BMJ Open Geographical and ethnic differences of osteoarthritis-associated hip and knee replacement surgeries in New Zealand: a population-based cross-sectional study

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ABSTRACT

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Dr Chunhuan Lao; chunhuan.lao@waikato.ac.nz **Objectives** To (1) explore the regional and ethnic differences in rates of publicly funded osteoarthritis-associated hip and knee replacement surgeries and (2) investigate the mortality after surgery.

Design Population-based, retrospective, cross-sectional study.

Setting General population in New Zealand. Participants Patients with osteoarthritis who underwent

publicly funded primary hip and knee replacement surgeries in 2005–2017. Patients aged 14–99 years were included. **Primary and secondary outcome measures** Agestandardised rate, standardised mortality ratio (SMR) and 30 days, 90 days and 1 year mortality.

Results We identified 53 439 primary hip replacements and 50072 primary knee replacements with a diagnosis of osteoarthritis. The number and age-standardised rates of hip and knee replacements increased over time. Maori had the highest age-standardised rate of hip replacements, followed by European/others and Pacific, and Asian had the lowest rate. Pacific had the highest age-standardised rate of knee replacements, followed by Maori and European/others, and Asian had the lowest rate. The Northern Health Network had the lowest rate of hip surgeries, and the Southern Health Network had the lowest rate of knee surgeries. The SMRs of patients undergoing hip and knee replacements were lower than the general population: 0.92 (95% Cl 0.89 to 0.95) for hip and 0.79 (95% CI 0.76 to 0.82) for knee. The SMRs were decreasing over time. The patterns of 30 days, 90 days and 1 year mortality were similar to the SMR.

Conclusions The numbers of publicly funded osteoarthritis-associated primary hip and knee replacements are steadily increasing. Māori people had the highest age-standardised rate of hip replacements and Pacific people had the highest rate of knee replacements. The Northern Health Network had the lowest rate of hip surgeries, and the Southern Health Network had the lowest rate of knee surgeries. Compared with the general population, patients who had hip and knee replacements have a better life expectancy.

INTRODUCTION

Osteoarthritis is the most common form of arthritis. In New Zealand, osteoarthritis affects 10.6% of adults.¹ European people

Strengths and limitations of this study

- This study is based on national data sets including over 100000 primary hip and knee replacement surgeries, with comprehensive data on patient characteristics, comorbidities and mortality.
- We used the WHO standard population as the reference to calculate the age-standardised rates of primary hip and knee replacement surgeries, to enable international comparisons on age-standardised rates of surgeries.
- We estimated the 30 days, 90 days and 1 year mortality after surgery, as well as standardised mortality ratio (SMR), which is easier for global comparison.
- Poisson regression modelling was used to calculate the rate ratios of SMR by subgroup after adjustment for other factors.
- One weakness is that this study does not have data on the prevalence of hip and knee osteoarthritis by subgroups to identify the reasons for lower rates of surgeries in some subgroups.

are more likely to have (12.5%) osteoarthritis than Māori (7.1%), Pacific (4.8%)and Asian people (2.5%).¹ Risk factors of osteoarthritis include systemic factors (such as genetics, dietary intake, oestrogen use and bone density) and local biomechanical factors (such as muscle weakness, obesity, occupation factors, sports participation and joint laxity).² ³ These risk factors partially explain the ethnic differences in prevalence of osteoarthritis.

Osteoarthritis of the hip and knee is one of the most common causes of reduced mobility. Hip and knee replacements for osteoarthritis can help to alleviate pain and improve function. The New Zealand Joint Registry (NZJR) reported osteoarthritis as the indication for 87% and 84% of primary hip and knee arthroplasties, respectively.⁴ Regional and ethnic disparities in hip and knee replacement surgeries have been demonstrated in other countries.^{5–12} It has been reported in

Australia that total hip and knee replacements are more likely to be performed for socially advantaged populations.¹³ ¹⁴ African–Americans, Asians and Hispanics are less likely to receive hip and knee replacement surgeries than American–European.⁵ ¹² Some studies have found variations in practice between different regions in New Zealand,^{15–18} but little has been reported in the differences in access to hip and knee replacement surgeries between different regions.

