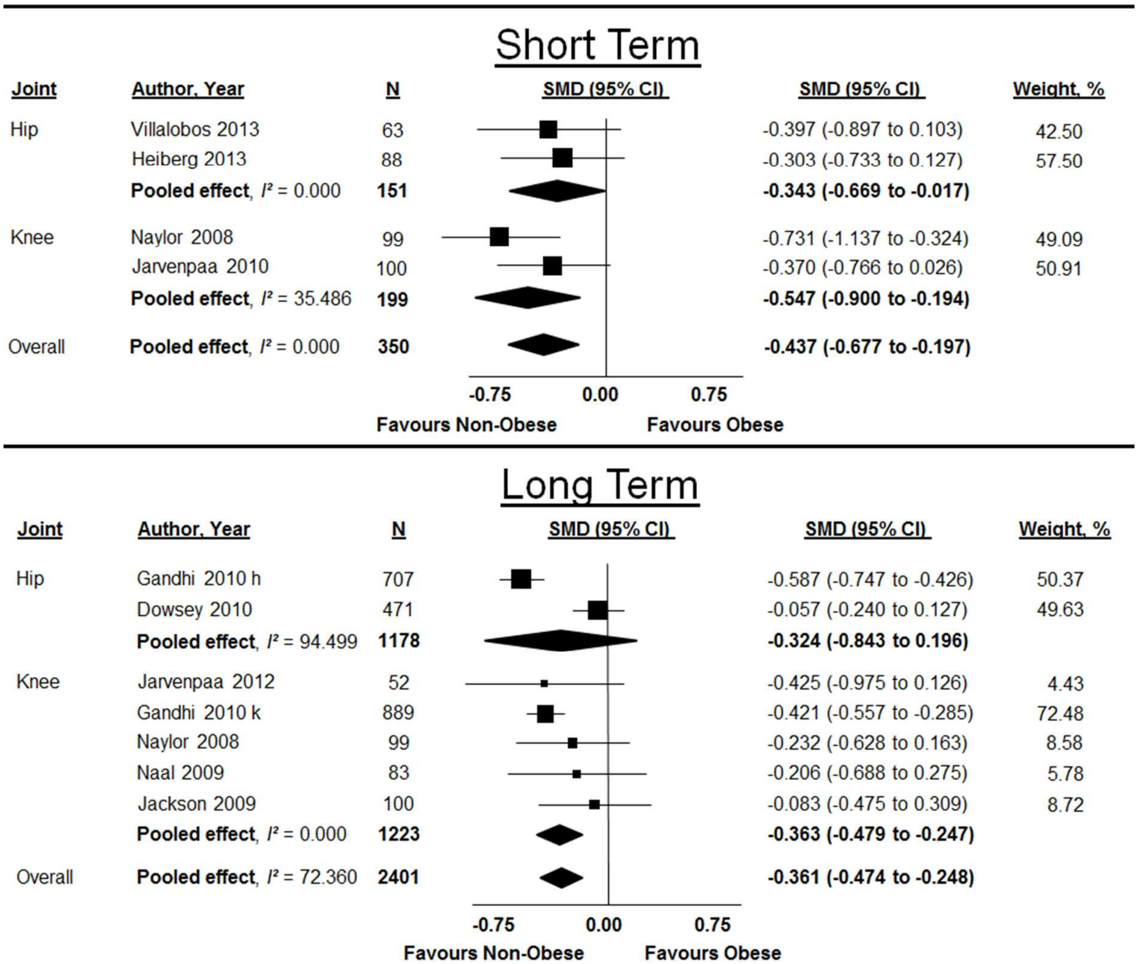


Fig 4 – Pooled standardised mean difference in disability at short and long term post-surgery between obese and non-obese patients.

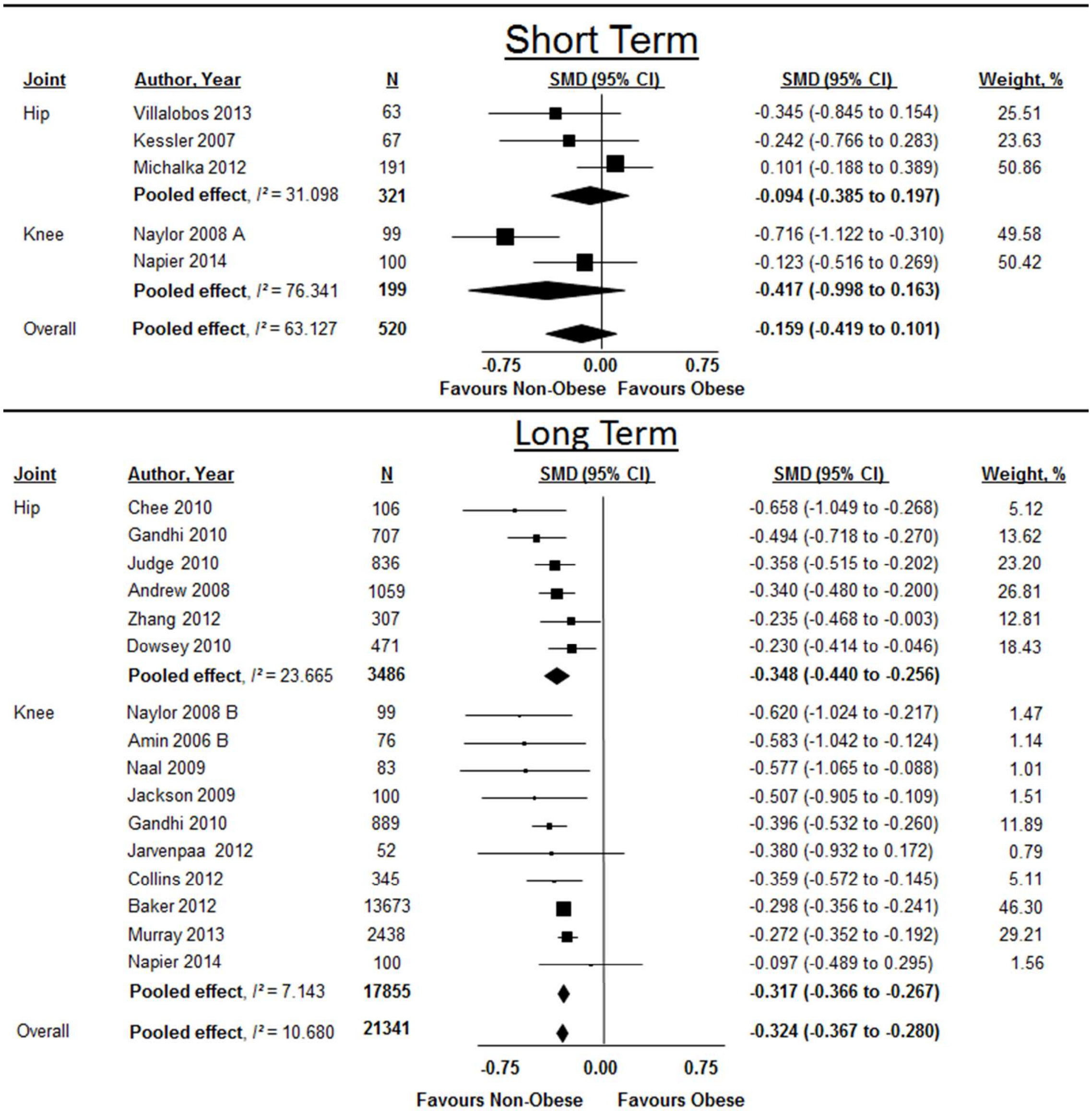
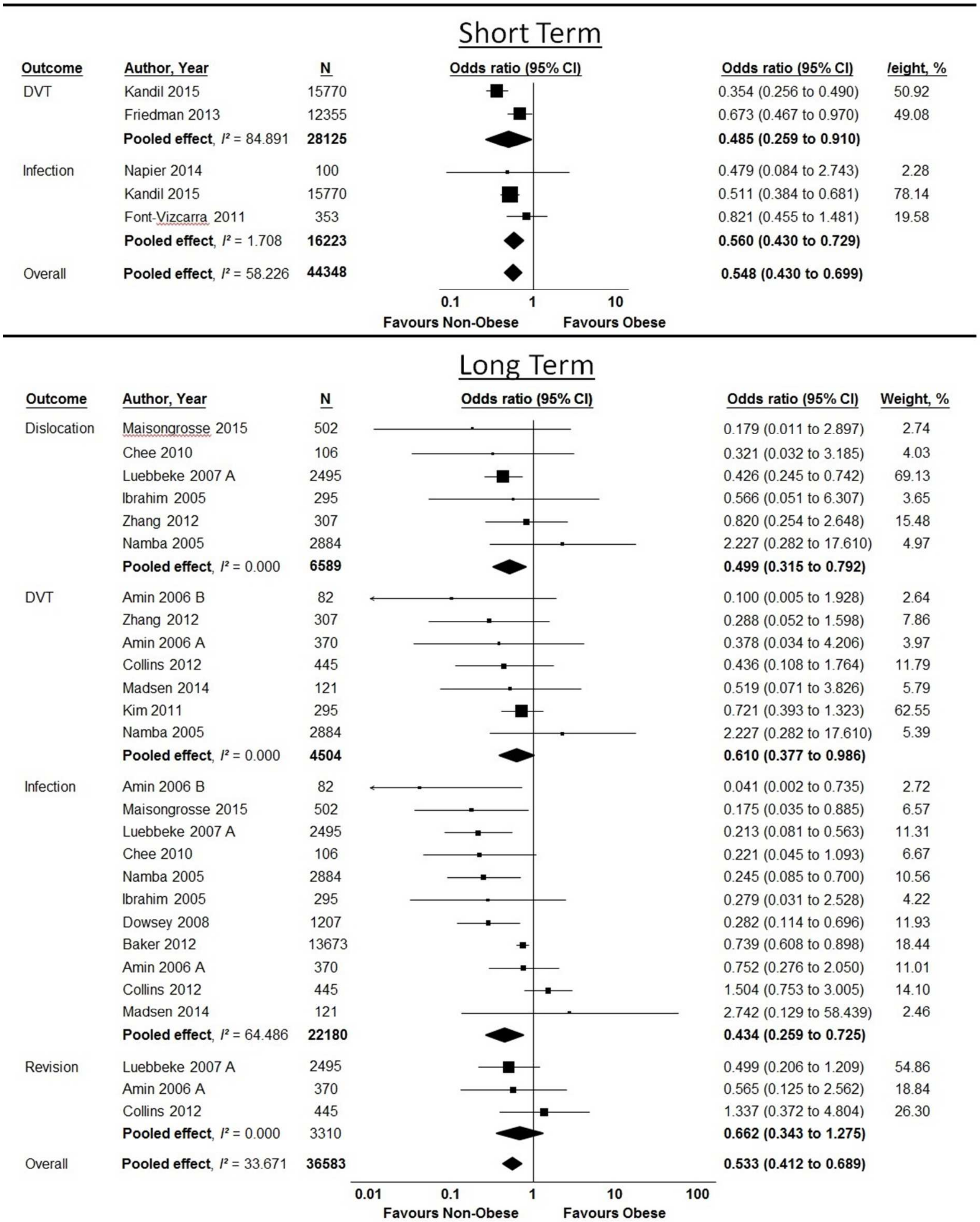


Fig 5 – Pooled association between complications and obesity at short term (A) and long term (B) follow-ups.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? – A meta-analysis of cohort studies.

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Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? – A meta-analysis of cohort studies.

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Word count: 3,799.

Abstract

Objective: The aim of this study was to systematically review the literature to identify whether obesity or the regular practice of physical activity are predictors of clinical outcomes in patients undergoing elective hip and knee arthroplasty due to osteoarthritis.

Design: Systematic review and meta-analysis.

Data Source and eligibility criteria: A systematic search was performed on the Medline, CINAHL, EMBASE, and Web of Science electronic databases. Longitudinal cohort studies were included in the review. To be included, studies needed to have assessed the association between obesity or physical activity participation at baseline and clinical outcomes (i.e. pain, disability, and adverse events) following hip or knee arthroplasty.

Data extraction: Two independent reviewers extracted data on pain, disability, quality of life, obesity, physical activity and any post-surgical complications.

Results: 63 full papers were included in this systematic review. From these, 31 were included in the meta-analyses. Our meta-analysis showed that non-obese participants tended to suffer less pain at both short (SMD -0.43; 95%CI: -0.67 to -0.19; p<0.001) and long term (SMD -0.36; 95%CI: -0.47 to -0.24; p<0.001), less disability at long term (SMD -0.32; 95%CI: -0.36 to -0.28; p<0.001) and report fewer post-surgical complications at short (OR: 0.48; 95% CI: 0.25 to 0.91; p<0.001) and long term (OR: 0.55; 95% CI: 0.41 to 0.74; p<0.001) and less post-surgical infections after hip arthroplasty (OR: 0.33; 95% CI: 0.18 to 0.59; p<0.001), and particularly when compared to morbidly obese participants after knee arthroplasty (OR: 0.42; 95% CI: 0.23 to 0.78; p=0.006).

Conclusions: Pre-surgical obesity is associated with worse clinical outcomes of hip or knee arthroplasty in terms of pain, disability, and complications in patients with osteoarthritis. No impact of physical activity participation has been observed.

Systematic review registration: PROSPERO registration CRD42016032711.

Keywords: Physical activity, obesity, arthroplasty, osteoarthritis, knee, hip, meta-analysis.

Strengths and limitations of this study

- The current review is the most comprehensive systematic review on the topic to date.

- The current review is the first review to use a quantitative approach to synthesize the results of pain, disability and surgical complications between non-obese and obese participants who underwent hip or knee arthroplasty due to osteoarthritis.

- The methodological quality of the included studies was in general poor.

- There was a substantial variability of follow-up duration across studies, ranging from 2 weeks to 11 years.

Introduction

Musculoskeletal pain, including pain from knee and hip osteoarthritis, is the leading cause of physical disability in the world and responsible for an increasing burden to patients and society.(1) This problem will increase over time, as the world population ages and physical disability resulting from declining health becomes increasingly prevalent.(2) The global health care expenditure for knee and hip osteoarthritis is substantial, and most of these costs are incurred by surgical management and associated hospital care.(3) For instance, in the UK the direct costs of osteoarthritis were estimated at more than £1 billion in 2010, of which £850 million was spent just on surgical procedures.(4)

Although management of the early stages of this condition consists of a combination of nonpharmacological and pharmacological therapies (e.g. anti-inflammatory and analgesic drugs), surgery has become the most common treatment option for severe cases, especially when nonsurgical therapies fail to provide sufficient pain relief.(5) Osteotomy, mosaicplasty, and arthroplasty are some of the existing types of surgery used to manage osteoarthritis of the hip and knee; with total or partial arthroplasty being the most commonly recommended.(6)

There are multiple risk factors for the development of knee OA. Among the most common of these are increased body weight and muscle weakness; often attributed to a sedentary lifestyle.(7) Obesity and sedentary lifestyle behaviour have also been associated with serious health conditions such as: coronary heart disease, type 2 diabetes, breast and colon cancers, and decreased life expectancy.(8) Although there is evidence for the role of obesity and physical inactivity in health conditions and quality of life in general,(9, 10) the actual impact of these factors, together or in isolation, on the outcomes of elective surgery of the knee and hip is still controversial.(11, 12) Although previous attempts to systematically review the literature have been made, these studies(13-15) have either failed to perform a quantitative summary of the evidence (i.e. meta-analysis), have excluded patients undergoing knee arthroplasty,(16) or have excluded pain outcomes.(13) No meta-analyses have been performed considering obesity and physical activity as predictors of surgical outcomes in terms of pain, disability, quality of life and complications after hip or knee arthroplasty for end stage osteoarthritis.

Identifying whether obesity and physical activity participation predict surgical outcomes in patients with knee and hip osteoarthritis will inform clinical practice in terms of prognosis and safety of an increasingly prevalent treatment approach. We have conducted a meta-analysis of cohort studies aiming to quantify the role of obesity and physical activity participation as predictors of clinical outcomes in terms of pain, disability, quality of life, and post-surgical complications. This review and meta-analysis focused on patients with knee and hip osteoarthritis undergoing hip or knee arthroplasty.

Methods

Data sources and searches

We conducted a systematic review following the PRISMA statement.(17) This review was prospectively registered on PROSPERO, registration number CRD42016032711. A systematic electronic search was performed in the following databases from inception to January 2017: MEDLINE, EMBASE, CINAHL, and Web of Science. We used a combination of relevant keywords to construct the search strategy including obesity, physical activity, knee osteoarthritis, hip osteoarthritis, arthroplasty, and elective surgery (appendix 1). The first screening of potentially relevant records was conducted by one author (DP) based on titles and abstract, and two authors (DP and GM) independently performed the final selection of included trials based on full-text evaluation. A third reviewer arbitrated in case of disagreement (MF). Moreover, the reference lists of included studies were checked for potential studies. An additional 26 references were screened, but none met our inclusion criteria. No restriction was applied on language.

Study selection

We included only longitudinal studies assessing the role of obesity or physical activity participation on the clinical outcomes following partial or total hip arthroplasty (THA) or partial or total knee arthroplasty (TKA) surgery. Clinical outcomes were defined in terms of pain, disability, quality of life, and complications post arthroplasty. To be eligible, studies had to be full reports; include participants who underwent elective arthroplasty of the hip or knee due to osteoarthritis; include data of pre-surgical and at least one post-surgical assessment of the clinical outcomes of interest; and assess the association between the predictors and outcomes of interest. Obesity and physical activity participation had to be

assessed at baseline. Studies on revision surgery were excluded. Studies were not excluded based on intensity or duration of symptoms.

Data extraction

Using a standardised form, data on study characteristics, predictors and outcome measures of interest were independently extracted from the included studies by two reviewers (DP and GM). A third author (MF) resolved any disagreement. Estimates of association between predictors and outcomes of interest were extracted as presented in each study and included odds ratios, risk ratios, correlations, mean differences or regression coefficients. When studies reported more than one tool regarding the same topic (e.g. WOMAC, HOOS, OHS, KOOS, KSS), estimates were extracted from the group with the largest sample size.

