Using linked clinical and hospital morbidity data to assess risk and outcomes of primary lower limb total joint replacement in elderly men

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"Savour your life. Chew every mouthful thirty times.

If you rush you will miss something remarkable."

Robert Allen

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Abstract

Background

Osteoarthritis is the most common musculoskeletal disorder affecting elderly Australians and is a leading cause of lower limb total joint replacement (TJR). The incidence of TJR has risen substantially over the past two decades, reflecting the ageing population, and increases in the prevalence of risk factors such as obesity. Primary TJR is considered to be relatively safe with low rates of adverse outcomes, however, there is increasing evidence that elderly, and male patients who undergo the procedure may be at higher risk for postoperative complications and mortality. The retrospective cohort studies presented in this thesis used data, drawn from Health In Men Study (HIMS), that were linked with Western Australia (WA) linked data system to assess risk and outcomes of primary TJR in a large population-based cohort of men. The studies closely examined three issues - obesity, co-morbidities, and smoking - about which there is continuing debate in regard to their association with the risk of undergoing the procedure, and their roles as determinants of outcome of TJR. These risk factors are particularly important because they are amenable to modification.

Objectives

The main objectives of this thesis were:

1. To validate WA hospital morbidity data (HMD) and to assess the performance of HMD-based co-morbidity adjustment methods in predicting mortality among men undergoing elective primary TJR.

2. To assess risk of undergoing elective primary TJR in elderly men.

3. To assess risk of adverse outcomes following elective primary TJR including:

   - in-hospital complications,

   - prolonged length of stay in hospital (LOS),

   - all-cause readmission, and

- short- and long-term mortality.

4. To assess the role of obesity in predicting postoperative complications following TJR.

Methods

The electronic records of 12,203 men from HIMS were linked with WA HMD, Cancer Registry, Mental Health Services System and mortality records. Linkage with hospital morbidity data was done to identify TJR, in-hospital complications, LOS, and readmission in the target population. Significant morbidity was retrieved from HMD in the period 1970-2007. Multivariable analyses including logistic, Cox proportional hazards, and competing risk regressions were undertaken to assess study outcomes.

Main findings

- WA HMD are more likely to identify major co-morbidities and major operations with relatively high sensitivities and positive predictive values than co-morbidities of a less serious nature.

- Co-morbidity as recorded in HMD, irrespective of method used to measure it, independently increased risk of adverse outcomes. Model discrimination of 5-year mortality following TJR improved by 13% when HMD-based Deyo-Charlson index (Deyo-CI) was added to the baseline model that only accounted for age (Harrell's C: 0.69 for baseline model vs. 0.78 for model including age and Deyo-CI).

- A dose-response relationship between both weight and smoking, and risk of TJR was observed. Being overweight independently increased the risk, while smoking lowered it. Engaging in vigorous exercise and having a high socioeconomic status were associated with higher risk of TJR.

- Of the 819 men who had had elective TJR, 331 (40.4%) developed an in-hospital complication of which 155 were major. Age and body mass index independently predicted major complications. Any in-hospital complications significantly increased

risk of short-term mortality. Morbid obesity was independently associated with 5-year mortality following TJR.

- Length of stay in hospital was significantly longer in the overweight or obese and those who had had a total knee replacement [TKR] (compared with total hip replacement [THR]) and these two groups were more likely to be readmitted. All-cause readmission was also significantly high among the socioeconomically disadvantaged patients.

- All-cause 90-day and 1-year readmission following TJR independently increased risk of postoperative 5-year mortality.

- Augmenting HMD with actual weight and height significantly improved the model fit when predicting major in-hospital complications following TJR.

Conclusions

- HMD-based co-morbidity adjustment methods (Deyo-Charlson, Enhanced-Charlson or Elixhauser) significantly improve HMD-based predictive models and are appropriate in epidemiological research.

- Compared to men with normal weight, the obese are at higher risk of undergoing elective TJR and are more likely to develop major complications, stay longer in hospital and be readmitted following the procedure.

- Adding minimal information to routinely collected HMD improves the latter's predictive ability. This study suggests making actual weight and height mandatory variables in any HMD system.

Declaration

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- Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Smoking, body weight, physical exercise, and risk of lower limb total joint replacement in a population-based cohort of men: reply to Letter to Editor. *Arthritis & Rheumatism* 2011; DOI 10.1002/art.34324. © 2011, American College of Rheumatology.

- Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Total joint replacement in men: old age, obesity and in-hospital complications. *ANZ Journal of Surgery* 2012; In press.

- Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Use of routine hospital morbidity data together with weight and height of patients to predict in-hospital complications following total joint replacement. Under review in the journal *BMC Health Services Research*.

- Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Length of stay in hospital and all-cause readmission following elective total joint replacement in elderly men. *Orthopedic Research and Reviews* 2012; 4:43-51.

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Manuscripts Contributing to this Thesis

1. Mnatzaganian G, Ryan P, Norman PE, Hiller JE. Accuracy of hospital morbidity data and the performance of comorbidity scores as predictors of mortality. *Journal of Clinical Epidemiology* 2012;65(1):107-15.

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6. Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Length of stay in hospital and all-cause readmission following elective total joint replacement in elderly men. *Orthopedic Research and Reviews* 2012; 4:43-51.

Presentations Arising out of this Thesis

- Mnatzaganian G. Obesity and excess long term mortality in men who undergo elective total joint replacement. School of Population Health and Clinical Practice Seminar Series. Adelaide, September 2011.

- Mnatzaganian G. A propensity score that accounts for pre-treatment patient selection bias and predicts major adverse outcomes after total joint replacement in men. School of Population Health and Clinical Practice Seminar Series. Adelaide, October 2010.

- Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Smoking, body weight, physical exercise and risk of lower limb total joint replacement in a population-based cohort of men. School of Population Health and Clinical Practice HDR Research Symposium. Adelaide, January 2010.

- Mnatzaganian G. Linking datasets from different sources to assess quality of care: Focusing on elective total joint replacements. 2009 State Population Health Conference. Adelaide, October, 2009.

- Mnatzaganian G. Elective total joint replacement in a population-based cohort of Australian men: modifiable risk factors, co-morbidities and outcomes. School of Population Health and Clinical Practice Seminar Series. Adelaide, September 2009.

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Iron sharpens iron; scholar, the scholar - William Drummond

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Abbreviations

AAA	Abdominal Aortic Aneurysm
BMI	Body Mass Index
CCI	Charlson Co-morbidity Index
CRR	Competing Risk Regression
Deyo-CI	Deyo Charlson co-morbidity Index
HIMS	Health In Men Study
HMD	Hospital Morbidity Data
ICD-9-CM	International Classification of Disease, Version 9, Clinical Modification
ICD-10-AM	International Classification of Disease, Version 10, Australian Modification
LOS	Length Of Stay in Hospital
OA	Osteoarthritis
ROC	Area under the Receiver Operator Curve
SEIFA	Socio-Economic Index For Areas
THR	Total Hip Replacement
TJR	Total Joint Replacement (synonymous with THR or TKR)
TKR	Total Knee Replacement
WALDS	Western Australia Linked Data System

Chapter 1

Introduction

Preface

The incidence of total hip replacement (THR) and total knee replacement (TKR) has increased steadily over the past two decades and continues to rise as global populations grow. (1-4) In both men and women the procedure rates increase with age as patients reach their late 70s, after which the rates decline. (1-8) Lower limb total joint replacement (TJR) has become an effective and successful treatment for osteoarthritis (OA) of the hip and knee. In TJR the worn-out parts of the diseased joint are removed and replaced by a prosthesis that substantially decreases pain, and improves the person's mobility and overall function of the joint. In persons with end stage degenerative joint disease, primary TJR has proven to be very cost-effective, (9-13) and relatively safe with low rates of adverse outcomes. (14) However, the procedure is associated with short- and long-term complications (15-23) which are more frequent in older patients, (16,17) particularly men, (15,20) in smokers, (19,21) and in the obese, (19,20,22,23) and a thorough understanding of potential complications in these groups is important for the delivery of high quality and safe medical care.

Using linked datasets, the studies presented in this thesis assessed the risk of undergoing an elective primary TJR in a large cohort of Australian men, focusing on body weight, co-morbidity, smoking and physical exercise. The studies also evaluated short- and long-term outcomes following the procedure including in-hospital complications, prolonged stay in hospital, readmission, and 1- and 5-year mortality following the procedure.

