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Brief Report

Association between bariatric surgery with long-term analgesic prescription and all-cause mortality among patients with osteoarthritis: a general population-based cohort study

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SUMMARY

Objectives: There is still a large unmet need for novel osteoarthritis (OA) treatments that could provide clinically important effects on long-term pain relief (≥12 months). We examined the relation of bariatric surgery along with weight loss to analgesic prescription and all-cause mortality among individuals with OA.

Methods: We conducted a cohort study among individuals with OA using The Health Improvement Network. We compared the rate of no analgesic prescription ≥12 consecutive months and the risk of all-cause mortality using inverse probability weighting Cox-proportional hazard models and the difference in number of analgesic prescriptions (non-steroidal anti-inflammatory drugs, opioids, and paracetamol) in the 50th, 75th and 90th percentiles using quantile regression model between bariatric and non-bariatric cohorts.

Results: Included were 588,494 individuals (694 had bariatric surgery). Compared with non-bariatric group, the rate of no analgesic prescription ≥12 consecutive months was higher (HR = 1.23, 95% CI: 1.08−1.38) in bariatric surgery group, and the number of analgesic prescriptions was lower in the 75th (44 vs 58) and 90th (74 vs 106) percentiles during a mean follow-up of 4.3 years. All-cause mortality in bariatric surgery group was lower than comparison group (HR = 0.46, 95% CI: 0.41−0.51).

Conclusion: This study presents the first evidence that bariatric surgery was associated with decreased long-term analgesic prescription and decreased all-cause mortality among individuals with OA. However, our findings may be overestimated owing to intractable confounding by indication for bariatric surgery; thus, future studies (e.g., clinical trials) are warranted.

Introduction

Joint pain from osteoarthritis (OA) is a major factor leading to the decision to seek medical care and an important antecedent to disability[1]. Although systemic analgesics, e.g., non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and opioids, have been widely used to relive pain from OA for decades, their adverse effects (e.g., cardiovascular and gastrointestinal diseases and addiction) and the subsequent socioeconomic costs are of great concern[1]. Furthermore, none of the currently available analgesics has shown a certainly long-term (≥12 months) efficacy in pain relief[2].

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Previous studies have shown that substantial weight loss from bariatric surgery led to marked pain reduction in obese individuals with knee pain or OA[3–7]; however, no study has examined whether it could reduce analgesic use among patients with OA. Furthermore, the net impact of improvement of both long-term pain relief and the overall general health from the bariatric surgery in OA remains unclear. To fill this knowledge gap, we conducted a cohort study to examine the relation of bariatric surgery to long-term analgesic prescription and all-cause mortality among individuals with OA.

Methods

Data source

The Health Improvement Network (THIN) is an electronic medical record database of records of general practitioners (GPs) in the United Kingdom (UK) and represents the UK population in demographics and medical conditions. THIN contains anonymized medical records from 790 general practices with approximately 17 million patients. Health care information is recorded at each practice on socio-demographics, anthropometrics, lifestyle factors, visits to GPs, diagnoses from specialists and hospital admissions, and laboratory test results. The Read classification system is used to code specific diagnoses and the Multilex classification system based on British National Formulary and Anatomical Therapeutic Chemical code is used for medications. The scientific review committee for the THIN database and the institutional review board at Xiangya Hospital, Central South University, China, approved this study, with waiver of informed consent. Details of THIN database have been described previously[8].

Study design and cohort definition

We conducted a cohort study to examine the relation of bariatric surgery to analgesic prescription and all-cause mortality. All participants who met the following inclusion criteria at the time of index date were included: (1) age between 40 and 90 years, (2) history of OA based on Read codes (Supplemental Table 1), (3) body mass index (BMI) 35 or greater, and (4) record in GP office during January 2000 to December 2018. All participants had at least 1 year of continuous enrollment with the general practice. Bariatric surgery was identified using Read codes. These included adjustable gastric banding, Roux-en-Y gastric bypass, sleeve gastrectomy, and other techniques (for example, gastrectomy, and malabsorptive procedures) (Supplemental Table 1). We divided the calendar time into 19 1-year blocks from January 2000 to December 2018. Within each time block, the date of bariatric surgery was used as the index date for the patient, and a random date was assigned as the index date for the matched subject without receiving bariatric surgery. Participants were excluded if they had no analgesic prescription before the index date, or had missing information on smoking status, alcohol drinking, or Socioeconomic Deprivation Index.