We contacted the authors to provide further information when there were insufficient data reported in the manuscript. When authors were unavailable we estimated data using the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions.(18)

Outcome measures

Data on pain intensity was extracted as visual analogue scale (VAS) scores ranging from 0 to 10 and measured directly or as part of the following measurement tools: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Hip disability and Osteoarthritis Outcome Score (HOOS), the Knee disability and Osteoarthritis Outcome Score (KOOS) or the Harris Hip Score (HHS). If studies reported more than one measure of pain intensity or disability for the cohort, the most severe measure at baseline was included in the pooled analyses. Disability measures included the Oxford Hip Score (OHS), ranging from 12 to 60 being 12 the best result; Oxford Knee Score (OKS) ranging from 0 to 60 being 60 the best result; the Harris Hip Score (HHS) ranging from 0 to 100 being 100 the best result; Knee Society Score (KSS) ranging from 0 to 100 being 100 the best result; WOMAC total score ranging from 0 to 96 being 0 the best result; or WOMAC function subscale, ranging from 0 to 10 being 10 the best result; and were converted into a uniform 0-100 scale where 0 meant less disability. Extracted data on complications included any descriptive measure of the number of complications or number of patients with a complication reported during the study. Only two of the screened studies had reported specific raw data on quality of life among the participants after joint arthroplasty, but due to differences in follow-up length, any meta-analysis made by merging this data would result in an unreliable measure.

Methodological Quality Assessment

The methodological quality of included studies was assessed by two independent reviewers using the Newcastle-Ottawa Scale (NOS)(19) recommended by the Cochrane Collaboration.(18) The NOS consists of eight items grouped into 3 categories, namely: selection, comparability, and outcome. A star system, ranging from zero to nine stars, is used to classify the quality of the study being reviewed (the more stars the study receives in each category, the higher its methodological quality). After the independent assessment of included studies by the leading author, each study received the following categorical score representing its quality: good (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain), fair (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain) or poor (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 star in outcome domain). A third reviewer (MF) resolved any disagreement between independent assessors.

Data analysis

Data on baseline (i.e. pre-surgical scores) and postoperative outcome scores were weighed by the inverse study variance and used in fractional polynomial regression modelling to build graphs depicting the course of pain and disability over time. STATA14 was used for the analyses (Stata Corp LP, College Station, TX).(20)

Meta-analyses were performed to assess the differences in pain, disability and complications post-surgery, between predictor groups (i.e. obese and non-obese groups as defined by included studies), using a random effects model. When possible, different analyses were performed for knee and hip arthroplasty and also for different levels of obesity (i.e. obesity and morbid obesity). When means and standard deviations of outcomes of interest were presented for multiple predictor groups in the same study (i.e. underweight (BMI<18), normal weight (BMI≥18<25), overweight (BMI≥25<30), and obese levels I (BMI≥30<35), II (BMI≥35<40) or III (BMI≥40)) these were combined into two groups (non-obese: BMI<30 and obese: BMI≥30) as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (18) before inclusion in the pooled analyses. Results were reported as standardised mean differences (SMD) and 95% confidence intervals (95%CI). Between-study heterogeneity was calculated using I^2 (I^2 <25%: small heterogeneity; 25% <I^2< 75%: moderate heterogeneity; I^2> 75%: large heterogeneity).(21) We have defined a standardised mean difference (SMD) of 0.2 as small difference, 0.5 as moderate difference and 0.8 as large difference.(22)

Assessment of publication bias was performed using funnel plots. The precision (i.e. standard error) of included studies was plotted against the difference in outcomes between groups (i.e. obese or non-obese) and results visually analysed. In the absence of publications bias or small study bias, smaller studies should be evenly spread around the base of the funnel, whilst the larger studies should be concentrated around the top of the funnel. Plot asymmetry was also quantified using the Egger's tests, for which a null hypothesis represents symmetry of plotted data.(23)

All meta-analyses were conducted using Comprehensive Meta-Analysis software (Comprehensive Meta-Analysis, Englewood, NJ). For studies not reporting enough data to be included in the meta-analyses, the reported individual associations were tabulated and qualitatively presented in the supplementary material.

Results

Our search strategy identified 11,990 studies. After removing 381 duplicates, 11,220 studies were screened and excluded based on keywords, titles, and abstracts. All the remaining 389 studies were written in English and were assessed by reading the full text, of which 327 were then excluded, yielding 62 studies to be included in the systematic review.(24-85) From these, 31 presented enough data to be included in at least one of the meta-analyses (Figure 1).

Figure 1 – Flowchart of search strategy and screening steps.

Included Studies

Included studies reported data from 18 different countries: Australia,(40, 47, 72, 85) Canada,(38, 43, 78) China,(84) Denmark,(60) England,(27, 30) Finland,(49-52), France,(65, 73) Germany,(55, 75, 81) Italy,(28, 29) Japan,(83) Netherlands,(57, 76) Norway,(45) Scotland (25, 36), South Korea,(56) Spain,(41, 80) Switzerland,(61, 62, 69) United Kingdom(26, 35, 37, 46, 48, 53, 63, 67, 68, 71, 74) and USA.(24, 31-34, 39, 42, 44, 54, 58, 59, 64, 66, 70, 77, 79, 82) Demographic data from each study are presented in table 1.

Methodological Quality

An overall quality assessment of the studies showed that 50% (n=31) of the included studies were considered as being of good methodological quality, whilst 1.5% (n=1) were considered fair and 48.5% (n=30) were considered of poor methodological quality. Of the screened studies, 56 (90%) had a follow-up rate of 80% or greater, and only half (n= 32 studies) assessed outcomes via retrospective analysis of medical records, conducted adjustment for potential confounders (e.g. age or sex) or investigated a representative sample of the population (Appendix 2).

Assessment of Publication Bias

Inspection of funnel plots and results of Egger's test confirmed no evidence of small study bias for those studies included in our pooled analyses, with p values ranging from 0.07 to 0.43 (Appendix 3, 4 and 5).

Table 1 - Included studies and characteristics.

Author, year	Country	Sample Size	Predictor	Outcomes	Surgery	Follow-Up Duration	Quality Score
AbdelSalam et al, 2012	USA	210	Obesity	Complications	Total Hip and Knee Arthroplasty	9 years	Fair
Amin et al, 2006 A	United Kingdom	328	Obesity	Complications; Disability	Total Knee Replacement	6, 18, 36 and 60 months	Poor
Amin et al, 2006 B	Scotland	82	Obesity	Complications	Total Knee Replacement	38.5 months	Poor
Andrew et al, 2008	England	1,059	Obesity	Complications; Disability	Total Hip Arthroplasty	3, 12, 24, 36 and 60 months	Poor
Azodi et al, 2006	Italy	3,309	Obesity	Complications	Total Hip Replacement	6 to 9 years	Fair
Azodi et al, 2008	Italy	2,106	Obesity	Complications	Total Knee Arthroplasty	2 years	Fair
Baker et al, 2012	England	13,673	Obesity	Complications; Disability	Total Hip Arthroplasty	6 months	Fair
Belmont et al, 2014	USA	17,514	Obesity	Complications	Total Knee Arthroplasty	1 month	Fair
Belmont et al, 2014	USA	15,321	Obesity	Complications	Total Knee Arthroplasty	1 month	Fair
Bozic et al, 2012 A	USA	40,919	Obesity	Complications	Total Hip Arthroplasty	10 years	Fair
Bozic et al, 2012 B	USA	83,011	Obesity	Complications	Total Knee Arthroplasty	10 years	Fair
Chee et al, 2010	United Kingdom	106	Obesity	Complications; Disability	Total Hip Arthroplasty	6, 18, 36 and 60 months	Good
Chesney et al, 2008	Scotland	1,278	Obesity	Complications	Total Knee Arthroplasty	6, 18 and 60 months	Poor
Collins et al, 2012	United Kingdom	385	Obesity	Complications; Disability	Total Knee Arthroplasty	6, 18 months, 3, 6, 9 years	Poor
Davis et al, 2011	Canada	931	Obesity	Pain	Total Hip and Knee Arthroplasty	2 weeks, 1, 3, 6, 12 months	Fair

Dewan et al, 2009	USA	220	Obesity	Complications; Disability	Total Knee Arthroplasty	5.4 years	Poor
Dowsey et al, 2008	Australia	1,207	Obesity	Complications	Hip Arthroplasty	1 year	Poor
Dowsey et al, 2010	Australia	471	Obesity	Complications; Pain; Disability	Total Hip Arthroplasty	1 year	Good
Font-Vizcarra et al, 2011	Spain	402	Obesity	Complications	Total Hip Arthroplasty	3 months	Fair
Friedman et al, 2013	USA	12,355	Obesity	Complications	Hip and Knee Arthroplasty	2 months	Poor
Gandhi et al, 2010	Canada	1,224	Obesity	Pain; Disability	Total Hip Arthroplasty	1 year	Good
Hamoui et al, 2006	USA	63	Obesity	Disability	Total Knee Arthroplasty	11.3 years	Poor
Heiberg et al, 2013	Norway	64	Obesity	Pain	Total Hip Arthroplasty	3 and 12 months	Good
Ibrahim et al, 2005	United Kingdom	343	Obesity	Complications	Total Hip Arthroplasty	1 year	Poor
Jackson et al, 2009	Australia	100	Obesity	Complications; Pain; Disability	Total Knee Replacement	9.2 years	Poor
Jameson et al, 2014	United Kingdom	5,535	Obesity	Disability	Hip Arthroplasty	6 months	Fair
Jamsen et al, 2010	Finland	2,647	Obesity	Complications	Total Knee Arthroplasty	1 year	Good
Jamsen et al, 2012	Finland	7,181	Obesity	Complications	Total Knee Arthroplasty	1 year	Good
Jarvenpaa et al, 2010	Finland	100	Obesity	Complications; Pain	Total Knee Arthroplasty	3 months	Poor
Jarvenpaa et al, 2012	Finland	52	Obesity	Pain; Disability	Total Knee Arthroplasty	10.8 years	Poor
Judge et al, 2010	United Kingdom	908	Obesity	Disability	Hip Replacement	1 year	Poor

Kandil et al, 2015	USA	15,770	Obesity	Complications	Unicompartimental Knee Arthroplasty	3 months	Poor
Kessler et al, 2007	Germany	67	Obesity	Disability	Total Hip Replacement	10 days and 3 months	Good
Kim et al, 2011	South Korea	227	Obesity	Complications	Total Knee Arthroplasty	6 months	Poor
Kort et al, 2007	Netherlands	46	Obesity	Complications	Unicompartimental Knee Replacement	2 years	Poor
Ledford et al, 2014	USA	316	Obesity	Complications	Total Hip and Knee Arthroplasty	2 months	Poor
Liabaud et al, 2013	USA	273	Obesity	Complications	Total Knee Arthroplasty	3 and 12 months	Poor
Liljensøe et al, 2013	Denmark	197	Obesity	Pain; Disability	Total Knee Arthroplasty	4 years	Poor
Luebbeke et al, 2007 A	Switzerland	2,495	Obesity	Complications; Disability	Total Hip Arthroplasty	5 years	Good
Luebbeke et al, 2007 B	Switzerland	325	Obesity	Disability	Total Hip Arthroplasty	5 years	Good
Mackie et al, 2015	United Kingdom	1,821	Obesity	Complications; Pain; Disability	Total Knee Arthroplasty	1 year	Poor
Madsen et al, 2014	USA	79	Obesity	Complications	Total Knee Arthroplasty	10 years	Poor
Maisongrosse et al, 2014	France	502	Obesity	Complications	Total Hip Arthroplasty	58 months	Poor
McLaughlin et al, 2006	USA	198	Obesity	Complications	Total Hip Replacement	14.5 years	Poor
Michalka et al, 2012	United Kingdom	191	Obesity	Complications; Pain; Disability	Hip Arthroplasty	6 weeks	Poor
Murray et al, 2013	United Kingdom	2,438	Obesity	Complications; Disability	Unicompartimental Knee Replacement	1 year	Poor
Naal et al, 2009	Switzerland	83	Obesity	Pain; Disability	Total Knee Arthroplasty	6 weeks, 3, 12 and 24 months	Poor
Namba et al, 2005	USA	1,813	Obesity	Complications	Total Hip and Knee Arthroplasty	1 year	Poor

Napier et al, 2014	United Kingdom	100	Obesity	Complications; Disability	Total Knee Arthroplasty	3 and 12 months	Poor
Naylor et al, 2008	Australia	99	Obesity	Pain	Total Hip and Knee Arthroplasty	2, 6, 12, 26 and 52 weeks	Good
Ollivier et al, 2012	France	210	Physical Activity	Disability	Total Hip Arthroplasty	10 years	Fair
Patel et al, 2008	United Kingdom	527	Obesity	Complications	Total Knee Replacement	4 weeks, 6 weeks and 1 year	Good
Pietschmann et al, 2013	Germany	171	Physical Activity	Disability	Unicompartimental Knee Arthroplasty	4.2 years	Poor
Poortinga et al, 2014	Netherlands	658	Physical Activity	Disability	Total Hip and Knee Arthroplasty	1 year	Good
Pulido et al, 2008	USA	9,245	Obesity	Complications	Total Hip and Knee Arthroplasty	1 year	Fair
Rajgopal et al, 2008	Canada	760	Obesity	Complications; Disability	Total Knee Arthroplasty	1 year	Fair
Sechriest et al, 2007	USA	34	Physical Activity	Disability	Total Hip Arthroplasty	5 years	Poor
Villalobos et al, 2013	Spain	63	Obesity	Pain; Disability	Total Hip Arthroplasty	3 months	Good
Vogl et al, 2014	Germany	281	Obesity	Disability	Total Hip Arthroplasty	6 months	Poor
Wang et al, 2010	USA	97	Obesity	Disability	Total Hip Arthroplasty	3 months, 1 and 2 years	Fair
Yasunaga et al, 2009	Japan	3,577	Obesity	Complications	Total Knee Arthroplasty	5 months	Fair
Zhang et al, 2012	China	714	Obesity	Complications; Disability	Total Hip Arthroplasty	5 years	Poor

The course of pain and disability over time

Figure 2 presents the course of disability over time for hip (A) and knee osteoarthritis (B) post-surgery; as well as pain for hip (C) and knee osteoarthritis (D). The central line represents the estimated pooled mean over time, and the shaded area circumscribes its 95% confidence intervals. A total of eight studies with complete data (i.e. estimates of central tendency and variance) were included in the pain analysis and 17 studies were included in the disability analysis.

The fractional polynomial regression model resulted in a pooled mean disability score and standard deviation before hip arthroplasty of 59.42 (SD: 10.94; n=5,250). At 12 months post-surgery it had decreased to a mean of 31.31 (SD: 24.28; n= 3,017) and a further reduction was observed at 120 months, when the mean disability score after hip arthroplasty was 24.32 (SD: 19.53; n= 210). For knee osteoarthritis, a pooled mean disability score of 56.88 (SD: 10.74; n= 17,225) was observed for patients undergoing arthroplasty. At 12 months after surgery this value decreased to 21.80 (SD: 13.51; n= 2,898), whilst at the 110-month follow-up, the mean disability score was 14.18 (SD: 0.77; n= 485). The pooled mean pain scores before hip arthroplasty was 54.86 (SD: 10.20; n= 2,517), decreasing to 13.76 (SD: 1.32; n= 1,058) 3 months after surgery, 10.8 (SD: 1.69; n= 1,212) at 6 months and slightly increasing to 13.45 (SD: 7.87; n= 2,173) at the 12 month follow-up. For patients undergoing knee arthroplasty, the pooled pain score at baseline was 57.78 (SD: 9.28; n= 2,211); which decreased to 25.67 (SD: 6.61; n= 1,222) at 6 months, and 14.18 (SD: 0.77; n= 1,820) at the 12-month follow-up (figure 2).

Figure 2 - Fractional polynomial analysis for hip (A) and knee (B) disability scores and hip (C) and knee (D) pain scores over time**.**

Association between obesity and post-surgical pain outcomes

Fourteen studies investigated the association between obesity and pain intensity in a total of 5,687 patients after hip or knee arthroplasty. Seven of the 14 studies presented enough data to be pooled in a meta-analysis. There was an overall moderate and statistically significant difference in post-surgical pain between obese and non-obese patients post arthroplasty, with non-obese patients having better outcomes at short (SMD -0.43; 95%CI: -

0.67 to -0.19; p<0.001), and long-term timepoints (SMD -0.36; 95%CI: -0.47 to -0.24; p<0.001). The pooled results for separate joints suggest non-obese participants have significantly less short-term (i.e. less than 6 months) post-surgical knee pain, compared to obese participants (SMD -0.54; 95%CI: -0.90 to -0.19; p=0.002) and post-surgical hip pain (SMD -0.34; 95%CI: -0.66 to -0.01; p=0.039). Obesity was defined as having a BMI over 30 kg/m^2. At long term (i.e. 6 months or longer), there was a significant moderate difference between obese and non-obese groups in terms of knee pain (SMD -0.36; 95%CI: -0.47 to -0.24; p<0.001), however there was no difference between groups for hip pain (SMD -0.32; 95%CI: -0.84 to 0.19; p=0.222)(figure 3). The results of individual studies not included in the pooled analyses are presented in table 2 below.

Figure 3 – Pooled standardised mean difference in pain at short and long term post-surgery between obese and non-obese patients.

