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The progression of end-stage osteoarthritis: analysis of data from the Australian and Norwegian joint replacement registries using a multi-state model

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SUMMARY

Objective: The incidence of joint replacements is considered an indicator of symptomatic end-stage osteoarthritis (OA). We analysed data from two national joint replacement registries in order to investigate whether evidence of a pattern of progression of end-stage hip and knee OA could be found in data from large unselected populations.

Design: We obtained data on 78,634 hip and 122,096 knee arthroplasties from the Australian Orthopaedic Association National Joint Replacement Registry and 19,786 hip and 12,082 knee arthroplasties from the Norwegian Arthroplasty Register. A multi-state model was developed where individuals were followed from their first recorded hip or knee arthroplasty for OA to receiving subsequent hip and/or knee arthroplasties. We used this model to estimate relative hazard rates and probabilities for each registry separately.

Results: The hazard rates of receiving subsequent arthroplasties in non-cognate joints were higher on the contralateral side than on the ipsilateral side to the index arthroplasty, especially if the index was a hip arthroplasty. After 5 years, the estimated probabilities of having received a knee contralateral to the index hip were more than 1.7 times the probabilities of having received a knee ipsilateral to the index hip.

Conclusion: The results indicate that there is an association between the side of the first hip arthroplasty and side of subsequent knee arthroplasties. Further studies are needed to investigate whether increased risk of receiving an arthroplasty in the contralateral knee is related to having a hip arthroplasty and/or preoperative factors such as pain and altered gait associated with hip OA.

Introduction

Osteoarthritis (OA) is a common chronic disease, leading to chronic pain, decreased quality of life and disability[1]. OA often involves multiple joints and the greatest disability is caused by hip and knee OA[2] for which joint replacement is often a successful treatment. The pathogenesis of OA is not clear. It is thought to be a combination of genetic factors, systemic risk factors and biomechanical factors[3–5]. The sequence of progression of OA to different joints can inform the understanding of the pathogenesis of OA. The incidence of joint replacements is considered by many an indicator of symptomatic end-stage OA[6–8], hence the progression of joint replacements in individuals is an indicator of the progression of end-stage OA. Evidence suggests that the pattern of progression of end-stage OA in large weight bearing joints is not a random process. For example, Shakoor *et al.*[8] found that a greater

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proportion of individuals who had received total hip arthroplasty (THA) or total knee arthroplasty (TKA) for OA, received their second arthroplasty in the cognate contralateral joint. Of those individuals who had received a unilateral THA followed by a TKA, a higher proportion received an arthroplasty in the contralateral knee than in the ipsilateral knee. This was in contrast to individuals with rheumatoid arthritis, where there was no difference between the sides of TKA following a THA.

Using joint replacements as an indicator of symptomatic end-stage OA, data from population-based arthroplasty registries can provide information on the progression of end-stage OA in large weight bearing joints. The objective of this study was to investigate whether evidence of a pattern of progression of joint replacements in large weight bearing joints could be found in independent data from two large national joint replacement registries using a multi-state model for each registry separately. The study hypothesis was that there is an association between the side of the first hip or knee arthroplasty and the side of subsequent arthroplasties in non-cognate large weight bearing joints.

Methods

We obtained data from the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR) and the Norwegian Arthroplasty Register (NAR). The NAR and the AOA NJRR are national registries that record and analyse data on subjects who have received joint replacements. The NAR has collected data on hip arthroplasties since 1987 and knee arthroplasties since 1994[9]. The AOA NJRR started collecting data on hip and knee arthroplasties in 1999 and became national in 2002[10].The NAR captures 97% of all hip and knee replacements performed in Norway[11].The AOA NJRR also has excellent coverage, after validation of its records against state hospital data, the AOA NJRR obtains an "almost complete dataset relating to hip and knee replacement in Australia"[10].

We obtained data on subjects who had received a first recorded hip or knee arthroplasty for OA in the period from January 1, 2002 to December 31, 2010 from the AOA NJRR and the NAR. Individuals who had received a hip or a knee arthroplasty before January 1, 2002 were excluded, as were individuals who were registered with a revision but without a primary arthroplasty. We also excluded individuals who had received two arthroplasties on the same day because the focus of the study was progression of OA. Some patients could have received arthroplasties prior to the time that the NAR and the AOA NJRR were established. Including these patients in the study sample would lead to inflation of the risk set and potentially bias the estimates. In order to minimise this complication, especially with regard to the Australian data, patients aged 55–74 years were selected because individuals within this age group compared to older individuals were less likely to have received an arthroplasty prior to 2002 that was not recorded in the joint registries. The lower age limit was selected because younger individuals had low prevalence of OA compared to the selected age group. For descriptive purposes, individuals were categorised into two groups based on age (55–64 years and 65–74 years).

