

Changes in hip fracture rate before and after total knee replacement due to osteoarthritis: a population-based cohort study

Daniel Prieto-Alhambra,¹⁻³ M Kassim Javaid,¹ Joe Maskell,^{1,4} Andrew Judge,¹ Michael Nevitt,⁵ Cyrus Cooper,^{1,4} Nigel K Arden^{1,4}

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¹NIHR Oxford Biomedical Research Unit, University of Oxford, Oxford, UK

²Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain

³IDIAP Jordi Gol i Gurina, Institut Català de la Salut, Barcelona, Spain

⁴MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton, UK

⁵Department of Epidemiology, University of California, San Francisco, California, USA

Correspondence to

Professor Nigel Arden, The Botnar Research Centre Institute of Musculoskeletal Sciences, University of Oxford, Nuffield Orthopaedic Centre, Windmill Road, Oxford OX3 7LD; nka@mrc.soton.ac.uk

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ABSTRACT

Objectives Patients with knee osteoarthritis have an increase in bone mass but no corresponding decrease in risk of fracture. This study describes the rates of hip fracture in subjects with knee osteoarthritis before and after having a total knee replacement (TKR), compared with matched controls.

Methods A population-based prospective cohort study was conducted. The study population included, from the General Practice Research Database (UK), patients 40 years and older, undergoing TKR between 1986 and end-2006 for knee osteoarthritis as 'cases' (n=20 033). Five disease-free controls (n=100 165) were randomly selected, and matched for age, gender and practice. Hip fractures were ascertained using READ codes, and yearly rates of hip fracture and rate differences were calculated for the 5 years before and after surgery, using Poisson regression. Stratified analyses were performed by age and history of fracture.

Results Hip fracture rates were non-significantly reduced compared with controls before the operation. In the year after TKR, risk increased significantly (RR 1.58; 95% CI 1.14 to 2.19). Rates then declined to equal those of controls by 3 years, and continued decreasing until the end of follow-up; corresponding RR were not significant. The increased risk is greatest in younger ages and in those without previous fracture.

Conclusions The association between knee osteoarthritis and fractures is time-dependent, which may explain the current controversy in the literature. The association is also modified by TKR: subjects have a higher rate of hip fracture than matched controls after TKR, although the rates may eventually decrease.

Osteoarthritis and osteoporosis are both common conditions in the elderly, associated with significant morbidity and healthcare costs. In 1990, an estimated 1.66 million people had a hip fracture, with an estimated cost of more than US\$7 billion in the USA alone. As the incidence of hip fracture continues to increase worldwide, projections indicate that the number of hip fractures occurring in the world each year will rise to 6.26 million by 2050, and costs of care will increase.¹ These include not only the cost of the initial hospital stay, but also subsequent costs after hospital discharge.² Osteoarthritis is the most prevalent joint disease: the prevalence of radiographic knee osteoarthritis is 33% in people over 63 years of age,³ the prevalence of clinically diagnosed knee osteoarthritis is 18.1% in those over 55 years,⁴ and significant knee pain has an annual prevalence of

25%.⁵ Moreover, osteoarthritis accounts for 80% of all total knee replacement (TKR) procedures,⁶ with reported costs of more than US\$20 000 per patient.⁷

A possible inverse association between osteoarthritis and osteoporosis (and fragility fractures) has been studied and reported in recent years, with discordant results. First observations⁸ showed that patients with hip fracture rarely had osteoarthritis, and so suggested a protective effect of osteoarthritis for osteoporosis and subsequent fractures. Several studies demonstrated an increased bone mineral density in patients with osteoarthritis, even measuring it at sites distant to the osteoarthritis affected joints. This association appeared to be stronger for knee and hip osteoarthritis than for generalised osteoarthritis or osteoarthritis in other sites,^{9 10} although recent studies using more accurate bone mineral density measuring tools, such as peripheral quantitative CT, have created some new doubts on this issue.¹¹ Some cohort studies have also shown no relationship between osteoarthritis and osteoporosis and/or fractures.^{12 13} Nevertheless, more recent, prospective cohort studies, have suggested an increased risk of fracture in patients with osteoarthritis.^{14 15} Furthermore, a recent prospective study that included more than 6500 men and women aged over 75 years, and followed them for 3 years, demonstrated that patients with a clinical diagnosis of knee osteoarthritis and with knee pain have a twofold increased risk of hip fracture.¹⁶ Different aetiologies for this association have been suggested: increased body sway in patients with knee osteoarthritis,¹⁷ increased risk of falling¹⁸ and higher severity of falls sustained¹⁶ are among them.