Obesity vs Pain			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
		Knee	
Davis 2011	NA	HOOS / KOOS	After adjusting for age, gender, joint, and presence of back pain, an increased BMI was associated with worst pain outcomes (p<0.02) at long term after THA or TKA.
Jarvenpaa 2010	29.7 (NA)	VAS	Increased BMI correlates significantly to VAS pain scale (r=0.236; p=0.018) at short term after TKA.
Liljensøe 2013	30 (NA)	SF-36	BMI was **not** associated with SF-36 pain scale (OR= 0.96; p=0.1) at long term after TKA.
Mackie 2015	NA	WOMAC	Increased BMI was associated with less improvement in WOMAC pain scale (t= -2.64; p<0.001) at long term after TKA.
		Hip	
Dowsey 2010	29.55 (5.64)*	Harris Hip Score	BMI was **not** associated with pain reduction (p=0.71) at long term after THA.
Heiberg 2013	27 (6.27)*	HOOS	BMI was **not** associated with HOOS pain scale (p>0.05) at short term after THA.

Table 2 – Results of individual studies on the association between post-surgical pain and baseline obesity.

BMI – Body Mass Index; SD – Standard deviation; THA – Total hip arthroplasty; TKA – Total knee arthroplasty; OR – Odds ratio; NA – None available; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; HOOS - Hip dysfunction and Osteoarthritis Outcome Score; KOOS - Knee dysfunction and Osteoarthritis Outcome Score; VAS – Visual Analogue Scale; SF-36 – Short Form 36 Questionnaire; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between obesity and post-surgical disability outcomes

The impact of obesity on disability was investigated by 32 studies which compared post-surgery disability scores in 35,286 obese and non-obese participants. Of these, 19 studies presented complete data that was included in the pooled analysis. At short term, no statistically significant difference in overall disability between obese and non-obese participants was observed (SMD -0.15, 95% CI -0.41 to 0.10, p=0.231). Likewise, no statistically significant difference was observed between obese and non-obese participants for post-surgical knee or hip disability (SMD -0.41, 95% CI -0.99 to 0.16, p=0.159 and SMD -0.09, 95% CI -0.38 to 0.19, p=0.527, respectively).

At long term follow-up, however, there was an overall moderate and statistically significant difference in post-surgical disability between obese and non-obese patients regardless of the joint affected (SMD -0.32; 95%CI: -0.36 to -0.28; p<0.001). That difference was still statistically significant and of moderate magnitude when knee and hip joints were analysed separately (SMD -0.31, 95% CI -0.36 to -0.26, p<0.001 and SMD -0.34, 95% CI -0.44 to -0.25, p<0.001, respectively and favouring non-obese patients)(figure 4). The results of individual studies not included in the pooled analyses are presented in table 3 below.

Figure 4 – Pooled standardised mean difference in disability at short and long term post-surgery between obese and non-obese patients.

Obesity vs Disability			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
		Knee	
Davis 2011	NA	WOMAC / KOOS	After adjusting for age, gender, joint, and presence of back pain, an increased BMI was associated with worst outcomes (p<0.02) at

			long term after TKA or THA.
Dewan 2009	31 (0.5)	Knee Society Score	BMI was **not** associated with worst knee function (p>0.119) at long term after TKA.
Hamoui 2006	27.93 (7.1)*	Knee Society Score	**No** significant association between BMI and KSS (p>0.05) were found at long term after TKA.
Kort 2007	NA	WOMAC	Obesity was **not** related to disability score (p>0.05) at long term after TKA.
Liljensøe 2013	30 (NA)	Knee Society Score	Increased BMI was associated with worst knee scores (OR 0.95, 95% CI 0.9 to 1.0, p=0.04) at long term after TKA. These results did not change significantly after adjusting for age, sex, primary disease and surgical approach (OR 0.94, 95% CI 0.90 to 0.99, p=0.02).
Mackie 2015	NA	WOMAC	Increased BMI was associated with less improvement in disability scores (WOMAC t= -2.13; p=0.033) at long term after TKA.
Rajgopal 2008	32.3 (6.58)*	WOMAC	The morbidly obese group (BMI ≥40, n=69) does **not** present a statistically significant difference in improvement in WOMAC score (p=0.669) when compared to others BMI groups at long term after TKA.
		Hip	
Heiberg 2013	27 (6.27)*	HHS	Increased BMI was associated with lower HHS (p<0.05) at short term after THA.
Jameson 2014	NA	OHS	Increased BMI was **not** associated with changes in OHS (p>0.05) at short term after THA.
Luebbeke 2007 B	26.4 (4.3)	HHS	Increased BMI was associated with lower hip score (r=-0.4, 95% CI -0.8 to -0.1) at long term after THA.
McLaughlin 2006	26 (NA)	HHS	The obese group (BMI ≥30; n=95) did **not** present any statistically significant difference from the non-obese group (BMI <30, n=103) with regards to clinical outcomes assessed by HHS (p>0.05) at long term after THA.
Vogl 2014	26.9 (4.9)	WOMAC	Obesity was associated with changes in WOMAC score (p<0.05) at short term after THA.
Wang 2010	29.14 (6.23)	WOMAC	Increased BMI was **not** associated with WOMAC score (p=0.114) at long term after THA.

Table 3 – Results of individual studies on the association between post-surgical disability and baseline obesity.

BMI – Body Mass Index; SD – Standard deviation; NA – None available; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; KOOS - Knee disability and Osteoarthritis Outcome Score; TKA – Total knee arthroplasty; THA – Total hip arthroplasty; KSS – Knee Society Score; OR – Odds ratio; CI

– Confidence interval; HHS – Harris Hip Score; OHS – Oxford Hip Score; r – coefficient of association; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between obesity and post-surgical complications

The association between obesity and complications after joint arthroplasty was assessed by 40 studies including a total of 245,433 patients who underwent knee or hip arthroplasty. Of these, 17 presented enough data and were included in the meta-analyses.

The pooled results suggest that at short term follow-up, non-obese participants are less likely to have post-surgical deep vein thrombosis (DVT) (OR 0.48; 95% CI 0.25 to 0.91; p=0.024) when compared with obese participants (figure 5). A total of 13 studies were pooled (n=22,782) showing non-obese patients are also less likely to present any long-term (i.e. ≥ 6 months) dislocation (OR: 0.49; 95% CI: 0.31 to 0.79; p=0.003) and DVT (OR: 0.61; 95% CI: 0.37 to 0.98; p=0.043). Non-significant difference between groups was observed between non-obese and obese participants for long-term revision surgery (OR: 0.66; 95% CI: 0.34 to 1.27; p=0.217).

The pooled analysis on short-term post-surgical infection for hip replacement showed that non-obese patients are less likely to develop infections compared to obese participants (OR 0.33; 95% CI 0.18 to 0.59; p<0.001)(Figure 6). For knee replacement separate analyses were conducted for studies comparing obese to non-obese participants and those comparing morbidly obese to non-obese participants (Figure 7). The results suggest that non-obese patients are less likely to develop infections when compared to morbidly obese patients (OR 0.42; 95% CI 0.23 to 0.78; p= 0.006). No association with post-surtical infection was observed when obese and non-obese participants were compared.

The overall pooled analysis for incidence of complications suggests that non-obese participants are less likely to present any post-surgical complication at the short or long term follow-ups (OR: 0.48; 95% CI: 0.25 to 0.91; p<0.001 and OR: 0.55; 95% CI: 0.41 to 0.74; p<0.001, respectively). The results of individual studies not included in the pooled analyses are presented in the table 4 below.

Figure 5 - Pooled association between complications and obesity at short term and long term follow-ups.

Figure 6 – Pooled association between post-surgical infections and obesity for hip surgery.

Figure 7 – Pooled association of post-surgical infections for knee surgery.*

Obesity vs Complications			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Ollivier 2012	25.13 (3.14)*	HHS / HOOS	At long term, high impact sports was associated with better HHS (p<0.001) after THA.
Pietschmann 2013	28.4 (4.62)*	OKS	At long term, physical activities were **not** related to complications (p<0.01). Physically active patients had less pain and better OKS scores after UKA.
Poortinga 2014	28.7 (4.9)	WOMAC	At long term, physical activity was **not** associated with WOMAC score (p>0.05) after THA or TKA.
Sechriest 2007	28.1 (8.3)	UCLA	At long term increased BMI was **not** correlated to UCLA physical activity score (R=-0.07; p=0.67) after TKA.

Table 4: Results of individual studies investigating the association between obesity and post-surgical complications.

BMI – Body Mass Index; SD – Standard deviation; HHS – Harris Hip Score; HOOS - Hip disability and Osteoarthritis Outcome Score; THA – Total hip arthroplasty; OKS – Oxford Knee Score; UKA - Unicompartimental knee arthroplasty; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; TKA – Total knee arthroplasty; UCLA - University of California, Los Angeles activity questionnaire; R – Correlation coefficient; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between physical activity participation and disability

The association between physical activity and disability was investigated by four studies (73, 75, 76, 79) or 1,033 participants undergoing hip or knee arthroplasty. Included studies have not provided enough data to be pooled. The overall results from these 4 papers suggest that participants who practice more physical activity before the surgeries were more likely to experience less pain after either hip or knee surgery, however the evidence regarding disability scores is still unclear with studies presenting contradictory results. Table 5 below presents the results of the individual studies.

Physical Activity vs Disability			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Ollivier 2012	25.13 (3.14)*	HHS / HOOS	At long term, high impact sports were associated with better HHS ($p<0.001$) and HOOS ($p<0.05$) after THA.
Pietschmann 2013	28.4 (4.62)*	OKS / KSS / WOMAC	At long term, physical activities were **not** related to complications. Physically active patients had less pain and better OKS, KSS and WOMAC scores ($p<0.05$) after UKA.
Poortinga 2014	28.7 (4.9)	WOMAC	At long term, physical activity was **not** associated with WOMAC score ($p>0.05$) after THA or TKA.
Sechriest 2007	28.1 (8.3)	UCLA	At long term increased BMI was **not** correlated to UCLA physical activity score ($R=-0.07$; $p=0.67$) after TKA.

Table 5 – Individual results on the association between physical activity and pain or disability.

BMI – Body Mass Index; SD – Standard deviation; HHS – Harris Hip Score; HOOS - Hip disability and Osteoarthritis Outcome Score; THA – Total hip arthroplasty; OKS – Oxford Knee Score; KSS – Knee Society Score; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; UKA - Unicompartimental knee arthroplasty; TKA – Total knee arthroplasty; UCLA - University of California, Los Angeles activity questionnaire; R – Correlation coefficient; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Discussion

Statement of principal findings

Our results suggest that following surgery, non-obese patients experience further reductions in both pain and disability post knee and hip arthroplasty when compared to obese patients, where obesity has been defined as having a BMI of 30 kg/m^2 or over. These differences seemed to be more accentuated for knee pain outcomes following arthroplasty, than for hip pain or disability outcomes. Non-obese participants also experienced significantly less post-surgical complications, including dislocation, DVT and infection especially following hip arthroplasty. Our analyses also demonstrate that obesity is a reliable predictor of complications after total hip arthroplasty and total knee arthroplasty, not only in the short term after the procedure but also at longer follow-ups. The evidence regarding pre-operative physical activity remains unclear due to conflicting results of included studies, especially in terms of post-operative disability. The four included cohort studies however, suggest that physical activity participation is associated with better pain outcomes following surgery.

Our results from the fractional polynomial analysis have also shown that all patients experienced an improvement in pain and disability post-surgery. The observed decrease in pain from baseline was approximately 70% at 6 months and 75% at 12 months, with decreases in disability of 55% at 12 months and 67% at 120 months. The interpretation of the postsurgical course of pain and disability, however, needs to be taken in the context of the inclusion criteria we have used in our review, given we have only included data from cohort studies that have assessed the role of obesity or physical activity participation on surgical outcomes.

Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

Our meta-analysis results regarding the association between obesity and post-surgical complications found that obese patients present higher complication rates than non-obese patients. These results are consistent with the findings of previous systematic reviews of Hofstede,(14) Samson(15) and Liu.(16) Our meta-analysis results regarding the association between obesity and post-surgery disability also agreed with the findings of Buirs et al(13) and Samson et al(15) which found that obesity (defined as having BMI over 30 kg/m^2), was associated with worst postsurgical functional score. The only previous review which has performed a meta-analysis on the association between obesity and post arthroplasty pain or disability limited its inclusion criteria to hip joint.(16) That review included a total of 15 studies in their meta-analysis and found that obesity increases the risk of post-surgical complications (RR: 1.68, 95% CI 1.23 to 2.30, P = 0.0004) and is associated with worse disability scores following surgery (MD: -2.75, 95% CI -4.77 to -0.6; P = 0.07). Our study has included 33 cohorts of hip arthroplasty participants in the qualitative analysis, 16 in the meta-analyses, and confirms past findings that obesity is associated with worse outcomes in terms of not only disability and complications, but also pain at both short and long term periods following surgery. Hofstede et al(14) have also conducted a systematic review of the literature on pre-operative predictors of surgical outcomes after hip replacement in patients with osteoarthritis. Although those authors included 35 studies, only 5 studies investigated the effect of obesity on post-surgical pain, disability and quality of life.(14) No meta-analysis was performed.

Implications for clinicians or policy makers

Our results have a direct impact on clinical practice as the results demonstrate that obese patients have a higher risk of complications and a poorer prognosis in terms of pain and disability post-operatively when compared with non-obese patients. These results also allude to the importance of identifying and implementing effective pre-surgical rehabilitation and weight loss approaches to optimise post-surgical outcomes and minimise harm to the patient. The importance of weight loss has been highlighted in international clinical guidelines on non-surgical management of knee osteoarthritis for instance, given the pain and disability reductions observed following weight loss regimes.(86) Past research also suggests there is a dose-response relationship between weight loss and clinical outcome improvement. A recent completer-type analysis of 1,383 participants with knee osteoarthritis showed that a weight loss of 7.7% of body weight or more is associated with clinically important changes in pain and disability, as measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS).(87) This evidence reinforces the importance of pre-surgical weight loss programs and strategies in order to optimize post-surgical recovery.

Strengths and weaknesses of the study

The current review has included 62 cohort studies and a total of 256,481 participants and is the most comprehensive systematic review on the topic to date. It is also the first review to use a quantitative approach to synthesize the results of pain, disability and surgical complications between non-obese and obese participants and consider the physical activity level of participants who underwent to hip or knee arthroplasty due to osteoarthritis.Our review has some limitations. The methodological quality of the included studies was in general poor. The most common methodological flaw among included cohorts was not controlling for confounding factors age, sex or BMI (32 studies, 51%) followed by not using a representative sample (n=30 studies, 48%). Moreover, we have observed great variability of follow-up duration across studies, ranging from 2 weeks to 11 years. We have used a cut-off of 6 months to define short (i.e. < 6 months) or long-term (i.e. ≥ 6 months) follow-ups, but acknowledge that within each follow-up category there was substantial variation in the duration of follow-up across studies.

Between-study heterogeneity has also been observed in some of the pooled analysis for obesity presented in this review. A potential source of between-study heterogeneity include the variability in the definition of obesity categories across studies. Although obesity was assessed using BMI scores in all studies some studies have used only two obesity groups (i.e. obese or non-obese) while others used several categories including underweight, normal or overweight, obese and morbidly obese. These needed to be combined for some of our pooled analyses.

Another potential source of between-study heterogeneity across is the difference in surgical procedures used across studies. For instance, in the pooled analysis of risk of post-surgical DVT and obesity, whislt Kandil et al (54) performed unicompartimental knee arthroplasties, Friedman et al (42)performed total arthroplasties on both hip and knee joints. That discrepancy might explain the different results reported by these two studies (figure 5). Likewise, the mean physical activity load reported by the included studies varied substantially, ranging from low to high frequency of participation in low and high impact activities. This should be taken into consideration when interpreting the physical activity results.

Conclusion

Our results have shown that obese patients undergoing hip or knee arthroplasty due to osteoarthritis have worse outcomes in terms of pain and complications when compared to non-obese patients, with differences more accentuated for patients with knee osteoarthritis. Likewise, obese patients will have worse surgical outcomes in terms of disability, but only at long-term follow-ups. It is still unclear whether pre-surgical physical activity participation has an impact on surgical outcomes. However, we acknowledge that the health benefits of physical activity participation for patients with knee and hip osteoarthritis are multiple and reach beyond those considered in this review.

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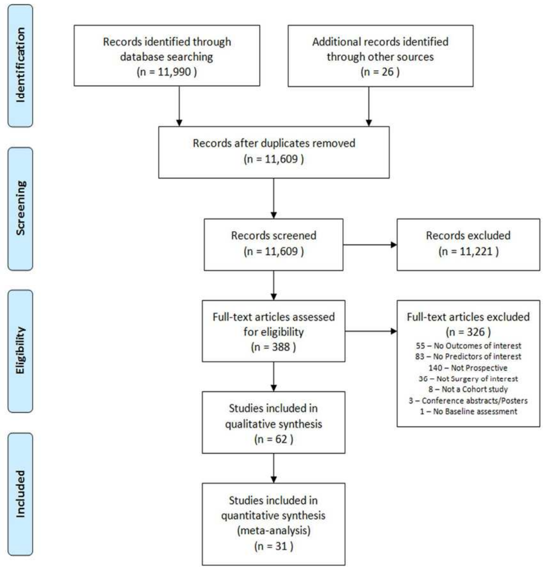

Figure 1. Flowchart of search strategy and screening steps.

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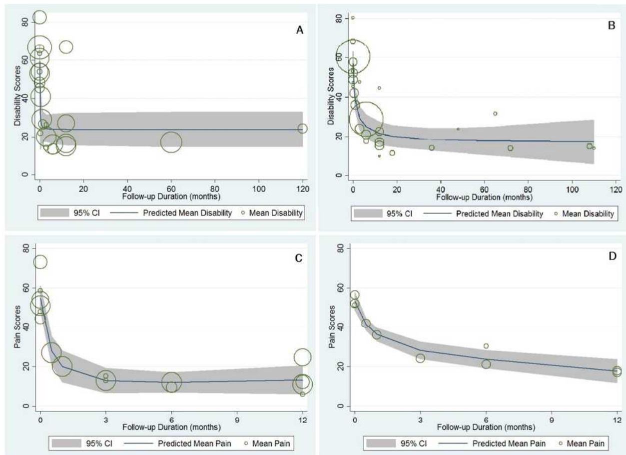

Figure 2 - Fractional polynomial analysis for hip (A) and knee (B) disability scores and hip (C) and knee (D) pain scores over time.