1.1 Epidemiology

1.1.1 Burden of disease: prevalence of osteoarthritis

Osteoarthritis (OA) of the hip and knee is the most common musculoskeletal disorder to cause pain and disability in elderly populations accounting for up to 60% of musculoskeletal complaints in individuals who are 64 years or older, and is a leading cause of total joint replacement. (14) Osteoarthritis is also a main cause of disability in ageing populations and has been estimated at a global level to be the fourth leading cause of total Years Lived with a Disability (YLD). (24) An estimated 33% of persons between the ages of 63 and 93 years have radiographic signs of arthritis of the knees. (25) Lohmander reported that 40% of patients 80 years or older showed evidence of knee OA and almost 12% demonstrate radiologic changes of the hip. (26) A much later report from the American Academy of Orthopedic Surgeons (AAOS) indicated that approximately one in every two adults aged 65 and over had some form of arthritis. (27) According to the report, data from 2004 indicated OA and rheumatoid arthritis were increasing in frequency among the ageing population of the United States (US) and other industrialized countries, and that arthritis was becoming more prevalent among younger populations 45 to 65 years of age. (27) Similarly, a high proportion of Australians report having a chronic musculoskeletal illness. In the 2004–05 Australian National Health Survey (NHS), 15% of the respondents reported that they currently had arthritis; 13% of males and 18% of females. Of those with arthritis, 16% had rheumatoid arthritis, 51% had osteoarthritis and 39% reported they had another type of arthritis or didn't know the type of arthritis they had. Of those who currently had arthritis, 78% reported their condition had been diagnosed by a doctor or nurse. The proportion of people with arthritis increased with age from less than 1% of people aged less than 25 years to 49% of people aged 65 years and over. (28) Another national survey (ABS Survey of Disability, Ageing and Carers) that also covered nursing homes not represented in the 2004-

05 NHS showed similar results with 14.9% self-reporting arthritis or another musculoskeletal condition as being long term. (29)

Osteoarthritis (OA) is the major condition leading to TJR. (8) A study involving 17,444 hip replacements in Norway found that 68.0% of total joint replacement procedures were undertaken for primary osteoarthritis (where the cause of the OA was unknown), 19.0% were due to secondary osteoarthritis (where the cause of the OA was known) and the rest, 13.0%, followed an injury. (30) In Australia, OA accounts for 88.7% of all total hip replacements and 97.1% of all total knee replacements. (8) For this reason, TJR is often considered as an acceptable surrogate indicator of severe OA, (31-33) and factors associated with OA are predictors of TJR. (32-34) While the exact aetiology of OA remains poorly understood, the association between OA and ageing is well documented. (35) Other risk factors that contribute to both the onset and progression of osteoarthritis-related disability include recurrent injury, genetic susceptibility, obesity, lifestyle, and occupational exposures. (35,36) Of these, this thesis will focus on three potentially modifiable risk factors: body weight, smoking, and physical exercise (for more detail, see Chapter 4).

1.1.2 Scope of demand: incidence of primary TJR

Globally, the incidence of joint replacement is rising. (1-3) According to data from the American National Hospital Discharge Survey (NHDS), US Census, and the Millennium Research Group, the incidence of total joint replacement worldwide has increased steadily over the past two decades and continues to rise as global populations grow and obesity becomes more prevalent. (37-39) A review by Lohmander et al. of national registries of hip replacement procedures in five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) showed a steady increase in crude incidence rates of primary THR for OA over a period of four years. The increase was observed in all countries except Iceland and it was seen in both men and women. For example, comparing 1996 with 2000, the Danish crude annual incidence rates of primary THR for OA increased by 17.6% (68 per 100,000 (overall

population) in 1996 compared with 80 per 100,000 in 2000). (40) Kurtz et al. noted that between 1990 and 2002 the annual rate of primary total hip replacement per 100,000 Americans increased by 46%, and the rate of primary total knee replacements almost tripled during the same time period. (37) Similarly, between 1990 and 2002 the authors reported significant increases in the annual rates of revision of these procedures. The rate of revision THR increased by 60%, whereas the rate of revision TKR increased by 166%. The demand for TJR procedures is projected to grow. In the US, it has been estimated that between 2005 and 2030, the demand for primary THR will grow by 174%, and for primary TKR by 673%. (3) In the United Kingdom (UK), between 1991 and 2000, the annual age standardised primary THR rates increased by 18%, from 65.5 per 100,000 in 1991 to 77.6 per 100,000 in 2000. (7) Considering demographic changes, Birrell et al. estimated that the demand for THR in the UK will increase by 40% by 2021. (1) A review of South Korean national registry data by Kim et al. suggested an almost two-fold increase in TKR from 2002 to 2005 in South Korea. (41) An increase in both TKR and THR is also reported in Australia; in 2009, there were 4.3% more primary TKR procedures reported than in 2008 and 55.9% more than in 2003. The increase is relatively less in THR; comparing 2008 with 2010, primary THR procedures escalated by 9.3% (23,849 in 2008 compared with 26,062 in 2010), whereas TKR increased by 15% (32,573 in 2008 compared with 37,443 in 2010). (8)

1.1.3 Complications following TJR: incidence

Primary total joint replacement is considered one of the safest and most effective surgical procedures. (14) Nevertheless, TJR procedures have been associated with various serious potentially life threatening complications and there is increasing evidence that elderly patients may be at higher risk for medical and prosthesis-related complications following the surgery. A large study of American Medicare claims data indicated that older age was a risk factor for an adverse outcome within 90 days following THR. These outcomes included dislocation, infection and death. (15) Higher rates of complications have also been associated

with increased co-morbidity. A study that assessed complications including death, postoperative myocardial infarction (MI), thromboembolism, urinary tract infection, and postoperative confusion in patients older than 80 years undergoing THR, found that the complications and postoperative morbidity were significantly associated with the American Society of Anaesthesiologists (ASA) score. Patients with an ASA rating of III or higher had a 15% risk of a perioperative complication, significantly greater than those with an ASA class I or II. (42) In general, the rates of complications are significantly higher after revision TJR than after primary TJR. Phillips et al. reported incidence rates of complications after primary or revision THR in the American Medicare population from July 1, 1995 to June 30, 1996 which included dislocation, pulmonary embolism, and deep infection. (43) Incidence rates were calculated per 10,000 person-weeks. For patients receiving a primary THR, 3.9% had a dislocation, 0.9% had a pulmonary embolism, and 0.2% had a deep hip infection in the first 26 postoperative weeks. In the revision THR group, 14.4% had a dislocation, 0.8% had a pulmonary embolism, and 1.1% had a deep hip infection. (43) According to the report, the incidence rates were highest immediately after the procedure but they continued to be elevated throughout the three months following surgery.

To study outcomes following total joint replacement, researchers have used existing large databases including registries of joint replacement procedures and hospital morbidity data (HMD). The latter have frequently been used to characterize the rates of immediate postoperative outcomes of both primary (15,18,19) and revision total joint replacement. (15, 44) In addition, these data have been used to assess risk factors associated with undergoing this procedure. (31,36) However, this was made possible only after linkage with information (provided by the researchers) on risk factors unavailable in hospital morbidity datasets including weight, height and smoking habits of study participants.

This thesis focuses on postoperative complications following primary TJR. Complications following a revision surgery were out of scope of this thesis. The electronic

records of 12,203 men who form the population-based Health In Men Study (HIMS) (45,46) were linked with hospital morbidity data, Cancer Registry, Mental Health Services System, and mortality records from the WA linked data system (WALDS). (47) Linkage with HMD (see page 27) was used to identify those participants who had had a primary total hip or knee replacement and to ascertain other endpoints in the target population including in-hospital complications, length of stay (LOS), and readmission. All-cause mortality following TJR was ascertained through linkage with WA mortality records.

1.2 Thesis Questions

The studies included in this thesis used WA HMD to assess risk and outcomes of TJR in elderly men. Since hospital morbidity data were not originally collected for the purpose of research, besides answering the research questions related to TJR, this thesis had first to assess the validity and accuracy of the information recorded in this database.

The following section outlines the main Thesis Questions.

HMD as a research tool

- Are the diagnoses and procedures recorded in WA HMD valid?

- Can HMD-based co-morbidity scores, such as HMD-based Charlson Index, predict major outcomes such as mortality following TJR?

- Do HMD-based co-morbidity scores provide significant improvement on age adjustment when predicting major outcomes following TJR in elderly men?

- Do repeated episodes of a major co-morbidity such as myocardial infarction or cerebrovascular accident have different associations with risk of adverse outcomes?

- Does the addition of minimal information to HMD make the latter a better tool to predict health outcomes in elderly men who undergo TJR?

Risk of undergoing an elective primary TJR

- Is obesity associated with increased risk of both total hip and total knee replacements?

- Is smoking associated with decreased risk of TJR?

- Is reporting vigorous exercise associated with increased risk of TJR in elderly men?

Risk of adverse outcomes following an elective primary TJR

- Are patient-related characteristics (e.g. age, body weight, smoking, presence of co-morbidities) independently associated with risk of major in-hospital complications following elective TJR?

- Do in-hospital complications increase the risk of adverse outcomes following TJR including prolonged stay in hospital (LOS), readmission and short- and long-term mortality?

- What are the risk factors associated with LOS, readmission and mortality following elective TJR in elderly men?

- Is LOS independently associated with readmission and mortality following TJR?

1.3 Thesis Objectives

The main objectives of the thesis were:

1. To validate the hospital morbidity data of Western Australia.

2. To assess the performance of three HMD-based co-morbidity adjusting methods in predicting mortality. The methods included Deyo adaptation of Charlson Index, Enhanced Charlson Index and Elixhauser adjusting method.

3. To assess risk of undergoing an elective primary total joint replacement in elderly men.

4. To assess risks of in-hospital complications and 1-year and 5-year mortality following elective primary total joint replacement, focusing on the modifiable factor of body weight.

