

# **Time to Event Analysis of Arthroplasty Registry Data**

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# ABSTRACT

**Background:** Arthroplasty registry data are traditionally analysed using standard survival methods, that is, Kaplan-Meier survival curves and the Cox proportional hazards model. The outcome of interest is usually the time from the primary procedure until occurrence of a single event – revision of the prosthesis. Other outcomes may also be of interest, for example, time to death, time to receiving another arthroplasty and the association between covariates and these events. The rise in life expectancy of the population combined with an increasing number of joint replacements being performed has resulted in many patients experiencing several joint replacement procedures during their lifetime. The analyses of registry data such as these require the use of more sophisticated statistical methods. Application and evaluation of statistical methods to analyse registry data containing complex arthroplasty histories are lacking.

**Aim:** The aim of this thesis was to investigate the use of statistical methods in the analysis of multiple event data contained in arthroplasty registries. Within this broad aim the objectives were to investigate the use of competing risks methods in estimating the risk and rate of revision, investigate methods for handling covariates with time-varying effect, investigate the use of multi-state modelling techniques in providing a more comprehensive analysis and description of complex arthroplasty histories than traditional survival methods and to develop a notation system to facilitate the description and analysis of arthroplasty event history data.

**Methods:** Data were obtained from the Australian Orthopaedic Association National Joint Replacement Registry and the Norwegian Arthroplasty Register. Estimates of revision from the Kaplan-Meier method were compared to estimates from the cumulative incidence function which accounts for the competing risk of death. Effects of covariates on the rate and risk of revision were estimated with competing risk regression and compared to estimates from the Cox proportional hazards model.

Multi-state models were set up and applied to the data. The Summary Notation for Arthroplasty Histories (SNAH) was developed in order to help manage and analyse this type of data.

**Results:** The Kaplan-Meier method substantially overestimated the risk of revision compared to estimates using competing risks methods when the incidence of the competing risk of death was high. The influence of some covariates on the hazard rate was different to the influence on the actual probability of occurrence of the event as this was modulated by their relationship with the competing event. Multi-state models, in combination with SNAH codes, were well suited to the management and analysis of arthroplasty registry data on patients who had multiple joint procedures over time. Multi-state modelling techniques proved useful in the investigation of the progression of end-stage osteoarthritis in data from two national arthroplasty registries.

**Conclusion:** In the presence of competing risks, the Kaplan-Meier method may lead to biased estimates of the risk of revision, and hazard ratios obtained from the Cox proportional hazards model and competing risks regression models need to be interpreted with care. Multi-state models provide a useful tool to analyse data containing complex arthroplasty histories.

# Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Signed: .....

Marianne KH Gillam (Candidate)

Date: .....

## Manuscripts Contributing to this Thesis

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Gillam MH, Ryan P, Graves SE, Miller LN, de Steiger RN, Salter A. Competing Risks Analysis Applied to Joint Replacement Registry Data. Faculty of Health Sciences 2010 Postgraduate Research Conference. Adelaide, September 2010.

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# Abbreviations

AOANJRR:	Australian Orthopaedic Association National Joint Replacement Registry
CIF:	Cumulative Incidence Function
Cox PH:	Cox Proportional Hazards
CPR:	Cumulative Percent Revision
FNOF:	Fractured Neck of Femur
HR:	Hazard Ratio
KM:	Kaplan-Meier
NAR:	Norwegian Arthroplasty Register
OA:	Osteoarthritis
RD:	Relative Differences
SNAH:	Summary Notation for Arthroplasty Histories
SubHR:	Subdistribution Hazard
THA:	Total Hip Arthroplasty
TKA:	Total Knee Arthroplasty

# 1 INTRODUCTION

This thesis investigates methods for analysis of time to event data in arthroplasty registry data. Arthroplasties—specifically joint replacements—are common surgical procedures. Registries collect and record data on these procedures and serve as important sources of data for evaluating specified outcomes of joint replacements. In order for arthroplasty registries to provide accurate information for their stakeholders, the use of appropriate statistical methods to analyse the data is of great importance. This thesis argues for the use of methods that appropriately account for the potential of multiple events, rather than standard univariate survival methods currently employed, when analysing time to event data contained in arthroplasty registries.

## 1.1 Background

Patient registries are organised systems that contain observational study data for populations characterised by particular diseases, conditions or exposures. They serve predetermined purposes such as monitoring safety of medical devices, measuring quality of care, describing the natural history of diseases, and determining health outcomes and treatment effects [1].

Patient registries are important sources of data for observational studies which are the mainstay of population health research. Traditionally, observational studies have had a lower ranking on the evidence scale than randomized controlled trials (RCTs) but the advantages of observational studies based on registry data are increasingly being recognized [2]. Some of these are that the data often come from large and varied groups of patients and the outcomes can therefore be generalized to a wide range of patients. They can be used pragmatically to evaluate treatments that are administered in the real world rather than those administered under what are often rigid RCT regimes and restrictive patient exclusion criteria. For rare diseases observational studies based on registry data can be used to measure outcomes where clinical studies are not feasible or

in situations where it is unethical to conduct RCTs. Furthermore, RCTs are often time consuming and resource intensive [3-6].

### 1.1.1 Arthroplasty registries

Patient registry data are particularly useful for evaluating outcomes of procedures which require relatively long follow up, such as the outcome of joint replacements [7, 8]. Sweden was the first country to establish a national joint replacement registry in 1975 [9], and following its success, several other countries have established national joint replacement registries [10]. One important purpose of these registries is to identify poorly performing prostheses thereby improving the quality of joint replacements [11]. In most countries prostheses are introduced on the market without prior clinical trials and thus continuous post marketing surveillance is important. Information on the collected data is typically disseminated in annual reports.

The incidence of joint replacements has been increasing in most countries over the past decade and it is expected that this will continue [12] as the incidence of the main risk factors such as osteoarthritis, age and obesity increase in the population. In the United States increases in primary hip and knee replacements of 174% and 673% respectively have been predicted for the period 2005 to 2030 [12]. In Australia there was an increase in primary total hip replacements and primary total knee replacements of 44% and 84% respectively from 2003 to 2012 [13].

### 1.1.2 Time to event analysis

In order to evaluate the outcome of joint replacement correctly, the use of appropriate statistical methods is important. Survival analysis, or time to event analysis, is commonly used in the analysis of registry data. The main outcome of interest in joint replacement registry data is 'time to revision' – the time interval between the date of

insertion of the prosthesis and the date of revision. Revision is a procedure where one or more of the prosthesis' components is removed and/or replaced. It signals failure of the prosthesis. A characteristic of time to event data<sup>1</sup> is that it may contain observations with incomplete information in that the exact survival time is not known, for example when a study ends before a revision is observed. These incomplete observations are called censored observations. The survival methods most commonly used in the analysis of joint replacement registry data are Kaplan-Meier survival curves [14] and Cox proportional hazards models [15]. These methods are extremely popular and the two papers introducing them are among the most cited statistical papers in the research literature [16]. The Kaplan-Meier method estimates a survival curve which indicates the proportion of subjects who have not yet experienced the event of interest at various time points. The method was initially based on actuarial life tables to estimate the proportion of subjects who had not yet died, but would eventually do so. The Kaplan-Meier method accounts for censored observations and thereby utilizes the information contained in the incomplete data. A crucial assumption is that censoring times and survival times are independent, that is, at time  $t$  patients whose time is censored will have the same risk of experiencing the event as those whose time is not censored, i.e. that censoring is non-informative. If patients are censored administratively this might be reasonable, but if they are lost to follow-up or have experienced another event then the assumption is often violated. For example, when estimating the risk of revision, subjects who have died (and therefore would be censored in the Kaplan-Meier method) clearly do not have the same risk of revision as subjects who are still alive, hence the censoring time is not independent. This violation of independence occurs due to a competing risk (where in this case the competing risk is death). Competing risks, where relevant, are

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<sup>1</sup> Treatment of the word “data” as singular or plural has been a vexed question in both scientific and non-scientific literature for almost a century. In this thesis I will generally treat the word as plural but when it is either obviously being used as a “mass noun” or it would otherwise sound peculiar, I will take the liberty of treating it as singular.

often not accounted for in statistical analyses of survival data, leading to potential biased estimates of the survival curves [17]. Understanding the role of competing risks in registry data is one of the objectives of this thesis.

Another important function in survival analysis is the hazard rate, which is the instantaneous rate of occurrence of an event, conditional on the event having not yet occurred. The Cox proportional hazards (PH) model enables estimation of the effect of covariates on the hazard rate. The model is regarded as a semi-parametric because the baseline hazard function is not explicitly estimated. The covariates act multiplicatively on the baseline hazard rate and the effects are expressed as ratios. One key assumption of the model is that the hazard ratio is constant, that is, independent of time. The assumption of proportionality is not always plausible and is often assumed without justification [18]. Causes of non-proportionality are omission of covariates, incorrect functional form of the covariate or the existence of time dependent covariates or covariates with time-varying effects. Time dependent covariates are covariates that change value over time, whereas covariates with time-varying effect are covariates whose effect on the hazard rate changes over time. Depending on the cause, different methods exist to deal with non-proportional hazards in the Cox model [19], but no consensus on which method is the best appears to have been reached. An alternative model to the Cox PH model is Aalen's additive hazard model [20]. In Aalen's additive model the effect of covariates acts additively on the baseline hazard rate and both time-dependent covariates and time-varying coefficients can easily be incorporated. The use of Aalen's model on registry data and exploration of methods for handling covariates with time-varying effects are also objectives of this thesis.

### 1.1.3 Regression models

In traditional survival analysis where the outcome is time to a single event, there is a one-to-one relationship between the hazard rate and the survival function. As a result, estimates from the Cox model can be used to directly estimate the effect of covariates on survival probabilities. However, in scenarios with competing risks this relationship is

more complicated because the probability of survival for one cause depends on the hazard rates for all the causes (cause specific hazards). One may find that some covariates have different effects on the cause specific hazard rates than they do on the survival probabilities. Hence, in the presence of competing risks the estimates from the Cox PH model require a different interpretation. Fine and Gray [21] have developed a method for competing risks scenarios to model the direct effect of covariates on survival probabilities for the event of interest. Regression methods for competing risks scenarios have not been used much in orthopaedic research, although they are often relevant. An objective of this thesis is to explore the use of competing risks regression models on arthroplasty registry data.

#### 1.1.4 Arthroplasty histories

An increasing number of individuals have several joint replacement procedures and, with time, joint replacement registries will contain increasing amounts of data on individuals with complex arthroplasty histories. These histories may contain information on primary arthroplasties in multiple joints with associated revisions and re-revisions. One issue that arises as a result of this expansion is the management and handling of large datasets that evolve over time and contain multiple events for each individual. Developing a notation system for recording and communicating patient-level arthroplasty histories is one of the objectives of this thesis. Another issue is that statistical methods other than those traditionally employed for single-outcome data are required. Several methods exist to deal with time to event data with multiple outcomes. One method is to represent longitudinal data with several events as a multi-state model where an individual occupies and moves between a finite number of states characterised by conditions such as having had a joint replacement or a revision. A multi-state model can account for time dependent covariates which can be included as transient states. The competing risks model is an example of a simple multi-state model with two or more mutually exclusive end-states. One of the objectives of this thesis is to investigate the use and suitability of multi-state modelling techniques in providing a comprehensive analysis and description of complex arthroplasty histories contained in joint

replacement registries. Furthermore, since joint replacement is most often performed for treatment of end-stage osteoarthritis, an objective is also to explore the use of multi-state models on arthroplasty registry data to provide information on the progression of osteoarthritis.

## 1.2 Thesis aim

The overall aim of this thesis is to investigate the use of statistical methods in the analysis of time to event data in arthroplasty registries allowing for the potential of multiple events. Within this broad aim, the objectives are to:

- Apply competing risks methods to arthroplasty registry data to investigate the degree to which the probability of revision is biased using the Kaplan-Meier estimates and if present, to comment on whether this bias is clinically relevant.
- Apply competing risks regression models to determine the effect of covariates on the rate and the risk of revision and death.
- Investigate methods of handling covariates with a time-varying effect.
- Investigate the use of multi-state modelling techniques in providing a more comprehensive analysis and description of complex arthroplasty histories held in arthroplasty registries than traditional survival methods.
- Develop a notation system to facilitate the description and analysis of arthroplasty event history data.
- Apply multi-state models to investigate the progression of joint replacements (a surrogate for end-stage osteoarthritis) in data from two national joint replacement registries.