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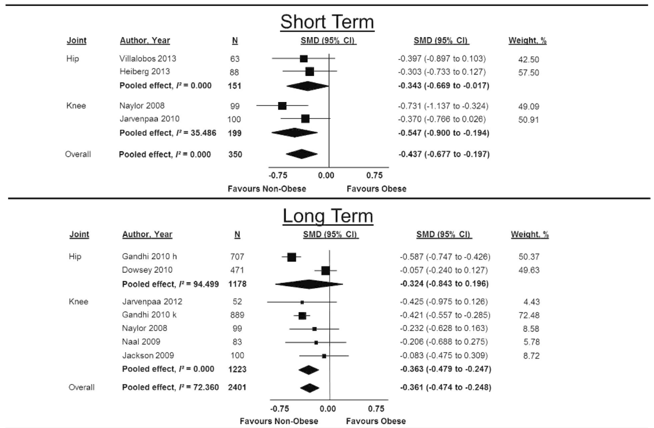

Figure 3 – Pooled standardised mean difference in pain at short and long term post-surgery between obese and non-obese patients.

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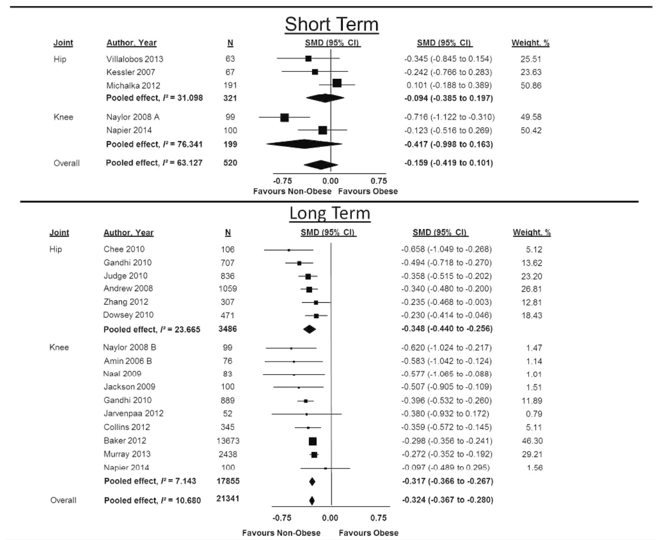

Figure 4 – Pooled standardised mean difference in disability at short and long term post-surgery between obese and non-obese patients.

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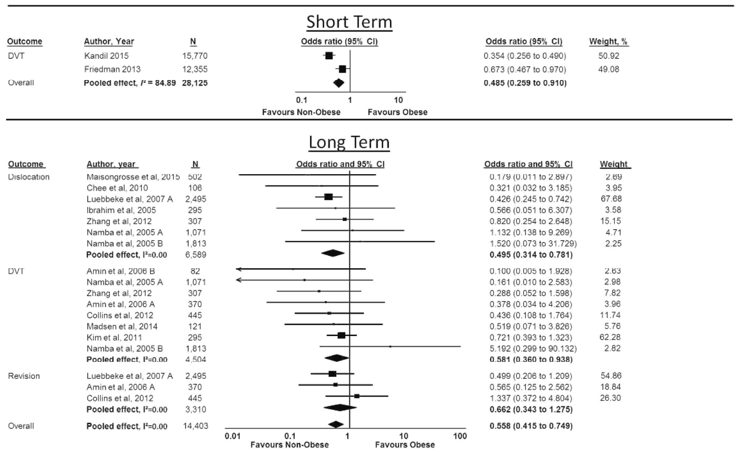

Figure 5 – Pooled association between complications and obesity at short term and long term follow-ups.

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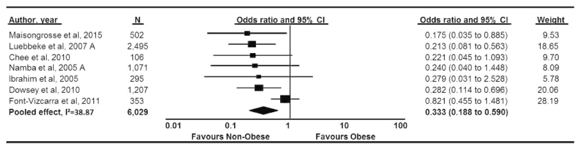

Figure 6 – Pooled association between post-surgical infections and obesity for hip surgery.

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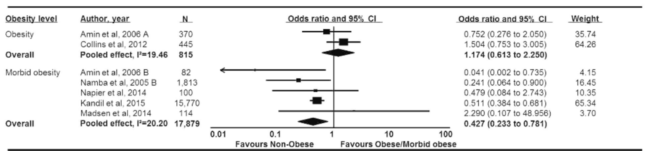

Figure 7 – Pooled association of post-surgical infections for knee surgery.*

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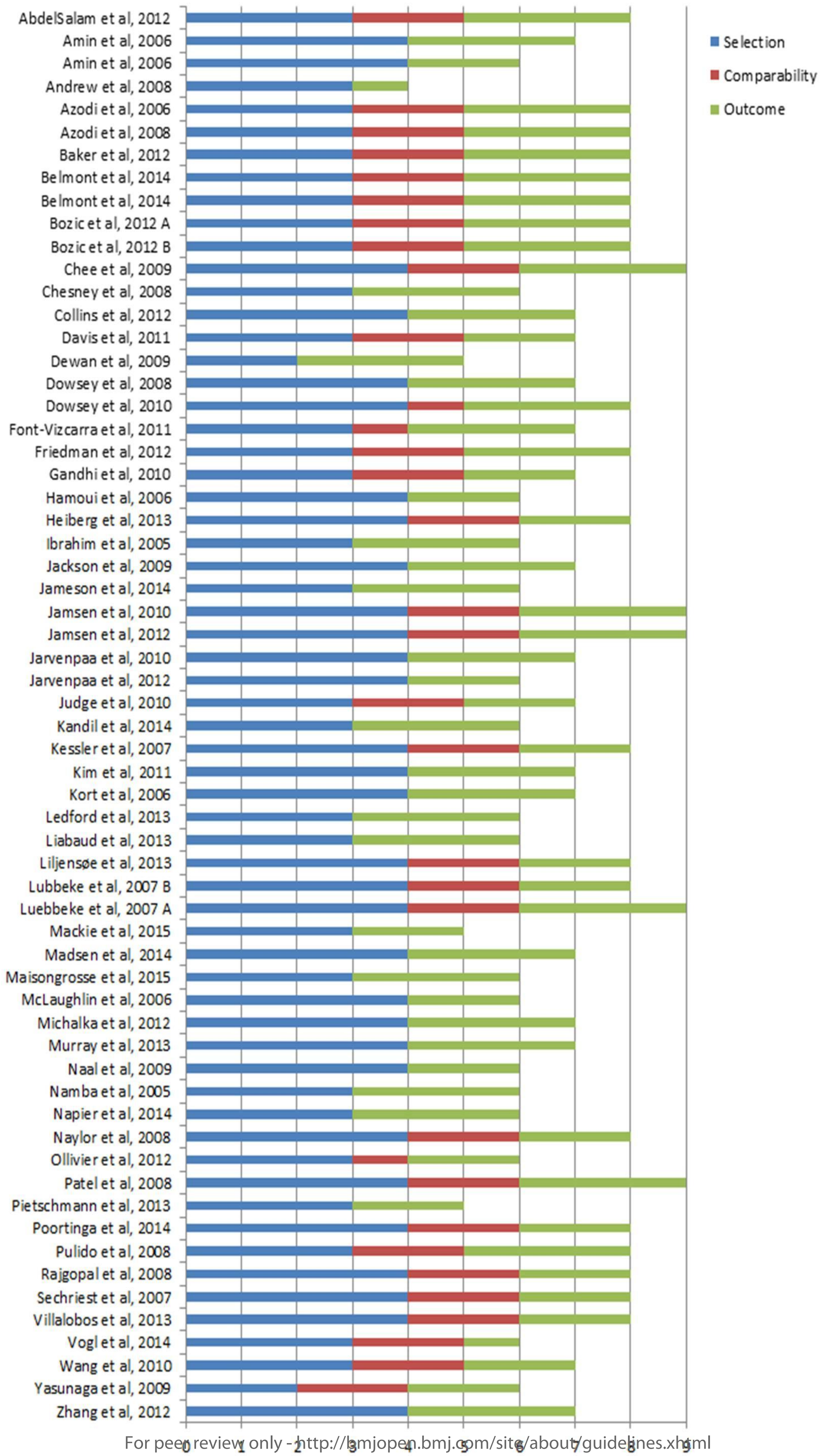
APPENDIX 1

MEDLINE search strategy terms used:

1	obesity.mp. or exp Obesity/ or exp Obesity, Abdominal/	197.941
2	Physical Activity.mp. or exp Motor Activity/	231.947
3	sedentar$.mp.	19.058
4	(time adj5 sitting).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	688
5	**1 or 2 or 3 or 4**	**414.967**
6	exp Postoperative Complications/ or exp Hip Prosthesis/ or exp Arthroplasty, Replacement, Hip/ or hip arthroplasty.mp. or exp Osteoarthritis, Hip/ or exp Hip Joint/	469.282
7	knee arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/	17.365
8	exp Elective Surgical Procedures/ or elective surgery.mp.	14.058
9	osteoarthritis.mp. or exp Osteoarthritis, Hip/ or exp Osteoarthritis/ or exp Osteoarthritis, Knee/	55.493
10	exp Osteonecrosis/ or Osteonecrosis.mp.	13.961
11	arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty, Replacement/ or exp Arthroplasty/ or exp Arthroplasty, Replacement, Hip/	53.979
12	**6 or 7 or 8 or 9 or 10 or 11**	**546.616**
13	exp Cohort Studies/ or cohort.mp.	1.526.984
14	incidence.mp. or exp Incidence/	587.274
15	exp Follow-Up Studies/ or follow-up.mp.	912.064
16	prognosis.mp. or exp Prognosis/	1.273.869
17	exp Prognosis/ or predictors.mp.	1.258.014
18	exp Time Factors/ or course.mp.	1.403.404
19	exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ or survival.mp.	843.771
20	logistic.mp.	198.801
21	cox.mp.	84.820
22	life table.mp. or exp Life Tables/	18.098
23	log rank.mp. or exp Follow-Up Studies/	533.280
24	**13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23**	**4.460.132**
25	Animals/	5.495.334
26	exp Editorial/ or editorial.mp.	376.114
27	case report.mp. or exp Case Reports/	1.754.352
28	letter.mp. or exp Letter/	895.420
29	25 or 26 or 27 or 28	8.184.015
30	**5 and 12 and 24**	**7.601**
31	**30 not 29**	**6.869**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Belmont et al, 2014
Bozic et al, 2012 A
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Chee et al, 2009
Chesney et al, 2008
Collins et al, 2012
Davis et al, 2011
Dewan et al, 2009
Dowsey et al, 2008
Dowsey et al, 2010
Font-Vizcarra et al, 2011
Friedman et al, 2012
Gandhi et al, 2010
Hamoui et al, 2006
Heiberg et al, 2013
Ibrahim et al, 2005
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Kessler et al, 2007
Kim et al, 2011
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Ledford et al, 2013
Liabaud et al, 2013
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Mackie et al, 2015
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Ollivier et al, 2012
Patel et al, 2008
Pietschmann et al, 2013
Poortinga et al, 2014
Pulido et al, 2008
Rajgopal et al, 2008
Sechriest et al, 2007
Villalobos et al, 2013
Vogl et al, 2014
Wang et al, 2010
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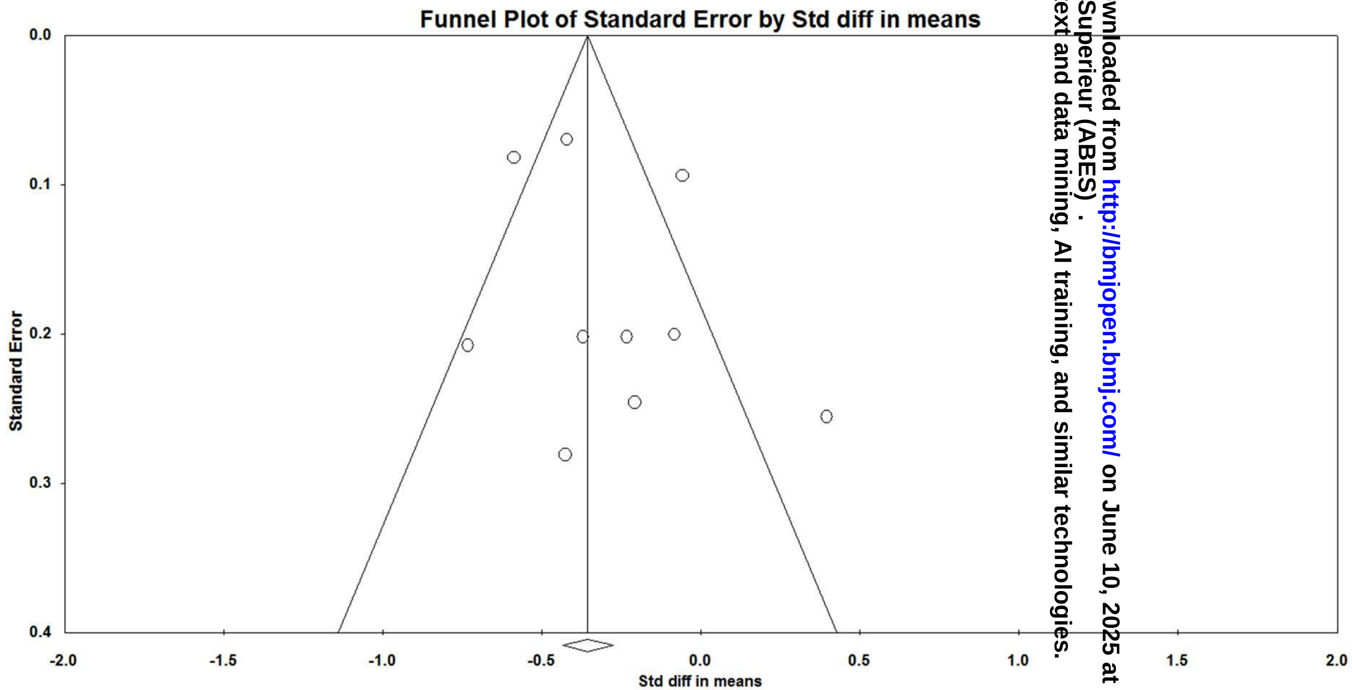
Funnel Plot of Standard Error by Std diff in means
Standard Error
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0.2
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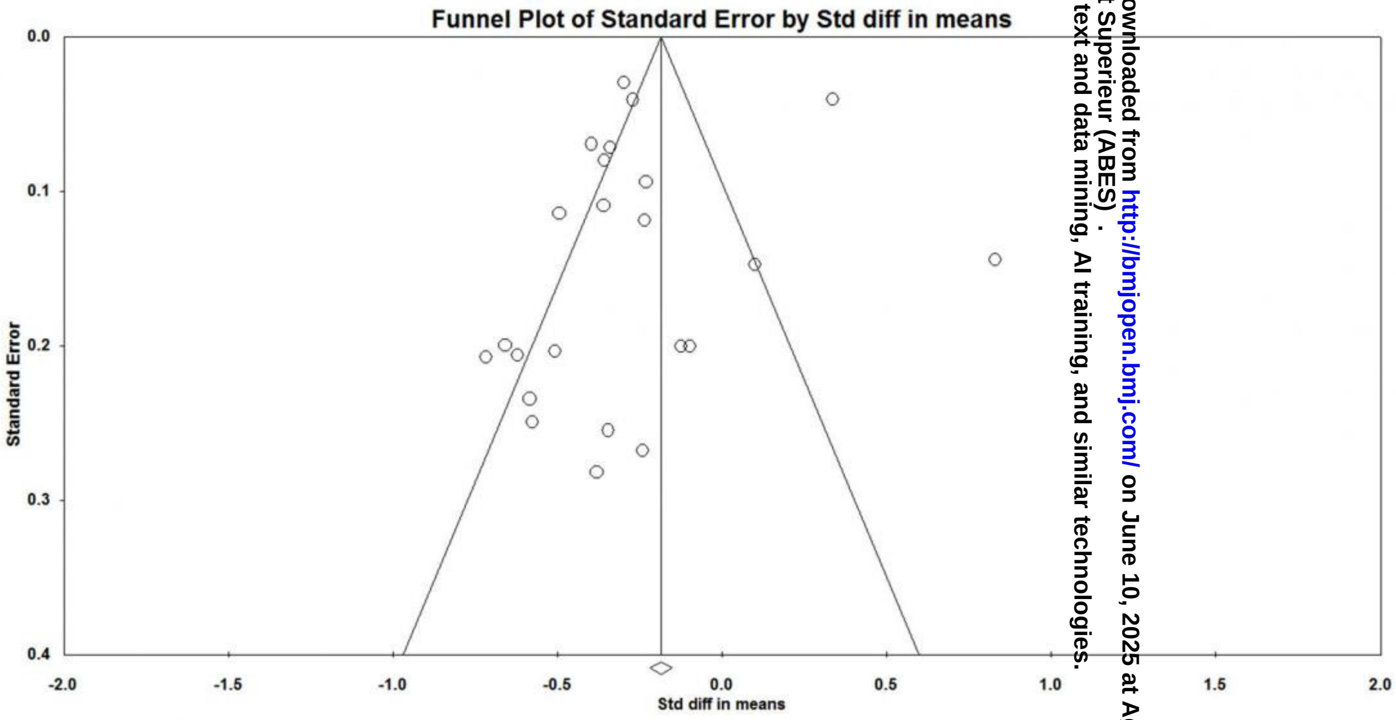
1.5
2.0
Std diff in means