Assessment of outcomes

The outcomes were rate of no analgesic prescription for ≥12 consecutive months, number of analgesic prescriptions, and all-cause mortality during the follow-up period. Analgesic prescription (NSAIDs, opioids or paracetamol) was identified according to the Multilex classification system based on a drug dictionary in British National Formulary and Anatomical Therapeutic Chemical code (Supplemental Table 2). Mortality was defined by the death date recorded in THIN, linked to the National Health Service[8].

Assessment of covariates

Covariates were listed in Table I. Socio-demographic and anthropometric characteristics and lifestyle factors were assessed using the nearest available datapoint prior to the index date. OA site and duration, duration of database data, comorbidities and medication use were assessed before the index date. Healthcare utilization was ascertained during the 1-year period before the index date.

Statistical analysis

Person-years of follow-up for each participant were calculated as the amount of time from the index date to the first of the following events: death, age 90 years, transferring out of the THIN GP practice, or December 31, 2019 when the study was closed. We examined the relation of bariatric surgery to the rate of no analgesic prescription for ≥12 consecutive months using Cox-proportional hazard models to account for the competing risk of death. If the proportional hazard assumption was violated, we conducted a weighted Cox regression to obtain a non-proportional hazard ratio (HR). Since the number of analgesic prescriptions was not normally distributed, we examined the association between bariatric surgery and number of analgesic prescriptions using the quantile regression models[9]. We compared the difference in number of analgesic prescriptions in 50th (i.e., median), 75th and 90th quantiles between two comparison groups, allowing us to assess the difference not only in the median number of analgesic use but also in the long-term and frequent use of analgesics (i.e., 75th or 90th percentile) between bariatric and non-bariatric cohorts. We used inverse probability weighting (IPW) to balance potential confounders between the compared groups. We also calculated the absolute rate differences (RDs) in no analgesic prescription for ≥12 consecutive months using the formula: $RD = \frac{e_1}{PY_1} - \frac{e_0}{PY_0}$, where e_i was the number of events and PY_i was the number of patient-years in the bariatric group ($i = 1$) and the comparison group ($i = 0$), respectively. Finally, we performed sub-cohort analyses according to substantial weight loss, defined as 20% of weight loss, after bariatric surgery[10], and conducted a sensitivity analysis by restricting analgesic prescriptions to opioid prescriptions. We took the same approach to examine the relation of bariatric surgery to mortality and conducted a sensitivity analysis by excluding participants with a history of ischemic heart disease, chronic renal disease, or cancer to test the robustness of our findings.

All P values were 2-sided and $P < 0.05$ was considered significant for all tests. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

The flowchart depicting the selection of participants is shown in Supplemental Figure 1. The baseline characteristics were well-balanced between 694 participants in the bariatric surgery group and 587,800 participants in the no-bariatric surgery group after IPW (Table I).

The rate of no analgesic prescription for ≥12 consecutive months was 238.2/1000 person-years in the bariatric group and 191.5/1000 person-years in the comparison group (Supplemental Table 3). The RD was 46.7 (95% CI: 22.2 to 71.3) and the HR was 1.23 (95% CI: 1.08 to 1.38). The difference in the rate of no analgesic prescription for ≥12 consecutive months was more pronounced among individuals with substantial weight loss from bariatric surgery (HR = 1.43, 95% CI: 1.25 to 1.62), but not among individuals without substantial weight loss (HR = 1.05, 95% CI: 0.90 to 1.21). The relation of bariatric surgery to the rate of no opioid prescription