It is difficult to disentangle the biomechanical consequences of knee osteoarthritis from the associated changes in bone quality and mass in current observational studies, and a good opportunity to assess this is by studying the effects of TKR, performed in patients with severe knee osteoarthritis, on the rate of hip fracture in these patients. TKR is the only intervention for knee osteoarthritis that has a large effect size on relieving chronic knee pain¹⁹ and improving physical function, and TKR should therefore be effective in decreasing the risk of falls and fractures in persons with knee osteoarthritis.²⁰

We report the results of a population-based parallel cohort study, with the aim of showing the relationship between the rate of hip fractures and severe knee osteoarthritis before and after TKR, compared with matched controls, using actual

practice data from a population-based database with prolonged periods of follow-up.

METHODS

Study population

The data were obtained from the General Practice Research Database (GPRD). The GPRD consists of computerised medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from 433 contributing practices chosen to be representative of the wider UK population. GPs in the UK play a key role in the delivery of health care by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD is administered by the Medicines and Healthcare products Regulatory Agency.²¹

The GPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, clinical events, specialist referrals, hospital admissions and their major outcomes. Data are stored using OXMIS and Read codes for diseases that are cross-referenced to the International Classification of Diseases, version 9. Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD.

We identified all patients in the database with a medical diagnosis code for knee replacement from 1986 to the end of 2006. Read/OXMIS codes were used to identify primary TKR. Patients were included in the analysis if aged 40 years or over at the time of the replacement. Five controls for each case were identified and matched on age (± 5 years), gender and practice, and selected using index date matching. All subjects without a clinical or referral record for knee arthroplasty, or knee osteoarthritis, or knee pain ever on the database were eligible for controls. Subjects with a medical diagnosis code for rheumatoid arthritis were excluded. These criteria identified 20 033 cases and 100 165 controls. To calculate the rate of hip fracture, patients were followed up for a maximum 5 years before and after TKR. Controls were assigned the same index date as their matched cases. Patients receiving a second TKR within the period of observation ($n=1308$) were censored at the time of this operation, as were their matched controls.

Ascertainment of hip fracture

Hip fractures were identified using the GPRD medical codes for hip fracture, which are based on the Read/OXMIS codes: S302.00, S30y.00, S10B400, S30.11, S302400, S130.00, S30.00, S305.00, S314.00, S31.00, S310100, S31z.00, 820 T, 7K1L400, S30y.11, S310.00, 808 A, 820 B, 8210, 820 A, 14G7.00. Previous studies have demonstrated good validity of hip fracture within the GPRD.²² When the same subject appeared to have two (or more) same-site fractures with less than a week's difference between them, they were considered duplicated registers, and the first date was taken into consideration for the analysis. The date of fracture is the date entered by the GP on which the fracture occurred.

Other covariates

For baseline clinical characteristics assessment, we took into consideration body mass index (BMI), smoking status and drinking habits recorded closest to the TKR date. Also, co-morbid conditions registered by the physician were identified using the GPRD

medical codes for: asthma, malabsorption syndromes, inflammatory bowel disease, hypertension, hyperlipidaemia, ischaemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure and cancer.

Statistical analyses

A Poisson regression model was fitted to calculate a rate (separately in both cases and controls) based on the number of hip fractures and person-years of observation at risk, in time intervals of 4–5, 3–4, 2–3, 1–2 and 0–1 years before and after the index TKR. Fracture rates and smoothed curve using loess line^{23 24} for hip fracture rates and 95% CI were plotted against time before and after TKR in months.

Hip fracture rate differences (absolute difference in hip fracture rate between cases and controls) and 95% CI were calculated using Poisson regression, and smoothed curves (loess lines) were plotted against time before and after TKR in yearly intervals.

Stratified analyses were then performed using age, based on median age in the study population: 71 years or less, over 71 years. The postoperative data were also stratified on the presence or absence of a fracture that occurred before the TKR. Subjects with a previous history of hip fracture were excluded from the analysis stratified by previous fracture, as they only had one hip susceptible to a further fracture. Only controls with the same fracture history as their matched cases were included in this analysis.