5. To assess risks of prolonged stay in hospital (LOS) and all-cause readmission following elective primary TJR.

6. To assess the association of LOS with readmission and mortality following TJR.

7. To assess the association of readmission following TJR with postoperative mortality.

8. To evaluate whether the augmentation of WA HMD with actual weight and height of patients and self-reported duration of smoking could improve its ability to a) assess risk factors associated with undergoing elective TJR, and b) predict major in-hospital complications following the procedure.

1.4 Thesis Outline

The remainder of this thesis is organised as follows. Chapter 2 introduces the data sources used in this thesis and also discusses the ethical implications of using linked datasets in research. In Chapters 3 and 4, I review the relevant literature to address each question of this thesis, introduced above. Chapter 3 reviews literature on the strengths and weaknesses of hospital morbidity data elaborating on the coding of diagnoses, the validity of information stored in HMD and the use of this routinely collected database in health research. I also introduce the most commonly used HMD-based co-morbidity scores and describe their performance in predicting outcomes in a hospitalized population. In Chapter 4, I discuss three modifiable risk factors that are associated with TJR: obesity, smoking, and physical exercise, while stressing the importance of co-morbidity. I also discuss some of the major adverse outcomes following this procedure including in-hospital complications, prolonged stay in hospital, readmission and mortality. Throughout Chapters 3 and 4, I identify gaps in research that will be addressed in this thesis. Chapter 5 describes the methods used in the various studies presented in this thesis. Publications arising from this thesis are included in Chapters 6 to 10. Each study is preceded by its main and specific objectives together with the rationale

for each main objective. In Chapter 11, I present my conclusions with a review of the findings of this thesis and an analysis of the potential utility of HMD in health research.

Chapter 2

Background to datasets

The longitudinal studies presented in this thesis are based on two main data sources: the Health In Men Study and the WA Linked Data System (WALDS). These two databanks were integrated and used in all the studies outlined in this thesis. As stated earlier, the electronic records of 12,203 men coming from Health In Men Study were integrated with WA HMD, Cancer Registry, Mental Health Services System, and mortality records. Linkage with HMD (see page 27) was used to identify total hip or knee replacement procedures, postoperative in-hospital complications, length of stay, and readmission. All-cause mortality following TJR was ascertained through linkage with WA mortality records. This section briefly introduces the data sources used in this thesis and also addresses some ethical issues related to the use of linked data in health research.

2.1 Datasets

2.1.1 Health In Men Study

The Health In Men Study (HIMS) arose from a randomised population-based trial of ultrasound screening for abdominal aortic aneurysm (AAA) in men aged 65-83 living in Perth, Western Australia, identified via the Electoral Roll (ER). (45,46) The WA Commonwealth ER includes all electors residing within Western Australian boundaries; for those entitled to vote, enrolling and attending the polls are prescribed by law. The accuracy and completeness of the ER are often assessed by the Australian National Audit Office (ANAO). In 2001, the ANAO matched data from the ER with Medicare and found that the Roll was 96% accurate. (48) The Medicare database contained some 18.4 million records

compared to the 12.6 million records on the Electoral Roll. This reflected the fact that the Medicare database includes information on people with Australian residency status rather than Australian citizens only. The Medicare database also includes records of persons under 17 years of age, that is, people who do not satisfy the age qualification to be on the ER.

During 1996-1999, 49,801 eligible men were identified via the WA Electoral Roll and were randomised into invited and control groups of equal size. The basic characteristics of the men eligible to be invited or to be controls are shown in Table 1. Of the 24,838 men randomised to be screened, 1,148 (4.6%) died before invitation and 4,338 (17.5%) were excluded because they lived outside Metropolitan Perth. Of the remaining 19,352 men who were invited, 12,203 (63.1%) agreed to participate and attended baseline screening in 1996-9. These participants were significantly younger and healthier (P<0.001) (illustrated in significantly lower Charlson co-morbidity index scores) than other men who were also eligible to participate but did not due to reasons shown in Table 2.

Table 1: Baseline characteristics[1] of men identified via the Electoral Role by invitation scheme

Baseline characteristic	To be invited for AAA screening N=24,838	Not invited for AAA screening N=24,963
Age, mean (SD)	71.4 (4.6)	71.4 (4.6)
Charlson co-morbidity index, mean (SD)	1.88 (2.5)	1.87 (2.5)
Charlson co-morbidity index categories, %		
0	40.4	40.9
1	18.7	18.9
2	14.2	13.8
3	8.7	8.3
4	5.1	5.0
5 +	12.8	13.0

[1] No significant differences in the characteristics of both groups were detected.

Table 2: Characteristics of study participants (group A) and other sub-groups initially eligible to participate in baseline screening

Baseline characteristic	A N=12,203	B N=7,149	C N=1,148	D N=4,338
Age, mean (SD)	70.9 (4.4)	71.3 (4.8)*	73.5 (4.6)*	72.1 (4.7)*
Charlson co-morbidity index, mean (SD)	1.47 (2.1)	2.06 (2.6)*	5.19 (3.4)*	1.85 (2.4)*
Charlson co-morbidity index categories, %				
0	46.2	36.8 *	6.0 *	39.5 *
1	19.4	18.8	8.2	19.7
2	14.4	13.9	13.2	14.4
3	7.7	9.9	11.7	8.5
4	3.9	5.8	10.3	5.8
5 +	8.3	14.7	50.4	12.0

A: Participated in baseline screening; B: Invited but refused to participate; C: Died before invitation; D: Excluded as they lived outside of Metropolitan Perth. * P<0.001 (compared with A)

At baseline, the participants provided detailed health and other information including information on diet, alcohol consumption, a comprehensive smoking history, medications used, presence of chronic diseases, and two questions on exercise during a usual week: a yes/no question on vigorous exercise activity (defined in the questionnaire as 'exercise that makes you breathe harder - e.g. jogging, aerobics, tennis, football, squash, etc.'), and a yes/no question on non-vigorous exercise (defined as 'exercise that does not make you breathe harder - e.g. slow walking or cycling, yoga, Tai Chi etc.'). In addition, study nurses recorded weight, height, and waist and hip circumferences. During 2001-04 the surviving men of the 12,203 initial participants were invited to a follow-up survey and 5,571 (45.7%) subjects agreed to participate providing detailed health information including smoking, medical history, and medications used. Of these 5,571 men, 4,263 were weighed a second time by research nurses while the remaining 1,308 returned a questionnaire but were not weighed.

2.1.2 Western Australia Linked Data System

The Western Australia Linked Data System (WALDS) links administrative health data of all 2.33 million inhabitants of Western Australia, (49) and it includes six core data elements: Birth Records, Midwives' Notification System, Cancer Registry, Hospital Morbidity Data System, Mental Health Services System and Mortality Records. This

population-based health information extends back to the early 1970s and is managed by the WA Department of Health and the WA Registrar-General's Office - Births, Deaths and Marriages. (47) The use of WA linked data system for research purposes is well established and the many benefits of using these linked datasets have been previously published. To name a few, WA linked data were used in studies such as the Safety and Quality of Surgical Care Program (50) and the WA Audit of Surgical Mortality which reduced preventable deaths from medical errors. (51) Another example is the Duty to Care Study of physical illness in people with mental health problems, which led to major legislative reforms. (52)

The WA HMD system is a key medical and administrative information source used throughout the WA Department of Health and public and private hospitals in Western Australia to meet mandatory and statutory reporting requirements. Records in the HMD contain information on items such as 1) date and location of service, 2) insurance payer type (public versus private hospitals), 3) beneficiary demographics such as age, gender, location of residence, country of birth, marital and employment status, 4) admission information (e.g. elective or unplanned), 5) diagnoses (main or chronic), 6) procedures performed, 7) patients' interdepartmental moves, 8) extent of service (e.g. hospital days), 9) separation mode (e.g. home, other specialised care, in-hospital death), and 10) other information needed for billing and mailing purposes. At the time of hospital discharge, the treating physician or surgeon writes a discharge summary that includes a list of diagnoses and procedures which are in turn coded as five-digit International Classification of Diseases (ICD) codes into the HMD system by professional coders). The coding of the medical information of each hospitalized patient is essential for many functional levels of a hospital including patient care and coordination of care at all levels, service utilization, billing, administration and planning, medical education, statistics, epidemiology and quality assurance (53) (full details given in Chapter 3). WA HMD allow the inclusion of up to 21 diagnoses and 11 procedure codes for each hospitalization in every hospital department. Patients may move between different hospital departments in a

single hospitalization episode and the HMD consider each of the departmental moves as a separate hospitalization.

Besides the HMD, this thesis used data from the WA Cancer Registry and Mental Health Services System (MHSS). The Cancer Registry records all results of pathology tests indicating a primary or secondary malignant disease (other than non-melanotic skin cancer). Reporting of such results is mandatory in Australia. The WA MHSS include all psychiatric diagnoses of patients who are admitted to a mental health institution in WA.

2.1.3 Linkage of datasets

All data linkage between the electronic files of the men belonging to the Health In Men Study and WA hospital morbidity data, WA Cancer Registry, WA Mental Health Services System and WA mortality records was performed by staff members in charge of data linkage in the Department of Health of Western Australia. The final data set that did not reveal the identity of the study participants was forwarded to the PhD candidate (GM). Date of birth was not omitted from the final data set since it was required to calculate the age of the participants over time as different events of interest took place (e.g. total joint replacement, readmission, death).