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Variable list	Bariatric surgery ($n = 694$)	No bariatric surgery ($n = 587{,}800$)	Standard difference before IPW	Standard difference after IPW
Demographics				
Age, mean (SD), y	55.0 (7.1)	59.8 (10.3)	0.543	0.081
Socioeconomic deprivation index score, mean (SD)*	2.9 (1.4)	3.0 (1.3)	0.067	0.055
Female (%)	76.1	70.1	0.135	0.040
BMI, mean (SD), kg/m^2	46.7 (6.9)	40.6 (5.8)	0.957	0.073
Lifestyle factors				
Drinking (%)			0.051	0.017
None	30.1	28.1		
Past	5.0	4.6		
Current	64.9	67.3		
Smoking (%)			0.114	0.054
None	53.5	54		
Past	38.8	35.3		
Current	7.8	10.8		
OA duration†, mean (SD), y	6.9 (5.7)	9.5 (7.4)	0.407	0.076
Duration of database data‡, median (IQR), y	8.6 (5.4, 11.3)	9.2 (5.9, 12.6)	0.224	0.019
OA site				
Knee OA	35.2	31.7	0.073	0.065
Hip OA	9.1	11.2	0.070	0.072
Hand OA	3.5	3.8	0.018	0.020
Comorbidity (%)				
Hypertension	55.8	65.1	0.193	0.093
Diabetes	42.1	30.9	0.233	0.034
Hyperlipidemia	16.0	19.6	0.094	0.064
Liver disease	3.9	4.3	0.018	0.005
Chronic kidney disease	6.3	15.6	0.301	0.088
Pneumonia or infection	9.1	9.1	<0.001	0.005
Chronic obstructive pulmonary disease	3.6	7.0	0.154	0.022
Cancer	7.9	11.3	0.116	0.018
Venous thromboembolism	7.3	7.0	0.015	0.015
Cerebrovascular accident	1.6	3.6	0.129	0.053
Atrial fibrillation	3.0	7.4	0.198	0.205
Ischemic heart disease	5.5	16.2	0.349	0.094
Peripheral vascular disease	0.4	1.5	0.110	0.024
Fracture	29.0	29.3	0.007	0.018
Gastroesophageal reflux disease	17.6	19.3	0.043	0.059
Gastrointestinal bleeding	2.0	2.7	0.044	0.019
Gout	7.1	10.5	0.121	0.045
Rheumatoid arthritis	2.9	2.4	0.028	0.044
Depression	32.7	20.0	0.291	0.031
Medication (%)				
NSAIDs	96.7	96.1	0.031	0.042
Opioids	72.0	63.9	0.175	0.068
Paracetamol	51.7	59.3	0.153	0.056
ACE inhibitors	48.7	52.5	0.075	0.098
Beta receptor inhibitors	35.2	42.9	0.159	0.075
Antihypertensive	79.8	81.6	0.044	0.073
Antidiabetic	32.1	23.9	0.183	0.075
Statin	44.2	54.1	0.197	0.031
Calcium channel blockers	35.6	44.8	0.189	0.022
PPIs	70.5	64.4	0.130	0.014
H2 blockers	25.5	25.6	0.002	0.002
Angiotensin receptor blockers	18.6	21.8	0.080	0.097
Loop diuretics	37.2	37.5	0.007	0.003
Thiazide diuretics	38.6	49.1	0.211	0.016
Glucocorticoids	37.9	32.4	0.116	0.022
Estrogen	37.6	29.2	0.179	0.077
Anticoagulants	9.9	12.1	0.068	0.018
Healthcare utilization, mean (SD)				
Hospitalizations§	0.8 (1.0)	0.5 (1.2)	0.284	0.015
General practice visits§	8.7 (6.8)	7.0 (7.2)	0.239	0.043
Specialist referrals§	1.2 (1.5)	0.7 (1.1)	0.425	0.077

OA, osteoarthritis; BMI, body mass index; n, number; y, years; SD, standard deviation; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin converting enzyme; PPIs, proton pump inhibitors; IPW, inverse probability weighting.

* The Socio-Economic Deprivation Index was measured by the Townsend Deprivation Index, which was grouped into quintiles from 1 (least deprived) to 5 (most deprived).