## 1.3 Thesis outline

Chapter 2 provides an introduction to time to event analysis, the important functions and issues with estimating the survival/failure curves and effects of covariates on the hazard rate. Multi-state models and competing risks are described. Literature pertaining to the specific aims (as outlined above) is reviewed and specific issues relating to the analysis of arthroplasty registry data are considered.

Chapter 3 describes the data sources in this thesis, the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR) and the Norwegian Arthroplasty Register (NAR).

Chapters 4 to 7 consist of articles, three of which have been published and one which has been accepted for publication<sup>2</sup>, each addressing different aspects of time to event analysis of arthroplasty registry data with multiple events. Chapter 4 contains a published article in which non-parametric competing risks methodology is applied to arthroplasty registry data and the results are compared to those obtained from the Kaplan-Meier method. In Chapter 5 the focus is on regression methods in competing risks scenarios and the inclusion of covariates with time-varying effects. The published article in this chapter investigates the effect of covariates on the rate and on the risk of revision.

Chapters 6 and 7 consider the use of multi-state models in the analysis of multiple events in joint replacement registry data. In Chapter 6, which contains a published article, the theory and issues with multi-state models are addressed and a multi-state model is developed. The Summary Notation for Arthroplasty Histories (SNAH) which facilitates the description and analysis of arthroplasty registry data is introduced. In Chapter 7 multi-state models are applied to data from the AOA NJRR and the NAR to

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<sup>2</sup> First published online 26<sup>th</sup> December 2012.



investigate the progression of hip and knee osteoarthritis. The article in this chapter has been accepted for publication.

Chapter 8 contains a summary of the findings and contributions to knowledge in the thesis, addresses limitations and outlines topics for further research in this area.

## 2 ANALYSIS OF TIME TO EVENT DATA

This chapter begins by describing the basic elements of survival analysis and then goes on to discuss some of the approaches used to model both single and multiple event (event history) survival data. The aim of the chapter is to review literature on survival analysis of relevance to the aims of this thesis and to provide a convenient summary orientation to many of the modern statistical approaches to modelling survival data, some of which will be discussed in more detail in succeeding chapters.

Survival analysis – or analysis of time to event – is the analysis of data where the outcome is the time to the occurrence of one or multiple event(s) of interest. A particular characteristic of these data is that they may contain incomplete observations if events are not observed within the study period. These incomplete observations are referred to as censored events. There are several forms of censoring and each requires the use of different statistical methods in its analysis. Right censoring occurs if it is known that a survival time is greater than that observed, for example if an individual is lost to follow up or a study is closed for administrative reasons before the event has occurred. Left censoring occurs if a subject has experienced the event before the beginning of the study, but the exact timing of this event is not known. A related term is left-truncation which relates to the design of the study and means that subjects have been at risk of the event before the start of the study. Interval censoring takes place when the event occurs during the study period but the exact time is not known, only that it occurred in a certain time interval. Right censoring is the most commonly occurring type and will be considered in the following discussion.

The risk set at a particular point in time consists of individuals who (at time  $t$ ) are at risk of experiencing the event of interest, that is, individuals who have entered the study and have survived up to time  $t$ . Individuals leave the risk set either when they experience the event, or when they are censored.

The main functions of interest in this context are *the survival function, the hazard function and the cumulative hazard function*. With  $T$  a random variable of survival times, the survival function is the probability of not experiencing the event by time  $t$ :

$$S(t) = P(T > t) = 1 - P(T \leq t) = 1 - F(t),$$

where  $F(t)$  is the cumulative distribution function. The hazard function is usually interpreted as the instantaneous rate of experiencing an event (given that the individual is at risk at the beginning of a short time interval):

$$\begin{aligned} \lambda(t) &= \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} P(t \leq T < t + \Delta t | T \geq t) \\ &= -\frac{d \log\{S(t)\}}{dt}, \end{aligned}$$

where  $\Delta t$  denotes a small interval of time and  $P$  is the conditional probability that the survival time of a subject is between  $t$  and  $t + \Delta t$ , given that a subject has survived up to time  $t$ .

The cumulative hazard function represents the total accumulated risk in the interval  $(0, t)$ :

$$\Lambda(t) = \int_{s=0}^{s=t} \lambda(s) ds.$$

The survival function, the hazard, and the cumulative hazard function are mathematically related such that:

$$S(t) = \exp\left(-\int_{s=0}^{s=t} \lambda(s) ds\right) = \exp(-\Lambda(t))$$

and

$$F(t) = 1 - \exp\left(-\int_{s=0}^{s=t} \lambda(s) ds\right).$$

Hence, there is a one-to-one correspondence between the risk and the rate functions [22].

## 2.1 Non-parametric methods

For discrete observations of time, the survival function is traditionally estimated non-parametrically by the Kaplan-Meier estimator [14]:

$$\hat{S}(t) = \prod_{t_j \leq t} \left( \frac{n_j - d_j}{n_j} \right)$$

where  $n_j$  is number of individuals in the risk set and  $d_j$  is number of events at time  $t_j$ . As stated in 1.1.2, an important assumption is that censoring is non-informative. Groups are often compared with different modifications of the log-rank statistic [23, 24]. The cumulative hazard function is typically estimated non-parametrically by the Nelson-Aalen [25, 26] estimator:

$$\hat{\Lambda}(t) = \sum_{t_j \leq t} \frac{d_j}{n_j}$$

In a plot of the Nelson-Aalen estimator versus time, the slope of the plot is an estimate of the hazard rate, e.g. a constant slope indicates a constant hazard. The results from non-parametric methods are presented in graphs and/or tables. Since the estimated distribution is discrete, the continuous hazard function needs to be estimated with the aid of smoothing techniques [27].

## 2.2 The Cox proportional hazards model

The standard method for regression analysis used to determine the effect of covariates on the hazard function is the Cox Proportional Hazards (PH) model [15]. In this model,

the hazard at time  $t$  for individuals with a vector of covariates  $\mathbf{X}$  and regression coefficients  $\boldsymbol{\beta}$  is:

$$\lambda(t) = \lambda_0(t)\exp(\boldsymbol{\beta}^T \mathbf{X}),$$

where the superscript “T” indicates the transpose of the column vector. Assuming that the baseline hazard function  $\lambda_0(t)$  is the same, the hazard (rate) ratio (HR) comparing subjects with covariate values  $\mathbf{X}_1$  relative to those with  $\mathbf{X}_0$  is:

$$HR = \exp\{\boldsymbol{\beta}^T(\mathbf{X}_1 - \mathbf{X}_0)\}.$$

Thus, the covariates are assumed fixed over time and the hazards over time are assumed to be proportional, that is, the HR is constant. Although a functional form for the covariates is specified, no particular distribution of survival times is postulated (indeed the baseline hazard function is not even estimated), and so the model is said to be semi-parametric. For single event survival data there is a direct relationship between the hazard function and the survival function, hence the Cox PH model can be used to estimate the effect of covariates on the survival function [28]. A stratified Cox PH model is fitted by allowing the baseline hazard function to be different for each value of the stratification variable. The obtained regression estimates are then the same within each stratum. In this scenario, the effect of the stratification variable on the hazard cannot be assessed. Specific estimates of these effects can be obtained by introducing interactions between strata and covariates. One advantage of the Cox PH model is that it is flexible in estimating the effects on the hazard for different values of a covariate [27], but the assumption of proportionality is not always plausible and is often assumed without justification [18]. Furthermore, the model is sensitive to omission of covariates, which can lead to biased regression coefficients or violation of the proportional hazards assumption [27, 29].

### 2.2.1 Time-dependent covariates

Time-dependent covariates are covariates whose values change over time. They are often classified into external and internal covariates [30] to aid interpretation of the results. External covariates are considered not to be generated by a subject and do not require a subject to be under observation. Examples might include air-pollution or age of a subject. Internal covariates change with the subject, for example a subject's blood pressure over time. Because the values of internal time-dependent covariates are only observed if the subject survives, it is not appropriate to use these covariates in time to event models to make predictions [31]. In the presence of internal time dependent covariates, the relationship between the survival function and hazard function do not hold [31].

When a time dependent covariate  $x(t)$  is introduced in the Cox PH regression model the hazard becomes:

$$\lambda(t) = \lambda_0(t)\exp\{\boldsymbol{\beta}^T \mathbf{X}(t)\}.$$

Modelling time-dependent covariates as time-fixed can lead to time-dependent bias. Van Walraven et al. [32] conducted a study of papers using survival analysis from a selection of medical journals and found that time-dependent bias was not only common, but that correction of the bias could have changed the conclusion in over half of the studies examined. Beyersmann [33] showed that treating time-dependent covariates as time-fixed generally leads to a smaller hazard ratio in a Cox PH model. However, using time-dependent covariates in the Cox PH model is more complicated than using time-fixed covariates and one has to pay careful attention to how the functional form of the covariates are specified and how the results are interpreted [34].

### 2.2.2 Time- varying coefficients

One cause of non-proportionality in the Cox PH model occurs when the effect of covariates on the hazard rate varies with time. If this is not accounted for, the results

may be biased [35]. There are several approaches to accommodate time-varying effects. Cox in his original article [15] suggested adding a time by covariate interaction in the model:

$$\lambda(t) = \lambda_0(t)\exp\{\beta x + \beta^* x f(t)\},$$

where  $f(t)$  can be any function of time. However, it may be difficult to choose an appropriate function and the wrong choice may result in incorrect interpretation of the results [36]. Other approaches to handle covariates with time-varying coefficients in the Cox PH model include stratifying on the covariate, using a weighted average of the hazard ratio, calculating piecewise constant hazard ratios, and methods based on splines or smooth functions [19, 36].

### 2.3 The additive Aalen model

An alternative to the Cox PH model is Aalen's non-parametric additive hazard regression model [20]. The model is well suited to handle time-dependent covariates and covariates with a time-varying effect. In this model the hazard for the  $i^{th}$  individual with vector of covariates  $\mathbf{X}_i(t) = (x_{i1}(t), x_{i2}(t), \dots, x_{ip}(t))^T$  is:

$$\lambda_i(t|x_i) = \beta_0(t) + \beta_1(t)x_{i1}(t) + \dots + \beta_p(t)x_{ip}(t),$$

where  $\beta_0(t)$  is the baseline hazard function and  $\beta_j(t)$  ( $j = 1, \dots, p$ ) are arbitrary regression functions which measure the effect of the respective covariates [37]. This model allows the effect of the covariates to change over time. In their book, Aalen et al. [37] provide several arguments for the use of this model over the standard Cox PH model. Amongst them are that the hazard ratio as calculated in the Cox PH model might not be a good measure of the effect when the risk factor is rare (risk differences may be better suited), time-dependent covariates are easily incorporated, the model is not vulnerable to neglected covariates, and it may be well suited for analysing excess hazard because the model is not forced to give positive estimates as are proportional

hazards models. Despite the obvious advantages, Aalen's additive model is not often used. One of the reasons may be that the regression coefficients are more difficult to estimate and interpret when compared with regression coefficients from the Cox PH model [38].

## 2.4 Multiple events

In traditional survival analysis, the outcome of interest is the time to occurrence of a single event. Event history analysis is concerned with the occurrence of multiple events over time for an individual. These data have a sequential structure where a subject may experience repeated events of the same type and/or events of different types over time.

The most commonly applied models in medical research for analysing these types of data are marginal [39, 40], conditional [41, 42], shared frailty [43] and multi-state models. For marginal and conditional models the dependence either within individuals in a group or within an individual for recurrent events is accounted for by a robust variance estimator, whereas for shared frailty models the dependence is accounted for by a random effect variable. In multi-state models, the events are seen as a stochastic process describing movements among a finite number of states. The application of these models to multiple event data are described in monographs by, for example, Hougaard [27] and Therneau and Grambsch [44].

The advantage of using multi-state models on survival data is that they easily incorporate time-dependent covariates as transient states, extend from single to multiple event survival analysis and account for left truncation. Multi-state models have been used considerably in analysing data from bone marrow transplant studies [45], and increasingly in cancer studies. In other fields of medical research they are not commonly used despite a rich literature on the theory and their advantages (see for example [27, 37, 46, 47]). One important reason why multi-state models have not been applied more often to survival data in the past may be the lack of available software to implement these models [48], although as this becomes increasingly available, the

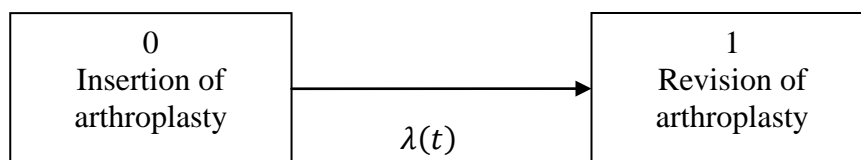


adoption of his approach is likely to increase. The next section provides a background on the multi-state modelling approach.