For multivariate analysis, we fitted a zero-inflated Poisson model. Zero-inflated Poisson regression is used to account for evidence of overdispersion due to the excess of zero counts in the dataset. The standard error was inflated using the square root of the χ^2 statistic because repeat fractures in the same person cannot be assumed to be independent. For the univariable analysis, the main exposure of interest is whether a person is a case or control, and we estimate the rate of hip fractures in cases versus controls. Multivariable models control for the following potential confounders: age, sex, BMI, smoking status (yes, no, ex-smoker), drinking status (yes, no, ex-drinker). All statistical analyses were carried out using Stata 10.1, R (version 2.9.1) and SPSS for Mac (version 17.0).

RESULTS

The baseline clinical characteristics of subjects with TKR and matched controls are shown in table 1. As expected, there are no significant differences in age and gender. Cases had available data for a significantly longer follow-up time; nevertheless, we only used a total of 10 years follow-up for our analysis in both cases and controls. Cases had also significantly higher BMI (mean difference 2.76 kg/m²; 95% CI 2.69 to 2.84), were more likely to be a current drinker, less likely to be a current smoker, and had a higher prevalence of previous fracture.

Control participants demonstrate the expected increase in hip fracture rate with time, due to increasing age (figure 1). Cases display similar, if not lower, rates of fracture until the TKR, when their rates increase more rapidly, only regaining an equivalent rate to the control group by 36 months post-operation (RR in years 2 to 3 post-TKR is 1.00; 95% CI 0.70 to 1.43). Figure 2 shows hip fracture rate differences for annual intervals in time. This confirms that the unadjusted rates in cases were lower, although not significantly reduced, in cases until their TKR, when they start to rise. During the last year before TKR, subjects with knee osteoarthritis are at a significantly lower risk of hip fractures than controls (rate difference -0.94 hip fractures per 1000 person-years; 95% CI -1.59 to -0.30). Fracture

Table 1 Baseline clinical characteristics of TKR cases and controls

	Cases		Controls	
	Mean (SD)	Mean (SD)	Mean difference (95% CI)	Significance (p value)
Total follow-up, years	23.62 (15.68)	21.95 (15.49)	1.67 (1.44 to 1.91)	<0.001
Age, years	70.53 (9.07)	70.53 (9.07)	0	>>0.05
Body mass index, kg/m ²	28.96 (4.90)	26.20 (4.64)	2.76 (2.69 to 2.84)	<0.001
Follow-up time, months	37.64 (20.76)	34.00 (20.94)	3.64 (3.32 to 3.95)	<0.001
	Frequency (%)	Frequency (%)	OR (95% CI)	Significance (χ^2 p value)
Gender, female	11 341 (56.6%)	56 699 (56.6%)	1 (0.97 to 1.03)	>>0.05
Alcohol, drinker				
Current	14 008 (69.9%)	63 930 (63.8%)	<0.001	
Ex	1302 (6.5%)	5395 (5.4%)		
No	2680 (13.4%)	13 910 (13.9%)		
Smoker				
Current	1942 (9.7%)	15 708 (15.7%)	<0.001	
Ex	6433 (32.1%)	27 811 (27.8%)		
No	11 063 (55.2)	48 249 (48.2%)		
Subjects wit fracture before TKR	3904 (19.5%)	15 955 (15.9%)	1.28 (1.23 to 1.33)	<0.001
Subjects with hip fracture before TKR	189 (0.9%)	1108 (1.1%)	0.85 (0.73 to 0.99)	0.042
Fractured (subjects) after TKR	1104 (5.5%)	4336 (4.3%)	1.29 (1.20 to 1.38)	<0.001
No of comorbid conditions*				
0	5378 (26.8%)	35 174 (35.1%)	<0.001	
1	6870 (34.3%)	32 342 (32.3%)		
2	4773 (23.8%)	19 882 (19.9%)		
3	2114 (10.6%)	8891 (8.9%)		
4	697 (3.5%)	2957 (3.0%)		
≥5	201 (1.0%)	908 (0.9%)		

*From the following: asthma, malabsorptive syndromes, inflammatory bowel disease, hypertension, hyperlipidaemia, ischaemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic renal failure, cancer.
TKR, total knee replacement.