Perioperative mortality is of great importance for assessing the safety of interventions, undertaking performance assessment and completing quality improvement initiatives.^{19 20} Hip and knee replacement surgeries are generally considered to be safe and successful procedures. Short-term and long-term mortality after hip and knee replacements has been reported to be lower or equivocal to the general population.²¹⁻²⁵

The New Zealand healthcare system is a mix of government-funded and private healthcare. The public-funded system is controlled and managed by the Ministry of Health.²⁶ The District Health Boards (DHBs) hold 75% of health funding in New Zealand. The public resources are limited and are allocated based on prioritisation.²⁷ Before 2017, the DHBs uses a clinical priority system specific to hip and knee primary and revision surgery for prioritising patients for surgery.²⁸ Since around 2017, the DHBs have shifted to using a generic prioritisation tool called Clinical Priority Assessment Criteria.²⁹ While the same scoring tool is used between DHBs, the score required to meet the commitment threshold is determined by individual DHBs, so varies between regions. It may be adjusted throughout the year based on available resources.

This study aims to (1) explore the regional and ethnic differences in rates of publicly funded osteoarthritis-associated hip and knee replacement surgeries and (2) investigate the mortality of patients having hip and knee replacement surgeries.

METHODS

Data sources

This study included patients with osteoarthritis who underwent publicly funded primary hip and knee replacement surgeries in 2005–2017. Patients aged between 14 and 99 years were included. These records were identified from the National Minimum Dataset (NMD) that stores all publicly funded and some privately funded hospital inpatient and day-patient discharge information nationally. The ICD-10-AM ACHI procedure codes (V.3) were used to extract the primary hip and knee replacement surgeries. These records were cross-referenced with the NZJR data to exclude the admissions not for primary hip or knee replacement surgery.

The NMD records patient's diagnosis for the admission and other comorbidities with a maximum of 30 diagnostic codes. Patients without a diagnosis of osteoarthritis were excluded. Comorbidities for calculating the Charlson Comorbidity Index score were identified from the diagnostic codes based on the coding algorithms developed by Quan *et al.*³⁰

Data from the NMD were linked to the Mortality Collection through patients' National Health Index (NHI) numbers.³¹ The NHI number is a unique identifier that is assigned to every person who uses health and disability support services in New Zealand. The combined data sets included: (1) demographic information: age, gender, ethnicity and location (DHBs); (2) treatment information: diagnosis, comorbidities and date of surgery; and (3) date of death.

Data analyses

Age-standardised rates of primary hip and knee replacement surgeries by gender, ethnicity (Māori, Pacific, Asian and European/others) and regional health network were calculated using the WHO standard population as the reference. There are four health networks in New Zealand: Northern Health Network, Midland Health Network, Mid Central Health Network, Midland Health Network, Mid Central Health Network and Southern Health Network. The Northern Health Network has a high Pacific population, the Midland Health Network has a high Māori population and is very rural, and the Southern Health Network is also rural but with low Māori and Pacific populations.^{32 33}

Because the population data by ethnicity and region provided by the Ministry of Health and Statistics New Zealand³³ was only available since 2006, the age-standardised rates by ethnicity and region were calculated for records in 2006–2017. Time trend analysis was performed on the number of surgeries as well as the age-standardised rates by subgroups.

Standardised mortality ratio (SMR) was estimated to compare the relative rate of observed deaths in the surgery group to expected deaths in the general population. The gender-specific, age-specific and year-specific mortality rate for the general population were from the Statistics New Zealand. The last updated date of the Mortality Collection was 31 December 2015; therefore, SMR was only estimated for patients in 2005-2014 to ensure all patients had at least 1-year follow-up after surgery. Subgroup analyses on SMR were performed by gender, age, ethnicity, Charlson score, year of surgery, health network and number of same type of surgeries. For patients who had two hip/knee (same type) surgeries, the first surgery date was used to calculate the SMR. Poisson regression modelling was used to calculate the adjusted rate ratios of SMR by subgroup. We have also estimated the 30 days, 90 days and 1 year mortality after surgery, and examined the differences by subgroup. All data cleaning and analyses were performed in R V.3.5.0.

Patient and public involvement

There was no active involvement of patients or the public in the research questions, study design and data analyses.



Figure 1 Number of publicly funded osteoarthritisassociated primary hip and knee replacements in 2005–2017.