The arthroplasty history of interest consisted of four possible arthroplasties; two hips and two knees. We developed a multi-state model where patients were followed as they moved through different possible states from a first arthroplasty (either hip or knee) to receiving subsequent hip or knee arthroplasties, death or until study closure (right-censored). The states describe conditions such as having had a joint replacement. When an event occurs, such as receiving a joint replacement, the individual changes state. Once the structure of the multi-state model is specified it can provide probabilities and hazard ratios (HRs) associated with states and with movements from one state to another[12].

The model with 14 possible states that can be occupied (boxes), and paths (arrows) that can be travelled, is illustrated in Fig. 1. The starting point for an individual is any one of four possibilities (left hip, right hip, left knee, right knee). After the first arthroplasty there is a total of three possible subsequent primary arthroplasties for an individual (contralateral cognate, left non-cognate, right cognate). The possibilities for the second primary arthroplasty is therefore one of the three remaining hip(s)/knee(s). The possibilities for the third primary arthroplasty is one of the remaining two hips(s)/knee(s) and so forth. At any time subjects could enter a so-called "absorbing" state, being dead (we adopt the naming convention that 'death' is an event and being 'dead' is a state[13]). Because the aim of the study was to investigate the progression of joint replacements for OA, individuals who received subsequent arthroplasties for other indications (e.g., fractured neck of femur) were merged with the state dead. The use of multi-state models and notation in analysing complex arthroplasty histories are described in more detail in a previous paper[14].

A Cox proportional hazards model[15] was used to estimate the effect of covariates on the transition hazards between states in the model, that is, the instantaneous risk (rate) of a subject moving from one state to another at a given point in time, conditional on being at risk for that particular transition at the time. In order to choose time scale in the model, preliminary analyses were performed to assess if the processes were Markov, that is, if the hazard rates were independent of past states and time spent in current state[16]. Time spent in previous states and in current states were included as covariates in the model and the results indicated that time spent in the current state, but not in the previous state affected the transition hazards. Therefore a model was chosen where time was reset (clock-reset model or semi-Markov[17]) after entering a new state. The Cox model was stratified on transitions such that transition hazards were calculated for each possible transition and the covariates were transition specific. The covariate of primary focus was the side (right or left) of the first arthroplasty as we wished to assess if the hazards of subsequent transitions were dependent on whether subjects received their first arthroplasty on the right side or on the left side. The HRs were adjusted for age, sex and which joint had a revision (time dependent covariate). The proportional hazards assumption in the Cox model was checked with Schoenfeld residuals for each transition and found to be satisfactory.

To illustrate the possible states through which individuals could move, the full model is presented in Fig. 1. However, we only present HRs that are relevant for the aim of the study, that is, HRs that compare the effect of side of the first arthroplasty (right vs left) on transitions to arthroplasties in non-cognate joints. The transition paths and states of interest are highlighted Fig. 1.

In order to further assess if there was a difference in the absolute risk of having received an arthroplasty in a hip or knee followed by an arthroplasty in a non-cognate joint at different points in time, we estimated the state probabilities for transitions from state 1 to state 3 and from state 1 to state 4 using the Aalen–Johansen estimator[18].

Observations were right-censored on December 31, 2010 after the last event (after last arthroplasty) if death had not yet occurred. For the data preparation and analyses we used the 'mstate' package[19] in the software environment 'R'[20] and Stata version 11.

Results

There were 200,730 subjects included from the AOA NJRR and 31,868 subjects from the NAR. The distribution of patients by type