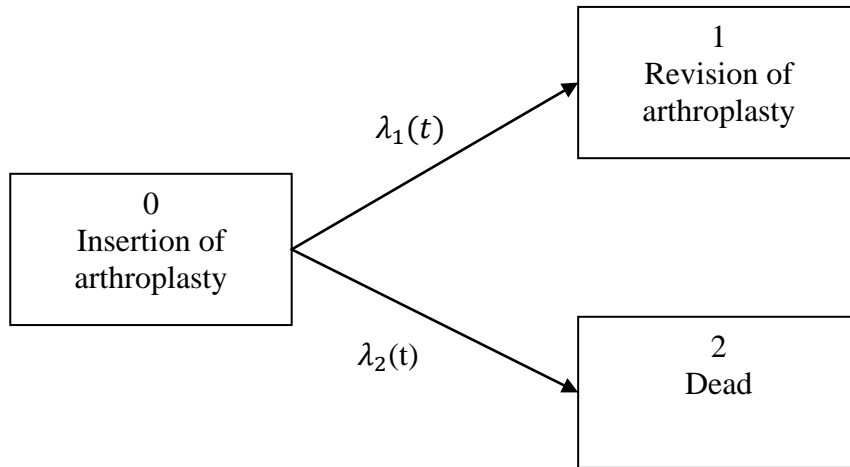
### 2.4.1 Multi-state models

Time to event data can be modelled as a multi-state stochastic process where an individual occupies a state and moves between states described by the events, that is, when an event occurs the individual changes state (unless prevented by right censoring). States are considered transient, if movement out of them is allowed, or absorbing, if no movement out is allowed. The structure of a multi-state model is often illustrated in diagrams where boxes represent states and arrows represent possible events [48-51].

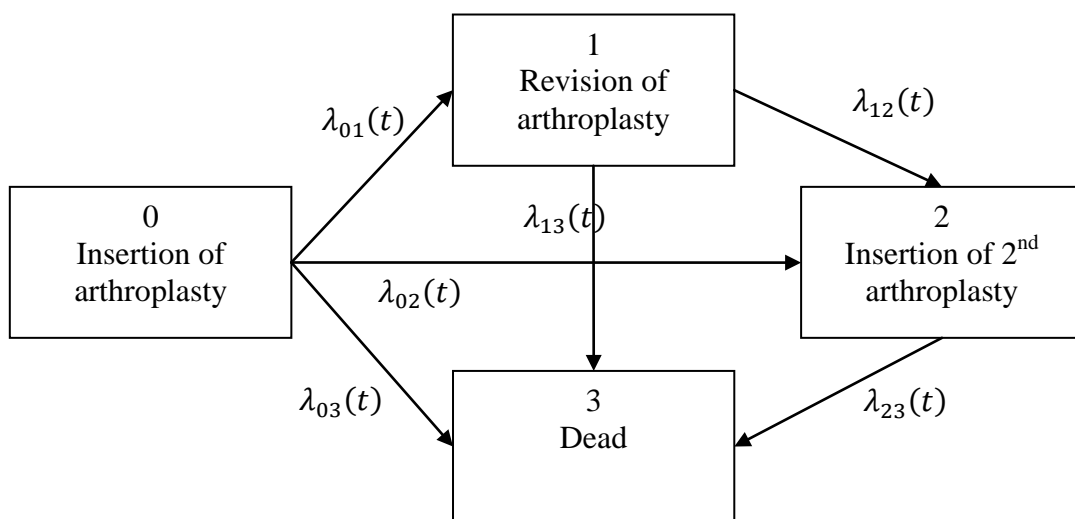
Considering survival analysis with a single outcome as a multi-state model, an individual can move from a starting state to the outcome state, for example from receiving a hip arthroplasty to having a revision of the arthroplasty (Figure 2.1). Another simple example in the context of competing risks concerns individuals who can move from a starting state into  $k$  different absorbing states (see for instance Figure 2.2 where  $k = 2$ ). In this model the transient state is insertion of an arthroplasty, and dead and revision are considered absorbing states (revision is an absorbing state because time to revision is the outcome of interest). A more complex multi-state model is illustrated in Figure 2.3 which includes three transient states (insertion of an arthroplasty, revision of this arthroplasty and receiving a second arthroplasty) and one absorbing state (dead).



**Figure 2.1: Traditional survival model with one event of interest and hazard rate  $\lambda(t)$ .**



**Figure 2.2:** Competing risks model with two absorbing states and cause specific hazards  $\lambda_1(t)$  and  $\lambda_2(t)$ .



**Figure 2.3:** Multi-state model with three transient states, one absorbing state (dead) and transition intensities  $\lambda_{gh}(t)$  from state  $g$  to state  $h$ , where  $g = 0, 1, 2$  and  $h = 1, 2, 3$ .

The movements between states are called transitions. The instantaneous rate of moving from state  $g$  to state  $h$  given that the individual is in state  $g$  just before time  $t$  is called the transition intensity,  $\lambda_{gh}(t)$ . This is equivalent to the hazard rate in traditional survival analysis with a single event. The transition probability,  $P_{gh}(s, t)$ , is the probability of moving from state  $g$  to  $h$ . The state occupation probability,  $P_h(t)$  is the probability that an individual is in state  $h$  at time  $t$ . When all individuals start in state 0 at  $t = 0$ , the state occupation probability is the same as the transition probability,  $P_{0h}(0, t)$  [37, 49]. If the process is Markovian, the transition probabilities can be calculated directly from the transition intensities, for example by using the Aalen-Johansen estimator [52]. A Markov chain is a process that has the Markov property: the future state depends only on the present state and not any past states. Hence, a Markov model is assumed to be independent of time spent in the current state, if not it is called a semi-Markov model. Further, a Markov model is considered time homogenous if the hazards do not depend on the time (because it is constant), and if it does it is non-homogenous [48]. In order to investigate if the process is Markovian, a function of current state duration can be included as a time dependent covariate in a Cox PH model (using time since the start of the process as baseline time variable) and testing if the estimated regression coefficient is equal to zero [52]. Datta and Sattten [53] showed that the Aalen-Johansen estimator is valid for estimating state occupation probabilities also in non-Markov models if censoring is independent of state occupied and censoring times. Gunnes et al. [54] showed that the Aalen-Johansen estimator may be valid for less stringent censoring assumptions (i.e. where censoring is allowed to depend on the past) in certain circumstances, such as for small sample sizes.

## 2.4.2 Competing risks

In survival analysis a competing risks model describes a situation where the occurrence of the event of interest may be precluded by another event, or the risk of the event of interest may be altered by the occurrence of another event [55]. This situation is sometimes (inappropriately) approached by ignoring the competing risks and treating them as censoring events when estimating the survival probability for the event of

interest. In this case the assumption of independence of the time to event and the censoring distribution is violated, often leading to a biased Kaplan-Meier estimate and an underestimation of the survival probability. This concept is well illustrated in Putter et al.'s article [51].

There are two mathematical approaches to modelling competing risks: either to model the lifetime as a multivariate random variable or as a multi-state model. The classic competing risks approach is the former: to model the competing risks as parallel latent failure times where there are several potential failure times for each individual. The assumption is that the latent times to failure are independent and that the first failure time determines the whole system failure [56]. The interpretation of the latent failure time is problematic. For example, it is speculative to assume that if a subject does not die from the first cause this will not alter the risk of dying from another cause (which obviously cannot be observed) [27]. This problem was first contemplated in a paper by Bernoulli in 1766 where competing risks were introduced in the context of vaccination for smallpox, see Dietz et al. [57].

The other approach which is increasingly being advocated [49] is to model the competing risks using a multi-state model where subjects pass from an initial state to one of several absorbing states (see for instance Figure 2.2 for  $k = 2$ ). The transition intensity for moving to one of these states, the instantaneous rate,  $\lambda_h(t)$ , is called the cause specific hazard rate. The process is Markovian. No assumption is made about independence of failure times but all hazard functions for leaving a state have to be interpreted in the full model [27]. The transition probabilities are known as the cumulative incidences [58]. The cumulative incidence function (CIF) for event type  $h$  is:

$$F_h(t) = Pr(T \leq t, \varepsilon = h) = \int_{s=0}^{s=t} \lambda_h(s) S(s) ds,$$

which can be estimated by the Aalen-Johansen estimator [22, 59]:

$$\hat{F}_h(t) = \sum_{t_j \leq t} \frac{d_{hj}}{n_j} \hat{S}(t_{j-1}), \text{ with } t_1 < t_2 < \dots < t_r$$

where  $\hat{S}(t_{j-1})$  is the Kaplan-Meier estimator of the survival function considering all events, that is, the probability of being event free prior to  $t_{hj}$ ,  $d_{hj}/n_j$  is the Nelson-Aalen estimator of the cumulative hazard of failure type  $h$  where  $n_j$  is number at risk at  $t_j$  and  $d_{hj}$  is the number of events of type  $h$  that occur at  $t_j$ .

### 2.4.3 Regression models for competing risks

Estimation of the effect of covariates on the cause specific hazard is often based on a Cox PH model. For example Kalbfleisch and Prentice [30] developed a method where each failure type is modelled separately and the other failure types are censored. Lunn and McNeil [60] developed a model with two versions referred to as method A and method B. In both versions the data are augmented  $k$  (failure type) times and a Cox PH model is fitted, method A unstratified and method B stratified. Tai et al. [61] compared four different approaches to analysing competing risks data and developed an extension of the Lunn and McNeil method. However, since the effect of a covariate on the cause specific hazard might be different to the effect on the cumulative incidence function [28, 62], much research has centred on developing regression models for the cumulative incidence function. Klein and Andersen [63] developed a regression method which is based on creating jack-knife pseudo values for the estimate of the cumulative incidence function at specified time points. The obtained pseudo values are then used in generalized estimating equations (GEEs) to model the effect of covariates on the outcome of interest. For the method to work, it is assumed that right censoring is independent on both the multi-state process and of the covariates [64].

The most frequently used method for regression of the cumulative incidence function was developed by Fine and Gray [21]. The model is based on the subdistribution hazard formulated by Gray [65]. For failure from cause 1, i.e.  $\varepsilon = 1$ , this is:

$$\lambda_1^*(t) = \lim_{\Delta t \rightarrow 0} \frac{1}{\Delta t} P\{t \leq T < t + \Delta t, \varepsilon = 1 | T \geq t \cup (T \leq t \cap \varepsilon \neq 1)\}$$

$$= -\frac{d \log\{1 - F_1(t)\}}{dt},$$

where  $F_1(t)$  is the cumulative incidence function for the failure from cause 1. The risk set associated with the subdistribution hazard consists of individuals who have not experienced the event by time  $t$  as well as individuals who have experienced the competing event. The cumulative incidence function and the subdistribution hazard are directly related as in survival analysis with a single event, with:

$$F_1(t) = 1 - \exp\left(-\int_{s=0}^{s=t} \lambda_1^*(s) ds\right).$$

The Fine and Gray is similar to the Cox PH model in that it is a proportional hazards model of the subdistribution hazard where the effect of the covariates is linear on a complementary log-log transformed cumulative incidence function, i.e.

$$\lambda^*(t) = \lambda_0^*(t) \exp(\boldsymbol{\beta}^T \mathbf{X}),$$

where  $\lambda^*(t)$  is the hazard of the subdistribution and  $\lambda_0^*(t)$  denotes the subdistribution baseline hazard function. As in the Cox PH model the subdistribution baseline hazard function is left unspecified and the subdistribution hazard ratio is:

$$HR_{sub} = \exp\{\boldsymbol{\beta}^T (\mathbf{X}_1 - \mathbf{X}_0)\},$$

comparing subjects with covariate values  $\mathbf{X}_1$  relative to those with  $\mathbf{X}_0$ . The model can be used to make predictions of the cumulative incidence function adjusted for covariates. However, because of the definition of the risk set, the subdistribution hazard ratios do not have a direct interpretation unlike the hazard ratios from the Cox PH model [28]. This fact is sometimes not appreciated by researchers, see e.g. [66-68]. The Fine and Gray model has become very popular, partly because of its similarity to the Cox PH model. Further, because commands for implementing the model are now

available in common software programs such as Stata and in R, its use will likely continue to increase. The model and its application to arthroplasty registry data are discussed further in Chapter 5.