The studies presented in this thesis were based on two main data linkages:

The principal data linkage

Studies reported in manuscripts 2 to 5 (see Chapters 7 to 10) are based on data linkage among the following databases: HIMS, WA HMD and WA mortality records. The electronic records of the 12,203 men belonging to HIMS cohort were integrated with HMD and mortality records. The linkage with HMD identified endpoints in the target population (i.e. total joint replacement, in-hospital complications, LOS and readmission). Significant

morbidity was retrieved from the HMD in the period 1970-2007. Deaths (both in-hospital and in community) were identified through linkage with WA mortality records.

Additional data linkage for the validation analysis

The study reported in the first manuscript contributing to this thesis (see Chapter 6) is based on data linkage of the following data sources: HIMS, WA HMD, WA mortality records, WA Cancer Registry, and WA MHSS. The HIMS data that were already linked with HMD and mortality records (presented in the above section) were further linked with WA Cancer Registry and WA Mental Health Services System. The purpose of this last linkage was to validate the diagnoses that were recorded in HMD. Cancer diagnoses recorded in the HMD were validated against diagnoses recorded in the Cancer Registry. Since reporting of such results is mandatory, the Cancer Registry data constituted the "Criterion Standard". Psychiatric diagnoses registered in the MHSS were used to validate the recorded psychiatric diagnoses in the HMD. The MHSS includes all psychiatric diagnoses of patients who were admitted to a mental health institution. Since not all patients with a mental illness are hospitalized in a mental institution, some of the psychiatric conditions recorded in the HMD may not be known to the MHSS. Despite this limitation, the MHSS was considered the "Criterion Standard".

2.2 Ethical implications of project

Linking information from different sources at an individual level is an acceptable and potent research tool, which is well established in Australia. Its use has been addressed in the National Statement on Ethical Conduct in Human Research: "The increased ability to link data has greatly enhanced the contribution that collections of data can make to research, as it enables researchers to match individuals in different data sets without being able to identify the person. For example, in epidemiological research, information about individuals and

groups may be collected so that features of groups of people can be investigated. These data may or may not have originally been obtained for research purposes." (54) Together with the benefits and advantages that come from linking datasets, one must never forget that such a resource is a collection of information on individuals whose privacy and confidentiality must be respected. The main ethical concerns in this study dealt with issues of privacy, consent and potential harm to the participants.

Accurate linkage necessitates the use of personal identifiers such as complete name, address, place of birth and sex. (47) However, the privacy and confidentiality of the participants were not breached in this study. Linkage between the electronic records of HIMS participants with WA hospital morbidity data, Cancer Registry, Mental Health Services System, and mortality records was performed exclusively by staff of the Government authorised WA Linked Data System (WALDS). A final anonymised dataset was created which had no personal identifiers except for date of birth, and all analyses were done on de-identified data thus assuring maximum privacy and confidentiality of the participants. The identities of the operating surgeons and hospitals also were not revealed.

Obtaining consent from the participants or their relatives in data-linkage studies is another ethical challenge. In the original study, the 12,203 men who became members of the HIMS cohort gave written consent to participate knowing that their information would be used for research purposes. The participants were also informed that data linkage would be performed to obtain nominated endpoints. Obtaining consent to new data linkage activities is probably impractical as some of the cohort members have died and tracing their relatives would be problematic. Furthermore, contacting the surviving participants was not feasible since some of them could have changed their addresses over the past decade, some could have left the country while others with their advanced ages could have fallen ill, with possible physical or cognitive impairment – something that potentially could undermine the validity of any consent obtained.

The Human Research Ethics Committees of WA Department of Health [custodians in charge of the datasets] and The University of Adelaide granted ethical approval to use the linked data in this thesis since the identity of the participants was hidden, and the likelihood of any potential harm, discomfort or inconvenience whether physical, psychological, personal, social, economic or legal to the participants, their relatives or to other third parties was extremely low. The Committees also determined that the potential benefits of this study outweighed any possible harm. These benefits lie in the potential for developing better ways of identifying men at higher risk for TJR and those with higher frequencies of adverse outcomes.

Details of ethical approvals:

- WA Department of Health: AHEC EC00422; October 12, 2009.
- The University of Adelaide: H-106-2009; August 10, 2009.

In conclusion, this thesis used linked datasets to assess risks and outcomes of elective primary total joint replacement in elderly men. Identification of patients who are at increased risk for experiencing adverse outcomes following a primary TJR may assist clinicians in selecting elderly patients for surgery, and may also help them take measures known to mitigate the risk.

Chapter 3

Hospital Morbidity Data: coding, validity, and use in research

Hospital morbidity data are frequently used in epidemiological research. These data have many advantages over the clinical data derived from chart review including their availability and coverage of large populations. However, research based on administrative data such as HMD requires a thorough assessment of their quality. This is particularly true given that HMD were not originally collected for the purpose of health research. This section describes some of the important aspects of hospital morbidity data collection including their coding, validity and use in health research. It also discusses the utility of commonly used HMD-based co-morbidity scores in predicting health outcomes among hospitalized patients.

3.1 Coding systems used in WA hospital morbidity data

The International Statistical Classification of Diseases and Related Health Problems (most commonly known by the abbreviation ICD) is the coding system used in WA HMD. The ICD-9-CM (9th Revision, Clinical Modification) (55) was used before July 1999, whereas the ICD-10-AM (Australian Modification) coding system (56) was implemented after that date. The ICD is a medical classification that provides codes to classify diseases, diagnostic and therapeutic procedures, and a wide variety of signs, symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or disease. The ICD was originally devised to record the cause of death (initially introduced in 1893 by a French physician, Jacques Bertillon, who named it the Bertillon Classification of Causes of Death), (57) but it quickly evolved to be used primarily to code the final diagnoses and procedures of a hospitalized patient (or the clinical problems of an outpatient). Beginning in 1900 with the

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ICD-1 version, this coding system evolved from 179 to over 120,000 total codes in ICD-10-CM. (56) The use of codes has expanded from classifying morbidity and mortality information for statistical purposes to diverse sets of applications, including reimbursement, administration, epidemiology, and health services research. With the introduction of DRG (Diagnosis Related Groups)-based billing, the ICD classification system was employed as the coding system for DRG although it was not originally developed for billing purposes. (58)

Upon discharge, the patient's medical record and all associated documentation are transferred to the medical record or health information management department. Before coding begins, technicians review the medical record to ensure its completeness (i.e. history and physical report, operative reports, radiology reports, physician's orders, progress and nursing notes, consultations, and discharge summary). Coders then begin the process of classifying documentation, including diagnoses and procedures, using rigid ICD coding guidelines and conventions. Under this coding system, every health condition can be assigned to a unique category and given a code, up to six characters long.

3.2 Sources of error in coding hospital morbidity data

Various sources of error are introduced between a person's true illness and the word label (the diagnosis) assigned by a clinician, and the final code applied to it by a medical coder. After reviewing all inpatient source documents for information, the attending physician may sometimes choose to document more serious clinical conditions, often leaving out "less serious" diagnoses like chronic illnesses thus underestimating co-morbidity. (59,60) Incomplete coding of secondary diagnoses may result in inadequate adjustment for illness-severity due to differences in case-mix reporting which may bias assessments of patient risks of poor outcomes, as demonstrated in a large study on in-hospital mortality among elderly patients. (60) Iezzoni et al. found that chronic conditions such as adult-onset diabetes mellitus, hypertension, angina pectoris, heart valve disease and previous myocardial infarction

significantly lowered the risk of in-hospital mortality. Since on a clinical basis, these conditions were expected to increase the risk of death, the researchers concluded that their findings were probably due to under-coding of chronic conditions for more severely ill patients. (60) Clinicians may also under-report socially stigmatised conditions such as drug abuse, minor procedures during hospitalization, medical errors, and iatrogenic complications including postoperative complications and hospital-acquired infections. (58-70) Mitchell et al. noted that surgeons may not charge a patient for treatment of iatrogenic complications, thus no billing record is generated. (70) Truncation of secondary diagnoses can also occur in administrative datasets that have limited coding spaces. (59)

Errors in assigning a code to a diagnosis (at the coder level) can occur because clinicians often use synonyms and abbreviations to describe the same condition. (58) For example, synonyms for ''stroke'' include cerebrovascular accident, cerebral occlusion, cerebral infarction, and apoplexy, among others. The presence of different terms may be problematic, as each diagnostic code should represent one and only one disease entity. From the clinician's recorded diagnosis label, the coder must select the ICD code that best seems to match the clinician's terminology. The use of synonyms leads to imprecision. For example, a patient who had a stroke can be described by one doctor as having had an intracerebral hemorrhage (ICD-9 code 431) and by another doctor as having had a cerebrovascular accident (ICD-9 code 436) and both doctors would be technically correct. The absence of an accurate operational definition for each code, the absence of prognostic information and the rigid nature of the ICD classification system may all be a source of coding errors and difficulties, (61) and the fact that the ICD contains different codes for various dimensions of the same disease (i.e., separate codes for coronary atherosclerosis, precordial chest pain, and angina pectoris) is often a cause of ambiguous coding and significant coding errors.