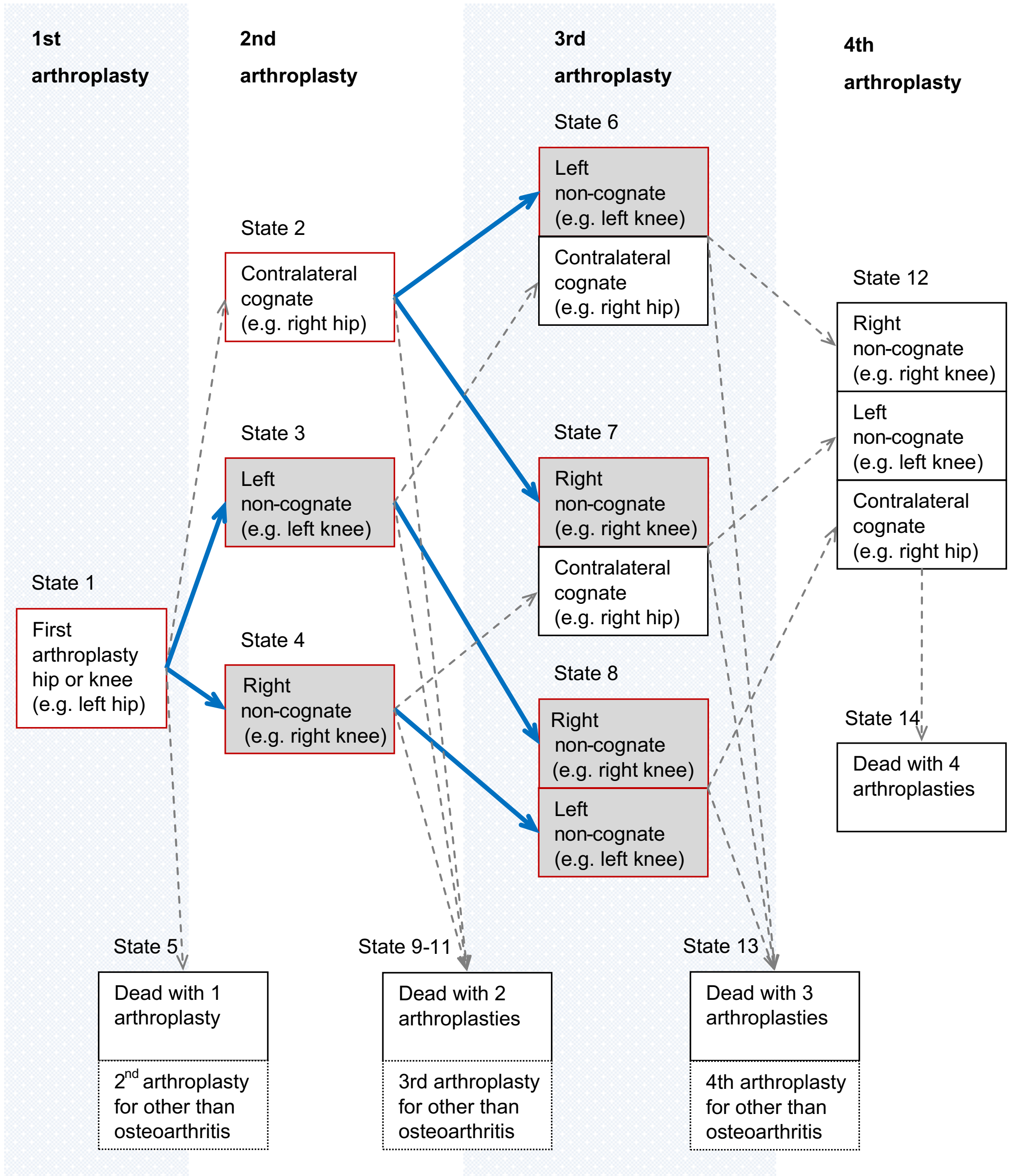

Fig. 1. Multi-state model.

of first arthroplasty (hip or knee), country, age, sex and side of first arthroplasty is presented in Table I. The data contain records on 98,420 first hip arthroplasties and 134,178 first knee arthroplasties. In Australia more subjects received first knee than first hip arthroplasties (61% vs 39%), whereas in Norway more subjects received first hip than first knee arthroplasties (62% vs 38%). For both countries there were more first arthroplasties on right sides with this being most pronounced for first hip arthroplasties from Norway. The Norwegian data had a lower proportion of males than females, especially for hip arthroplasties. In the Australian data, this was also the case for knee arthroplasties, whereas in the hip data there were equal proportions of males and females. For both hip and knee arthroplasties there were more subjects in the oldest age group.

Table I
Distribution of individuals according to covariates

		First arthroplasty hip		First arthroplasty knee	
		Australia	Norway	Australia	Norway
Age:	55–64 years	34,093 (43%)	7,691 (39%)	50,854 (42%)	5,286 (44%)
	65–74 years	44,541 (57%)	12,095 (61%)	71,242 (58%)	6,796 (56%)
Sex:	Males	39,435 (50%)	6,816 (34%)	54,462 (45%)	4,554 (38%)
	Females	39,199 (50%)	12,970 (66%)	67,634 (55%)	7,528 (62%)
Side:	Left	34,715 (44%)	8,003 (40%)	55,149 (45%)	5,447 (45%)
	Right	43,919 (56%)	11,783 (60%)	66,947 (55%)	6,635 (55%)
Total		78,634	19,786	122,096	12,082