RESULTS

We identified 60527 admissions for publicly funded primary hip replacements and 52098 admissions for primary knee replacements in 2005-2017 from the NMD. After cross-referencing with the NZJR, 500 (0.8%)admissions coded for primary hip replacements and 483 (0.9%) admissions coded for primary knee replacements were excluded. Of the eligible surgeries (60027 primary hip surgeries and 51615 primary knee surgeries), 53439 (89.0%) primary hip replacements and 50072 (97.0%)primary knee replacements had a diagnosis of osteoarthritis. The number of hip replacements has steadily increased from 3283 in 2005 to 5272 in 2017 (by 60.6%), and the number of knee replacements increased from 3093 in 2005 to 5263 in 2017 (by 70.2%) (figure 1). While more total hip than total knee replacement surgeries were performed in 2005, the total numbers of hip and knee replacement surgeries performed per year have converged over recent years.

The number of surgeries by ethnicity varied in different health network (appendix tables 1 and 2). For primary hip replacement surgeries, 17.4% of surgeries in the Midland Health Network were performed in Māori patients compared with only 4.3% in the Southern Health Network. For primary knee replacement surgeries, 10.0% of surgeries in the Northern Health Network were performed in Pacific patients compared with only 0.9% in the Southern Health Network and 1.6% in the Midland Health Network.

The overall age-standardised rates of hip and knee surgeries both increased over time (figures 2 and 3): from 59.7 per 100 000 in 2005 to 69.8 per 100 000 in 2017 for hips, and from 55.1 to 68.1 per 100 000 for knees, respectively. The rates of hip and knee replacement surgeries between women and men were similar. There were great ethnic disparities in rates of hip and knee replacement surgeries. Māori had the highest age-standardised rate of hip surgeries (105.6 per 100 000 in 2017), followed by European/others (74.0 per 100 000) and Pacific (30.0 per 100 000), and Asian (5.3 per 100 000) had the lowest rate. Pacific had the highest age-standardised rate of knee replacements (108.9 per 100 000 in 2017), followed



Figure 2 Age-standardised rates of primary hip replacement surgeries by subgroup: (A) overall and by gender; (B) by ethnicity; (C) by health network.

by Māori (72.5 per 100 000) and European/others (68.5 per 100 000), Asian (39.3 per 100 000) had the lowest rate. The Northern Health Network had the lowest rate of hip surgeries, and the Southern Health Network had the lowest rate of knee surgeries.

Patients undergoing hip and knee surgeries had a longer life expectancy compared with the general population of the same gender and age in recent years. The SMRs of patients undergoing hip and knee surgeries were 0.92 and 0.79, respectively (table 1). The SMRs were decreasing over time, from 1.05 (95% CI 0.97 to 1.13) in 2005 to 0.62 (95% CI 0.47 to 0.81) in 2014 for hip surgeries, and from 0.94 (95% CI 0.87 to 1.01) in 2005 to 0.46 (95% CI 0.33 to 0.63) in 2014 for knee surgeries. Women had a lower SMR than men and patients aged 70+ years had lower SMRs than younger patients, in terms of both hip and knee surgeries. The SMRs increased with Charlson score, from 0.70 for patients with a Charlson score 0 to 2.37 for patients with a Charlson score 3+ for hip surgery, and from 0.70 for Charlson score 0 to 1.93 for Charlson score 3+ for knee surgery. Māori patients undergoing hip and knee surgeries had a shorter life expectancy than the general population (SMR>1), but all other ethnic groups had a longer life expectancy than the general population (SMR<1). Patients in the Northern Health Network had



Figure 3 Age-standardised rates of primary knee replacement surgeries by subgroup: (A) overall and by gender; (B) by ethnicity; (C) by health network.

the lowest SMR. Patients who had two hip/knee surgeries had a much lower SMR (0.57 and 0.52) than patients who only had one hip/knee surgery (0.98 and 0.87).

Poisson regression (table 2) showed that the adjusted rate ratio of SMR between men and women was 0.96 (95% CI 0.91 to 1.02) for hip replacements and 1.03 (95% CI 0.97 to 1.10) for knee replacements. Māori patients had a higher rate ratio of SMR compared with other ethnic groups, and all other health networks had high rate ratios (>1) compared with the Northern Health Network. The rate ratio decreased with age and year, and increased with Charlson score.

The patterns of 30 days, 90 days and 1 year mortality after replacement surgery (appendix tables 3 and 4) by gender, Charlson score, year and number of surgeries were consistent with the SMR. The 30 days, 90 days and 1 year mortality all increased with age.