An overview of the above and other competing risks regression models is provided by Zhang et al. [69] and more recently by Haller et al.[70].

## 2.5 Analysis of joint replacement registry data

A number of joint replacement registries have been established worldwide. Results from the analysis of registry data are typically presented in annual reports and publications in journals [71, 72].

Data in joint replacement registries are traditionally analysed with survival methods where the outcome of the analysis is ‘time to revision’, that is, the time interval between the operation date of insertion of the prosthesis and the operation date of revision. Revision is the main indicator of failure of a joint replacement. It is a crude measure of failure as it depends on many factors such as the health of the patient, waiting lists, the surgeon threshold for operation etc., but in its favour it is an unambiguous outcome [73]. The survival function is commonly estimated with the Kaplan-Meier method and results are presented in figures and tables [13, 74]. Patients are censored either administratively (at the end of each year) or because of death. Groups are compared with log-rank tests. Revision rates of different prostheses are compared using the Cox PH model, adjusting for covariates such as age and sex [75].

This approach to analysis is followed for example by the Nordic countries’ arthroplasty registries and the Australian registry. The National Joint Registry (NJR) in the United Kingdom use a flexible parametric model [76] to model the hazard rates of revision, thereby obtaining both absolute and relative risks. An extension of the model is also used to estimate the cumulative incidence function and the effect of covariates in the presence of the competing risk of death [77].

Several registries compare risk of revision between different types of prostheses using revision rate per 100 or 1000 component years [78]. This method adjusts for the different lengths of time the prostheses have been at risk of failure, but it does not provide information on how the risk of revision may change over time.

When data in the AOA NJRR are analysed, proportionality in the Cox PH model is checked and, if evidence of a time varying effect is found, time points are chosen iteratively for calculating hazard ratios for each selected time period.

As the main outcome of interest in analysis of joint replacement data is failure of the prosthesis, data are analysed at the prosthesis-level. The consequence is that a patient who has several joint replacements may appear several times in the same analysis. For the purpose of data management and linkage, the NJR have restructured their data from procedure-level to person-level, but the data are analysed at procedure-level. With increasing amounts of data in joint replacement registries, the system for data management will become increasingly important.

This Chapter has provided an introduction to time to event analysis. The relevant literature has been reviewed and some issues related to the analysis of event histories have been discussed. In Chapters 4 to 7, these issues are considered in more detail, specifically with respect to the analysis of joint replacement registry data.



## 3 DATA SOURCES

Arthroplasty is surgical reconstruction or replacement of a joint. In this thesis, arthroplasty means joint replacement surgery. In addition to collecting data on hip and knee replacements, some arthroplasty registries also collect data on replacements of other joints such as elbow, shoulder, ankle and fingers. This thesis considers only data on hip and knee replacements, but the statistical methods discussed are applicable to data on other types of joint replacements.

There are two main categories of hip replacement, total hip replacement and partial hip replacement. In the former, the articular surfaces of both the acetabulum and femur are replaced. The main indication for this procedure is symptomatic osteoarthritis. In partial hip replacement (hemiarthroplasty) only the femoral component is replaced. This procedure is mainly performed as treatment for fractured neck of femur.

The main categories of knee replacements are partial and total knee replacements. In partial knee replacements only parts of the femur and/or tibia articular surface are replaced whereas in total knee replacement the entire femorotibial articulation is replaced with a single femoral and a single tibial prosthesis. Again, the main indication is symptomatic osteoarthritis.

In the following I provide a short description of the two registries used as data sources for this thesis, the Australian Orthopaedic Association National Joint Replacement Registry and the Norwegian Arthroplasty Register.

### 3.1 The Australian Orthopaedic Association National Joint Replacement Registry

The Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR) was established and began data collection in 1999, but was not fully national until 2003. The need to establish a joint replacement registry in Australia was inspired

by the success of the Swedish Knee Arthroplasty Registry in improving standards and reducing costs of joint replacement surgery. The purpose of the AOA NJRR is to “*define, improve and maintain the quality of care for individuals receiving joint replacement surgery*”[13].

The AOA NJRR is owned by the Australian Orthopaedic Association and its technical support is provided by the Data Management & Analysis Centre (DMAC), University of Adelaide. Until 2008, the AOA NJRR was only collecting data on hip and knee replacements, but since then data on other joints (shoulder, elbow, ankle, etc.) replacements have been included. Data are recorded on both primary procedures and revisions. The Registry now (as of December 2012) has data on more than 700,000 procedures. Almost 100% of hip and knee procedures performed in Australia are reported. The amount of data recorded for each procedure is relatively small, which contributes to good compliance and reporting. The AOA NJRR obtain mortality data on patients who have received joint replacements (which are necessary for the appropriate analysis of the data) from the National Death Index, a data base maintained by the Australian Institute of Health and Welfare.

Information from the analysis of the Registry data is disseminated through annual and supplementary reports. There is an online facility where surgeons can access their individual data and for prosthesis companies and regulatory bodies to monitor prostheses.

Up until 31 December 2011, 332,351 hip procedures in 273,534 individual patients were recorded in the AOA NJRR. Approximately 12% of these procedures were revisions and 16% of the primary hip procedures were partial. Of 36,503 bilateral hip procedures, 4.6 % of patients had both hips operated upon the same day and 20% between 1 day and 6 months. The number of patients who received a hip replacement and have since died is 57,586 (21.1%).

For knee procedures, 380,726 were reported in 285,474 individual patients, 8% of which were revisions. The number of bilateral knee procedures was 72,788, 22.5% of

patients had both knees operated upon the same day and 13% performed between 1 day and 6 months. The number of patients who received a knee replacement and have since died is 27,597 (9.7%)[13].

## 3.2 The Norwegian Arthroplasty Register

The Norwegian Hip Arthroplasty Register (NAR) was established in 1987 in response to high failure rates of some prostheses that had been introduced to the market without prior clinical studies [79]. In 1994 it was extended to register all types of joint replacements performed in Norway. The main purpose of the NAR is to “*function as a surveillance tool to identify inferior implants as early as possible*”[80].

The NAR has excellent coverage. It has been reported that the NAR registered 97% of hip arthroplasties patient recorded in the Norwegian Patient Register 1999-2002 [81, 82]. The data are linked through patients’ national social security number to the Norwegian Population Register so that information about emigration and death are obtained when the NAR data base is updated.

The 2012 annual report [74] includes 162,971 hip procedures performed between 1987 and 2012; approximately 14% of these were revision procedures. In 2011, 7,360 primary hip procedures were performed. In the period 1994 to 2012, 51,337 knee procedures were recorded, 8% of these were revision procedures. In 2011, 4,526 primary knee procedures were performed.

## 3.3 Ethical considerations

The AOA NJRR is a Declared Federal Quality Assurance Activity and is required by law to abide by certain specified requirements, for example, protect information that identifies individuals in the AOA NJRR. It has been subjected to ethics approval. The AOA NJRR only releases de-identified data. The data released for this project had the patients' identifiers removed. Further, there were no other characteristics in the data used in this thesis from which to identify any particular patient or surgeon.

Prior to undergoing their arthroplasty patients are informed about the AOA NJRR and informed that they may 'opt-off', that is, choose not to be included in the Registry database. They are given a phone number to ring for further information. Surgeons are not identified on the database unless they choose to be.

The data obtained from the NAR are also de-identified. The NAR obtains permission from each patient to collect information on their procedure.

# 4 COMPETING RISKS SURVIVAL ANALYSIS APPLIED TO DATA FROM THE AUSTRALIAN ORTHOPAEDIC ASSOCIATION NATIONAL JOINT REPLACEMENT REGISTRY

## 4.1 Preface

This chapter contains the first of four articles that contribute to this thesis. The article has been published in *Acta Orthopaedica* [83]. It investigates the use of the Kaplan Meier (KM) method and the Cumulative Incidence Function (CIF) in the analysis of arthroplasty registry data. The aim of the study was to compare the estimates of risk of revision from the two methods while treating death as a competing risk. The purpose was to demonstrate the degree to which the risk of revision is biased using the KM method, compared to estimates using competing risks methods, on subsets of data from the AOA NJRR with different incidences of the competing risk death.

The article also explains the problems associated with using the KM method in competing risks scenarios and reasons why KM estimates are often biased.

Of note is that the competing risks model is equivalent to a simple multi-state model with two or more absorbing states and one transient state. Multi-state models with a more complex structure are described in Chapters 6 and 7.

## 4.2 Statement of Authorship

Gillam MH, Ryan P, Graves SE, Miller LN, de Steiger RN, Salter A. Competing risks survival analysis applied to data from the Australian Orthopaedic Association National Joint Replacement Registry. *Acta Orthop* 2010;81(5):548-55.

Doi: [10.3109/17453674.2010.524594](https://doi.org/10.3109/17453674.2010.524594)

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### **Philip Ryan**

Contributed to the design of the study, interpretation of the results and reviewed the manuscript. I give consent for Marianne Gillam to present this paper towards examination for the Doctor of Philosophy.

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### 4.3 Article

Marianne H Gillam 1, Philip Ryan, Stephen E Graves, Lisa N Miller, Richard N de Steiger, and Amy Salter (2010) Competing risks survival analysis applied to data from the Australian Orthopaedic Association National Joint Replacement Registry. *Acta Orthopaedica*, v. 81 (5), pp. 548-555, October 2010

NOTE: This publication is included in the print copy of the thesis held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.3109/17453674.2010.524594>



## 4.4 Additional Discussion

The data in the published article were obtained from the AOA NJRR. The Australian registry achieved full national coverage in 2002 and at the time of analysis the data consisted of records covering a 7-year period. In the discussion in the article, it was pointed out that scope for further research would entail applying competing risks methods to data with a much longer follow-up time.

The same analysis was subsequently performed on data from the Norwegian Arthroplasty Register (NAR) which has records on hip replacements in Norway from 1987. The data consist of 78,102 first recorded hip arthroplasties in patients who received THA for OA from 1987 to 2010. As in the published article, results were compared for patients younger than 70 years with those from patients who were 70 years or older. These results are presented in Table 4.5 and Figures 4.8 and 4.9 below. The KM and CIF estimates, differences and relative differences are similar to the estimates based on the Australian data at 1 year and at 5 years (Table 4.4). Because mortality in this group of patients was relatively low for the first 5 years after receiving the arthroplasty, there was little difference between the KM and CIF estimates of risk of revision at these time points. However, with increasing mortality over time with increasing age of the patients, it is evident that the KM method eventually overestimates the risk of revisions to a substantial degree in this group, as was the case in the group of patients from the AOA NJRR who received arthroplasty for fractured neck of femur. For example, after 20 years the relative difference in the youngest age group was 21.5% whereas in the oldest age group it was 68.9% (Table 4.5). Because CIF estimates of the risk of the event of interest should be interpreted in conjunction with estimates of the competing event(s), the figures for the estimates of risk of death over the period are also presented (Figure 4.9). The CIF estimates are somewhat lower than the KM estimates for the risk of death and represents estimates of the risk of death over time without first having had a revision. When revision is not considered a competing event to death, which is most commonly the case, the KM estimates are the appropriate estimates of risk of death at specific points in time. The

results demonstrate that even in a population with relative low mortality such as individuals who have received THA for OA [101], accounting for competing risks is important in analysis with long follow-up time.