† The duration of OA was calculated by using the year of index date minus year of OA diagnosis.

‡ The duration of database data was calculated by using the year of index date minus year of entry date.

§ Frequency during the past 1 year.

Table I Baseline characteristics of patients with OA

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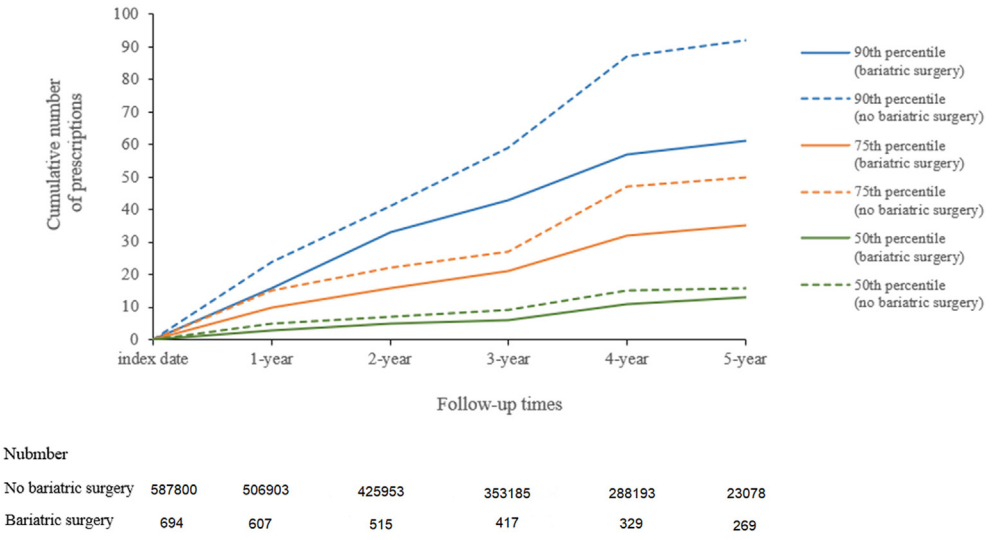

Fig. 1 Association between bariatric surgery with number of analgesic prescriptions among patients with OA. OA, osteoarthritis.

for ≥12 consecutive months remained similar (Supplemental Table 4).

As shown in Fig. 1 and Supplemental Table 5, the number of analgesic prescriptions among the bariatric surgery group was lower than that among the comparison group. While there was no difference in median number of analgesic prescriptions between the two groups (0.0, 95% confidence interval [CI]: −6.4 to 6.4), the numbers of analgesic prescriptions in the 75th and 90th percentiles in the bariatric group were much lower than that in the non-bariatric group during the follow-up period, with the corresponding differences being −10.0 (95% CI: −16.3 to −3.7) and −36.0 (95% CI: −56.7 to −15.3), respectively. The reduction in the number of analgesic prescriptions at the 75th or 90th percentile was more pronounced among individuals with substantial weight loss from bariatric surgery (−15.0, 95% CI: −19.4 to −10.6; −40.0, 95% CI: −55.6 to −24.4) than among individuals without substantial weight loss (−10.0, 95% CI: −24.8 to 4.8; −34.0, 95% CI: −76.0 to 8.0) when compared with the comparison group. Similar association between bariatric surgery and number of opioid prescriptions was observed (Supplemental Table 6).

During the follow-up period, 21 deaths occurred in the bariatric group (6.9/1000 person-years) and 64,858 deaths occurred in the non-bariatric group (24.1/1000 person-years). Compared with those without bariatric surgery, HR of mortality for bariatric surgery was 0.46 (95% CI: 0.41–0.51) (Supplemental Table 7), and sensitivity analysis by excluding participants with ischemic heart disease, chronic renal disease or cancer did not materially change the results (Supplemental Table 8).

Discussion

Bariatric surgery was associated with an increased rate of no analgesic prescription for ≥12 consecutive months by 23%, a reduced number of analgesic prescriptions, and a decreased risk of mortality by 54% compared with the no-bariatric surgery group.