DISCUSSION

Among the total numbers of publicly and privately funded primary hip and knee replacements in 2005– 2016, publicly funded primary hip and knee replacements accounted for 54% and 59%, respectively.⁴ The annual proportion of publicly funded surgeries over the total public and private surgeries has been stable. The total number of publicly funded hip and knee replacements has been increasing over time as have the age-standardised rates of surgery.

In a paper by Pabinger and Geissler comparing the utilisation rates of hip replacements among 27 OECD (Organisation for Economic Co-operation and Development) countries,³⁴ New Zealand ranked 17th in 2011 with a rate of 141 hip replacements per 100000 total population, and Switzerland had the highest rate of 306 per 100 000, followed by Germany (286 per 100 000) and Austria (273 per 100 000). The rates in this paper were not age-standardised and included all publicly and privately funded surgeries. These explained the difference between the rate of 141 per 100000 in Pabinger's paper and the age-standardised rate of 60 per 100000 in our study. Hooper *et al*³⁵ estimated an age-standardised rate of total hip and knee replacements of 285 and 250 per 100000, respectively, in 2011 in New Zealand. The gaps between Hooper's and our estimations can be explained by all publicly and privately funded surgeries included in their study and the population used for estimating age-standardised rate, only including people aged 35+ years. We decided to use the WHO standard population including all age groups as the reference, because the Ministry of Health reports all use the WHO standard population to calculate the age-standardised rates and it enables head-to-head comparisons with overseas studies.

Interestingly, we found that Māori people had the highest age-standardised rate of publicly funded hip surgeries and Pacific people had the highest rate of publicly funded knee surgeries. Hooper's study showed that New Zealand Europeans had the highest rate of hip replacements and a second-highest rate of knee replacements, which was slightly lower than Pacific people.³⁵ This is possibly because New Zealand Europeans are more likely to have privately funded surgeries than other ethnic groups.³⁶ Asian people had the lowest rate of hip (less than 10% the rate for all patients) and knee (58% of the rate for all patients) surgeries. This corresponds to the low prevalence of osteoarthritis for Asian people (1.9%).¹

The Northern Health Network had the lowest rate of hip surgeries, and has a high urban population compared with the other regions. Research has shown that farmers have high rates of hip osteoarthritis,³⁷ and the Northern Health Network has a smaller population of rural residents than other health networks. The Southern Health Network had the lowest rate of knee surgeries. This may be related to the access problems. The Southern Health Network has a big rural population but low Māori and Pacific populations who had high needs of primary knee replacement surgeries as shown in our results. Other reasons may include the variations in the distribution of different ethnicities and people of different socio-economic status in different health network. Socially disadvantaged populations are more likely to have better