**Table 4.5: Data from the Norwegian Arthroplasty Register. Percent estimates (with 95% confidence interval) of revision in patients with osteoarthritis who underwent total hip replacement – by age group.**

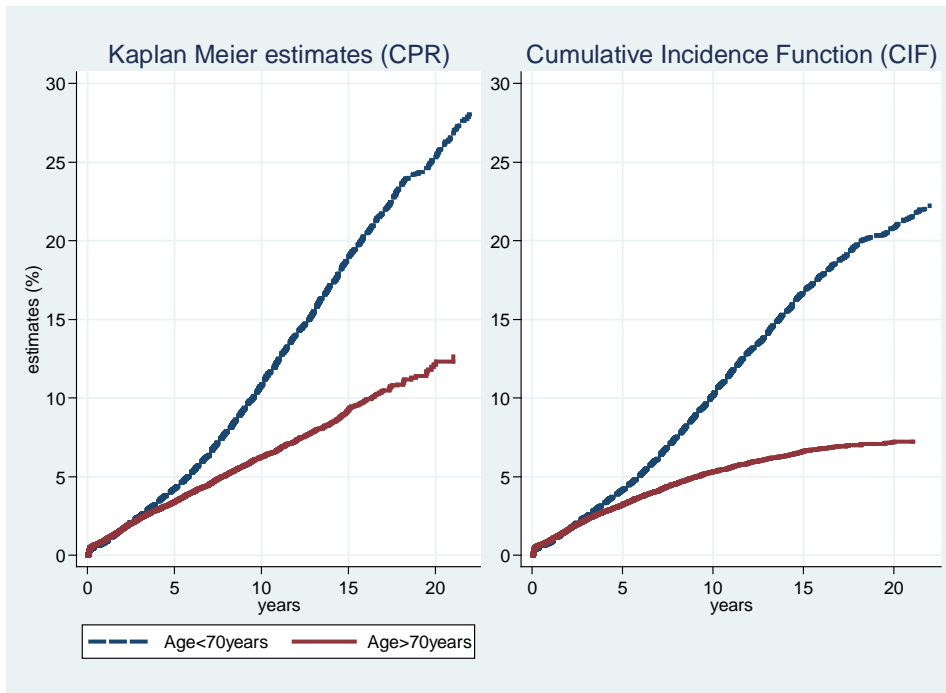
	<b>1 Yr</b>	<b>5 Yrs</b>	<b>10 Yrs</b>	<b>15 Yrs</b>	<b>20 Yrs</b>
<b>Age &lt; 70 years</b>					
<b>At risk</b>	31,634	22,010	12,211	5,413	1,549
<b>KM</b> <sup>a</sup>	0.8 (0.7-0.9)	4.2 (4.0-4.5)	10.8 (10.4-11.3)	19.0 (18.3-19.7)	25.3 (24.3-26.3)
<b>CIF</b> <sup>b</sup>	0.8 (0.7-0.9)	4.2 (3.9-4.4)	10.2 (9.8-10.6)	16.8 (16.2-17.3)	20.8 (20.1-21.5)
<b>Diff</b> <sup>c</sup>	0.002	0.08	0.62	2.21	4.47
<b>RD</b> <sup>d</sup>	0.2%	1.9%	6.2%	13.2%	21.5%
<b>Age ≥70 years</b>					
<b>At risk</b>	40,398	27,552	12,243	3,573	514
<b>KM</b>	1.0 (0.9-1.1)	3.4 (3.2-3.6)	6.3 (6.0-6.5)	9.2 (8.8-9.8)	12.1 (11.1-13.2)
<b>CIF</b>	1.0 (0.9-1.0)	3.2 (3.1-3.4)	5.3 (5.1-5.5)	6.6 (6.3-6.9)	7.2 (6.9-7.5)
<b>diff</b>	0.01	0.2	0.94	2.64	4.95
<b>RD</b>	0.9%	5.7%	17.7%	39.9%	68.9%

<sup>a</sup> Kaplan-Meier estimate of Cumulative Percent Revised.

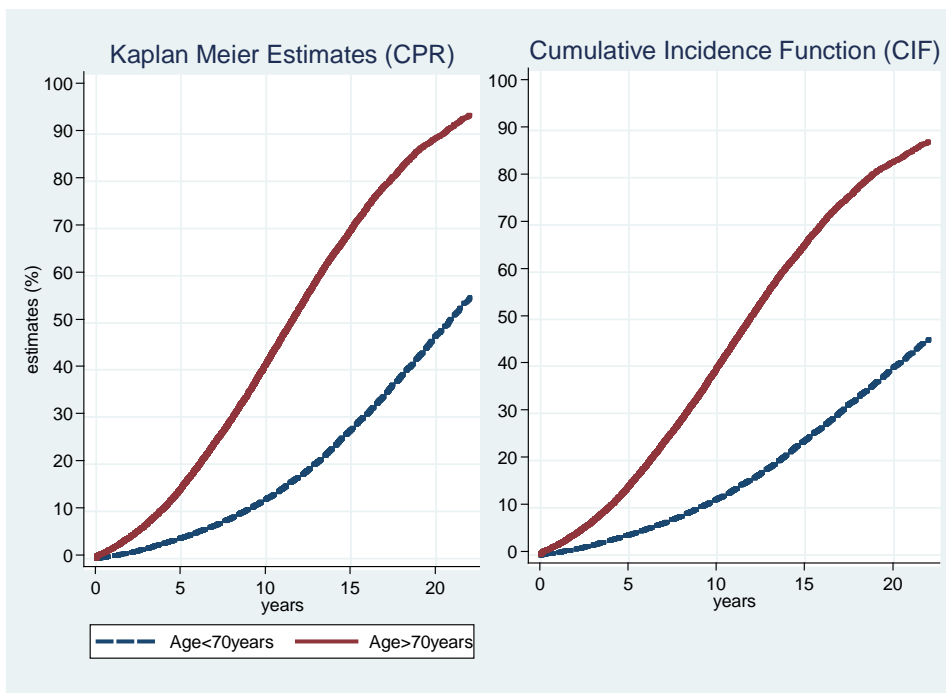
<sup>b</sup> Cumulative Incidence Function.

<sup>c</sup> Difference (bias of the KM estimate).

<sup>d</sup> Relative Difference (bias of KM estimate relative to the CIF).



**Figure 4.8: Estimates of revision by age group in patients with OA and THA (data from the NAR)**



**Figure 4.9: Estimates of death by age group in patients with OA and THA (data from the NAR)**

# 5 DIFFERENT COMPETING RISKS MODELS APPLIED TO DATA FROM THE AUSTRALIAN ORTHOPAEDIC ASSOCIATION NATIONAL JOINT REPLACEMENT REGISTRY

## 5.1 Preface

In the previous chapter, non-parametric methods for estimating the risk of revision in the presence of the competing risk of death were compared. It was shown that when the risk of death was high, the KM method substantially overestimated the risk of revision compared to estimates using competing risks methods, and that the bias increased with time as the incidence of the competing risk of death increased.

This chapter deals with estimating the effect of covariates on the hazard rate and on the risk of revision and death. The hazard rate of revision is the instantaneous risk of revision at any given time whereas the risk of revision, as estimated by the CIF, is the accumulated risk before a certain time. Since the latter estimates depend on the hazard rates of both death and revision, the effects of covariates on the rate and risk of revision may differ.

In the following article, which has been published in *Acta Orthopaedica* [102], the aim was to examine the use of different models in analysing arthroplasty registry data in the presence of competing risks. It illustrates the use of methods for assessing the effect of covariates on the revision rate and methods for assessing the effect on the risk of revision. Methods for handling covariates with time dependent effects are also addressed, and guidance is provided on how to interpret estimates from competing risks analysis.

## 5.2 Statement of authorship

Gillam MH, Salter A, Ryan P, Graves SE. Different competing risks models applied to data from the Australian Orthopaedic Association National Joint Replacement Registry. *Acta Orthop* 2011;82(5):513-20. Doi: 10.3109/17453674.2011.618918.

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### **Amy Salter**

Contributed to the design of the study, interpretation of the results, and reviewed the manuscript. I give consent for Marianne Gillam to present this paper towards examination for the Doctor of Philosophy.

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### **Philip Ryan**

Contributed to the design of the study, interpretation of the results, and reviewed the manuscript. I give consent for Marianne Gillam to present this paper towards examination for the Doctor of Philosophy.

Signed: ..... Date: .....

### **Stephen E Graves**

Contributed to the acquisition of the data, interpretation of the results, and reviewed the manuscript. I give consent for Marianne Gillam to present this paper towards examination for the Doctor of Philosophy.

Signed: ..... Date: 27<sup>th</sup>.December.2012.....

### 5.3 Article

Marianne H Gillam, Amy Salter, Philip Ryan, and Stephen E Graves (2011)  
Different competing risks models applied to data from the Australian Orthopaedic  
Association National Joint Replacement Registry  
*Acta Orthopaedica*, v. 82 (5), pp. 513-520, October 2011

NOTE: This publication is included in the print copy of the thesis  
held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.3109/17453674.2011.618918>

## 5.4 Additional discussion

In traditional survival analysis with a single outcome there is a one-to-one correspondence between the hazard rate and the survival function so that the effect of covariates as estimated by the Cox PH model corresponds directly to the effect on the survival function [22]. The previous article demonstrates that in competing risks scenarios the effect of covariates on the risk of revision may be different to the effect on the hazard rate of revision. This is evident for example when comparing the effect of sex on revision: males had a significantly higher hazard of revision than females whereas there was no evidence of a difference between the sexes in the actual risk of revision. In a competing risks scenario with one event of interest and one competing event and with cause specific hazards  $\lambda_1(t)$  and  $\lambda_2(t)$  respectively, the relationship between  $\lambda_1(t)$  and the subdistribution hazard  $\lambda_1^*(t)$  for the event of interest is [121, 122]:

$$\lambda_1(t) = \left(1 + \frac{P(T \leq t, \varepsilon = 2)}{P(T > t)}\right) \times \lambda_1^*(t) = \left(1 + \frac{F_2(t)}{P(T > t)}\right) \times \lambda_1^*(t),$$

where  $F_2(t)$  is the CIF of the competing event and

$$P(T > t) = \exp\left(-\int_{s=0}^{s=t} \lambda_1(s) + \lambda_2(s) ds\right)$$

Proportionality of either the Cox PH model or the Fine and Gray model does not imply proportionality of the other. However, even if the model for the subdistribution hazard is misspecified, it may still be useful for estimating average effects of covariates on the CIF [123, 124].

The relationship between the hazard ratios (HRs) from the Cox PH model and the Fine and Gray model are described by Lau et al. [109]. Table 5.3 shows how the HR of the event of interest relates to the subdistribution HR in a scenario with one competing risk. For example, if the HRs indicate a decreasing effect of a covariate ( $HR < 1$ ) on the cause specific hazards for both the event of interest and the competing event, the subdistribution HR will be larger than the cause specific HR for this event (Table 5.3). In general, it appears that if a covariate influences both cause specific hazards in the same direction, it can potentially result in the covariate having an opposite effect on the hazard rate to the actual risk of an event. See also articles by Allignol et al. and Dignam et al. [125, 126].

The relationship between the cause specific hazards and the subdistribution hazard is further complicated in that the numerical values of the subdistribution HRs cannot be interpreted quantitatively, unlike HRs obtained from Cox PH models, but only as qualitative relative effects on the CIF [22]. This is because the risk set associated with the subdistribution hazard for the event of interest at any time consists of individuals who have not experienced any event in addition to individuals who have experienced the competing event(s) [21].

Table 5.4 provides results from a stratified Cox PH model and the modified Fine and Gray model applied to the registry data from the AOA NJRR in the previous article (Table 5.4 is similar to Table 5.2 in the article except that it also includes HRs for death). The results in table 5.4 are consistent with the relationship between the cause specific HRs and the subHRs as described in Table 5.3 below.



**Table 5.3: Relationship between HRs and subHRs, modified from Lau et al. [109]**

$HR_1$	$HR_2$	
< 1	< 1	$subHR_1 > HR_1$
< 1	> 1	$subHR_1 < HR_1$
> 1	< 1	$subHR_1 > HR_1$
> 1	> 1	$subHR_1 < HR_1$

$HR_1$  and  $HR_2$ : cause specific hazard ratios for event of interest and competing event respectively.  $subHR_1$ : subdistribution hazard ratio for event of interest.