"Over-coding" or "up-coding" of diagnoses in for-profit hospitals has also been reported in situations where coding practices influence reimbursement. (71) Up-coding, or

assigning codes of higher reimbursement value over codes with lesser reimbursement value may occur at any level of assigning a diagnosis but is more often seen at the coder level. (72) Diagnosis codes are associated with different levels of payment for hospitals; for example, in traditional US Medicare, hospitals are reimbursed more than twice as much per admission for cases of "respiratory infections and inflammations" as for "pneumonia without complications." (71) In one example of up-coding in traditional fee-for-service US Medicare, when Medicare implemented a new way of paying for inpatient hospital care called the Prospective Payment System, the number of patients assigned diagnosis codes that yield higher payments increased significantly and the RAND study found that much of this increase reflected changes in documentation and coding practices that were not related to changes in patients' health status or care needs. (73) As a result, payments to hospitals increased more than was warranted. Up-coding was deemed serious enough that in 2006, as part of the Deficit Reduction Act, the American Congress sought to address the problem of up-coding by requiring the Centers for Medicare and Medicaid Services to take up-coding into account in setting Medicare payments to private plans for the 2008-2010 period. (74) Hospitals concerned about publicly reported quality assessments based on risk-adjusted models from administrative data could over-report diagnoses as present on admission to hospital thus making their patients look sicker and thereby improve their publicly reported risk-adjusted mortality rates. (58,71) Although up-coding may occur in any for-profit health system, research indicates that it is less common in Australia. A study by Steinbusch et al. compared the American and Australian healthcare systems and found that the US case-mix system tends to be more open to up-coding than the Australian one. (75)

Coding accuracy may also be influenced by the annual expansion and change in ICD codes and coding rules. For example, a comparison of ICD-9-CM with ICD-10-CM indicates that the number of categories doubled from 4,000 to 8,000 and the number of death causes increased from 72 to 113. (76) Changes in codes may also include the deletion of old codes

and reclassification of others, such as moving of haemorrhage from the ''circulatory'' chapter to the ''signs and symptoms'' chapter, and changing of the four-digit numeric codes of ICD-9 to the four-digit alphanumeric codes of ICD-10. (55,56) Without continuous education on code changes, accuracy of coding may easily be jeopardised. Furthermore, some of the codes used in ICD are imprecise and inaccurate. (65,76) For example in ICD-9-CM, urosepsis is coded the same as urinary tract infection (code 599.0), although in a clinical setting, urosepsis may indicate a more serious condition with usually a systemic infection that has originated from the urinary tract. (77)

Another disadvantage in the coding of hospital morbidity data is its inability to differentiate co-morbidities from complications. (69) However, Roos et al. showed that the impact of misinterpreting complications as co-morbidities on the Charlson index is minor in surgical procedures. (78)

3.3 Validity of HMD

The purpose of most epidemiological research is to demonstrate a relationship between an outcome of interest and one or more variables or characteristics. Our ability to identify and measure the relationships of interest depends on our capacity to accurately measure both the outcome variable of interest and those variables tentatively believed to be associated with the outcome. The accuracy of a variable, (e.g. diagnosis as recorded in HMD), is the degree of closeness of that variable (e.g. recorded diagnosis of left lower lobe acute myocardial infarction) to the actual truth (i.e. the patient actually did have a left lower lobe acute myocardial infarction). It is the measure of exactness or correctness of such a recording in HMD, whereas validity refers to the extent that something measures what it is supposed to measure. For example, one may ask how valid are the HMD as a tool to measure the chronic or the acute diseases presented during an episode of hospitalisation. The term "valid" implies that there is some sort of external standard, or "Criterion Standard", against which the current

diagnosis is being compared. Such validity can be rigorously defined by the sensitivity and specificity of the tool we are investigating. The tool (e.g. HMD) needs to be sensitive enough to detect the relevant problem (i.e. diagnosis describing a medical condition) if it is present (and therefore avoid too many false negative results), but specific enough not to detect other conditions (and therefore avoid too many false positive results).

Several studies have attempted to validate diagnoses reported in administrative hospital morbidity datasets against various data sources, including patients' medical charts, (79-81) discharge summaries (82) or patient self-reported conditions. (83-85) Of these methods, patient self-report has been mostly criticized as underestimating the accuracy of the diagnostic codes in HMD since patients are not necessarily aware of all the diagnoses recorded by their physicians. (86) In contrast, the medical chart is often regarded the "Criterion Standard", as in any inpatient setting care tends to be extensively documented and clinical events are temporally recorded. On the other hand, discharge summaries may contain selected data from the patient file, possibly underestimating chronic conditions and iatrogenic complications. (59,60)

Findings from validation studies of administrative databases vary. The highest agreement has been shown for demographic characteristics with average kappa=0.92. (87) Agreement for inpatient principal diagnosis based on three-digit ICD-9-CM codes was found in 78.2% of cases with the National DRG Validation Study (65) and in 92% of cases with the California Office of State-wide Health Planning and Development. (63) However, agreement may significantly differ with the condition studied. Jollis et al. studied 12,937 patients undergoing cardiac catheterization showing that agreement rates between the clinical and claims data (administrative data) ranged from 0.83 for the diagnosis of diabetes to 0.09 for the diagnosis of unstable angina with an overall agreement of 0.75. Claims data failed to identify one half of the patients with prognostically important conditions including mitral insufficiency, congestive heart failure, peripheral vascular disease, old infarction,

cerebrovascular disease and unstable angina when compared with the clinical data. (68) Conditions with complex coding rules, such as acute myocardial infarction tended to have relatively poor agreement (kappa=0.36) for Medicare claims. (68) It has been reported that 10% to 24% of clinically identified acute myocardial infarctions were not coded by ICD-9-CM codes. (65,68)

Western Australia HMD have 21 quality-of-data checks that are built into the provision of data from all public and private hospitals and there are periodic audits of random selections of hospital-assigned codes to ensure quality and validity of the data. A coding audit of 1,050 records at seven hospitals in 1996-97 found the coding accuracy for Australian National Diagnosis-Related Group (ANDRG) to average at 87%. (47) Besides the audits, a few validation studies have been conducted to assess the accuracy of various coded diagnoses in this HMD; however, the findings of these studies were inconsistent. A retrospective chart review of a sample of 1,006 patients found that WA HMD perform well in identifying patients with the principal diagnosis of heart failure (positive predictive value=0.99), (79) whereas another study has shown that of all surgery-related endophthalmitis cases coded in WA HMD, only 50.9% were found to be valid cases. (88) In another validation study of 2,037 patients, using patients' chart review as the Criterion Standard, Preen et al. found a high proportion of false negatives in the WA HMD in many co-morbid conditions such as any malignancy (sensitivity of 0.53), myocardial infarction (sensitivity of 0.26) and congestive heart failure (sensitivity of 0.44). (80) This study further reported that WA HMD contained only 45.5% of the co-morbidities recorded in hospital charts. However, this study may have been disadvantaged by the methods employed to collect information on co-morbidity from the administrative database. Preen et al. retrieved information on co-morbid conditions as reported in the HMD from admissions that occurred within 5 years from the index hospitalization. This most probably led to an underestimation of the prevalence of many diagnoses as demonstrated in another validation study. (85) Robinson et al. have shown how

using additional years of administrative data can increase the agreement among data sources. (85) Preen et al. study design may have limited the data collection to a time period that did not include all relevant or complete information on the patients' co-morbid conditions.

3.4 Co-morbidity recorded in HMD

In hospitalized populations, co-morbidity is one of the main factors associated with adverse outcomes. Studies have consistently shown that co-morbidity (either acute or chronic illness) is associated with in-hospital mortality, postoperative complications, longer stay in hospital, higher hospital costs and readmissions. (15,18,89-98) Consequently, in clinical settings, co-morbidities influence how a clinical decision is made or how a treatment strategy is planned. For example, unlike in randomised controlled trials (RCT), allocation of patients to TJR or non-TJR alternative therapies is not random and therefore patients selected for different therapies (i.e. surgery versus non-surgery) may differ considerably. (99,100) Often patients with clinical indications for TJR are never proposed for surgery because of medical concerns regarding worse outcomes. This potential selection for surgery may be present if, for instance, factors such as advanced age or co-morbidities exclude patients from undergoing the surgical procedure. (101) Therefore, since in clinical practice (or in observational studies) randomisation is usually not feasible, presence of co-morbidity must be accounted for in any non-RCT study. However, in studies that use administrative data such as the hospital morbidity data, adjusting for co-morbidity may prove difficult and often unattainable as demonstrated by numerous studies. Using large administrative databases from Denmark, England and Canada, Roos et al. retrospectively assessed 54,077 men who had prostatectomy and found that, compared to supra-pubic prostatectomy for benign prostatic hyperplasia, transurethral prostatectomy (TURP) was associated with a higher postoperative 5-year mortality after controlling for co-morbidity that was based on discharge information (relative risk[RR]=1.45, 95% CI: 1.15-1.83). (96) To explore whether differences in co-morbidity

unaccounted by administrative data explained this finding, the same research team reviewed the medical charts of selected 485 Canadian patients who had undergone the procedure and reported similar findings with a significantly higher risk of death in those patients who had a transurethral prostatectomy. (97) On a much smaller sample (n=252), Concato et al. repeated the study and found similar elevated risk of mortality in the transurethral group. (98) Nonetheless, this elevated risk in mortality was not statistically significant (RR=1.03, 95% CI: 0.51-2.07) when the same adjustment method was based on medical record review. The authors concluded that administrative databases may tend to underestimate co-morbidities and results should be interpreted cautiously especially because men who are selected for TURP are generally sicker and older than those who undergo an open surgery. (98) This may indicate that the performance of administrative-data-based adjustment co-morbidity indices may be influenced by the accuracy of information stored in these databases, and therefore, the quality of these data must be rigorously assessed and considerable effort must be invested in data validation before their use in any health research. (102)

Ideally in hospital settings, co-morbidity should be based on chart review, but this is rarely feasible and too expensive for large numbers of patients. Therefore, interest in developing co-morbidity adjustment methods that are based on administrative data has grown in the past few decades and many researchers have developed coding algorithms that suit administrative data to account for patients' co-morbid conditions. (103-111) Among the ICD coding algorithms, Charlson co-morbidity index (103,104) with its many adaptations (105-110) and Elixhauser co-morbidities (111) are the most widely used in administrative datasets to measure and control for the effects of co-morbid illness.