Table II shows the numbers and proportions of arthroplasty events that had occurred at the end of the study period. Between 72% and 74% of the subjects did not receive another arthroplasty within the study period. Between 16% and 22% of subjects who had a first hip or knee arthroplasty received a second hip or knee arthroplasty respectively. If the second arthroplasty was in the

Table II
Numbers and percent of events in the multi-state model (Fig. 1) at the end of the study period for patients whose first arthroplasty was either a hip or a knee arthroplasty for OA

	First arthroplasty hip		First arthroplasty knee	
	Australia	Norway	Australia	Norway
	n (%*)	n (%*)	n (%*)	n (%*)
1 arthroplasty	78,634 (100)	19,786 (100)	122,096 (100)	12,082 (100)
No event	58,303 (74)	14,414 (73)	87,874 (72)	8714 (72)
State 1 → state 2	12,668 (16)	3867 (20)	26,433 (22)	2521 (21)
State 1 → state 3	1828 (2)	228 (1)	1348 (1)	133 (1)
State 1 → state 4	2072 (3)	257 (1)	1772 (1)	222 (2)
State 1 → state 5	3763 (5)	1020 (5)	4669 (4)	492 (4)
State 2 → state 6	172 (1)	26 (1)	268 (1)	27 (1)
State 2 → state 7	232 (2)	46 (1)	335 (1)	46 (2)
State 3 → state 6	127 (7)	14 (6)	134 (10)	10 (8)
State 3 → state 8	208 (11)	26 (11)	159 (12)	23 (17)
State 4 → state 7	153 (7)	26 (10)	196 (11)	17 (8)
State 4 → state 8	241 (12)	33 (13)	158 (9)	27 (12)
State 2–4 → state 9–11	574 (3)	154 (4)	952 (3)	94 (3)
State 6–8 → state 12	97 (10)	20 (12)	127 (10)	8 (5)
State 6–8 → state 13	20 (2)	3 (2)	25 (2)	3 (2)
State 12 → state 14	1 (1)	0 (0)	4 (3)	0 (0)

* Percent of number of individuals who entered the state(s).

same type of joint (cognate joint) as the first, only 1–2% went on to have a third arthroplasty. If the second arthroplasty was in a non-cognate joint (e.g., hip followed by knee), 9–17% of subjects went on to have another arthroplasty in the contralateral joint to the second arthroplasty (state 3→8 and state 4→8). The highlighted transitions in Table II correspond to the HRs presented in Table III.

Table III shows the effect of side of first arthroplasty (either hip or knee) adjusted for age and sex on the transition hazards between the states highlighted in Fig. 1 and Table II. Occurrence of revision was included in transitions where it had a significant effect. After the first hip arthroplasty the hazard of receiving a knee on the contralateral side was higher than the hazard of receiving a knee on the ipsilateral side. That is, for subjects who had received a hip first, the HR (right vs left first hip) of receiving a left knee (state 1→3) was 1.83 [95% confidence interval (CI): 1.65, 2.02) and 2.97 (95% CI: 2.10, 4.20] for Australian and Norwegian subjects respectively (illustrated in Fig. 2), whereas for receiving a right knee (state 1→4) the HR was 0.52 (95% CI: 0.48, 0.57) for Australians and 0.51 (95% CI: 0.40, 0.65) for Norwegians.

For subjects who received a second knee following a hip and a knee (state 3→8 and state 4→8), there was a higher hazard of receiving a knee contralateral than ipsilateral to the index hip. That is, the HR (right vs left first hip) of receiving a subsequent right knee (state 3→8) was 0.74 (95% CI: 0.56, 0.99) and 0.72 (95% CI: 0.26, 1.95) for Australian and Norwegian subjects respectively (illustrated in Fig. 3), whereas for receiving a subsequent left knee (state 4→8) the HR was 1.62 (95% CI: 1.26, 2.10) for Australians and 2.09 (95% CI: 1.01, 4.35) for Norwegians. For subjects who received a knee as a first arthroplasty evidence of a pattern was less consistent than for subjects who received a hip first (Table III). The transition hazard of receiving a third arthroplasty after two arthroplasties of the same type of joint (e.g., after bilateral hip arthroplasties) did not show a consistent association with the side of the first arthroplasty (Table III, state 2→6 and state 2→7).