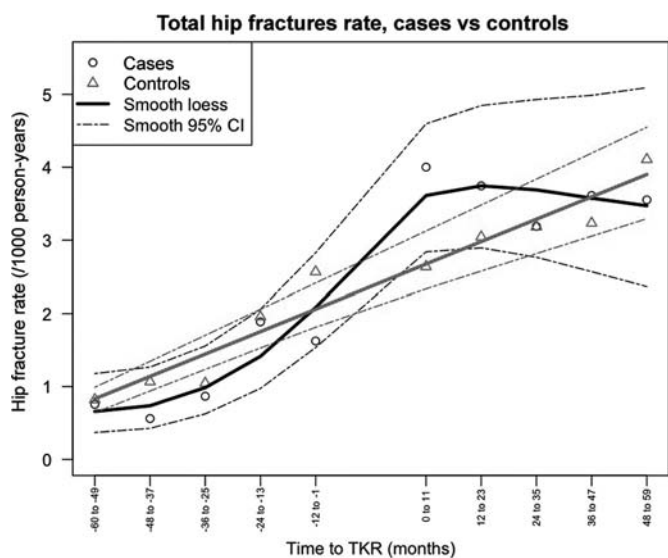


Figure 1 Hip fracture rates in cases and controls. TKR, total knee replacement.

rates among cases then increase further post-TKR, peaking at the 0–12 month interval with a rate difference of 1.36 (95% CI 0.39 to 2.34) hip fractures per 1000 person-years. The rates then become non-significantly different, and hip fracture rates among cases decrease eventually equally to those of controls after 24 months post-operation, further decreasing more importantly among cases during the last year of follow-up. Nevertheless, no further significantly reduced risk of hip fracture is observed for cases when compared with controls for the 5 years post-surgery. The RR for hip fracture adjusted for age, gender, BMI, smoking

and alcohol status were 1.27 (0.85 to 1.90) the year before surgery and 1.58 (1.14 to 2.19) the year after surgery, falling to 0.73 (0.45 to 1.20) in the fifth year post-operation (table 2).

Figures S1a and b (see supplementary figures S1a and b, available online only) show different patterns among younger and older individuals (as defined by an age of ≤71 or >71 years): older subjects show a significantly protective effect at year –4 and –1, and from then onwards a similar pattern to the whole cohort, not observed among younger individuals. In addition, we repeated these analyses after stratification using 65 and 75 years old as alternative thresholds, and the results remained unchanged (data not shown).

Figure 3A,B shows the rate difference of hip fracture limited to the postoperative period for patients with or without a non-hip fracture before the time of operation. An excess post-TKR risk is most marked in non-fracture subjects (figure 3A). Conversely, in patients with a history of previous fracture, there is a non-significantly increased risk during the first year post-operation, but then the rate difference decreases significantly during the second and third year, and continues to decrease slowly.

DISCUSSION

Our results demonstrate, for the first time, an increased risk of hip fracture in patients with knee osteoarthritis following a TKR. This risk varies according to the clinical stage of disease, as defined by the time before their operation: being reduced before the operation, it is greatest for 1–2 years following the TKR, only returning to normal after 3 years. We have also shown that this excess risk differs among different patient groups, being highest in younger ages, women and subjects without a previous fracture.

The relationship between osteoarthritis and osteoporosis is complex; numerous studies have shown an increased bone mass

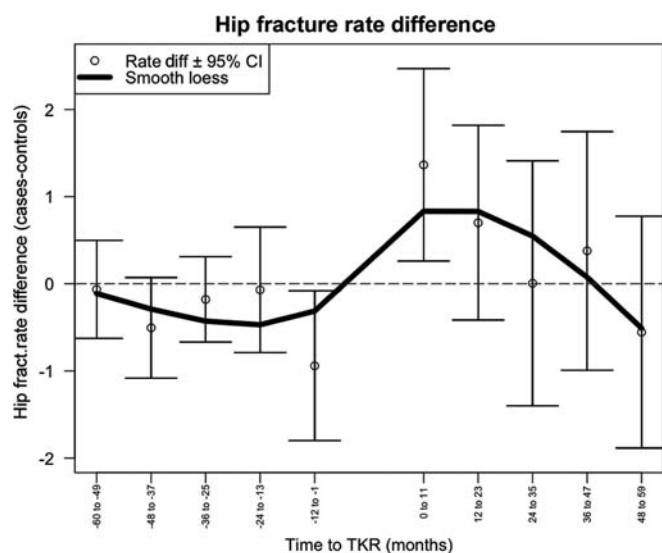


Figure 2 Hip fracture rate difference in time. TKR, total knee replacement.