3.5 Charlson co-morbidity index

Charlson co-morbidity index (CCI) was developed by Mary Charlson and her colleagues, who assessed the medical records of 559 medical patients to form a weighted co-

morbidity index that is a simple, valid, and readily applicable method of estimating risk of mortality from co-morbidity. (103) The index is based on 19 co-morbid conditions with assigned weights of 1, 2, 3, or 6, which were derived from relative risk estimates of a proportional hazard regression model. The scores are summed to give a total score that predicts the event of interest. The researchers found significant associations of their newly developed score with increased 1-year mortality following index admission. The index was further validated on a second cohort of 685 breast cancer patients during a 10-year follow-up period and showed a 2.3 fold (95% CI: 1.9-2.8) increase in risk of 10-year mortality per unit increase in CCI. (103) Similar results were reported for postoperative survival in patients with diabetes or hypertension. (104)

However, since researchers may not always have access to patients' medical records, several adaptations of the original CCI have been developed to enable its application in research that relies on administrative data; to name a few versions are those developed by Deyo et al, (105) D'Hoore et al., (106) Ghali et al., (107) and Roos et al., (78) [also known as Dartmouth-Manitoba version] which was further updated by Romano et al.. (108) The Deyo Charlson version was most recently modified by Quan et al., (109) producing the Enhanced Charlson Co-morbidity Index.

Deyo et al. adapted the original CCI for use with ICD-9-CM diagnosis and procedure codes in a group of 27,111 Medicare beneficiaries (mean age of 71.8 years and 57.1% women) who underwent a predominantly elective lumbar spine surgery. (105) The researchers reported statistically significant associations of their adapted index with increased number of blood transfusions, in-hospital complications, length of stay, hospital costs, discharge to nursing homes, and 6-week post operative mortality. (105) Magnitudes of these associations were not reported, but the authors reported that the associations remained statistically significant after adjusting for age, which suggested that the adapted index explained additional variances in these outcomes compared with a model that only accounted for age.

However, the authors did not show how much variation was explained by the outcomes studied. In another administrative claims data study, Melfi et al. used Deyo-Charlson index (Deyo-CI) to predict length of stay and 30-day mortality in 249,744 Medicare patients who had had a total knee replacement, (112) and found that an increase in Deyo-CI of one point increased the probability of 30-day mortality by 17%, however, including the index in the model marginally improved model discrimination by 1.2% (C-statistic change from 0.645 to 0.653). These authors further showed that a simple count of the unique diagnosis codes listed on the discharge summary was predictive of hospital length of stay and 30-day mortality, performing better than Deyo-CI with C=0.733 for the mortality model. A clear advantage in this simple adjusting method is the fact that number of the coded diagnoses may not be affected by miscoding, (113) however, a simple count does not account for the degree of severity inherent in different conditions and also this method of adjustment may be influenced by the general under-reporting of diagnoses which is not uncommon in administrative databases. (114)

Using large hospital discharge datasets from a Canadian health region, Quan et al. adapted the Deyo-CI ICD-9-CM codes with ICD-10 coding algorithms and introduced a few changes in the codes that were included in the final index. The authors also adapted the ICD-9-CM codes that are used in Elixhauser's co-morbidities (see below) with ICD-10 codes. The translation of the ICD-9-CM codes and development of ICD-10 coding algorithms was achieved by a consensual approach among three international research groups in Canada, Switzerland and Australia. (109,110) Using population-based administrative hospital morbidity data from Australia, Sundarajan et al. further adapted the Deyo-CI to the ICD-10-AM (Australian Modification) codes. (110)

ICD-9 and ICD-10 coding algorithms for Charlson co-morbidities are presented in Appendix I, pp: 214-5.

3.6 Elixhauser co-morbidities

In 1998, Elixhauser et al. used a larger administrative data set (n=1,779,167) of medical patients to develop a comprehensive set of 30 co-morbid conditions in a risk adjustment model. Diagnoses that represented potential complications were excluded and no distinction was made among diagnoses recorded during the index hospitalization or during prior admissions. Moreover, co-morbid conditions were considered only when they did not relate to the diagnosis-related group (DRG) of each admission. For example, secondary diagnosis codes that were used to detect cardiac arrhythmias as co-morbidity were excluded when the DRG for a patient specified that his/her principal diagnosis was a cardiac disease related condition. In contrast with Charlson index and its many adaptations, Elixhauser adjustment method does not sum up to a single score. The conditions are retained as separate dichotomous (presence yes/no of a condition), and independent measures thus allowing the assessment of the association of different co-morbid conditions with different outcomes. (111) The method developed by Elixhauser independently predicted length of stay, hospital charges, and in-hospital mortality. Most of the conditions included in the Charlson index are also included in Elixhauser method with the exception of a few major co-morbid conditions such as past myocardial infarction and leukaemia which were excluded from Elixhauser method due to their lack of significant associations with in-hospital mortality. (111)

Elixhauser method has been often criticized as being cumbersome because of its many co-morbid groups that do not sum into an index. (115) van Walraven et al. modified the 30-co-morbidity method into a single numeric score. The authors used a large set of 345,795 hospital admission data to both develop the score and to validate it on a subset of their population. In their analyses, 21 of the 30 original Elixhauser groups were independently associated with in-hospital mortality and these formed the single score which was, similar to Elixhauser method, discriminative for death in hospital. (115) However, this new score was

based on data coming from a single medical centre and it has not been validated on an external and independent sample.

ICD-9 and ICD-10 coding algorithms for Elixhauser co-morbidities are presented in Appendix II, pp: 216-8.

3.7 Performance of HMD-based co-morbidity adjusting methods

Since administrative-data-based co-morbidity adjustment methods have no "Criterion Standard", researchers validate a method and assess its preference over another by how each predicts worse health outcomes. (102,109,112,115-124) The predictive ability of these adjusting methods may vary among studies as their overall performance may be affected by various factors such as accuracy of the data. This is especially true because hospital morbidity databases have been initially designed for billing purposes and not for use with co-morbidity adjustment measures. That is, such databases may reflect the intensity of resource utilization more accurately than they reflect a patient's health status. (4,71,74) Prior research has shown that coding practices for billing purposes may vary among hospitals and are influenced by factors including hospital characteristics, and physician documentation. (125-127) Furthermore, a patient's co-morbid conditions may not be fully captured if these were retrieved from a single index admission. (116) Often, some co-morbid diagnoses may not be relevant to the principal diagnosis when the patient received medical care and thus not recorded during that particular admission. Consequently, the predictive power of these co-morbidity adjustment methods is limited by the availability and accuracy of the data. Besides accuracy of HMD, the performance of these measures may be influenced by factors including 1) the endpoint studied, for example, 30-day, 1-year survival, or all-cause readmission, 2) the prevalence of co-morbidity in the study population, for example, old versus young patients, 3) and the clinical co-morbidities included in the adjustment method and the relative weights given to each condition. (116,117) Therefore, the performance of different adjustment

methods should be compared on the same population and for the same endpoint. (102,107,112)

For dichotomous outcomes, the performance of prediction models is often evaluated using the area under the receiver-operator curve (ROC), or the C statistic, which indicates a model's discriminatory power. The ROC curve is a graphical plot of the sensitivity, or true positive rate, versus false positive rate (1-specificity), for a binary classifier system as its discrimination threshold is varied and ROC analysis provides tools to select possibly optimal models and to discard suboptimal ones. (128) Depending on study population and variables included into model or exposure under study, predictive validities of the co-morbidity adjusting methods were stated to vary between C=0.61 and C=0.88 for in-hospital or 1-year mortality, (109,112,115-123) and some have reported that introducing the co-morbidity adjustment method into the model produced only a slight improvement over age adjustment. (112)

The performances of Charlson Index and Elixhauser method have been compared and both methods were found to either perform equally well, (118) or Elixhauser method outperforming the former. (109,116,121,122) Several studies have shown that Elixhauser method that used information only from an index hospitalization performed best, better than Charlson Index that used information from the index and prior hospitalizations. (116,121). In the most recent update of Charlson index, Quan et al. reported that their enhanced index either matched or outperformed the original Deyo-Charlson and Elixhauser ICD-9-CM coding algorithms in predicting in-hospital mortality. (109)