Figures 4 and 5 show the estimated probabilities of occupying state 3 and 4 (Fig. 1) over a period of 5 years after the first arthroplasty. Figure 4 shows the estimated probabilities for individuals who had received a hip arthroplasty followed by a knee arthroplasty (state 3 on the left panel and state 4 on the right panel). The figure indicates that from approximately half a year after the initial arthroplasty the probabilities of having received a contralateral knee were consistently higher than the probabilities of having received an ipsilateral knee. For example, after 5 years the estimated probabilities of having received a left knee (contralateral) after a right hip were approximately 2.9% and 1.5% for Australians and Norwegians respectively, whereas the probabilities of having received a left knee (ipsilateral) after a left hip were approximately 1.5% and 0.4% respectively (left panel Fig. 4). Figure 5 shows the estimated probabilities for individuals who had received a knee arthroplasty followed by a hip arthroplasty (state 3 on the left panel and state 4 on the right panel). For both countries, there was less difference in the probabilities between receiving a contralateral hip and an ipsilateral hip. For example, after 5 years the estimated probabilities of having received a left hip (contralateral) after a right knee were approximately 1.2% and 1.1% for Australians and Norwegians respectively. The probabilities of having received a left hip (ipsilateral) after a left knee were approximately 0.9% and 1.1% for Australians and Norwegians respectively. The probabilities of having received a left hip after a knee arthroplasty were also similar for the two countries, but the probabilities of having received a right hip after a knee was somewhat higher for the Norwegians than Australians over the 5-year period.

Discussion

We used a multi-state model to investigate the progression of joint replacements in large weight bearing joints. The majority of individuals who received a second arthroplasty did so in the cognate contralateral joint. If the first arthroplasty was a hip, the hazards of receiving subsequent knee arthroplasties were higher on the contralateral side than on the ipsilateral side to the index arthroplasty. This was most pronounced for progression from hip arthroplasty to first knee arthroplasty but was also evident on the transition to receiving another (second) knee. Hence the side of first hip arthroplasty affected the rate of receiving subsequent knee arthroplasties. If the first arthroplasty was a knee, the hazards of receiving subsequent hip arthroplasties were generally higher on the contralateral side, but were not statistically significant.

Table III
Effect of side of first arthroplasty (hip or knee) on hazards for selected transitions in the model

	Right vs left hip		Right vs left knee	
	Australia	Norway	Australia	Norway
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
State 1 → 3	1.83 (1.65, 2.02)***	2.97 (2.10, 4.20)***	1.10 (0.99, 1.23)	1.08 (0.76, 1.52)
State 1 → 4	0.52 (0.48, 0.57)***	0.51 (0.40, 0.65)***	0.87 (0.79, 0.95)*	0.77 (0.59, 1.001)
State 2 → 6	1.25 (0.92, 1.69)	1.12 (0.52, 2.46)	0.95 (0.74, 1.20)	1.36 (0.63, 2.93)
State 2 → 7	0.74 (0.58, 0.96)*	0.97 (0.54, 1.74)	1.05 (0.85, 1.30)	0.83 (0.47, 1.49)
State 3 → 8	0.74 (0.56, 0.99)*	0.72 (0.26, 1.95)	0.87 (0.65, 1.22)	0.64 (0.26. 1.53)
State 4 → 8	1.62 (1.26, 2.10)***	2.09 (1.01, 4.35)*	1.34 (0.98, 1.84)	0.97 (0.45, 2.08)