Funnel Plot of Standard Error by Std diff in means
Standard Error
0.0
0.1
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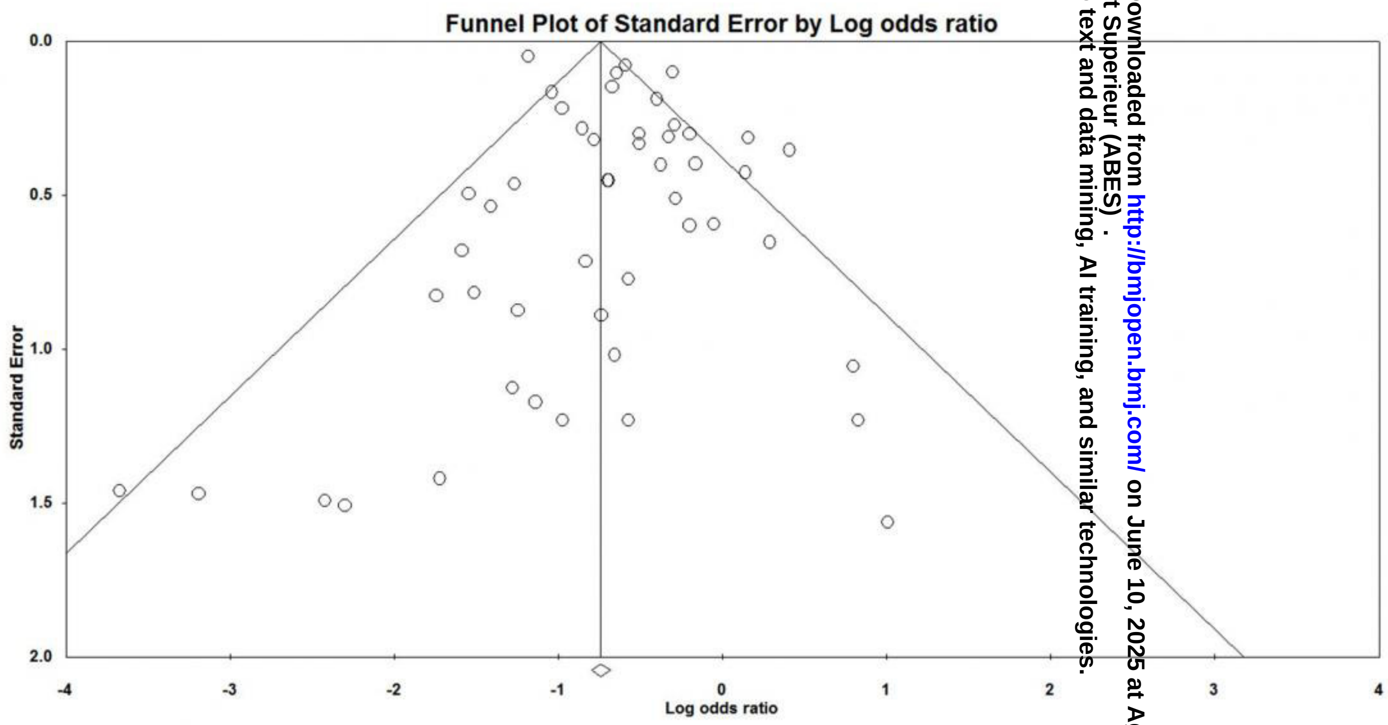
Std diff in means


Funnel Plot of Standard Error by Log odds ratio
Standard Error
0.0
0.5
1.0
1.5
2.0
-4
-3
-2
-1
0
1
2
3
4
Log odds ratio

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? – A meta-analysis of cohort studies.

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Can obesity and physical activity predict outcomes of elective knee or hip surgery due to osteoarthritis? – A meta-analysis of cohort studies.

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Word count: 3,799.

Abstract

Objective: The aim of this study was to systematically review the literature to identify whether obesity or the regular practice of physical activity are predictors of clinical outcomes in patients undergoing elective hip and knee arthroplasty due to osteoarthritis.

Design: Systematic review and meta-analysis.

Data Source and eligibility criteria: A systematic search was performed on the Medline, CINAHL, EMBASE, and Web of Science electronic databases. Longitudinal cohort studies were included in the review. To be included, studies needed to have assessed the association between obesity or physical activity participation at baseline and clinical outcomes (i.e. pain, disability, and adverse events) following hip or knee arthroplasty.

Data extraction: Two independent reviewers extracted data on pain, disability, quality of life, obesity, physical activity and any post-surgical complications.

Results: 63 full papers were included in this systematic review. From these, 31 were included in the meta-analyses. Our meta-analysis showed that non-obese participants tended to suffer less pain at both short (SMD -0.43; 95%CI: -0.67 to -0.19; $p<0.001$) and long term (SMD -0.36; 95%CI: -0.47 to -0.24; $p<0.001$), less disability at long term (SMD -0.32; 95%CI: -0.36 to -0.28; $p<0.001$) and report fewer post-surgical complications at short (OR: 0.48; 95% CI: 0.25 to 0.91; $p<0.001$) and long term (OR: 0.55; 95% CI: 0.41 to 0.74; $p<0.001$) and less post-surgical infections after hip arthroplasty (OR: 0.33; 95% CI: 0.18 to 0.59; $p<0.001$), and particularly when compared to morbidly obese participants after knee arthroplasty (OR: 0.42; 95% CI: 0.23 to 0.78; $p=0.006$).

Conclusions: Pre-surgical obesity is associated with worse clinical outcomes of hip or knee arthroplasty in terms of pain, disability, and complications in patients with osteoarthritis. No impact of physical activity participation has been observed.

Systematic review registration: PROSPERO registration CRD42016032711.

Keywords: Physical activity, obesity, arthroplasty, osteoarthritis, knee, hip, meta-analysis.

Strengths and limitations of this study

- The current review is the most comprehensive systematic review on the topic to date.

- The current review is the first review to use a quantitative approach to synthesize the results of pain, disability and surgical complications between non-obese and obese participants who underwent hip or knee arthroplasty due to osteoarthritis.

- The methodological quality of the included studies was in general poor.

- There was a substantial variability of follow-up duration across studies, ranging from 2 weeks to 11 years.

Introduction

Musculoskeletal pain, including pain from knee and hip osteoarthritis, is the leading cause of physical disability in the world and responsible for an increasing burden to patients and society.[1] This problem will increase over time, as the world population ages and physical disability resulting from declining health becomes increasingly prevalent.[2] The global health care expenditure for knee and hip osteoarthritis is substantial, and most of these costs are incurred by surgical management and associated hospital care.[3] For instance, in the UK the direct costs of osteoarthritis were estimated at more than £1 billion in 2010, of which £850 million was spent just on surgical procedures.[4]

Although management of the early stages of this condition consists of a combination of nonpharmacological and pharmacological therapies (e.g. anti-inflammatory and analgesic drugs), surgery has become the most common treatment option for severe cases, especially when nonsurgical therapies fail to provide sufficient pain relief.[5] Osteotomy, mosaicplasty, and arthroplasty are some of the existing types of surgery used to manage osteoarthritis of the hip and knee; with total or partial arthroplasty being the most commonly recommended.[6]

There are multiple risk factors for the development of knee OA. Among the most common of these are increased body weight and muscle weakness; often attributed to a sedentary lifestyle.[7] Obesity and sedentary lifestyle behaviour have also been associated with serious health conditions such as: coronary heart disease, type 2 diabetes, breast and colon cancers, and decreased life expectancy.[8] Although there is evidence for the role of obesity and physical inactivity in health conditions and quality of life in general,[9, 10] the actual impact of these factors, together or in isolation, on the outcomes of elective surgery of the knee and hip is still controversial.[11, 12] Although previous attempts to systematically review the literature have been made, these studies[13-15] have either failed to perform a quantitative summary of the evidence (i.e. meta-analysis), have excluded patients undergoing knee arthroplasty,[16] or have excluded pain outcomes.[13] No meta-analyses have been performed considering obesity and physical activity as predictors of surgical outcomes in terms of pain, disability, quality of life and complications after hip or knee arthroplasty for end stage osteoarthritis.

Identifying whether obesity and physical activity participation predict surgical outcomes in patients with knee and hip osteoarthritis will inform clinical practice in terms of prognosis and safety of an increasingly prevalent treatment approach. We have conducted a meta-analysis of cohort studies aiming to quantify the role of obesity and physical activity participation as predictors of clinical outcomes in terms of pain, disability, quality of life, and post-surgical complications. This review and meta-analysis focused on patients with knee and hip osteoarthritis undergoing hip or knee arthroplasty.

Methods

Data sources and searches

We conducted a systematic review following the PRISMA statement.[17] This review was prospectively registered on PROSPERO, registration number CRD42016032711. A systematic electronic search was performed in the following databases from inception to January 2017: MEDLINE, EMBASE, CINAHL, and Web of Science. We used a combination of relevant keywords to construct the search strategy including obesity, physical activity, knee osteoarthritis, hip osteoarthritis, arthroplasty, and elective surgery (appendix 1). The first screening of potentially relevant records was conducted by one author (DP) based on titles and abstract, and two authors (DP and GM) independently performed the final selection of included trials based on full-text evaluation. A third reviewer arbitrated in case of disagreement (MF). Moreover, the reference lists of included studies were checked for potential studies. An additional 26 references were screened, but none met our inclusion criteria. No restriction was applied on language.

Study selection

We included only longitudinal studies assessing the role of obesity or physical activity participation on the clinical outcomes following partial or total hip arthroplasty (THA) or partial or total knee arthroplasty (TKA) surgery. Clinical outcomes were defined in terms of pain, disability, quality of life, and complications post arthroplasty. To be eligible, studies had to be full reports; include participants who underwent elective arthroplasty of the hip or knee due to osteoarthritis; include data of pre-surgical and at least one post-surgical assessment of the clinical outcomes of interest; and assess the association between the predictors and outcomes of interest. Obesity and physical activity participation had to be

assessed at baseline. Studies on revision surgery were excluded. Studies were not excluded based on intensity or duration of symptoms.

Data extraction

Using a standardised form, data on study characteristics, predictors and outcome measures of interest were independently extracted from the included studies by two reviewers (DP and GM). A third author (MF) resolved any disagreement. Estimates of association between predictors and outcomes of interest were extracted as presented in each study and included odds ratios, risk ratios, correlations, mean differences or regression coefficients. When studies reported more than one tool regarding the same topic (e.g. WOMAC, HOOS, OHS, KOOS, KSS), estimates were extracted from the group with the largest sample size.

We contacted the authors to provide further information when there were insufficient data reported in the manuscript. When authors were unavailable we estimated data using the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions.[18]

Outcome measures

Data on pain intensity was extracted as visual analogue scale (VAS) scores ranging from 0 to 10 and measured directly or as part of the following measurement tools: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Hip disability and Osteoarthritis Outcome Score (HOOS), the Knee disability and Osteoarthritis Outcome Score (KOOS) or the Harris Hip Score (HHS). If studies reported more than one measure of pain intensity or disability for the cohort, the most severe measure at baseline was included in the pooled analyses. Disability measures included the Oxford Hip Score (OHS), ranging from 12 to 60 being 12 the best result; Oxford Knee Score (OKS) ranging from 0 to 60 being 60 the best result; the Harris Hip Score (HHS) ranging from 0 to 100 being 100 the best result; Knee Society Score (KSS) ranging from 0 to 100 being 100 the best result; WOMAC total score ranging from 0 to 96 being 0 the best result; or WOMAC function subscale, ranging from 0 to 10 being 10 the best result; and were converted into a uniform 0-100 scale where 0 meant less disability. Extracted data on complications included any descriptive measure of the number of complications or number of patients with a complication reported during the study. Only two of the screened studies had reported specific raw data on quality of life among the participants after joint arthroplasty, but due to differences in follow-up length, any meta-analysis made by merging this data would result in an unreliable measure.

Methodological Quality Assessment

The methodological quality of included studies was assessed by two independent reviewers using the Newcastle-Ottawa Scale (NOS)[19] recommended by the Cochrane Collaboration.[18] The NOS consists of eight items grouped into 3 categories, namely: selection, comparability, and outcome. A star system, ranging from zero to nine stars, is used to classify the quality of the study being reviewed (the more stars the study receives in each category, the higher its methodological quality). After the independent assessment of included studies by the leading author, each study received the following categorical score representing its quality: good (3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain), fair (2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome domain) or poor (0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 star in outcome domain). A third reviewer (MF) resolved any disagreement between independent assessors.

Data analysis

Data on baseline (i.e. pre-surgical scores) and postoperative outcome scores were weighed by the inverse study variance and used in fractional polynomial regression modelling to build graphs depicting the course of pain and disability over time. STATA14 was used for the analyses (Stata Corp LP, College Station, TX).[20]

Meta-analyses were performed to assess the differences in pain, disability and complications post-surgery, between predictor groups (i.e. obese and non-obese groups as defined by included studies), using a random effects model. When possible, different analyses were performed for knee and hip arthroplasty and also for different levels of obesity (i.e. obesity and morbid obesity). When means and standard deviations of outcomes of interest were presented for multiple predictor groups in the same study (i.e. underweight (BMI<18), normal weight (BMI≥18<25), overweight (BMI≥25<30), and obese levels I (BMI≥30<35), II (BMI≥35<40) or III (BMI≥40)) these were combined into two groups (non-obese: BMI<30 and obese: BMI≥30) as recommended in the Cochrane Handbook for Systematic Reviews of Interventions[18] before inclusion in the pooled analyses. Results were reported as standardised mean differences (SMD) and 95% confidence intervals (95%CI). Between-study heterogeneity was calculated using I^2 (I^2 <25%: small heterogeneity; 25% <I^2< 75%: moderate heterogeneity; I^2> 75%: large heterogeneity).[21] We have defined a standardised mean difference (SMD) of 0.2 as small difference, 0.5 as moderate difference and 0.8 as large difference.[22]

Assessment of publication bias was performed using funnel plots. The precision (i.e. standard error) of included studies was plotted against the difference in outcomes between groups (i.e. obese or non-obese) and results visually analysed. In the absence of publications bias or small study bias, smaller studies should be evenly spread around the base of the funnel, whilst the larger studies should be concentrated around the top of the funnel. Plot asymmetry was also quantified using the Egger's tests, for which a null hypothesis represents symmetry of plotted data.[23]

All meta-analyses were conducted using Comprehensive Meta-Analysis software (Comprehensive Meta-Analysis, Englewood, NJ). For studies not reporting enough data to be included in the meta-analyses, the reported individual associations were tabulated and qualitatively presented on tables 2, 3, 4 and 5.

Results

Our search strategy identified 11,990 studies. After removing 381 duplicates, 11,220 studies were screened and excluded based on keywords, titles, and abstracts. All the remaining 389 studies were written in English and were assessed by reading the full text, of which 327 were then excluded, yielding 62 studies to be included in the systematic review.[24-85] From these, 31 presented enough data to be included in at least one of the meta-analyses (Figure 1).

Figure 1 – Flowchart of search strategy and screening steps.

Included Studies

Included studies reported data from 18 different countries: Australia,[40, 47, 72, 85] Canada,[38, 43, 78] China,[84] Denmark,[60] England,[27, 30] Finland,[49-52], France,[65, 73] Germany,[55, 75, 81] Italy,[28, 29] Japan,[83] Netherlands,[57, 76] Norway,[45] Scotland [25, 36], South Korea,[56] Spain,[41, 80] Switzerland,[61, 62, 69] United Kingdom[26, 35, 37, 46, 48, 53, 63, 67, 68, 71, 74] and USA.[24, 31-34, 39, 42, 44, 54, 58, 59, 64, 66, 70, 77, 79, 82] Demographic data from each study are presented in table 1.

Methodological Quality

An overall quality assessment of the studies showed that 50% (n=31) of the included studies were considered as being of good methodological quality, whilst 1.5% (n=1) were considered fair and 48.5% (n=30) were considered of poor methodological quality. Of the screened studies, 56 (90%) had a follow-up rate of 80% or greater, and only half (n= 32 studies) assessed outcomes via retrospective analysis of medical records, conducted adjustment for potential confounders (e.g. age or sex) or investigated a representative sample of the population (Appendix 2).

Assessment of Publication Bias

Inspection of funnel plots and results of Egger's test confirmed no evidence of small study bias for those studies included in our pooled analyses, with p values ranging from 0.07 to 0.43 (Appendix 3, 4 and 5).

Table 1 - Included studies and characteristics.