3.8 Use of routinely collected HMD in research

The utility of hospital morbidity data as a resource for medical research has been keenly investigated in recent years. (62-64,129-131) While clinical data usually retrieved from patients' files are considered the gold standard for accurate clinical information, these

are costly and time consuming to obtain and often large clinical databases for comparative purposes are not easily available. Therefore, administrative data or claims data such as HMD are being increasingly used to assess clinical outcomes and monitor, evaluate and improve the quality of care. These data have many advantages over the clinical data derived from chart review including their availability and coverage of large populations, thus avoiding the potential of a possible selection bias. These large and routinely collected data also offer additional advantages in regulatory and surveillance settings in that the data have been collected in a reasonably consistent manner over a number of years, and will continue to be collected, using similar procedures, into the future. Owing to their many advantages, researchers have tried to improve these data and augment them with additional information in order to use them in health care research. Increasingly, studies show how the augmentation of administrative data with minimal clinical data may improve the former's predictive power. (132-135) In a retrospective study of 46,769 patients in 30 acute care hospitals, Pine et al. demonstrated how the addition of laboratory data to hospital administrative datasets could provide accurate predictions of inpatient mortality from acute myocardial infarction, cerebrovascular accident, congestive heart failure or pneumonia with significant improvements in models' discrimination. (132) Other studies (134,135) showed how models using claims data to predict mortality following cardiac bypass surgery can be improved with the addition of minimal clinical variables. Hannan et al. (134) have reported how the addition of three risk factors: cardiac ejection fraction, re-operation and more than 90% narrowing of the left main trunk improved the C-statistic of the in-hospital mortality predicting model from 0.74 to 0.79. The model with the additional clinical variables predicted in-hospital mortality better and this added information did contribute to the fit of the data for this outcome.

In conclusion, routinely collected WA hospital morbidity data are frequently used in epidemiological research. This thesis used this database to assess risk and outcomes of

elective total joint replacement in elderly men. The literature review presented in this chapter identified the following gaps in research that were addressed in the studies contributing to this thesis:

- Validation of WA HMD that relies on all previous hospital admissions for various diagnoses and procedures has not been reported.

- The performance of the Enhanced version of Charlson Index and that of the original Deyo adaptation of Charlson Index has been compared by Quan et al., (109) but never on another independent sample.

- Methods to improve hospital morbidity data to predict complications following TJR have never been documented.

Chapter 4

Total joint replacement

The studies presented in this thesis focused on primary total joint replacement. I chose a high-volume procedure such as TJR because it is predominantly performed in the elderly and the overweight or the obese who present an increasing proportion of the population. In Chapter 1, I presented the scope of demand for TJR; in this chapter, I discuss the associations of three modifiable factors (body weight, smoking and physical exercise) with TJR, I introduce the major adverse outcomes following this procedure and I indicate the gaps in research that will be addressed in this thesis.

4.1 Modifiable risk factors

Patient-lifestyle and disease related factors have been extensively investigated in various centres in the world. In Scandinavia, Canada, England and Australia, (6,8,30,136-138) data on these high volume operations are stored in national registries which enable the investigation of large samples of patients undergoing TJR. In countries that do not yet have a national registry, such as the United States, researchers mainly rely on administrative hospital discharge records to retrieve large samples of subjects undergoing this procedure. (3,15)

While TJR can be performed at any age, it is more frequent in middle-aged and older people (7) since these are more likely to suffer from end-stage joint disease than the younger population. Besides old age, independent risk factors for this disorder include female gender, (1,3,139) obesity, (36,139-141) physical activity, (139,141) and never-smoking. (31,139,140) However, the reported association of some of these factors with an increased risk of OA or subsequent TJR has not been consistent. Being overweight shows the most consistent

association with OA (31,36,139,140) and with TJR (32,33,141) while the results for physical activity and smoking have been the most inconsistent. (31,32,139-152)

In the following sections I briefly review some of the literature covering three modifiable factors: body weight, smoking and physical exercise.

4.1.1 Body weight

Body weight is one of the most investigated factors in the study of osteoarthritis or total joint replacement. In many studies, being overweight (body mass index [BMI] 24.9-29.9kg/m^2) or obese (BMI $\geq$30kg/m^2) and measures of relative body mass have been associated with an increased risk of OA (31,36,139,140) and TJR (32,33,141), with some showing a stronger association in knee OA (36), suggesting a biomechanical component in the relationship between body weight and OA. However, more studies are showing a positive relationship between being overweight and OA at different body sites including knee and hip (33,36), and non-weight bearing joints such as small joints of the hands (153,154) suggesting a connection between OA and metabolically active adipose tissue. Two recent population-based prospective studies, the Swedish Malmo Diet and Cancer study (36) and a large Australian prospective cohort study that involved healthy volunteers, (33) demonstrated a positive association of different measures of body mass including body mass index, waist circumference, waist-to-hip ratio and percentage body fat with risk of hip and knee replacement. The significant associations between obesity and OA persist after controlling for important confounding factors such as sex, physical activity, smoking, and diabetes. (155) Some studies assessed whether reduction in weight is associated with lowering the risk for OA (156) or TJR. (141) A Norwegian prospective study based on a large sample of 50,034 subjects estimated a theoretical reduction of 35.0% in the hip replacements performed had the participants had lower body mass indices. (141)

4.1.2 Smoking

The association between smoking and osteoarthritis or subsequent TJR is not clear, as research in the field continues to show contradictory and confusing results. Smoking has variously shown a negative association with OA (31,139,140,144,145,152) or TJR, (146) a positive association with OA (147,148) or TJR, (32) and no significant association with OA. (142,149,151) One of the first publications on this topic came from the cross sectional population-based first Health and Nutrition Examination Survey (HANES I) in the United States (157) which found an age-adjusted significant inverse association of number of cigarettes smoked per day and radiographic knee OA among both men and women. To test for confounding, researchers from the Framingham Study controlled for age, sex, BMI, physical activity and past knee injury and found a similar negative association in two separate studies. (139,140) In the first prevalence analysis of 1,424 participants, the adjusted OR for knee OA was 0.74 (P<0.05) among the smokers. (140) The second analysis investigated the incidence of radiographic knee OA and showed that heavy smokers had significantly lower risk of developing new knee OA among a cohort of 598 participants initially free of OA (OR=0.4; 95% CI: 0.2-0.8). (139) A similar decrease in risk was reported in a large longitudinal population-based cohort of construction workers. (31) Never-smokers had an increased relative risk of about 40% of undergoing hip replacement due to severe OA, while ex-smokers had an increased risk of 20% compared with smokers. (31) A British case-control study did not find an overall association between smoking and hip OA, though in men, smoking appeared to have a significant protective effect against hip OA (OR=0.4; 95% CI: 0.2-0.9). (144) The mechanisms behind this apparent decrease in risk are not clear. There is some evidence that smoking may directly reduce the severity of OA. An in vitro study found a relationship between nicotine and stimulation of the anabolic activity of the chondrocytes (cells found in joint cartilage). (158) This was supported by an Australian population-based

prospective cohort study that showed a positive dose-response between pack-years of smoking and knee cartilage volume among healthy individuals. (152)

On the other hand, the prospective Nurses' Health Study demonstrated that among a selected sample of 568 participants, the risk of hip replacement was significantly higher for those who had smoked in the past. However a non-significant protective effect was seen among the current smokers. (32) A higher crude risk of self-reported OA was demonstrated among ever-smokers in the Florey Adelaide Male Ageing Study (FAMAS). (148) The age-adjusted risk was still higher in those who smoked compared with the never-smokers, though the association was not statistically significant. A prospective cohort study that investigated self-reported physician-diagnosed osteoarthritis of the knee and/or the hip among 16,961 participants found a positive association between smoking cigarettes and risk of OA, however, this positive association was not statistically significant. (159) Furthermore, a New Zealand two-year prospective study on 252 subjects demonstrated a significant association between smoking and cartilage loss – a sign of OA. (160)

The conflicting findings of these studies could have been caused by various factors such as differences in study populations, study design, and lack of adjustment for co-morbidities, but are also possibly due to differences in the definitions of OA and of smoking. Summarizing smoking habits is not that straightforward since they involve both duration of exposure and intensity of smoking. Some studies have defined smoking as a dichotomous variable without proper distinction made between current and past smoking; for example 'smokers' sometimes included present and past smokers (148) while 'non-smokers' often included former smokers and never-smokers. (36,157) These two definitions are problematic since neither gives information about duration of exposure (years of smoking) and about the intensity of exposure (cigarettes per day). The Framingham Study (139) did not consider years of exposure to tobacco use, and the Swedish, (31) Finnish, (151) and Nurse's cohort

(32) studies disregarded duration and intensity of exposure to tobacco. The Clearwater Osteoarthritis Study ignored duration of exposure. (142)

Gap in research addressed in this thesis: Given the known hazards of smoking, it is vital to understand better the association of this habit and the risk of undergoing TJR after controlling for important confounding factors including weight, co-morbidity, socioeconomic status and physical activity.