in osteoarthritis patients,^{9, 10} which should reduce their risk of osteoporotic fracture; however, cohort studies have not found a reduction in fracture rates, with some showing an increased rate.^{14, 15} Falls, due to pain and/or biomechanical effects, may explain this apparent paradox: lower limb osteoarthritis is associated with an increased risk of falling,^{17, 18} and the increased risk of falls may attenuate the beneficial effects of higher bone mass on fracture rates. In two cohort studies,^{16, 18} the increased risk of fracture was independent of the number of falls; however, fall data collection is often incomplete, but more importantly, often does not describe the details of the fall. The nature of a fall can determine whether or not it is likely to result in a hip fracture: those that result in hip fractures often occur at slower walking speeds and directly onto the hip, and this type of fall may be more common in patients with knee pain.¹⁸ This study shows, for the first time, that the association between osteoarthritis and hip fracture is time dependent, with a reduction in the rate of hip fractures before knee replacement, with an increasing rate towards the date of their knee surgery, which can be used as a surrogate for severe clinical disease. This may represent an increased risk of falling with more severe knee pain, and may explain some of the discrepancy between previous studies. Unfortunately, we did not collect reliable data on falls; however, there is indirect support for this hypothesis from a case-control study, which demonstrated that the relationship between osteoarthritis and the risk of fractures²⁵ changed with time, becoming non-significant 10 years after the diagnosis of osteoarthritis. The exception to this trend is the year before surgery, when the rate of hip fracture is significantly reduced. The reason for this is unclear. However, there are several possibilities: subjects may be less active and using a walking aid and therefore at a lower risk of falls, as suggested by bibliography;²⁶ alternatively this may be a statistical anomaly.

This study shows that the risk of hip fracture is increased for 12–24 months after the operation. This period of time includes the postsurgical rehabilitation period, when residual knee pain and stiffness may remain. Further work is needed to demonstrate whether lifestyle, physical therapy and/or pharmacological interventions can modify this risk. Patients who are highly sedentary in the last year waiting for a TKR appear to be at a significantly lower risk of hip fracture. They may then become very active post-surgery (both for rehabilitation and because of pain relief); this abrupt increase in exposure to fall risk may contribute to the

Table 2 RR for hip fracture (cases/controls) in time to and after TKR

	Unadjusted RR (95% CI)	Final adjusted model†
Year -5 to -4	0.93 (0.50 to 1.73)	0.98 (0.34 to 2.78)
Year -4 to -3	0.42* (0.21 to 0.84)	0.49 (0.21 to 1.15)
Year -3 to -2	0.97 (0.55 to 1.69)	1.60 (0.86 to 2.97)
Year -2 to -1	0.89 (0.60 to 1.30)	1.51 (0.97 to 2.34)
Year -1 to date of TKR	0.80 (0.55 to 1.17)	1.27 (0.85 to 1.90)
Date of TKR to Year +1	1.27 (0.96 to 1.68)	1.58** (1.14 to 2.19)
Year +1 to +2	1.14 (0.84 to 1.54)	1.35 (0.95 to 1.91)
Year +2 to +3	1.00 (0.70 to 1.43)	1.11 (0.75 to 1.65)
Year +3 to +4	1.04 (0.70 to 1.56)	1.39 (0.89 to 2.15)
Year +4 to +5	0.72 (0.46 to 1.13)	0.73 (0.45 to 1.20)

* $p < 0.05$; ** $p < 0.005$.

†Adjusted by age, gender, body mass index, smoking and alcohol intake status. TKR, total knee replacement.

described increase in hip fracture risk. The risk stratification suggests that most of the excess risk of fracture is concentrated in younger patients and those who have not previously sustained a fracture, and as such are less likely to be assessed for fracture risk preoperatively by healthcare professionals.

The decrease in risk observed presurgery among patients at younger ages (figure S1a, available online only) remains unexplained, but could possibly be due to a selection bias, in which younger patients undergoing a TKR might be different to those of older ages. We conducted a sensitivity analyses in order to test for consistency, changing the age threshold used for stratification to: 65 years or less versus over 65, 71 years or less versus over 71 and 75 years or less versus over 75. The results did not change (data not shown), suggesting that this might not be due to chance, but this needs further validation in other studies.

The differences observed in terms of fracture risk after TKR between subjects with and without a previous fracture constitute a novel finding, and additional exploration in different cohorts should be carried out to confirm this.

Important strengths of our study are that the GPRD is highly representative of the whole UK population and contains comprehensive data before and after TKR. Furthermore, large samples from GPRD data, similar to ours, have already been successfully used to assess fracture risk prediction²⁷ and epidemiology of fractures in England and Wales.²⁸ The longitudinal nature of the dataset allows the temporal trends in the association between osteoarthritis and hip fracture to be explored for the first time.