Table 1 Standardised mortality ratio (SMR) of studied patients compared with general population										
	Primary hip replacem	ent	Primary knee replacer	ment						
Subgroups	Number of patients	SMR (95% CI)	Number of patients	SMR (95% CI)						
Gender										
Female	18336	0.90 (0.86 to 0.95)	16205	0.76 (0.72 to 0.81)						
Male	15797	0.93 (0.89 to 0.98)	14136	0.82 (0.78 to 0.86)						
Ethnicity										
European/others	29853	0.88 (0.84 to 0.91)	25692	0.77 (0.74 to 0.80)						
Māori	3671	1.64 (1.43 to 1.89)	2317	1.41 (1.20 to 1.66)						
Pacific	419	1.02 (0.62 to 1.68)	1345	0.76 (0.58 to 1.00)						
Asian	190	0.95 (0.51 to 1.80)	987	0.58 (0.44 to 0.78)						
Age (years)										
<40	518	1.81 (0.48 to 6.89)	52	4.72 (0.18 to 127.22)						
40–49	2127	1.32 (0.84 to 2.06)	719	1.35 (0.63 to 2.92)						
50–59	5515	1.37 (1.13 to 1.66)	4681	1.11 (0.90 to 1.38)						
60–69	9924	1.12 (1.02 to 1.23)	10144	0.88 (0.80 to 0.97)						
70–79	11300	0.84 (0.80 to 0.89)	10928	0.74 (0.70 to 0.78)						
80+	4749	0.88 (0.83 to 0.93)	3817	0.79 (0.75 to 0.84)						
Charlson Comorbidity Index										
0	29663	0.79 (0.76 to 0.82)	25538	0.70 (0.67 to 0.73)						
1	2236	1.37 (1.24 to 1.52)	2260	1.17 (1.05 to 1.30)						
2	1598	1.68 (1.45 to 1.95)	1874	1.12 (0.96 to 1.30)						
3+	636	2.37 (1.97 to 2.85)	669	1.93 (1.59 to 2.35)						
Year										
2005	3176	1.05 (0.97 to 1.13)	2970	0.94 (0.87 to 1.01)						
2006	3149	1.04 (0.96 to 1.13)	2835	0.86 (0.79 to 0.94)						
2007	3520	0.97 (0.90 to 1.06)	3109	0.84 (0.76 to 0.92)						
2008	3312	0.98 (0.89 to 1.08)	2828	0.79 (0.71 to 0.88)						
2009	3473	0.87 (0.78 to 0.97)	3009	0.84 (0.75 to 0.95)						
2010	3356	0.79 (0.70 to 0.90)	2849	0.66 (0.58 to 0.76)						
2011	3305	0.75 (0.65 to 0.87)	2981	0.68 (0.58 to 0.80)						
2012	3426	0.72 (0.60 to 0.85)	3097	0.49 (0.40 to 0.61)						
2013	3541	0.63 (0.50 to 0.78)	3020	0.47 (0.36 to 0.60)						
2014	3875	0.62 (0.47 to 0.81)	3643	0.46 (0.33 to 0.63)						
Health network										
Northern	8956	0.90 (0.83 to 0.96)	9996	0.72 (0.67 to 0.77)						
Mid Central	7040	0.96 (0.89 to 1.04)	6448	0.82 (0.75 to 0.89)						
Midland	8308	0.94 (0.88 to 1.01)	6834	0.84 (0.78 to 0.91)						
Southern	9807	0.88 (0.83 to 0.95)	7046	0.83 (0.77 to 0.89)						
Unknown	22	1.21 (0.25 to 5.84)	17	0.47 (0.05 to 4.65)						
Number of same type of surgeries in 2005–2017										
1	28804	0.98 (0.94 to 1.02)	24128	0.87 (0.83 to 0.91)						
2	5329	0.57 (0.51 to 0.64)	6213	0.52 (0.47 to 0.57)						
Total	34133	0.92 (0.89 to 0.95)	33 825	0.79 (0.76 to 0.82)						

Table 2 Rate ratios of standardised mortality ratio from Poisson regression model									
	Primary hip replacements			Primary knee	Primary knee replacements				
Variables	Rate ratio	95% CI	P value	Rate ratio	95% CI	P value			
Gender									
Female	Ref			Ref					
Male	0.96	0.91 to 1.02	0.216	1.03	0.97 to 1.10	0.308			
Ethnicity									
European/others	Ref			Ref					
Māori	1.61	1.46 to 1.78	<0.001	1.71	1.52 to 1.92	<0.001			
Pacific	0.96	0.67 to 1.39	0.829	0.98	0.79 to 1.22	0.883			
Asian	1.00	0.62 to 1.61	0.997	0.78	0.61 to 0.99	0.045			
Age (years)									
<40	Ref			Ref					
40–49	0.72	0.31 to 1.69	0.451	0.29	0.07 to 1.28	0.102			
50–59	0.75	0.34 to 1.70	0.494	0.26	0.06 to 1.04	0.058			
60–69	0.60	0.27 to 1.34	0.213	0.21	0.05 to 0.83	0.026			
70–79	0.45	0.20 to 0.99	0.048	0.17	0.04 to 0.68	0.012			
80+	0.46	0.21 to 1.03	0.060	0.18	0.05 to 0.73	0.016			
Charlson Comorbidity Index									
0	Ref			Ref					
1	1.69	1.55 to 1.84	< 0.001	1.63	1.49 to 1.79	<0.001			
2	2.25	2.02 to 2.50	<0.001	1.76	1.56 to 1.98	<0.001			
3+	3.01	2.66 to 3.41	<0.001	2.88	2.51 to 3.29	<0.001			
Year (first surgery date)									
2005	Ref			Ref					
2006	0.98	0.89 to 1.07	0.648	0.92	0.83 to 1.01	0.085			
2007	0.92	0.83 to 1.01	0.066	0.89	0.81 to 0.99	0.026			
2008	0.96	0.86 to 1.06	0.378	0.86	0.77 to 0.96	0.009			
2009	0.88	0.79 to 0.98	0.020	0.94	0.84 to 1.06	0.302			
2010	0.81	0.71 to 0.91	<0.001	0.74	0.65 to 0.85	<0.001			
2011	0.75	0.66 to 0.86	<0.001	0.76	0.66 to 0.88	<0.001			
2012	0.69	0.60 to 0.81	<0.001	0.52	0.43 to 0.62	<0.001			
2013	0.56	0.46 to 0.67	<0.001	0.47	0.37 to 0.59	<0.001			
2014	0.56	0.45 to 0.70	<0.001	0.46	0.35 to 0.60	<0.001			
Health network									
Northern	Ref			Ref					
Mid Central	1.08	1.00 to 1.18	0.065	1.10	1.01 to 1.21	0.032			
Midland	1.07	0.99 to 1.16	0.095	1.16	1.06 to 1.26	0.001			
Southern	1.04	0.96 to 1.13	0.298	1.12	1.03 to 1.22	0.008			
Number of same type of surgeries in 2005–2017									
One	Ref			Ref					
Two	0.53	0.48 to 0.58	<0.001	0.56	0.51 to 0.61	<0.001			
Ref, reference.									