***$P < 0.001$; *$P < 0.05$; HR.

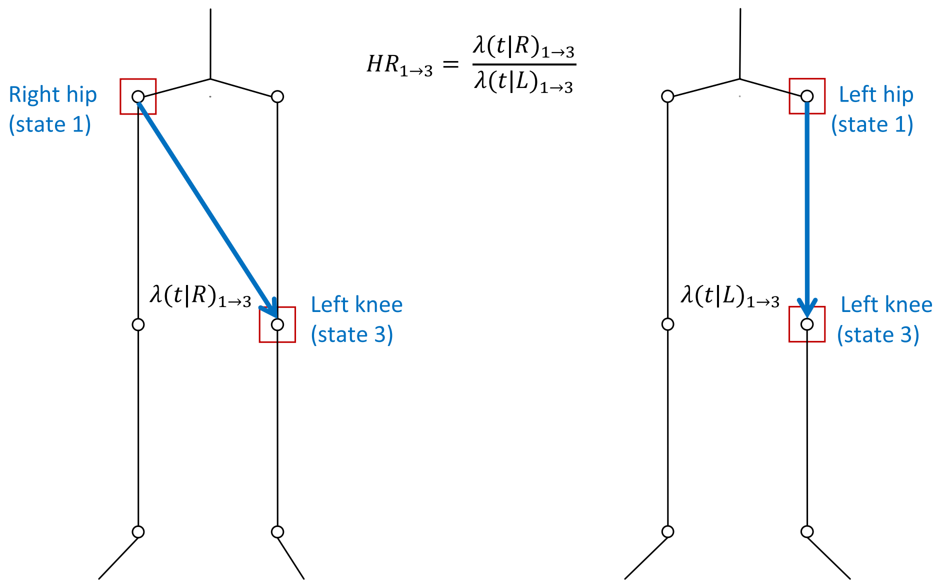

Fig. 2. Comparing hazards of receiving a left knee arthroplasty between individuals who had received a right hip arthroplasty with individuals who had received a left hip arthroplasty. HR, $\lambda(t|R)_{1\to3}$: hazard of receiving a left knee given that first hip was a right hip, $\lambda(t|L)_{1\to3}$: hazard of receiving a left knee given that first hip was a left hip.

The estimated HRs express the relative effect of side of the first arthroplasty on the subsequent transitions to arthroplasties in other joints, but not the absolute probabilities of individuals receiving further arthroplasties. We therefore also estimated probabilities for transitions from the first hip or knee arthroplasty to a second arthroplasty in a non-cognate joint. They showed the same pattern as the estimated HRs for the respective transitions. After 5 years, the probabilities of having received a knee contralateral to the index hip was more than 1.7 times the probabilities of having received a knee ipsilateral to the index hip, whereas there was little difference between the sides of hips relative to the previous knee arthroplasties. This was evident in data from both countries, but the probabilities for Australians to have received a knee after a hip were higher than for Norwegians (Fig. 4). Australia has a higher incidence of knee arthroplasties than Norway[21], and the difference in probabilities may be partially explained by this. The somewhat higher probabilities for Norwegians compared to Australians to receive a right hip (but not left hip) after a knee arthroplasty are difficult to explain. They may be related to particular risk factors for OA in the Norwegian population as it has previously been reported that Norway has much higher incidence ratios (female/male) for THA than the other Nordic countries[22].

Our study has some limitations. Joint replacements may not be an ideal measure of the incidence of symptomatic end-stage OA. Several factors contribute to regional and national variation in rate of surgical treatment for OA, such as access to treatment, disparity by race or ethnic group, surgical waiting lists, socio-economic status, patient or orthopaedic surgeon preferences[23–26]. However, our

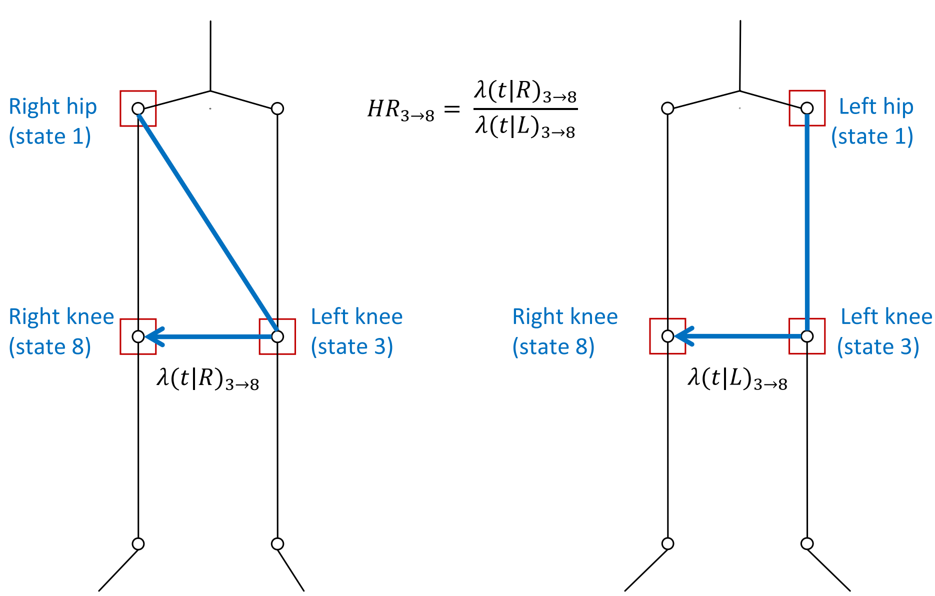

Fig. 3. Comparing hazards of receiving a right knee between individuals who had received arthroplasties in right hip and left knee with individuals who had received arthroplasties in left hip and left knee. HR, $\lambda(t|R)_{3\to8}$: hazard of receiving a right knee given that first hip was a right hip, $\lambda(t|L)_{3\to8}$: hazard of receiving a right knee given that first hip was a left hip.