The most important potential limitations of our study are the non-validation of fractures at an individual level; however, the fracture data have been widely validated in GPRD.²⁹ It is possible that there are some missing fractures in our dataset; the GPRD is highly specific for fracture (95% correctly coded) but likely to be insensitive.²⁹ However, this is a random misclassification bias, and would serve to adjust the OR downwardly, rather than inflate it. Furthermore, we only took into consideration hip fractures, which are almost always hospitalised, and so, more reliably registered. The GPRD has limited individual information on falls, and so, unfortunately, we could not assess the suggested association between knee osteoarthritis, TKR, falls and hip fractures. Information on ethnic origins is also not available in GPRD data. Our results are not necessarily generalisable to other populations and healthcare systems.

Patients with knee osteoarthritis have a variable risk of hip fracture depending on the time around knee replacement. TKR, in the long term, appears to be effective in reducing the risk of fracture among patients with knee osteoarthritis; however, the risk of hip fracture is increased for up to 2 years before and after surgery, but reduced further away from this period. This suggests

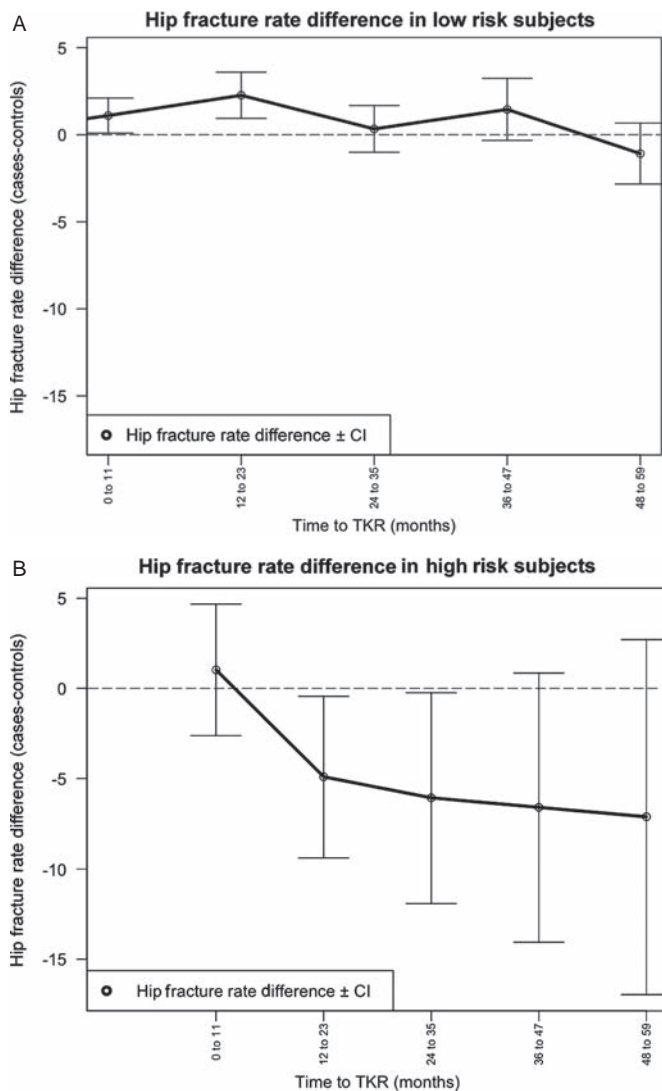


Figure 3 (A) Hip fracture difference in time. Subjects with no previous fracture. Hip fracture difference in time. Subjects with a previous fracture. (B) Hip fracture rate difference: subjects with a previous fracture. TKR, total knee replacement.

that the increased risk of hip fracture is mediated by pain and biomechanical changes leading to an increased risk of falls. We show that particularly during the postoperative hospitalisation and rehabilitation phases, there is a definite increased risk of hip fracture that needs to be recognised by rehabilitation professionals. Strategies should be implemented to reduce hip fractures in those patients undergoing a TKR, both before and after surgery.

Contributions DPA, MKJ, NKA and AJ were involved in the analysis and interpretation of data, and NKA and MKJ in the conception and design of the study. DPA drafted the manuscript. All authors had full access to all of the data in the study, and reviewed the manuscript. NKA is the guarantor.

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Competing interests None.

Ethics approval The GPRD group obtained ethical approval from a multicentre research ethics committee for all purely observational research using GPRD data, such

as ours. This study obtained approval from the GPRD Independent Scientific Advisory Committee, responsible for reviewing protocols for scientific quality.

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