**Table 5.4: Cause specific hazard ratios (HRs) and subdistribution hazard ratios (subHRs) for different covariate for a stratified Cox PH model and a modified Fine and Gray model respectively.**

Models Event type	Cox PH				Modified Fine and Gray	
	Revision		Death		Revision	
	HR (95% CI)	P	HR (95% CI)	P	subHR (95% CI)	P
<b>Age: young vs. old<sup>a</sup></b>	1.28 (1.05, 1.56)	0.01	0.81 (0.77, 0.86)	<0.001	1.36 (1.10, 1.67)	0.004
<b>Male vs. female<sup>b</sup></b>	1.37 (1.10, 1.70)	0.005	1.94 (1.83, 2.05)	<0.001	1.94 (0.83, 1.31)	0.73
<b>Fixation type</b>	stratified	-	stratified	-	time dependent	-
<b>Monoblock vs. bipolar<sup>b</sup></b>	1.45 (1.09, 1.94)	0.01	1.85 (1.71, 1.99)	<0.001	1.30 (0.97, 1.74)	0.08
<b>Unipolar vs. bipolar<sup>c</sup></b>	1.38 (1.02, 1.88)	0.04	1.04 (0.96, 1.14)	0.36	1.44 (1.04, 1.98)	0.03
<b>Unipolar vs. monoblock<sup>d</sup></b>	0.95 (0.74, 1.23)	0.71	0.56 (0.52, 0.61)	<0.001	1.11 (0.85, 1.45)	0.46

<sup>a</sup> $HR_{revision} > 1$  and  $HR_{death} < 1$  HR,  $subHR_{revision} > HR_{revision}$

<sup>b</sup> $HR_{revision} > 1$  and  $HR_{death} > 1$  HR,  $subHR_{revision} < HR_{revision}$

<sup>c</sup> $HR_{revision} > 1$  and  $HR_{death} \approx 1$  HR,  $subHR_{revision} > HR_{revision}$

<sup>d</sup> $HR_{revision} < 1$  and  $HR_{death} < 1$  HR,  $subHR_{revision} > HR_{revision}$

# 6 MULTI-STATE MODELS AND ARTHROPLASTY HISTORIES AFTER UNILATERAL TOTAL HIP ARTHROPLASTIES

## Introducing the Summary Notation for Arthroplasty Histories

### 6.1 Preface

In the two previous chapters methods for analysing arthroplasty registry data in the presence of competing risks have been applied and discussed. The competing risks model is an example of a simple multi-state model with two or more absorbing states. In more complex multi-state models individuals can move into a finite number of different transient states before reaching absorbing states.

With a well documented increasing proportion of elderly people in the population and an increasing incidence of joint replacements in the population, progressively more individuals are expected to experience several joint procedures during their lifetime. The following article, which has been published in *Acta Orthopaedica* [127] with supplementary article data, investigates the use and suitability of multi-state modelling techniques in analysing data on complex arthroplasty histories. The aim of this article was to develop a model that could be used to describe arthroplasty histories and estimate transition intensities and probabilities associated with multiple joint procedures in an individual.

As joint replacement registries grow larger over time, management of the resultant data becomes increasingly complex. Joint replacement registries record each primary joint replacement with associated revisions, such that each individual may be recorded several times. Another aim of this article was to develop a notation that would enable identification and management of the complete arthroplasty history of each individual.

## 6.2 Statement of Authorship

Gillam MH, Ryan P, Salter A, Graves SE. Multi-state models and arthroplasty histories after unilateral total hip arthroplasties. *Acta Orthop* 2012;83(3):220-6.

Doi: 10.3109/17453674.2012.684140.

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### **Philip Ryan**

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### **Amy Salter**

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### **Stephen E Graves**

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27<sup>th</sup> December 2012

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## 6.3 Article

Marianne H Gillam, Philip Ryan, Amy Salter and Stephen E Graves (2012)  
Multi-state models and arthroplasty histories after unilateral total hip arthroplasties:  
introducing the Summary Notation for Arthroplasty Histories.  
*Acta Orthopaedica*, v. 83 (3), pp. 220-226, June 2012

NOTE: This publication is included in the print copy of the thesis  
held in the University of Adelaide Library.

It is also available online to authorised users at:

<http://dx.doi.org/10.3109/17453674.2012.684140>

# 7 THE PROGRESSION OF END-STAGE OSTEOARTHRITIS: ANALYSIS OF DATA FROM THE AUSTRALIAN AND NORWEGIAN JOINT REPLACEMENT REGISTRIES USING A MULTI- STATE MODEL

## 7.1 Preface

In Chapter 6 the use of a multi-state model for analysing the rates and probabilities of revision and receiving a second arthroplasty was investigated. The Summary Notation for Arthroplasty Histories, SNAH, was developed as a tool to manage data in arthroplasty registries on patients with multiple joint procedures and also to facilitate multi-state modelling. This chapter contains an article which has been accepted (16<sup>th</sup> December 2012) for publication in *Osteoarthritis and Cartilage* [135] where rather than focussing on revision of prostheses, a multi-state modelling technique is applied to the investigation of progression of osteoarthritis. Osteoarthritis is a common chronic disease and the pathogenesis is not clear. Symptomatic osteoarthritis is by far the most common indication for joint replacement surgery. The article investigates the progression of osteoarthritis using joint replacements as an indicator of the incidence of symptomatic osteoarthritis. The aim of the article was to determine if evidence of a pattern in the progression of osteoarthritis in large weight bearing joints could be found in independent data from two large national joint replacement registries.

**7.2 Statement of Authorship**

Gillam MH, Lie SA, Salter A, Furnes O, Graves SE, Havelin LI, Ryan P. The progression of end-stage osteoarthritis: Analysis of data from the Australian and Norwegian joint replacement registries using a multi-state model.

Accepted for publication in Osteoarthritis and Cartilage 17 December 2012

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Designed the study, performed all analysis, interpreted the results, drafted the manuscript and acted as corresponding author.

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*December 27<sup>th</sup> 2012*

**Leif I Havelin**

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Date:

*December 20, 2012*

**Philip Ryan**

Contributed to the design of the study, interpretation of the results and reviewed the manuscript. I give consent for Marianne Gillam to present this paper towards examination for the Doctor of Philosophy.

Signed:

Date:

.....

.....



## 7.3 Article

### 7.3.1 Abstract

*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.

### 7.3.2 Introduction

Osteoarthritis (OA) is a common chronic disease, leading to chronic pain, decreased quality of life and disability [136]. OA often involves multiple joints and the greatest disability is caused by hip and knee OA [137] 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 [138-140]. 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 [129, 141, 142], 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. [129] found that a greater 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.

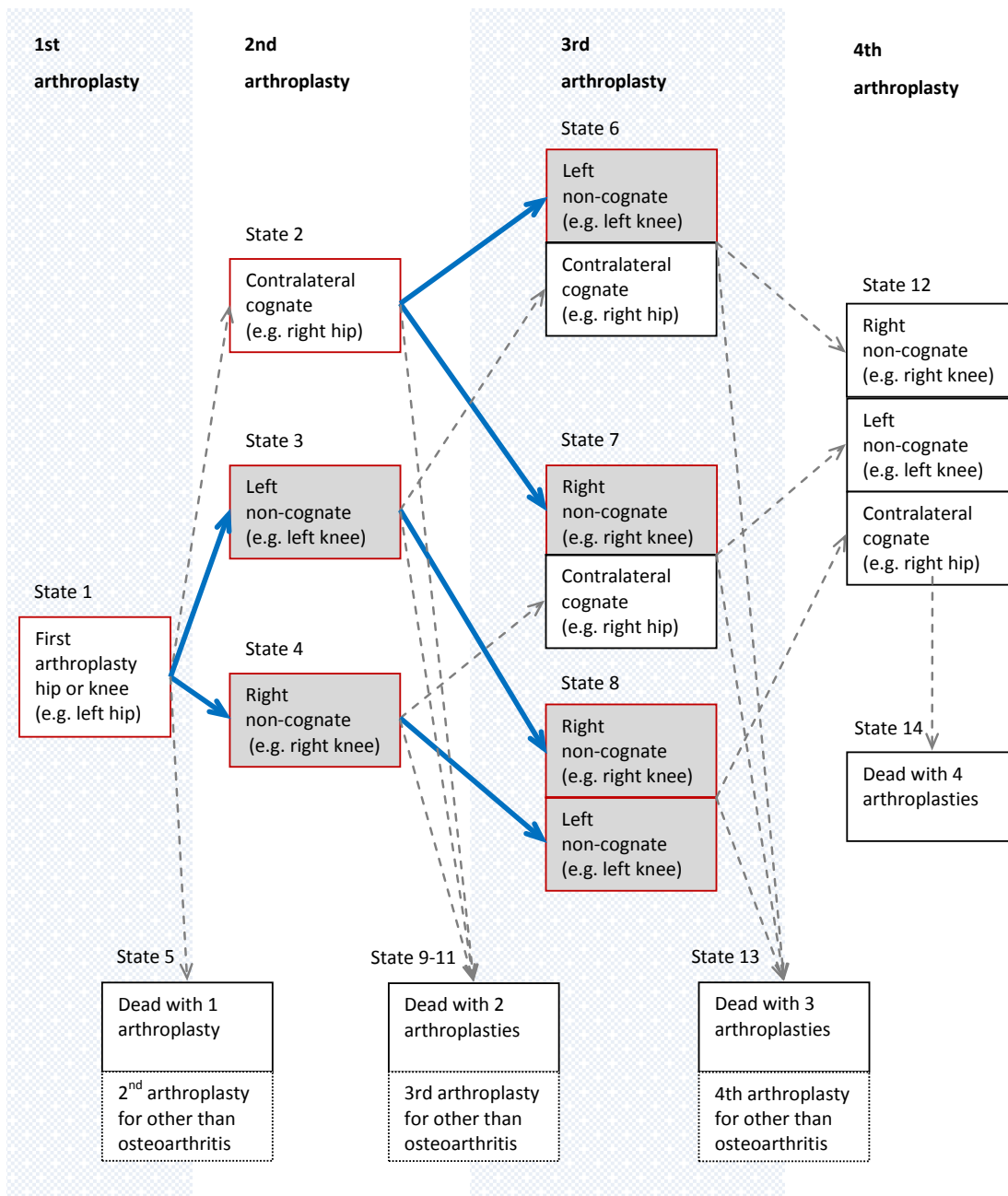
### 7.3.3 Material and methods

We obtained data from the Australian Orthopaedic Association National Joint Replacement Registry (AOA NJRR) and the Norwegian Arthroplasty Register (NAR). The Norwegian Arthroplasty Register and the Australian Orthopaedic Association National Joint Replacement Registry 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 [79]. The AOA NJRR started collecting data on hip and knee arthroplasties in 1999 and became national in 2002 [143]. The NAR captures 97% of all hip and knee replacements performed in Norway [81]. 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”[143].

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 [52].

The model with 14 possible states that can be occupied (boxes), and paths (arrows) that can be travelled, is illustrated in Figure 7.1. 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 [50]). 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 [127].



**Figure 7.1: Multi-state model**

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 [144]. 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 [51]) 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 Figure 7.1. 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 Figure 7.1.

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 [59].

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 [128] in the software environment 'R' [108] and Stata version 11.

### 7.3.4 Results

There were 200,730 subjects included from the AOA NJRR and 31,868 subjects from the NAR. The distribution of patients by type of first arthroplasty (hip or knee), country, age, sex and side of first arthroplasty is presented in Table 7.1. 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 7.1: Distribution of individuals according to covariates.**

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

**Table 7.2: Numbers and percent of events in the multi-state model (Figure 7.1) 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 (%*)
<b>1 arthroplasty</b>	78,634 (100)	19,786 (100)	122,096 (100)	12,082 (100)
<b>No event</b>	58,303 (74)	14,414 (73)	87,874 (72)	8714 (72)
<b>state 1 → state 2</b>	12,668 (16)	3867 (20)	26,433 (22)	2521 (21)
<b>state 1 → state 3</b>	1828 (2)	228 (1)	1348 (1)	133 (1)
<b>state 1 → state 4</b>	2072 (3)	257 (1)	1772 (1)	222 (2)
<b>state 1 → state 5</b>	3763 (5)	1020 (5)	4669 (4)	492 (4)
<b>state 2 → state 6</b>	172 (1)	26 (1)	268 (1)	27 (1)
<b>state 2 → state 7</b>	232 (2)	46 (1)	335 (1)	46 (2)
<b>state 3 → state 6</b>	127 (7)	14 (6)	134 (10)	10 (8)
<b>state 3 → state 8</b>	208 (11)	26 (11)	159 (12)	23 (17)
<b>state 4 → state 7</b>	153 (7)	26 (10)	196 (11)	17 (8)
<b>state 4 → state 8</b>	241 (12)	33 (13)	158 (9)	27 (12)
<b>state 2-4 → state 9-11</b>	574 (3)	154 (4)	952 (3)	94 (3)
<b>state 6-8 → state 12</b>	97 (10)	20 (12)	127 (10)	8 (5)
<b>state 6-8 → state 13</b>	20 (2)	3 (2)	25 (2)	3 (2)
<b>state 12 → state 14</b>	1 (1)	0 (0)	4 (3)	0 (0)

\*Percent of number of individuals who entered the state

Table 7.2 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 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 7.2 correspond to the HRs presented in Table 7.3.