Author, year	Country	Sample Size	Predictor	Outcomes	Surgery	Follow-Up Duration	Quality Score
AbdelSalam et al, 2012	USA	210	Obesity	Complications	Total Hip and Knee Arthroplasty	9 years	Fair
Amin et al, 2006 A	United Kingdom	328	Obesity	Complications; Disability	Total Knee Replacement	6, 18, 36 and 60 months	Poor
Amin et al, 2006 B	Scotland	82	Obesity	Complications	Total Knee Replacement	38.5 months	Poor
Andrew et al, 2008	England	1,059	Obesity	Complications; Disability	Total Hip Arthroplasty	3, 12, 24, 36 and 60 months	Poor
Azodi et al, 2006	Italy	3,309	Obesity	Complications	Total Hip Replacement	6 to 9 years	Fair
Azodi et al, 2008	Italy	2,106	Obesity	Complications	Total Knee Arthroplasty	2 years	Fair
Baker et al, 2012	England	13,673	Obesity	Complications; Disability	Total Hip Arthroplasty	6 months	Fair
Belmont et al, 2014	USA	17,514	Obesity	Complications	Total Knee Arthroplasty	1 month	Fair
Belmont et al, 2014	USA	15,321	Obesity	Complications	Total Knee Arthroplasty	1 month	Fair
Bozic et al, 2012 A	USA	40,919	Obesity	Complications	Total Hip Arthroplasty	10 years	Fair
Bozic et al, 2012 B	USA	83,011	Obesity	Complications	Total Knee Arthroplasty	10 years	Fair
Chee et al, 2010	United Kingdom	106	Obesity	Complications; Disability	Total Hip Arthroplasty	6, 18, 36 and 60 months	Good
Chesney et al, 2008	Scotland	1,278	Obesity	Complications	Total Knee Arthroplasty	6, 18 and 60 months	Poor
Collins et al, 2012	United Kingdom	385	Obesity	Complications; Disability	Total Knee Arthroplasty	6, 18 months, 3, 6, 9 years	Poor
Davis et al, 2011	Canada	931	Obesity	Pain	Total Hip and Knee Arthroplasty	2 weeks, 1, 3, 6, 12 months	Fair

Dewan et al, 2009	USA	220	Obesity	Complications; Disability	Total Knee Arthroplasty	5.4 years	Poor
Dowsey et al, 2008	Australia	1,207	Obesity	Complications	Hip Arthroplasty	1 year	Poor
Dowsey et al, 2010	Australia	471	Obesity	Complications; Pain; Disability	Total Hip Arthroplasty	1 year	Good
Font-Vizcarra et al, 2011	Spain	402	Obesity	Complications	Total Hip Arthroplasty	3 months	Fair
Friedman et al, 2013	USA	12,355	Obesity	Complications	Hip and Knee Arthroplasty	2 months	Poor
Gandhi et al, 2010	Canada	1,224	Obesity	Pain; Disability	Total Hip Arthroplasty	1 year	Good
Hamoui et al, 2006	USA	63	Obesity	Disability	Total Knee Arthroplasty	11.3 years	Poor
Heiberg et al, 2013	Norway	64	Obesity	Pain	Total Hip Arthroplasty	3 and 12 months	Good
Ibrahim et al, 2005	United Kingdom	343	Obesity	Complications	Total Hip Arthroplasty	1 year	Poor
Jackson et al, 2009	Australia	100	Obesity	Complications; Pain; Disability	Total Knee Replacement	9.2 years	Poor
Jameson et al, 2014	United Kingdom	5,535	Obesity	Disability	Hip Arthroplasty	6 months	Fair
Jamsen et al, 2010	Finland	2,647	Obesity	Complications	Total Knee Arthroplasty	1 year	Good
Jamsen et al, 2012	Finland	7,181	Obesity	Complications	Total Knee Arthroplasty	1 year	Good
Jarvenpaa et al, 2010	Finland	100	Obesity	Complications; Pain	Total Knee Arthroplasty	3 months	Poor
Jarvenpaa et al, 2012	Finland	52	Obesity	Pain; Disability	Total Knee Arthroplasty	10.8 years	Poor
Judge et al, 2010	United Kingdom	908	Obesity	Disability	Hip Replacement	1 year	Poor

Kandil et al, 2015	USA	15,770	Obesity	Complications	Unicompartimental Knee Arthroplasty	3 months	Poor
Kessler et al, 2007	Germany	67	Obesity	Disability	Total Hip Replacement	10 days and 3 months	Good
Kim et al, 2011	South Korea	227	Obesity	Complications	Total Knee Arthroplasty	6 months	Poor
Kort et al, 2007	Netherlands	46	Obesity	Complications	Unicompartimental Knee Replacement	2 years	Poor
Ledford et al, 2014	USA	316	Obesity	Complications	Total Hip and Knee Arthroplasty	2 months	Poor
Liabaud et al, 2013	USA	273	Obesity	Complications	Total Knee Arthroplasty	3 and 12 months	Poor
Liljensøe et al, 2013	Denmark	197	Obesity	Pain; Disability	Total Knee Arthroplasty	4 years	Poor
Luebbeke et al, 2007 A	Switzerland	2,495	Obesity	Complications; Disability	Total Hip Arthroplasty	5 years	Good
Luebbeke et al, 2007 B	Switzerland	325	Obesity	Disability	Total Hip Arthroplasty	5 years	Good
Mackie et al, 2015	United Kingdom	1,821	Obesity	Complications; Pain; Disability	Total Knee Arthroplasty	1 year	Poor
Madsen et al, 2014	USA	79	Obesity	Complications	Total Knee Arthroplasty	10 years	Poor
Maisongrosse et al, 2014	France	502	Obesity	Complications	Total Hip Arthroplasty	58 months	Poor
McLaughlin et al, 2006	USA	198	Obesity	Complications	Total Hip Replacement	14.5 years	Poor
Michalka et al, 2012	United Kingdom	191	Obesity	Complications; Pain; Disability	Hip Arthroplasty	6 weeks	Poor
Murray et al, 2013	United Kingdom	2,438	Obesity	Complications; Disability	Unicompartimental Knee Replacement	1 year	Poor
Naal et al, 2009	Switzerland	83	Obesity	Pain; Disability	Total Knee Arthroplasty	6 weeks, 3, 12 and 24 months	Poor
Namba et al, 2005	USA	1,813	Obesity	Complications	Total Hip and Knee Arthroplasty	1 year	Poor

Napier et al, 2014	United Kingdom	100	Obesity	Complications; Disability	Total Knee Arthroplasty	3 and 12 months	Poor
Naylor et al, 2008	Australia	99	Obesity	Pain	Total Hip and Knee Arthroplasty	2, 6, 12, 26 and 52 weeks	Good
Ollivier et al, 2012	France	210	Physical Activity	Disability	Total Hip Arthroplasty	10 years	Fair
Patel et al, 2008	United Kingdom	527	Obesity	Complications	Total Knee Replacement	4 weeks, 6 weeks and 1 year	Good
Pietschmann et al, 2013	Germany	171	Physical Activity	Disability	Unicompartimental Knee Arthroplasty	4.2 years	Poor
Poortinga et al, 2014	Netherlands	658	Physical Activity	Disability	Total Hip and Knee Arthroplasty	1 year	Good
Pulido et al, 2008	USA	9,245	Obesity	Complications	Total Hip and Knee Arthroplasty	1 year	Fair
Rajgopal et al, 2008	Canada	760	Obesity	Complications; Disability	Total Knee Arthroplasty	1 year	Fair
Sechriest et al, 2007	USA	34	Physical Activity	Disability	Total Hip Arthroplasty	5 years	Poor
Villalobos et al, 2013	Spain	63	Obesity	Pain; Disability	Total Hip Arthroplasty	3 months	Good
Vogl et al, 2014	Germany	281	Obesity	Disability	Total Hip Arthroplasty	6 months	Poor
Wang et al, 2010	USA	97	Obesity	Disability	Total Hip Arthroplasty	3 months, 1 and 2 years	Fair
Yasunaga et al, 2009	Japan	3,577	Obesity	Complications	Total Knee Arthroplasty	5 months	Fair
Zhang et al, 2012	China	714	Obesity	Complications; Disability	Total Hip Arthroplasty	5 years	Poor

The course of pain and disability over time

Figure 2 presents the course of disability over time for hip (A) and knee osteoarthritis (B) post-surgery; as well as pain for hip (C) and knee osteoarthritis (D). The central line represents the estimated pooled mean over time, and the shaded area circumscribes its 95% confidence intervals. A total of eight studies with complete data (i.e. estimates of central tendency and variance) were included in the pain analysis and 17 studies were included in the disability analysis.

The fractional polynomial regression model resulted in a pooled mean disability score and standard deviation before hip arthroplasty of 59.42 (SD: 10.94; n=5,250). At 12 months post-surgery it had decreased to a mean of 31.31 (SD: 24.28; n= 3,017) and a further reduction was observed at 120 months, when the mean disability score after hip arthroplasty was 24.32 (SD: 19.53; n= 210). For knee osteoarthritis, a pooled mean disability score of 56.88 (SD: 10.74; n= 17,225) was observed for patients undergoing arthroplasty. At 12 months after surgery this value decreased to 21.80 (SD: 13.51; n= 2,898), whilst at the 110-month follow-up, the mean disability score was 14.18 (SD: 0.77; n= 485). The pooled mean pain scores before hip arthroplasty was 54.86 (SD: 10.20; n= 2,517), decreasing to 13.76 (SD: 1.32; n= 1,058) 3 months after surgery, 10.8 (SD: 1.69; n= 1,212) at 6 months and slightly increasing to 13.45 (SD: 7.87; n= 2,173) at the 12 month follow-up. For patients undergoing knee arthroplasty, the pooled pain score at baseline was 57.78 (SD: 9.28; n= 2,211); which decreased to 25.67 (SD: 6.61; n= 1,222) at 6 months, and 14.18 (SD: 0.77; n= 1,820) at the 12-month follow-up (figure 2).

Figure 2 - Fractional polynomial analysis for hip (A) and knee (B) disability scores and hip (C) and knee (D) pain scores over time.

Association between obesity and post-surgical pain outcomes

Fourteen studies investigated the association between obesity and pain intensity in a total of 5,687 patients after hip or knee arthroplasty. Seven of the 14 studies presented enough data to be pooled in a meta-analysis. There was an overall moderate and statistically significant difference in post-surgical pain between obese and non-obese patients post arthroplasty, with non-obese patients having better outcomes at short (SMD -0.43; 95%CI: -0.67 to -0.19; p<0.001), and long-term timepoints (SMD -0.36; 95%CI: -0.47 to -0.24; p<0.001). The pooled results for separate joints suggest non-obese participants have significantly less short-term (i.e. less than 6 months) post-surgical knee pain, compared to obese participants (SMD -0.54; 95%CI: -0.90 to -0.19; p=0.002) and post-surgical hip pain (SMD -0.34; 95%CI: -0.66 to -0.01; p=0.039). Obesity was defined as having a BMI over 30 kg/m^2. At long term (i.e. 6 months or longer), there was a significant moderate difference between obese and non-obese groups in terms of knee pain (SMD -0.36; 95%CI: -0.47 to -0.24; p<0.001), however there was no difference between groups for hip pain (SMD -0.32; 95%CI: -0.84 to 0.19; p=0.222)(figure 3). The results of individual studies not included in the pooled analyses are presented in table 2 below.

Figure 3 – Pooled standardised mean difference in pain at short and long term post-surgery between obese and non-obese patients.

Obesity vs Pain			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Knee			
Davis 2011	NA	HOOS / KOOS	After adjusting for age, gender, joint, and presence of back pain, an increased BMI was associated with worst pain outcomes (p<0.02) at long term after THA or TKA.
Jarvenpaa 2010	29.7 (NA)	VAS	Increased BMI correlates significantly to VAS pain scale (r=0.236; p=0.018) at short term after TKA.
Liljensøe 2013	30 (NA)	SF-36	BMI was **not** associated with SF-36 pain scale (OR= 0.96; p=0.1) at long term after TKA.
Mackie 2015	NA	WOMAC	Increased BMI was associated with less improvement in WOMAC pain scale (t= -2.64; p<0.001) at long term after TKA.
Hip			
Dowsey 2010	29.55 (5.64)*	Harris Hip Score	BMI was **not** associated with pain reduction (p=0.71) at long term after THA.
Heiberg 2013	27 (6.27)*	HOOS	BMI was **not** associated with HOOS pain scale (p>0.05) at short term after THA.

Table 2 – Results of individual studies on the association between post-surgical pain and baseline obesity.

BMI – Body Mass Index; SD – Standard deviation; THA – Total hip arthroplasty; TKA – Total knee arthroplasty; OR – Odds ratio; NA – None available; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; HOOS - Hip dysfunction and Osteoarthritis Outcome Score; KOOS - Knee dysfunction and Osteoarthritis Outcome Score; VAS – Visual Analogue Scale; SF-36 – Short Form 36 Questionnaire; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between obesity and post-surgical disability outcomes

The impact of obesity on disability was investigated by 32 studies which compared post-surgery disability scores in 35,286 obese and non-obese participants. Of these, 19 studies presented complete data that was included in the pooled analysis. At short term, no statistically significant difference in overall disability between obese and non-obese participants was observed (SMD -0.15, 95% CI -0.41 to 0.10, p=0.231). Likewise, no statistically significant difference was observed between obese and non-obese participants for post-surgical knee or hip disability (SMD -0.41, 95% CI -0.99 to 0.16, p=0.159 and SMD -0.09, 95% CI -0.38 to 0.19, p=0.527, respectively).

At long term follow-up, however, there was an overall moderate and statistically significant difference in post-surgical disability between obese and non-obese patients regardless of the joint affected (SMD -0.32; 95%CI: -0.36 to -0.28; p<0.001). That difference was still statistically significant and of moderate magnitude when knee and hip joints were analysed separately (SMD -0.31, 95% CI -0.36 to -0.26, p<0.001 and SMD -0.34, 95% CI -0.44 to -0.25, p<0.001, respectively and favouring non-obese patients)(figure 4). The results of individual studies not included in the pooled analyses are presented in table 3 below.

Figure 4 – Pooled standardised mean difference in disability at short and long term post-surgery between obese and non-obese patients.

Obesity vs Disability			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
	Knee		
Davis 2011	NA	WOMAC /	After adjusting for age, gender, joint, and

		KOOS	presence of back pain, an increased BMI was associated with worst outcomes (p<0.02) at long term after TKA or THA.
Dewan 2009	31 (0.5)	Knee Society Score	BMI was **not** associated with worst knee function (p>0.119) at long term after TKA.
Hamoui 2006	27.93 (7.1)*	Knee Society Score	**No** significant association between BMI and KSS (p>0.05) were found at long term after TKA.
Kort 2007	NA	WOMAC	Obesity was **not** related to disability score (p>0.05) at long term after TKA.
Liljensøe 2013	30 (NA)	Knee Society Score	Increased BMI was associated with worst knee scores (OR 0.95, 95% CI 0.9 to 1.0, p=0.04) at long term after TKA. These results did not change significantly after adjusting for age, sex, primary disease and surgical approach (OR 0.94, 95% CI 0.90 to 0.99, p=0.02).
Mackie 2015	NA	WOMAC	Increased BMI was associated with less improvement in disability scores (WOMAC t= -2.13; p=0.033) at long term after TKA.
Rajgopal 2008	32.3 (6.58)*	WOMAC	The morbidly obese group (BMI ≥40, n=69) does **not** present a statistically significant difference in improvement in WOMAC score (p=0.669) when compared to others BMI groups at long term after TKA.
		Hip	
Heiberg 2013	27 (6.27)*	HHS	Increased BMI was associated with lower HHS (p<0.05) at short term after THA.
Jameson 2014	NA	OHS	Increased BMI was **not** associated with changes in OHS (p>0.05) at short term after THA.
Luebbeke 2007 B	26.4 (4.3)	HHS	Increased BMI was associated with lower hip score (r=-0.4, 95% CI -0.8 to -0.1) at long term after THA.
McLaughlin 2006	26 (NA)	HHS	The obese group (BMI ≥30; n=95) did **not** present any statistically significant difference from the non-obese group (BMI <30, n=103) with regards to clinical outcomes assessed by HHS (p>0.05) at long term after THA.
Vogl 2014	26.9 (4.9)	WOMAC	Obesity was associated with changes in WOMAC score (p<0.05) at short term after THA.
Wang 2010	29.14 (6.23)	WOMAC	Increased BMI was **not** associated with WOMAC score (p=0.114) at long term after THA.

Table 3 – Results of individual studies on the association between post-surgical disability and baseline obesity.

BMI – Body Mass Index; SD – Standard deviation; NA – None available; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; KOOS - Knee disability and Osteoarthritis Outcome Score;

TKA – Total knee arthroplasty; THA – Total hip arthroplasty; KSS – Knee Society Score; OR – Odds ratio; CI – Confidence interval; HHS – Harris Hip Score; OHS – Oxford Hip Score; r – coefficient of association; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between obesity and post-surgical complications

The association between obesity and complications after joint arthroplasty was assessed by 40 studies including a total of 245,433 patients who underwent knee or hip arthroplasty. Of these, 17 presented enough data and were included in the meta-analyses.

The pooled results suggest that at short term follow-up, non-obese participants are less likely to have post-surgical deep vein thrombosis (DVT) (OR 0.48; 95% CI 0.25 to 0.91; p=0.024) when compared with obese participants (figure 5). A total of 13 studies were pooled (n=22,782) showing non-obese patients are also less likely to present any long-term (i.e. ≥ 6 months) dislocation (OR: 0.49; 95% CI: 0.31 to 0.79; p=0.003) and DVT (OR: 0.61; 95% CI: 0.37 to 0.98; p=0.043). Non-significant difference between groups was observed between non-obese and obese participants for long-term revision surgery (OR: 0.66; 95% CI: 0.34 to 1.27; p=0.217) (figure 5).

The pooled analysis on short-term post-surgical infection for hip replacement showed that non-obese patients are less likely to develop infections compared to obese participants (OR 0.33; 95% CI 0.18 to 0.59; p<0.001)(Figure 6). For knee replacement separate analyses were conducted for studies comparing obese to non-obese participants and those comparing morbidly obese to non-obese participants (Figure 7). The results suggest that non-obese patients are less likely to develop infections when compared to morbidly obese patients (OR 0.42; 95% CI 0.23 to 0.78; p= 0.006). No association with post-surtical infection was observed when obese and non-obese participants were compared.

The overall pooled analysis for incidence of complications suggests that non-obese participants are less likely to present any post-surgical complication at the short or long term follow-ups (OR: 0.48; 95% CI: 0.25 to 0.91; p<0.001 and OR: 0.55; 95% CI: 0.41 to 0.74; p<0.001, respectively). The results of individual studies not included in the pooled analyses are presented in the table 4 below.

Figure 5 - Pooled association between complications and obesity at short term and long term follow-ups.

Figure 6 – Pooled association between post-surgical infections and obesity for hip surgery.

Figure 7 – Pooled association of post-surgical infections for knee surgery.*

*Comparison for both pooled analysis is non-obese participants.

Obesity vs Complications			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Ollivier 2012	25.13 (3.14)*	HHS / HOOS	At long term, high impact sports was associated with better HHS (p<0.001) after THA.
Pietschmann 2013	28.4 (4.62)*	OKS	At long term, physical activities were **not** related to complications (p<0.01). Physically active patients had less pain and better OKS scores after UKA.
Poortinga 2014	28.7 (4.9)	WOMAC	At long term, physical activity was **not** associated with WOMAC score (p>0.05) after THA or TKA.
Sechriest 2007	28.1 (8.3)	UCLA	At long term increased BMI was **not** correlated to UCLA physical activity score (R=-0.07; p=0.67) after TKA.