Comparison with previous studies

To date, several studies have reported bariatric surgery led to the short-term (≤12 months) pain reduction among individuals with knee pain or OA[3,5,7], however, there is a paucity of data on its long-term effect. Results from the Longitudinal Assessment of Bariatric Surgery-2 showed significantly reduced knee pain among 633 individuals with severe obesity and knee pain or disability 1 year post following bariatric surgery[4]. Such an improvement remained at year three[4]. In a small observational study of 13 patients with knee OA bariatric surgery was associated with a statistically significant reduction in pain at year five after surgery[6]. Our study provided the first population-based empirical evidence that bariatric surgery greatly decreased the long-term analgesic prescription. The beneficial effect of bariatric surgery may be partially explained by the improvement in pain sensitization and depressive symptoms after substantial weight loss[5,7]. Our finding of lower mortality after bariatric surgery was consistent with those of other cohort studies[11–14], including two studies with much longer median follow-up time (e.g., over 11 years)[13,14], indicating that bariatric surgery appears to have a beneficial effect on many diseases, including OA patients with severe obesity.

Limitations

Our study has several limitations. First, although we made allowances for many potential confounders, residual confounding cannot be ruled out in an observational study. For example, prognosis-based selection for bariatric surgery may lead to intractable confounding by indication; hence, the protective effect of bariatric surgery on all-cause mortality may be overestimated. Second, the use of over-the-counter analgesics was not recorded in the THIN database; thus, our estimates of analgesic use may be underestimated. Such bias, if it occurs, would affect the observed association either toward the null or away the null. Since the National Health Service England provides free health care for most services,

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including medications prescribed by GPs for the elderly, it is unlikely that many patients would purchase analgesics over the counter without a prescription. Last, prognosis-based selection for bariatric surgery may lead to intractable confounding by indication; hence, its protective effect on mortality may be overestimated.

Clinical implications

Effective management of OA with chronic pain requires long-term treatment strategies. However, a recent network meta-analysis found that none of the included 33 pharmacological interventions was superior when compared with placebo for knee OA[2]. In addition, analgesics are often recommended for short-term or intermittent use considering their safety profiles, especially for the patients with multiple comorbidities, such as OA. Owing to the lack of randomized controlled trials, large cohort studies, such as the present study, could provide the best empirical evidence for clinical practice. Furthermore, the overall all-cause mortality is critically important because mortality, regardless of its causes, represents the overall net health impact of various benefits and risks related to bariatric surgery. As a result, bariatric surgery may be considered as one alternative treatment strategy for certain morbidly obese patients with OA[15].

Conclusion

Bariatric surgery was associated with decreased long-term analgesic prescription and risk of all-cause mortality among individuals with OA. However, our findings may be overestimated owing to intractable confounding by indication for bariatric surgery; thus, future studies (e.g., clinical trials) are warranted.

Author contributions

Drs. Zhang and Lei had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Lei and Zhang are joint corresponding authors. All authors have read, provided critical feedback on intellectual content, and approved the final manuscript. Concept and design: Lei, Zhang, Zeng. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Zeng, Lei, Zhang, Lane. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Li, Wei, Zhang. Obtained funding: Zeng, Wei, Lei. Administrative, technical, or material support: Zeng, Lei, Zhang. Supervision: Lei, Zhang.

Conflict of Interest

No conflict of interest for any of the authors.

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Role of the funder/sponsor

The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. Dissemination of the findings to participants is not possible owing to the use of an anonymised dataset.

Ethical approval

This study received approval from the medical ethical committee at Xiangya Hospital (2018091077), with waiver of informed consent.

Scientific approval

This study was approved by the THIN Scientific Review Committee (21SRC005).

Statement

THIN is a registered trademark of Cegedim SA in the United Kingdom and other countries. Reference made to the THIN database is intended to be descriptive of the data asset licensed by IQVIA World Publications Ltd. (IQVIA). This work uses de-identified data provided by patients as a part of their routine primary care.

Disclaimer

The interpretation of these data is the sole responsibility of the authors.

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Everyone who contributed significantly to the work has been listed.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2021.05.063.

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