Table 7.3 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 Figure 7.1 and Table 7.2. 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 hazard ratio (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 Figure 7.2), whereas for receiving a right knee (state 1 → 4) the hazard ratio 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 hazard ratio (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 Figure 7.3), whereas for receiving a subsequent left knee (state 4 → 8) the hazard ratio 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 7.3). The transition hazard of receiving a third arthroplasty after two arthroplasties of the same

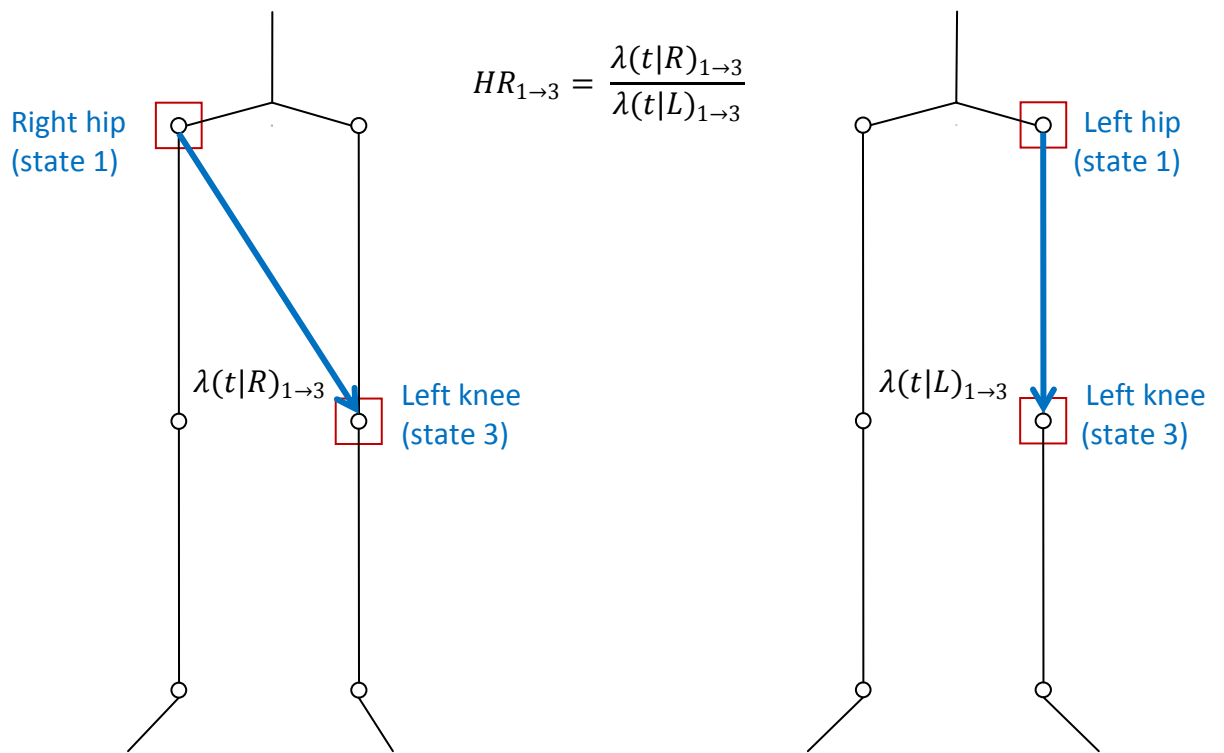
type of joint (e.g. after bilateral hip arthroplasties) did not show a consistent association with the side of the first arthroplasty (Table 7.3, state 2 → 6 and state 2 → 7).

Figures 7.4 and 7.5 show the estimated probabilities of occupying state 3 and 4 (Figure 7.1) over a period of 5 years after the first arthroplasty. Figure 7.4 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 Figure 7.4). Figure 7.5 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.

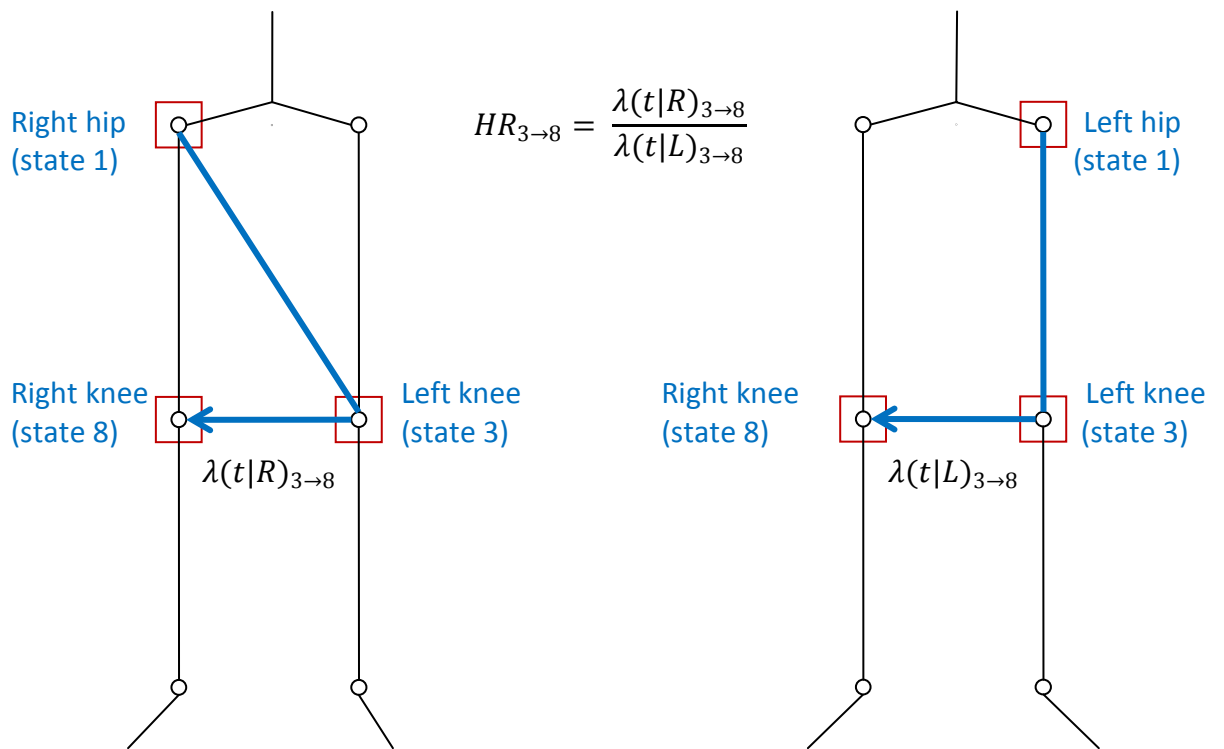
**Table 7.3: Effect of side of first arthroplasty (hip or knee) on hazards for selected transitions in the model.**

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

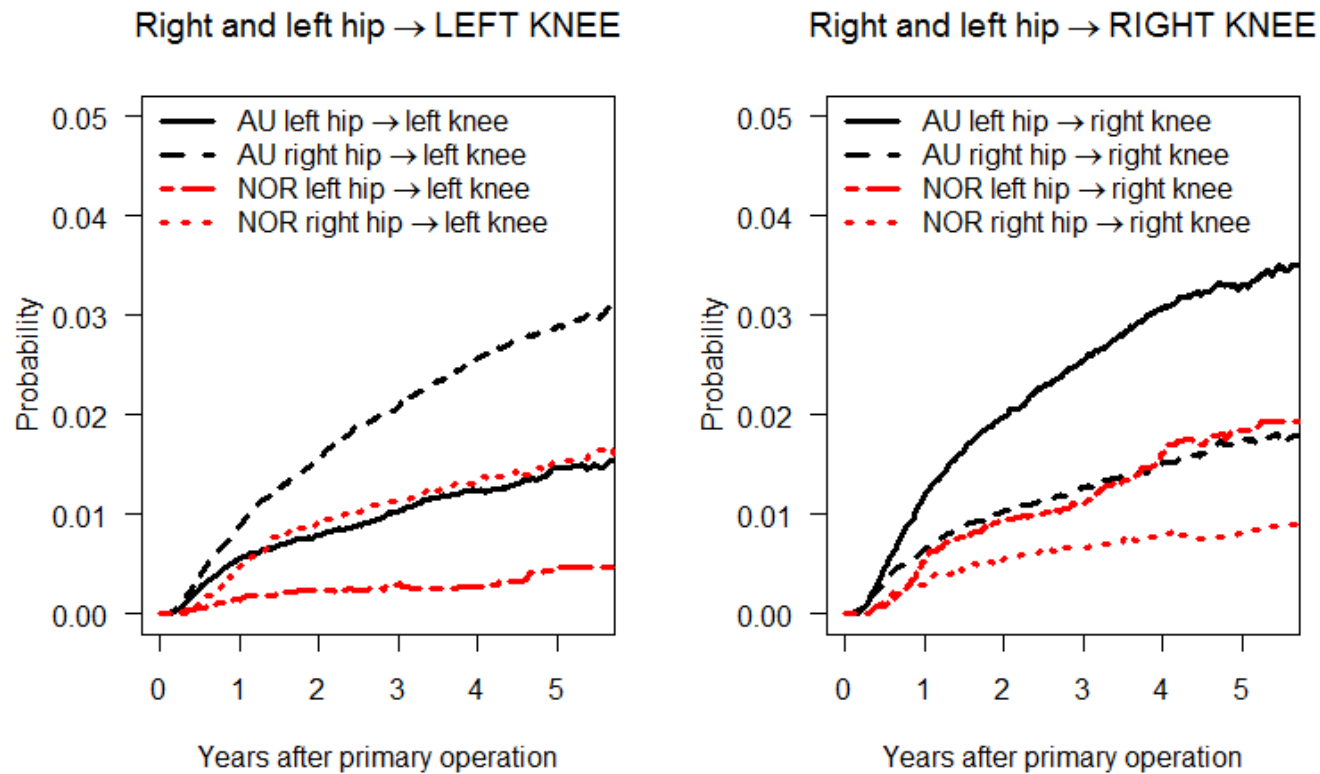
\*\*\*P<0.001; \*P<0.05. HR: Hazard ratio



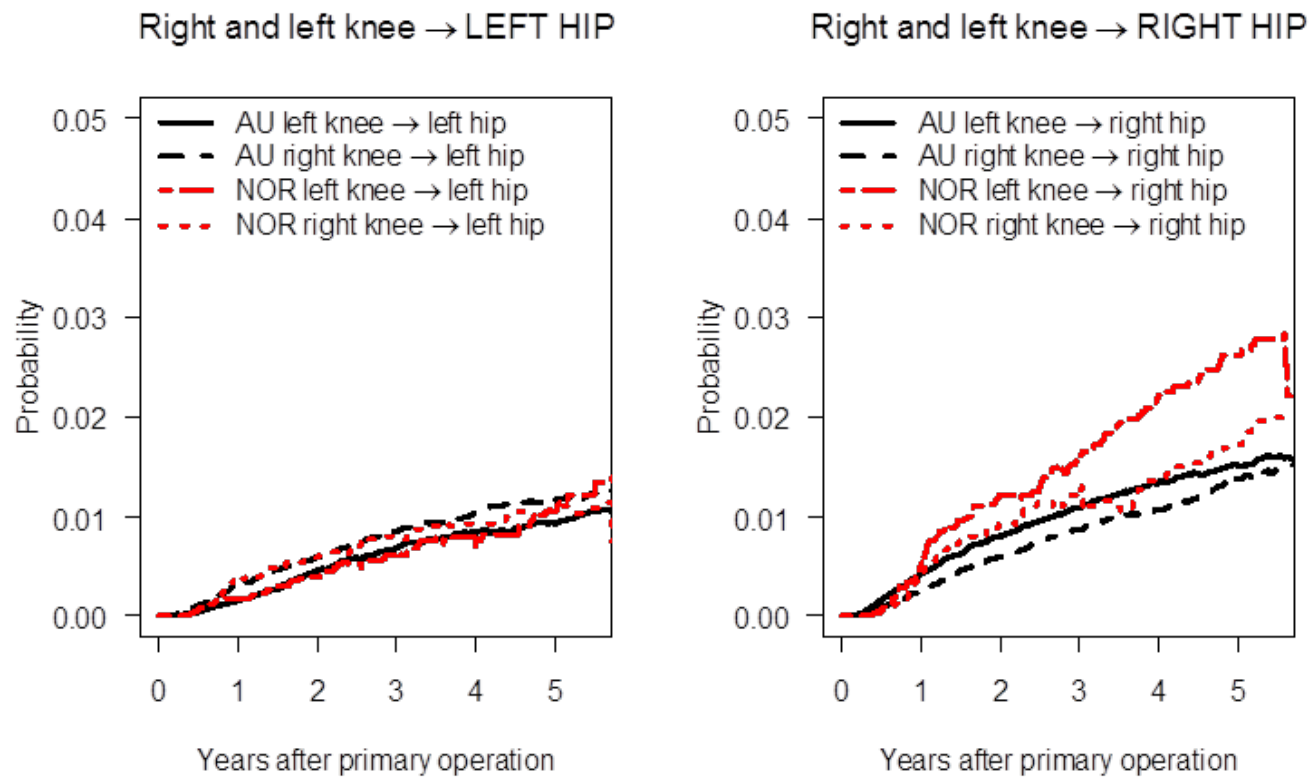
**Figure 7.2: Comparing hazards of receiving a left knee arthroplasty between individuals who had received a right hip arthroplasty with individuals who had received a left hip arthroplasty. HR: hazard ratio,  $\lambda(t|R)_{1 \rightarrow 3}$ : hazard of receiving a left knee given that first hip was a right hip,  $\lambda(t|L)_{1 \rightarrow 3}$ : hazard of receiving a left knee given that first hip was a left hip.**



**Figure 7.3: 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: hazard ratio,  $\lambda(t|R)_{3 \rightarrow 8}$ : hazard of receiving a right knee given that first hip was a right hip,  $\lambda(t|L)_{3 \rightarrow 8}$ : hazard of receiving a right knee given that first hip was a left hip.**



**Figure 7.4: 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).**



**Figure 7.5: 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).**

### 7.3.5 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.

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 (Figure 7.4). Australia has a higher incidence of knee arthroplasties than Norway [9], 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 [145].