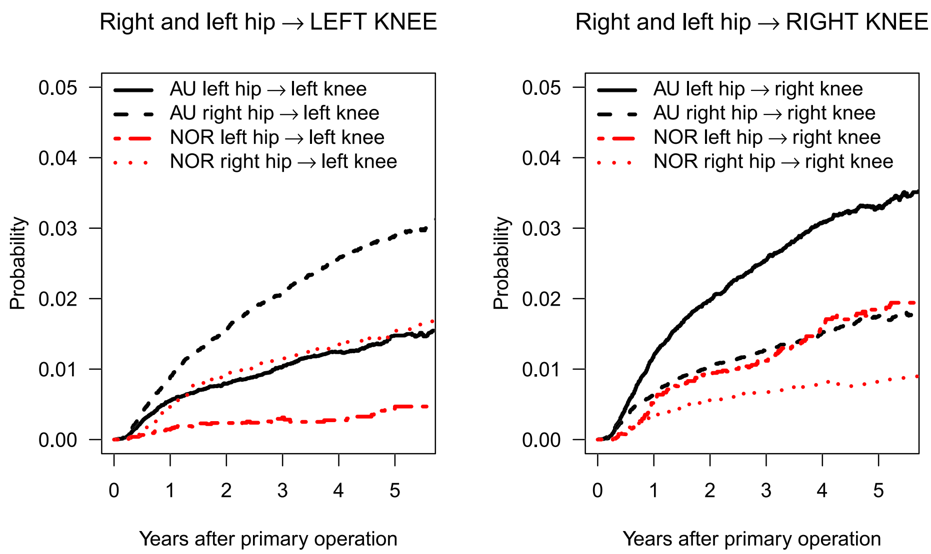

Fig. 4. Estimated probabilities for receiving a knee arthroplasty after having received a hip arthroplasty (AU: Australia, NOR: Norway, left panel: state 3, right panel: state 4).

study sample consisted of individuals who had received one arthroplasty for OA and some of the above factors would likely have less influence since the subjects already had been selected once for the same treatment. Furthermore, although there were differences in the relative proportion of hip and knee replacements in the Australian and the Norwegian registry data, the pattern of subsequent arthroplasties were similar between the two countries and are therefore likely to reflect the sequence of OA progression.

The results are consistent with those of other studies that have shown the progression of end-stage OA in large weight bearing joints to be a non random process[8,27,28], but we did not find clear evidence of a difference in association between side of the first knee arthroplasty and the following hip arthroplasty as has been described by others[8]. This may be due to differences in study design. Our use of the multi-state modelling technique allows for a more comprehensive analysis of the data than previous studies. It enables the analysis of the entire arthroplasty history of interest which in our study was the sequence and timing of joint replacements after the first hip or knee to subsequent hip(s)/knee(s). The multi-state model, which is a generalisation of standard survival analysis of time to one event, not only takes the time to different events into account but also incorporates incomplete observations, that is, the information contained in the time that some subjects have been under observation without experiencing the event(s). Another strength of this study is that it is the first study using data from two large, independent population-based national arthroplasty registries showing that there is evidence for a pattern in the progression of OA. Previous studies have involved far fewer subjects, from 50 to 3000, compared to our study, which entails more than 230,000 subjects. Both registries have excellent coverage of joint replacement procedures performed in the respective countries[10,11] and the two countries have developed health systems[29]. The Australian registry is comparatively large whereas the Norwegian registry has been operating for more than 20 years, thus data from the two registries complement each other.

Several studies have found evidence of bilateral symmetrical OA in large weight bearing joints[30] which may indicate that some individuals have an increased susceptibility to develop OA, due to