Table 4: Results of individual studies investigating the association between obesity and post-surgical complications.

BMI – Body Mass Index; SD – Standard deviation; HHS – Harris Hip Score; HOOS - Hip disability and Osteoarthritis Outcome Score; THA – Total hip arthroplasty; OKS – Oxford Knee Score; UKA - Unicompartimental knee arthroplasty; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; TKA – Total knee arthroplasty; UCLA - University of California, Los Angeles activity questionnaire; R – Correlation coefficient; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Association between physical activity participation and disability

The association between physical activity and disability was investigated by four studies[73, 75, 76, 79] or 1,033 participants undergoing hip or knee arthroplasty. Included studies have not provided enough data to be pooled. The overall results from these 4 papers suggest that participants who practice more physical activity before the surgeries were more likely to experience less pain after either hip or knee surgery, however the evidence regarding disability scores is still unclear with studies presenting contradictory results. Table 5 below presents the results of the individual studies.

Physical Activity vs Disability			
Author, year	**BMI:** Mean (SD)	**Measure**	**Results**
Ollivier 2012	25.13 (3.14)*	HHS / HOOS	At long term, high impact sports were associated with better HHS (p<0.001) and HOOS (p<0.05) after THA.
Pietschmann 2013	28.4 (4.62)*	OKS / KSS / WOMAC	At long term, physical activities were **not** related to complications. Physically active patients had less pain and better OKS, KSS and WOMAC scores (p<0.05) after UKA.
Poortinga 2014	28.7 (4.9)	WOMAC	At long term, physical activity was **not** associated with WOMAC score (p>0.05) after THA or TKA.
Sechriest 2007	28.1 (8.3)	UCLA	At long term increased BMI was **not** correlated to UCLA physical activity score (R=-0.07; p=0.67) after TKA.

Table 5 – Individual results on the association between physical activity and pain or disability.

BMI – Body Mass Index; SD – Standard deviation; HHS – Harris Hip Score; HOOS - Hip disability and Osteoarthritis Outcome Score; THA – Total hip arthroplasty; OKS – Oxford Knee Score; KSS – Knee Society Score; WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index; UKA - Unicompartimental knee arthroplasty; TKA – Total knee arthroplasty; UCLA - University of California, Los Angeles activity questionnaire; R – Correlation coefficient; *Calculated following guidelines from Cochrane Handbook for Systematic Reviews of Interventions.

Discussion

Statement of principal findings

Our results suggest that following surgery, non-obese patients experience further reductions in both pain and disability post knee and hip arthroplasty when compared to obese patients, where obesity has been defined as having a BMI of 30 kg/m^2 or over. These differences seemed to be more accentuated for knee pain outcomes following arthroplasty, than for hip pain or disability outcomes. Non-obese participants also experienced significantly less post-surgical complications, including dislocation, DVT and infection especially following hip arthroplasty. Our analyses also demonstrate that obesity is a reliable predictor of complications after total hip arthroplasty and total knee arthroplasty, not only in the short term after the procedure but also at longer follow-ups. The evidence regarding pre-operative physical activity remains unclear due to conflicting results of included studies, especially in terms of post-operative disability. The four included cohort studies however, suggest that physical activity participation is associated with better pain outcomes following surgery.

Our results from the fractional polynomial analysis have also shown that all patients experienced an improvement in pain and disability post-surgery. We also highlight that although non-obese patients experience further improvements in pain and disability compared to obese participants, both groups improved significantly following surgery as depicted in figure 2. The observed decrease in pain from baseline was approximately 70% at 6 months and 75% at 12 months, with decreases in disability of 55% at 12 months and 67% at 120 months. The interpretation of the postsurgical course of pain and disability, however, needs to be taken in the context of the inclusion criteria we have used in our review, given we have only included data from cohort studies that have assessed the role of obesity or physical activity participation on surgical outcomes.

Strengths and weaknesses in relation to other studies, discussing particularly any differences in results

Our meta-analysis results regarding the association between obesity and post-surgical complications found that obese patients present higher complication rates than non-obese patients. These results are consistent with the findings of previous systematic reviews of Hofstede,[14] Samson[15] and Liu.[16] Our meta-analysis results regarding the association between obesity and post-surgery disability also agreed with the findings of Buirs et al[13] and Samson et al[15] which found that obesity (defined as having BMI over 30 kg/m^2), was associated with worst postsurgical functional score. The only previous review which has performed a meta-analysis on the association between obesity and post arthroplasty pain or disability limited its inclusion criteria to hip joint.[16] That review included a total of 15 studies in their meta-analysis and found that obesity increases the risk of post-surgical complications (RR: 1.68, 95% CI 1.23 to 2.30, P = 0.0004) and is associated with worse disability scores following surgery (MD: -2.75, 95% CI -4.77 to -0.6; P = 0.07). Our study has included 33 cohorts of hip arthroplasty participants in the qualitative analysis, 16 in the meta-analyses, and confirms past findings that obesity is associated with worse outcomes in terms of not only disability and complications, but also pain at both short and long term periods following surgery. Hofstede et al[14] have also conducted a systematic review of the literature on pre-operative predictors of surgical outcomes after hip replacement in patients with osteoarthritis. Although those authors included 35 studies, only 5 studies investigated the effect of obesity on post-surgical pain, disability and quality of life.[14] No meta-analysis was performed.

Implications for clinicians or policy makers

Our results have a direct impact on clinical practice as the results demonstrate that obese patients have a higher risk of complications and a poorer prognosis in terms of pain and disability post-operatively when compared with non-obese patients. These results also allude to the importance of identifying and implementing effective pre-surgical rehabilitation and weight loss approaches to optimise post-surgical outcomes and minimise harm to the patient. The importance of weight loss has been highlighted in international clinical guidelines on non-surgical management of knee osteoarthritis for instance, given the pain and disability reductions observed following weight loss regimes.[86] Past research also suggests there is a dose-response relationship between weight loss and clinical outcome improvement. A recent completer-type analysis of 1,383 participants with knee osteoarthritis showed that a weight loss of 7.7% of body weight or more is associated with clinically important changes in pain and disability, as measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS).[87] This evidence reinforces the importance of pre-surgical weight loss programs and strategies in order to optimize post-surgical recovery.

Strengths and weaknesses of the study

The current review has included 62 cohort studies and a total of 256,481 participants and is the most comprehensive systematic review on the topic to date. It is also the first review to use a quantitative approach to synthesize the results of pain, disability and surgical complications between non-obese and obese participants and consider the physical activity level of participants who underwent to hip or knee arthroplasty due to osteoarthritis.Our review has some limitations. The methodological quality of the included studies was in general poor. The most common methodological flaw among included cohorts was not controlling for confounding factors age, sex or BMI (32 studies, 51%) followed by not using a representative sample (n=30 studies, 48%). Moreover, we have observed great variability of follow-up duration across studies, ranging from 2 weeks to 11 years. We have used a cut-off of 6 months to define short (i.e. < 6 months) or long-term (i.e. ≥ 6 months) follow-ups, but acknowledge that within each follow-up category there was substantial variation in the duration of follow-up across studies.

Between-study heterogeneity has also been observed in some of the pooled analysis for obesity presented in this review. A potential source of between-study heterogeneity include the variability in the definition of obesity categories across studies. Although obesity was assessed using BMI scores in all studies some studies have used only two obesity groups (i.e. obese or non-obese) while others used several categories including underweight, normal or overweight, obese and morbidly obese. These needed to be combined for some of our pooled analyses.

Another potential source of between-study heterogeneity across is the difference in surgical procedures used across studies. For instance, in the pooled analysis of risk of post-surgical DVT and obesity, whislt Kandil et al [54] performed unicompartimental knee arthroplasties, Friedman et al [42]performed total arthroplasties on both hip and knee joints. That discrepancy might explain the different results reported by these two studies (figure 5). Likewise, the mean physical activity load reported by the included studies varied substantially, ranging from low to high frequency of participation in low and high impact activities. This should be taken into consideration when interpreting the physical activity results.

Conclusion

Our results have shown that obese patients undergoing hip or knee arthroplasty due to osteoarthritis have worse outcomes in terms of pain and complications when compared to non-obese patients, with differences more accentuated for patients with knee osteoarthritis. Likewise, obese patients will have worse surgical outcomes in terms of disability, but only at long-term follow-ups. It is still unclear whether pre-surgical physical activity participation has an impact on surgical outcomes. However, we acknowledge that the health benefits of physical activity participation for patients with knee and hip osteoarthritis are multiple and reach beyond those considered in this review.

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Contributors: DP, GCM, PHF, FB and MF were involved in the conception and design of the review. DP, GCM and MF developed the search strategy and performed study selection. DP and GCM extracted data from included studies. DP and GV assessed the methodological quality of included studies. DP and MLF were involved in the data analysis. DP, GCM, PHF, FB and MF were involved in the interpretation and discussion of results. DP drafted the manuscript, and GCM, PHF, FB and MF contributed to the drafting of the review. GCM, PHF, FB and MF revised it critically for important intellectual content. All authors approved the final version of the article. All authors had access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing Interests Statement

All authors have completed the ICMJE uniform disclosure form www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: All data extracted from papers and used to write this paper is available to whoever ask. Contact the correspondence author for further information.

Transparency: The lead author (Daniel Pozzobon) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

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FIGURE LEGEND

Figure 1 – Flowchart of search strategy and screening steps.

Detailed steps of references screening process of results from database searches.

Figure 2 - Fractional polynomial analysis for hip (A) and knee (B) disability scores and hip (C) and knee (D) pain scores over time**.**

A - Graphic representation of results from fractional polynomial analysis of disability scores evolution over time after hip surgeries;

B - Graphic representation of results from fractional polynomial analysis of disability scores evolution over time after knee surgeries;

C - Graphic representation of results from fractional polynomial analysis of pain scores evolution over time after hip surgeries;

D - Graphic representation of results from fractional polynomial analysis of pain scores evolution over time after knee surgeries.

Figure 3 – Pooled standardised mean difference in pain at short and long term post-surgery between obese and non-obese patients.

Results from meta-analysis of included studies presented as standardised mean difference of pain scores at short (<6 months) and long term (≥6 months) follow-up between non-obese and obese groups.

Figure 4 – Pooled standardised mean difference in disability at short and long term post-surgery between obese and non-obese patients.

Results from meta-analysis of included studies presented as standardised mean difference of disability scores at short (<6 months) and long term (≥6 months) follow-up between non-obese and obese groups.

Figure 5 - Pooled association between complications and obesity at short term and long term follow-ups.

Results from meta-analysis of included studies presented as incidence of complications at short (<6 months) and long term (≥6 months) follow-up between non-obese and obese groups.

Figure 6 – Pooled association between post-surgical infections and obesity for hip surgery.

Results from meta-analysis of included studies presented as incidence of infections after hip surgery between non-obese and obese groups.

Figure 7 – Pooled association of post-surgical infections for knee surgery.

Results from meta-analysis of included studies presented as incidence of infections after hip surgery comparing the non-obese group to obese group and the non-obese group to morbid obese group.

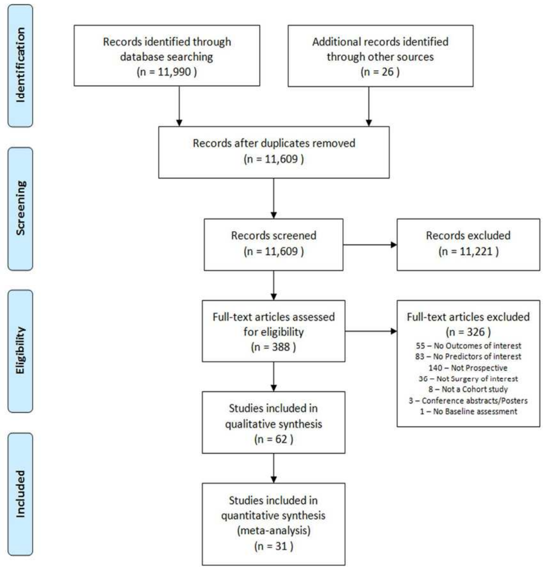

Figure 1. Flowchart of search strategy and screening steps.

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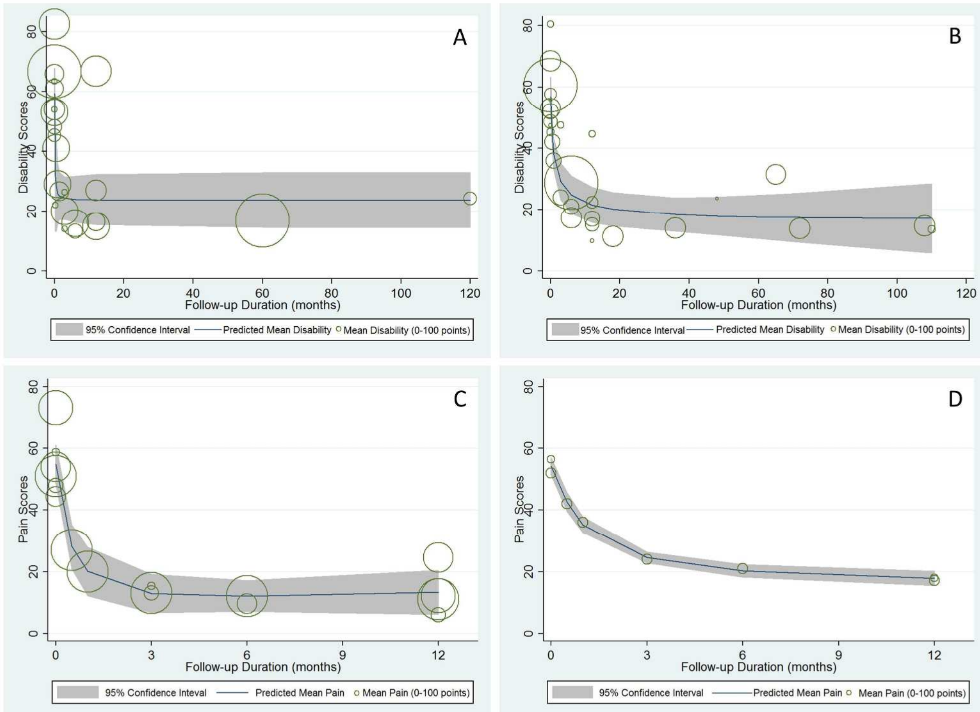

Figure 2 - Fractional polynomial analysis for hip (A) and knee (B) disability scores and hip (C) and knee (D) pain scores over time.

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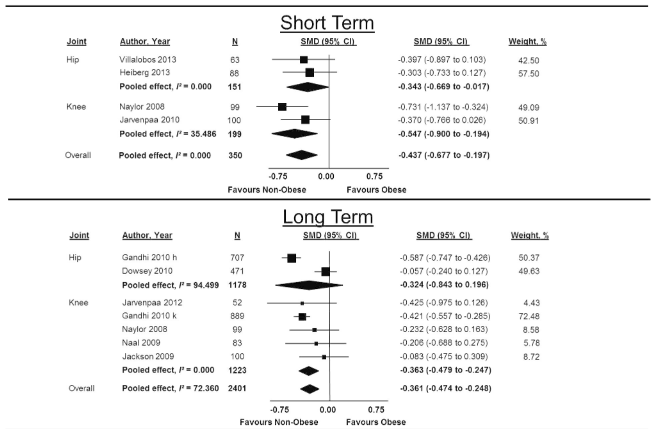

Figure 3 – Pooled standardised mean difference in pain at short and long term post-surgery between obese and non-obese patients.

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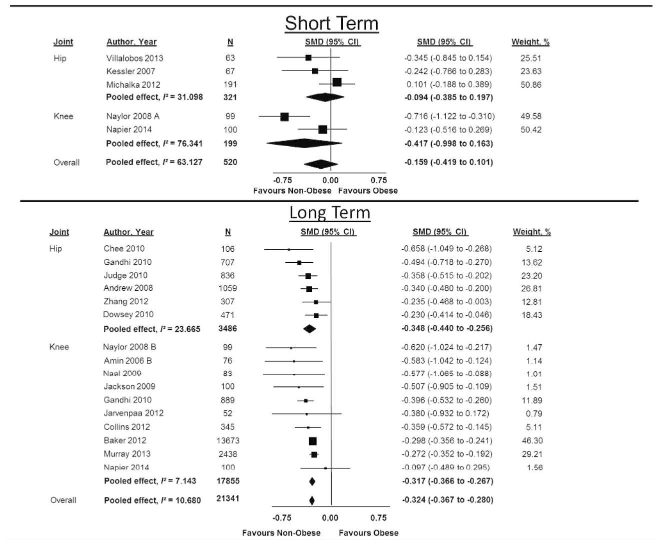

Figure 4 – Pooled standardised mean difference in disability at short and long term post-surgery between obese and non-obese patients.

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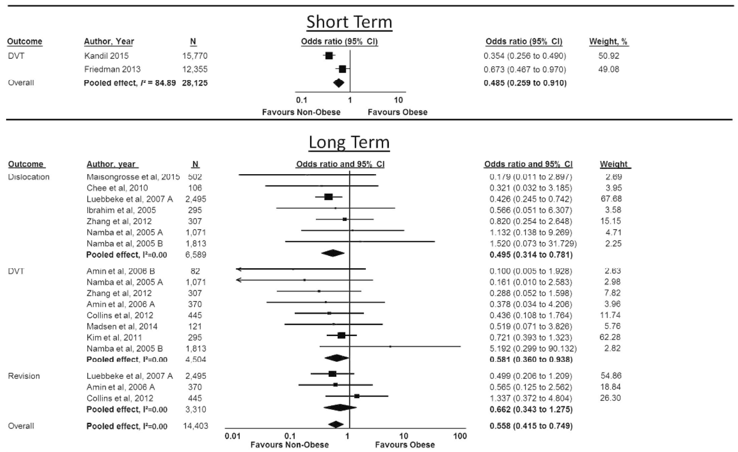

Figure 5 – Pooled association between complications and obesity at short term and long term follow-ups.