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 [146-149]. However, our 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 [129, 150, 151], 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 [129]. 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[81, 143] and the two countries have developed health systems [152]. 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 [153] which may indicate that some individuals have an increased susceptibility to develop OA, due to 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.[154] 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 [155-159] which may explain the progression of OA in the non-operated limbs. Umeda et al. [150] 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 [160].Tanaka et al.[161] 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. [162] 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.

**END OF PUBLISHED ARTICLE**

## 8 SUMMARY AND CONCLUSIONS

In this thesis statistical methods for analysing joint replacement registry data have been investigated. Joint replacement registries are important sources of data for evaluating outcomes of joint replacements. The use of appropriate statistical methods to analyse the data is of great importance. The overall aim of the thesis was to explore methods for analysing time to event data contained in joint replacement registries. The emphasis has been on multiple event data, more specifically methods for competing risks scenarios and multi-state modelling.

In this final chapter, I summarise the main findings and contributions to knowledge, discuss limitations and address topics for future research.

### 8.1 Main findings and contributions

#### 8.1.1 Non-parametric competing risks methods and arthroplasty data

The Kaplan-Meier (KM) method is generally known to overestimate the probability of failure in the presence of competing risks. An important aim of joint registries is to identify poorly performing prostheses. Revision surgery is considered the main indicator of failure of the prosthesis. In Chapter 4, the aim was to apply KM methods to arthroplasty data and compare the estimates of risk of revision with estimates accounting for the competing risk of death. In order to evaluate the magnitude of the potential bias when using the KM method, subsets of data with different incidence of the competing risk of death were examined.

It was evident that when the risk of the competing event death was high, such as that in individuals who received arthroplasty for fractured neck of femur, the KM method substantially overestimated the risk of revision. For example, 5 years after insertion of the primary procedure, the relative difference between the KM and CIF estimates was 79% for the group of patients with the highest mortality and 1.4% for the group with the

lowest mortality. The relative difference increased with time due to the incidence of death increasing with increasing age.

The results from this thesis are important since survival (or failure) curves are often used to estimate the risk of revision of prostheses over time, and as this work demonstrates, these estimates may be substantially biased if competing risks are not taken into account. Scenarios where accounting for competing risks in joint replacement registries are especially relevant include those where the incidence of death is high, where one reason for revision competes with other reasons for revision, or where there are long follow-up times. Prior to publication of the article in Chapter 4, only a few studies in orthopaedic research had been published addressing competing risks. This was the first article to show evidence of clinically relevant bias in the KM method on data from a large joint replacement registry. The article makes recommendations for analysis of joint replacement data and informs clinicians and other readers on how to interpret results from the KM method published in registry reports.

### **8.1.2 Competing risks regression and arthroplasty data**

Joint replacement registries collect and record information on a number of characteristics of the recipients of joint prostheses such as age and sex, type of prosthesis, type of fixation, indication for the procedure etc. In the analysis of these data, it is of interest to obtain estimates of effects on hazards and risks of failures adjusted for appropriate covariates. Several approaches for regression modelling in competing risks scenarios exist, but prior to the article presented in Chapter 5, their use had not been examined in the analysis of joint replacement registry data. The aim of the article in Chapter 5 was to describe some of the available models for dealing with competing risks in the analysis of joint replacement registry data and use them to examine the effects of covariates on the hazard rates and the risks of revision.

The effects of various covariates on the hazard of revision were modelled with a Cox-Aalen model, allowing the effect of fixation (cementless vs. cemented) to vary with time. The effect on the actual risk of revision, treating death as a competing risk, was

modelled with an extension of the Fine and Gray model, also allowing the effect of fixation to vary with time. The key finding in the article was that some covariates had a different effect on the hazard of revision than on the actual risk of revision, thus demonstrating that in competing risks scenarios, the effect on the risk of an event depends on the cause specific hazard for every event. Further, predictions based on both models showed that estimates based on the Cox-Aalen model overestimated the risk of revision compared to estimates from the modified Fine and Gray model. This was most pronounced for the group with the highest incidence of the competing risk of death.

The article in Chapter 5 is the first to demonstrate that the effect of covariates on the hazard rate and risk of revision may be different. Thus, as discussed in Chapter 4, results from joint replacement registries must be interpreted with care when competing risks are present. The articles in Chapters 4 and 5 should contribute to increased awareness of competing risks issues in the orthopaedic research and registry community and alert analysts to use appropriate tools in the presence of competing risks. Furthermore, although the Cox PH model is the standard regression model in time to event analysis, Aalen's additive model has many advantages as demonstrated in the article in Chapter 5 where the changing effect of a time-varying covariate can be visualised and thereby provide a clearer understanding of the data.

### **8.1.3 Multi-state models and arthroplasty histories**

With the increases in life expectancy of the population, the increase in the rate of joint replacements is predicted to continue, meaning also that patients are likely to have several joint replacement procedures during their lifetime. Thus, data contained in joint replacement registries is expanding and is getting more complex. The aim of the article in Chapter 6 was to examine the use of multi-state modelling techniques in the analysis of data on complex arthroplasty histories with several outcomes of interest occurring over time. The aim was also to develop a system of notation that could assist in the management and analysis of large joint replacement data sets.

A multi-state model was developed where individuals were followed as they moved through different possible states from their first hip arthroplasty to receiving a second arthroplasty, to revision, death or until study closure. The model presented in Chapter 6 was used to describe numbers and proportions of patients in the cohort who experienced these events, their transition probabilities and the effect of sex on the transition intensities in the model. It was demonstrated that multi-state modelling techniques were well suited to the analysis and description of complex arthroplasty histories. The Summary Notation for Arthroplasty Histories (SNAH) code proved to be extremely useful when managing the large and complex data set.

The article in Chapter 6 contributes to the increasing research literature on the application and use of multi-state modelling techniques in medical research. The development has been facilitated by more advanced computer capabilities and increased availability of necessary software. The work presented in Chapter 6 will lead to increased awareness of advantages and possibilities of multi-state models in the analysis of multiple events amongst researchers using arthroplasty data. No system for managing complex arthroplasty histories has existed until now. The SNAH code could prove useful not only in the management of arthroplasty data, but also in a clinical context describing a patient's arthroplasty history.

#### **8.1.4 Application of multi-state models and osteoarthritis**

Data from joint replacement registries contain unique information on joint replacements in the population. For example, the indication for patients receiving an arthroplasty is recorded. Joint replacement is often a successful treatment for end-stage osteoarthritis and symptomatic osteoarthritis is the most common indication for joint replacement. Subsequently, the incidence of joint replacement is considered an indicator of the incidence of end stage osteoarthritis. The aim of the article in Chapter 7 was to apply multi-state modelling methods to joint replacement registry data to investigate progression of hip and knee osteoarthritis.

Data were obtained from two national joint replacement registries. A multi-state model was developed where individuals were followed from a first hip or knee arthroplasty for osteoarthritis to subsequent hip or knee arthroplasties, death or study closure. The effect of side of the first arthroplasty on the transition intensities and transition probabilities was estimated. The article demonstrated that there was evidence of an association between the side of the first hip arthroplasty and the side of subsequent knee arthroplasty.

Osteoarthritis is a common chronic disease. Factors such as older age and obesity are known to increase the risk, but the pathogenesis of osteoarthritis is not clear. Results from the article in Chapter 7 contribute to an understanding of the pathogenesis of osteoarthritis informed by the sequence of progression of osteoarthritis to different joints. This has implications for further research into causes, prevention and treatment of osteoarthritis. This article also illustrates the application of multi-state models to this important area of research and contributes information about alternative approaches to the analysis and use of arthroplasty registry data.

## 8.2 Limitations and future directions

Analysis of time to event data is a research area with a high level of activity. This thesis has focused on multi-state modelling to explore event histories contained in arthroplasty data, both in competing risks scenarios and when there are multiple joint procedures per patient. There are other approaches to analysing time to event data with multiple events. It would be of interest to examine how multi-state models compare with other models, such as marginal and conditional models in the analysis of arthroplasty data. Although the role of frailties in multi-state models is not clear [163], future work may consider their use accounting for clustering of events in arthroplasty data, for example by hospitals. Further, in this thesis, data on patients who received two arthroplasties on the same day were excluded and the performance of different types of models to analyse multivariate event data such as these would be of interest.



The most commonly used methods to analyse arthroplasty registry data are the Kaplan-Meier survival curves and the Cox PH model. Further investigation into the use of alternatives to the Cox PH model is warranted. An extension of one of these alternatives, Aalen's additive model, was used in this thesis and Aalen's additive model should be used more widely in the analysis of time to event data. The National Joint Registry in the United Kingdom, which is the largest joint replacement registry in the world, use a flexible parametric model to obtain relative and absolute hazards as well as to account for time varying effect and competing risks. Comparisons of this approach with the multi-state model used in this thesis would be interesting as both approaches have theoretical advantages over other (more commonly utilised) models. A related issue of interest is collaboration between national registries in evaluating statistical methods to analyse the registry data. Although national joint replacement registries operate mainly for their own use and have national characteristics [164], standardisation in reporting and analysis methods would be useful in disseminating and comparing results amongst stakeholders in registries worldwide. Continued evaluation of statistical methods to analyse the data presented in annual reports is of utmost importance. Because national regulations differ, various restrictions exist in gaining access to data in national joint replacements registries [71]. The data for this thesis were raw de-identified data obtained from the Australian and Norwegian registries offering a unique opportunity to examine characteristics of both registries. Continued collaboration of this kind is important and sharing of information across countries is beneficial for all parties involved.

In many joint replacement registries such as the AOA NJRR and the NAR, the amount of data collected on each joint replacement procedure is relatively small which contributes to good compliance and reporting. However, the resulting outcome measure, such as revision, consequently becomes crude as it may depend on many factors that are not recorded. One way to handle this issue, which will become increasingly important, is to link joint replacement data to other types of registries and data bases. Some of these other data bases may contain important measurements that are continually updated. An interesting approach advocated by Aalen [165], makes use of these

additional data by integrating time to event and longitudinal measurement data in the analysis and may prove to be a very useful tool in describing complex arthroplasty histories.

The SNAH code described in the article in Chapter 6 was developed to describe and manage arthroplasty history event data. Future developments could consider a similar approach for the notation of sequential events in other types of registry data where there is interest in analysing and keeping track of patients' event histories. For example, outcomes of cancer treatment are often modelled with a multi-state model and a similar summary notation could be used to describe the sequence of treatments and relapses after the diagnosis of cancer for each individual patient.

### **8.3 Conclusion**

This thesis has investigated methods for analysing time to event data contained in joint replacement registry data. The focus has been on exploring how multi-state models can be used to handle multiple events in these data. It has been demonstrated that in the presence of a competing risk such as death, the Kaplan-Meier method might lead to clinically relevant biased estimates of the risk of revision. The effect of covariates on the risk and on the rate of revision may differ and it is important that estimates obtained from the Cox PH model and competing risks regression models are interpreted correctly. Multi-state models provide a useful tool to describe and analyse data containing complex arthroplasty histories.

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