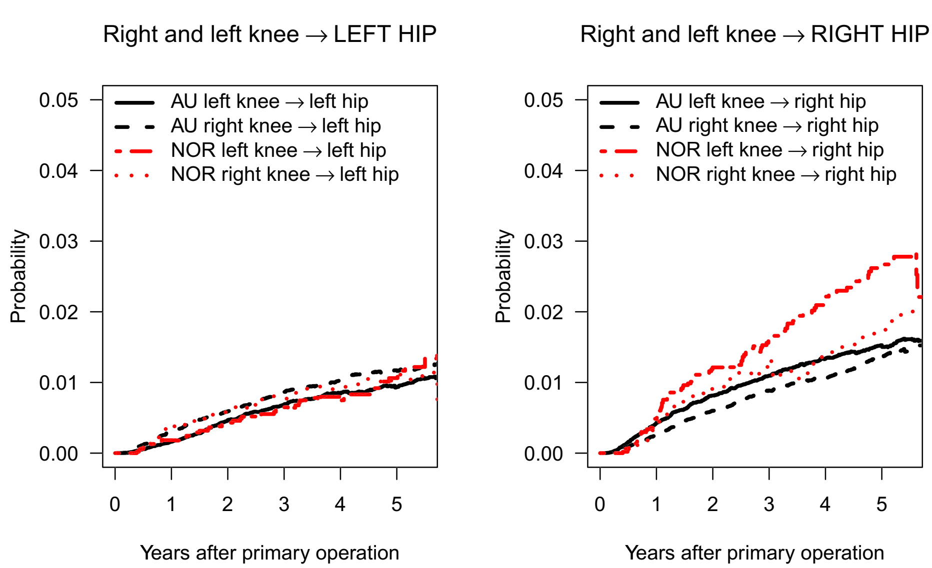

Fig. 5. Estimated probabilities for receiving a hip arthroplasty after having received a knee arthroplasty (AU: Australia, NOR: Norway, left panel: state 3, right panel: state 4).

systemic factors and/or genetic factors. In addition, biomechanical factors may contribute to the progression of end-stage OA to the contralateral joint. Shakoor *et al.*[31] performed a gait study in 62 patients with unilateral symptomatic and radiological hip OA, and found evidence that the contralateral asymptomatic knee and hip had increased dynamic loading as well as increased medial compartment tibial bone mineral density. Hence, the consequence of gait alterations due to a diseased hip may be responsible for the subsequent development of OA in the contralateral knee. Furthermore, several studies have found that gait does not return to normal after THA and TKA[32–36] which may explain the progression of OA in the non-operated limbs. Umeda *et al.*[27] did a longitudinal study in 30 women who had received hip arthroplasty, most for developmental dysplasia. Baseline radiographs showed no difference in knee OA between the operated and the non-operated side. At follow up, after minimum 10 years, there was significantly more severe knee OA medially in the non-THA side than the THA side. The authors concluded that this could be related to reduced offset of conventional femoral prostheses leading to shifts in mechanical axes. Further, leg length discrepancy (LLD) after THA is common[37].Tanaka *et al.*[38] found that postoperative LLD and stage of preoperative hip OA were the factors that had the largest influence on gait abnormalities after THA. Hence, the pattern of progression of joint replacements in large weight bearing joints, especially after the first hip replacement, may be related to LLD and associated pre and/or postoperative gait abnormalities. This is consistent with the work of Harvey *et al.*[39] who found that LLD was associated with prevalence, incidence and progression of knee OA. However, the registries have no access to data on LLD so we can make no definite statement about this. Further studies are needed to investigate whether the increased risk of receiving an arthroplasty in the contralateral knee is related to having a THA and/or preoperative factors such as pain and altered gait associated with hip OA.

In conclusion, we have demonstrated in data from two large population-based national arthroplasty registries of 55–74-year-old subjects who received arthroplasties for OA, that there is evidence of an association between the side of the first hip arthroplasty and side of subsequent knee arthroplasties. This is indicative of a pattern of progression of OA in large weight bearing joints. The evidence of a pattern in the progression of joint replacements and the nature of this pattern are important for the understanding of the pathogenesis of OA as well as for prevention and treatment.

Author contributions

Marianne H. Gillam: conception and design of the study, analysis and interpretation of the data, drafting of the article and critical revision of the article for important intellectual content. Stein Atle Lie: acquisition of the data, analysis and interpretation of the data and critical revision of the article for important intellectual content. Amy Salter: analysis and interpretation of the data and critical revision of the article for important intellectual content. Ove Furnes: acquisition of the data and critical revision of the article for important intellectual content. Stephen E. Graves: acquisition of the data and critical revision of the article for important intellectual content. Leif I. Havelin: acquisition of the data and critical revision of the article for important intellectual content. Philip Ryan: analysis and interpretation of the data and critical revision of the article for important intellectual content. All authors have given their final approval of the submitted article.

Marianne H. Gillam, Amy Salter and Philip Ryan take responsibility for the integrity of the work as a whole, from inception to finished article.

Role of the funding source

Marianne H. Gillam received PhD scholarship from the University of Adelaide. The funding source had no role in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication.

Conflict of interest

There was no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interests that any of the authors may have, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work.

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