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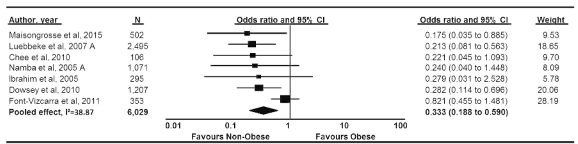

Figure 6 – Pooled association between post-surgical infections and obesity for hip surgery.

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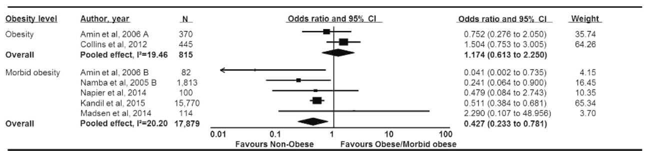


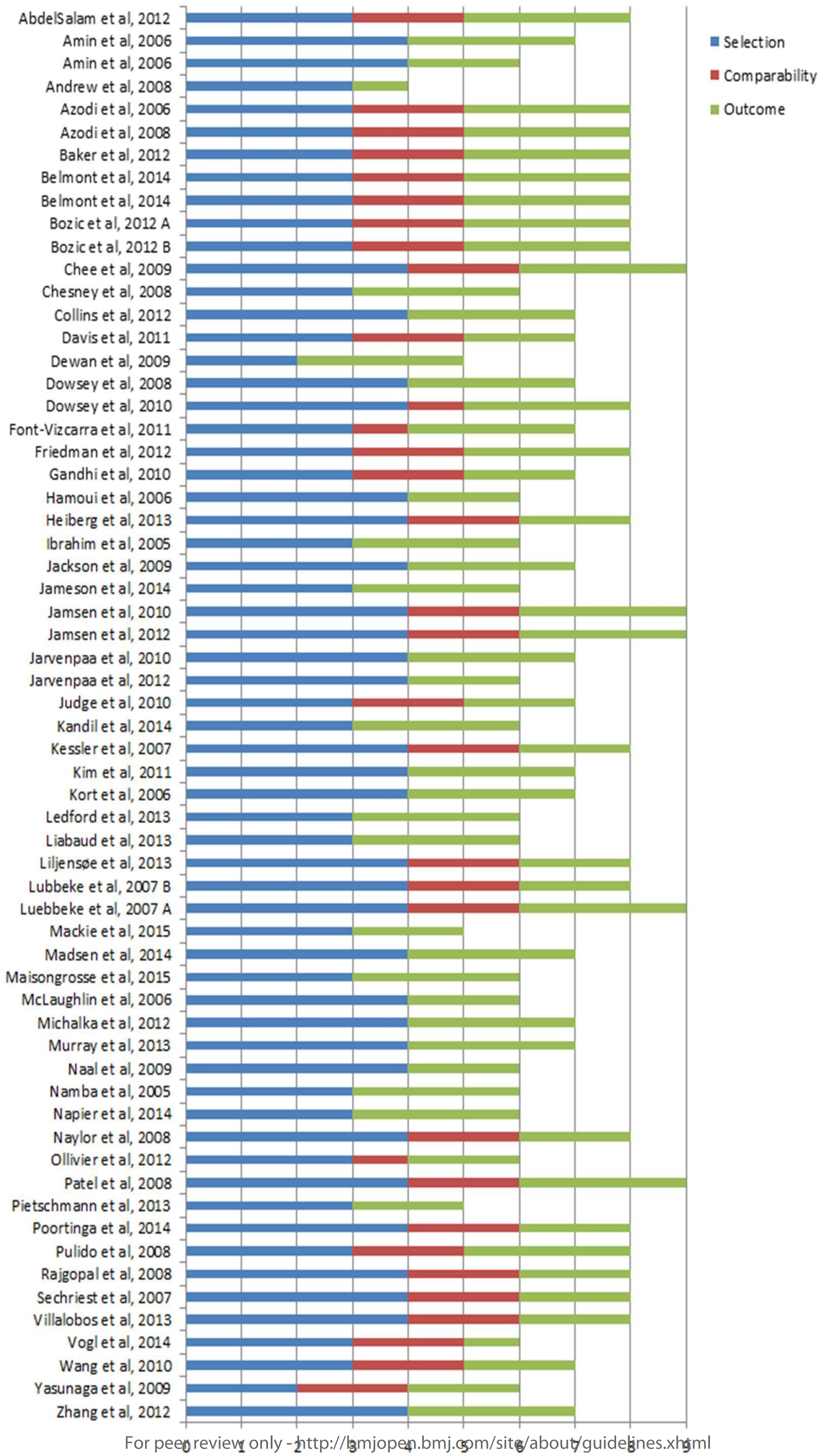
Figure 7 – Pooled association of post-surgical infections for knee surgery.*

254x142mm (300 x 300 DPI)

APPENDIX 1

MEDLINE search strategy terms used:

1	obesity.mp. or exp Obesity/ or exp Obesity, Abdominal/	197.941
2	Physical Activity.mp. or exp Motor Activity/	231.947
3	sedentar$.mp.	19.058
4	(time adj5 sitting).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	688
5	**1 or 2 or 3 or 4**	**414.967**
6	exp Postoperative Complications/ or exp Hip Prosthesis/ or exp Arthroplasty, Replacement, Hip/ or hip arthroplasty.mp. or exp Osteoarthritis, Hip/ or exp Hip Joint/	469.282
7	knee arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/	17.365
8	exp Elective Surgical Procedures/ or elective surgery.mp.	14.058
9	osteoarthritis.mp. or exp Osteoarthritis, Hip/ or exp Osteoarthritis/ or exp Osteoarthritis, Knee/	55.493
10	exp Osteonecrosis/ or Osteonecrosis.mp.	13.961
11	arthroplasty.mp. or exp Arthroplasty, Replacement, Knee/ or exp Arthroplasty, Replacement/ or exp Arthroplasty/ or exp Arthroplasty, Replacement, Hip/	53.979
12	**6 or 7 or 8 or 9 or 10 or 11**	**546.616**
13	exp Cohort Studies/ or cohort.mp.	1.526.984
14	incidence.mp. or exp Incidence/	587.274
15	exp Follow-Up Studies/ or follow-up.mp.	912.064
16	prognosis.mp. or exp Prognosis/	1.273.869
17	exp Prognosis/ or predictors.mp.	1.258.014
18	exp Time Factors/ or course.mp.	1.403.404
19	exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ or survival.mp.	843.771
20	logistic.mp.	198.801
21	cox.mp.	84.820
22	life table.mp. or exp Life Tables/	18.098
23	log rank.mp. or exp Follow-Up Studies/	533.280
24	**13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23**	**4.460.132**
25	Animals/	5.495.334
26	exp Editorial/ or editorial.mp.	376.114
27	case report.mp. or exp Case Reports/	1.754.352
28	letter.mp. or exp Letter/	895.420
29	25 or 26 or 27 or 28	8.184.015
30	**5 and 12 and 24**	**7.601**
31	**30 not 29**	**6.869**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Belmont et al, 2014
Bozic et al, 2012 A
Bozic et al, 2012 B
Chee et al, 2009
Chesney et al, 2008
Collins et al, 2012
Davis et al, 2011
Dewan et al, 2009
Dowsey et al, 2008
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Font-Vizcarra et al, 2011
Friedman et al, 2012
Gandhi et al, 2010
Hamoui et al, 2006
Heiberg et al, 2013
Ibrahim et al, 2005
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Lubbeke et al, 2007 B
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McLaughlin et al, 2006
Michalka et al, 2012
Murray et al, 2013
Naal et al, 2009
Namba et al, 2005
Napier et al, 2014
Naylor et al, 2008
Ollivier et al, 2012
Patel et al, 2008
Pietschmann et al, 2013
Poortinga et al, 2014
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Villalobos et al, 2013
Vogl et al, 2014
Wang et al, 2010
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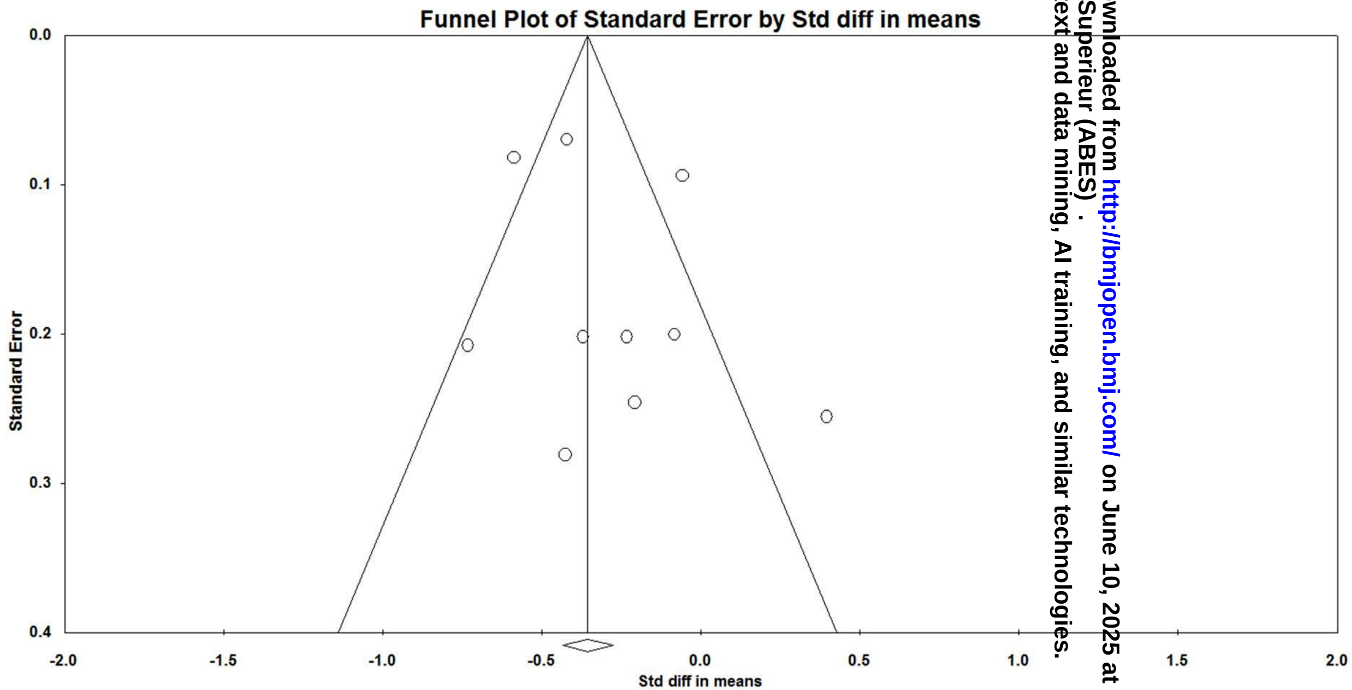
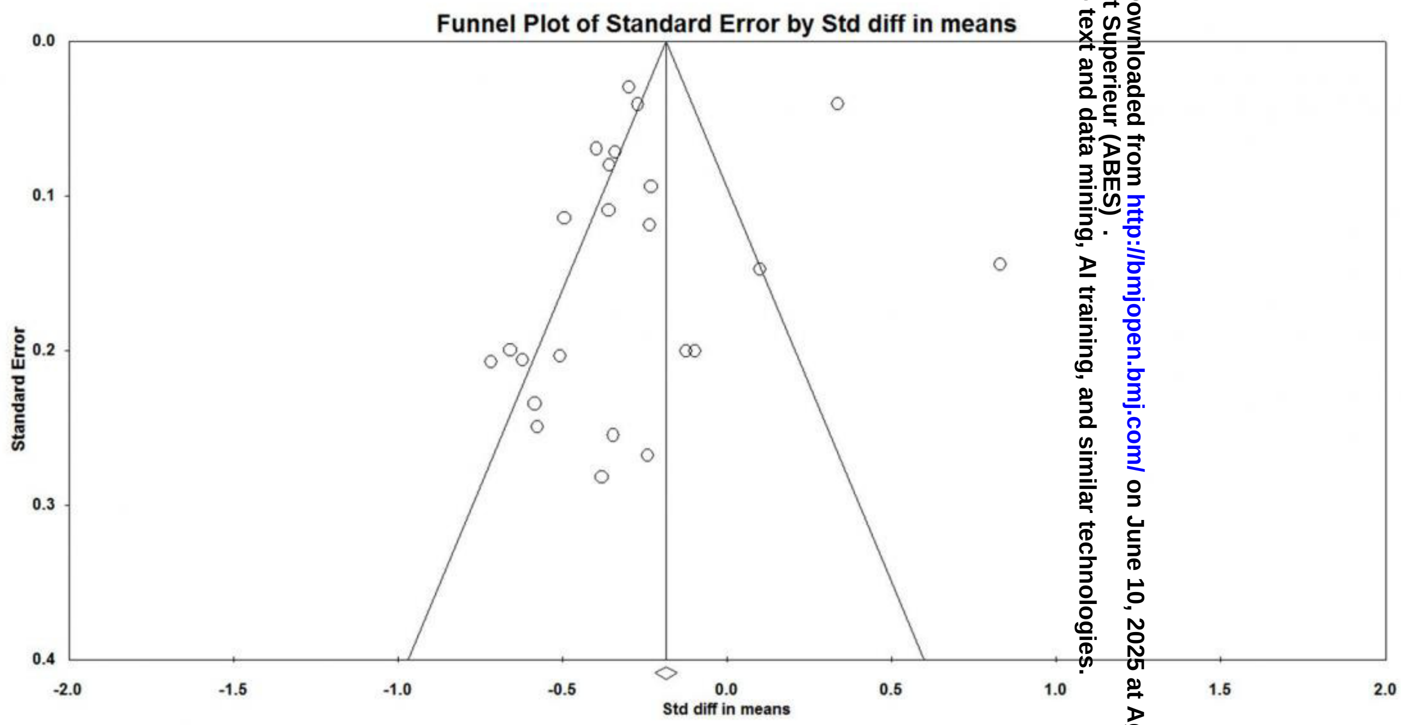
Outcome


Funnel Plot of Standard Error by Std diff in means
Standard Error
0.0
0.1
0.2
0.3
0.4
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
Std diff in means


Funnel Plot of Standard Error by Std diff in means
Standard Error
0.0
0.1
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0.4
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-1.5
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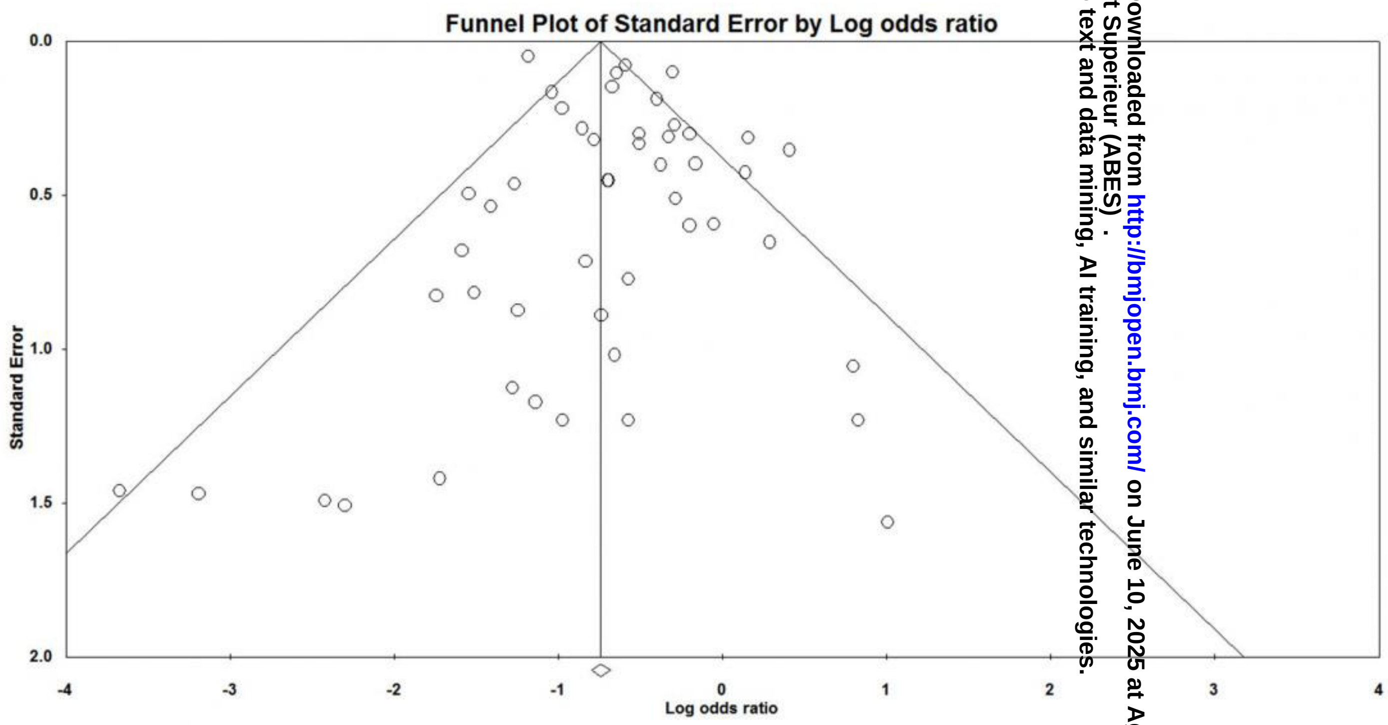
-0.5
0.0
0.5
1.0
1.5
2.0
Std diff in means


Funnel Plot of Standard Error by Log odds ratio
Standard Error
0.0
0.5
1.0
1.5
2.0
-4
-3
-2
-1
0
1
2
3
4
Log odds ratio

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-13
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	14-20
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-13
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-23
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	24

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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