access to hip and knee replacements compared with their less disadvantaged counterparts.^{13 14}

This study showed that patients who had primary hip and knee replacement surgeries had longer life expectancy than the general population (SMR<1). This again confirms that hip and knee replacement surgeries are safe and successful procedures. This is consistent with findings from other studies²¹ ²² ²⁴ ²⁵ reporting better mortality following total hip and knee replacements than the general population, although individuals with osteoarthritis have a shorter life expectancy.²³ Possible explanations include selection of healthier individuals to undergo surgery and benefits of increased mobility and activity levels after surgery.²² ²⁵

The high SMR and rate ratio (from Poisson regression) for Māori patients can be attributed to the overall shorter life expectancy for Māori³⁸ and the SMR was calculated by comparing Māori with the general population. The gender-specific, age-specific and year-specific mortality rate by different ethnic populations were not available. This also explains why the Midland Health Network that has the highest proportion of Māori patients (15% vs 4%–10% in other health networks) had the highest SMR. For hip replacement surgeries, 19% of Māori patients had a Charlson score of 1+ compared with 12% of European/others, and for knee replacements, 23% of Māori patients had a Charlson score of 1+ compared with 14% of European/others.

Mortality declined with increasing age at surgery, which was reported in previous studies assuming younger patients may have more comorbidities and higher risk of death.^{22 25} In our cohort, 5% of patients aged less than 50 years had one or more comorbidities. Other investigators observed a convergence of mortality after 5 years following surgery.^{39 40} This corresponds to the similar mortality to the general population (SMR close to 1) for patients having surgeries in 2005–2008.

The strength of this study is that it is based on national data sets including over 100000 primary hip and knee replacement surgeries. These data sets collect comprehensive data on patient characteristics, comorbidities and mortality. One weakness is that this study does not have data on the prevalence of hip and knee osteoarthritis by subgroups. Therefore, we cannot ascertain whether the lower rates of surgeries in some subgroups (eg, lower rates of hip surgeries in Pacific and Asian people) was because of the lower prevalence of hip and knee osteoarthritis in these subgroups or barriers of access to public health services. The mortality data were only available till 31 December 2015, and we could not examine the mortality of patients in 2015–2017.

CONCLUSIONS

The numbers of publicly funded osteoarthritis-associated primary hip and knee replacement surgeries are steadily increasing. Māori people had the highest age-standardised rate of publicly funded primary hip replacements and Pacific people had the highest rate of publicly funded knee replacements. The Northern Health Network had the lowest rate of hip surgeries, and the Southern Health Network had the lowest rate of knee surgeries. Compared with the general population, patients who had hip and knee replacements had a better life expectancy.

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Contributors CL, DL, RL, DW and SP conceived of and designed the study. CL did all the data cleaning and analyses, and wrote the first draft of the main paper. All the authors discussed the results and were involved in the critical revisions of the manuscript. All the authors have read and approved the final version of the manuscript.

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Competing interests None declared.

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