4.1.3 Physical activity

Similarly, the association of physical activity with the risk of OA is unclear. An example of contradictory findings was demonstrated in two studies based on the population-based Framingham cohort. In the first publication on this topic, based on a sub-population from the first cohort enrolled, patients in the highest quartile of physical activity had 3.3 times the odds of developing OA compared with those in the lowest quartile of physical activity. (139) However, in a second publication, based on a sub-population of the first cohort's children and their spouses, the association between physical activity and radiographic OA was weaker and did not reach statistical significance (adjusted OR=1.20, 95% CI 0.65 - 2.21). (143) Based on kilocalories of energy used at each level of activity (e.g. walking, sleeping, jogging, etc.), the researchers from the Framingham study formed an index that defined physical activity. The overall physical activity index was derived as a weighted sum of activity over 24 hours. (139)

While repetitive joint use may lead to cartilage loss, (161,162) physical activity may help prevent OA through other mechanisms: 1) physical activity helps reduce weight - a well established risk factor for OA; 2) physical activity may strengthen the muscular support around the joint and in turn reduce risk of joint injury (the association of muscle weakness and OA is well established); (35) and finally, 3) since cartilage has no blood vessels or nerves, nourishment reaches these cells through diffusion of substances across the cartilage matrix from joint fluid, and physical activity may improve this process. (163) However, there is

increasing evidence to indicate that individuals who participate in competitive sports and some occupational activity may be at higher risk of OA (139,151,159,164) or TJR. (141,165) Cheng et al. found that high levels of physical activity (running 20 or more miles per week) were associated with osteoarthritis among men under age 50 after adjusting for body mass index, smoking, and use of alcohol or caffeine (hazard ratio=2.4, 95% CI: 1.5-3.9), while no relationship was suggested among women or older men. (159) A large prospective study, the Melbourne Collaborative Cohort Study (n=39,023) found a positive association between vigorous physical exercise and risk of primary total knee replacement due to end-stage OA. A total physical activity level was computed, incorporating both intensity and frequency for different forms of physical activity obtained by questionnaire at baseline attendance. In contrast, the frequency of less vigorous activity, as well as the frequency of walking, was not related to risk of undergoing TKR for OA. At the same time, none of these measures of physical activity were associated with risk of undergoing a total hip replacement. (165)

4.2 Adverse outcomes following a primary TJR

First primary TJR is considered to be relatively safe with low rates of adverse outcomes. (14) However, there is increasing evidence that elderly patients may be at higher risk for postoperative complications and mortality following the procedure. (15-18,166) Besides old age, other independent risk factors for these adverse outcomes include male gender, (15,18) presence of co-morbidity, (15,18,89,95) smoking, (19,21) and obesity. (19,20,22,95) Nonetheless, the reported association of some of these factors with an increased risk of an adverse outcome following TJR has not been consistent. Old age and presence of co-morbidity show the most consistent associations with postoperative complications and mortality, (15,16,18) while the results for being overweight or obese have been the most inconsistent. (20,22,167-175)

4.2.1 Obesity and adverse outcomes

Some studies have reported higher rates of postoperative complications among the obese who undergo TJR including higher risk of systemic complications, (19) venous thromboembolic disease, (17,169) prolonged wound drainage and wound infection, (20,22,168,172) and dislocation, (20) while others did not find any significant increased risk of either short- (167,170,171) or long-term (173-175) complications. Furthermore, Patel et al. (22) reported that morbid obesity was significantly associated with prolonged wound drainage in patients who undergo THR (P=0.001) but not in those who have TKR (P=0.590). In contrast, Namba et al. found a high risk for infections in obese patients who have either a TKR or a THR, however, the risk was higher in the TKR group (OR=6.7 for TKR, and OR=4.2 for THR). (172) In addition, a recent publication suggested that the association of obesity with adverse outcomes following THR may be gender-specific. In a prospective cohort study, obesity was found to increase postoperative infection, dislocation, and revision in women but not in men, although infection was higher in men compared with women. (20) Inconsistencies in the findings of these and other studies may be attributed to various factors including relatively small sample sizes, (170,173) and lack of or insufficient adjustment for the confounding effect of co-morbidity. (22,168,170,172-175)

Being overweight or obese has also been associated with increased consumption of hospital resources (167,175-177) including significantly longer operative times, (167,175,177) and prolonged length of stay in hospital (LOS). (19) A retrospective cohort study of 3,309 patients undergoing primary THR reported a median LOS that increased from nine days for patients with a normal BMI to 10 days in the obese. In a multivariable analysis, the authors showed that increasing BMI was significantly associated with an increased mean length of stay in hospital (P<0.001). (19) In contrast, another prospective study of 1,416 patients undergoing THR found no significant differences in mean LOS between the non-obese, obese, and morbidly obese patients (9.8 days [SD 7.2], 9.1 days [SD 4.5], and 8.9 days [SD 3.1], respectively, P=0.232). (175)

4.2.2 Old age and adverse outcomes

Postoperative complications following elective total joint replacement are not uncommon in the elderly. (16,23,178-184) A retrospective study that assessed perioperative complications in 10,244 patients following TJR found significantly higher frequencies of incident myocardial infarction (MI), pulmonary embolism (PE), deep vein thrombosis (DVT), and death in the older patients compared to younger patients in the study. (16) Incidence of MI was also significantly higher in male compared to female patients. For male patients aged 60–69 yr, 70–79 yr, and 80 yr or more, the corresponding incidence rates of MI were 0.4, 0.7, and 2.2%. Another prospective study that assessed new onset heart arrhythmias in 1,210 patients who had total hip or knee replacement, reported an atrial fibrillation or supra-ventricular tachycardia (AF/SVT) rate of 4.8%, however, this rate increased to 18.2% in patients 60 years of age or older who had other risk factors for AF/SVT, (179) with atrial fibrillation being the most common arrhythmia encountered. (184) A survey of the demographics of blood use in north England in the year 2000 showed that patients undergoing major orthopaedic surgery including TKR and THR consumed 8% of all transfused units and these procedures were the leading indication for blood transfusion in surgical patients. (180) Rosencher et al. (182) found that 51% of 3,996 orthopaedic surgical patients had prevalent postoperative anaemia. Other common complications following TJR include urinary retention (incidence of 10% to 38.1%), (183) and electrolyte imbalance that may be as high as 15%. (178)

A limitation of studies that report a restricted set of postoperative complications following TJR (16-18,20,179,183) is their underestimation of the overall rates of all complications. A prospective study that reported all incident complications (in-hospital or six weeks following a primary TJR) in 1,636 patients found that 6.4% and 1.0% developed a major systemic or local complication, respectively, and 21.6% and 6.1% had a minor systemic or local complication, respectively. (23) Moreover, classification of a complication as major

or minor may differ among studies. This classification can be researcher-biased if the investigators are not blinded to the outcomes that follow these conditions as demonstrated in two studies published by the same researchers. (23,185) In one study some conditions (such as transient ischemic attack and deep vein thrombosis) were classified as major while in the other as minor.

Gap in research addressed in this thesis: Classification of in-hospital complications following elective TJR, retrieved from HMD, by independent orthopaedic surgeons has not been reported.

4.3 Length of stay in hospital and readmission following TJR

Comparisons of length of stay (LOS) and readmission among hospitals and studies can be difficult as differences in LOS or readmission rates among patients may or may not indicate differences in the quality of care that the patients received. This is because these differences may be attributed to many factors including differences in age, co-morbid conditions, but also differences in administrative and policy factors that are often not accounted for in such analyses. (186,187) Examples of factors that may affect both the LOS and readmission and that may be unrelated to quality of care include the availability of hospital beds, and the availability of intermediate or step-down units. (187) Additionally, thresholds for readmission may vary by physicians and the same complication may be treated in an outpatient setting in one hospital but during readmission in another. (188,189) Nevertheless, LOS and subsequent short-term readmission are considered key performance indicators and a measure of quality of hospital care and these measures are often used to compare patients and hospitals. (190,191) In a large case-control study, Ashton et al. showed that lower quality of inpatient care independently increased risk of 14-day readmission among men who were initially admitted for diabetes, chronic obstructive lung disease or heart failure. (191) A recent study reported that a reduction in LOS is associated with an increase in short-term readmission following total hip replacement. Using Medicare data on more than one

million THR procedures done in the United States between 1991 and 2008, Cram et al. showed that while the median LOS dropped over the years from 9 to 4 days, 30-day or 90-day all-cause readmission increased from 5.9% to 8.5%, P<0.001. (192) The researchers also showed that mean age and co-morbidity of the surgical patients who were selected for THR increased significantly over time, however, this increase in patients' age and co-morbidity was not accounted for in their analysis.

Length of stay in hospital following an elective procedure is often used to assess hospital management, planning and efficiency (190) as it determines number of beds to be provided. Reducing LOS may mean that more beds would be available for a high-volume procedure such as TJR that is ever increasing in demand, (3) which may lead to a substantial reduction in waiting time for surgery. This is especially important since long waiting periods for elective total joint replacement in an elderly population may lead to clinical deterioration, which in turn is associated with worse postoperative outcomes. (193)

In conclusion, the studies contributing to this thesis used hospital morbidity data and mortality records that were linked to minimal clinical data including actual weight and height of 12,203 elderly male study participants and their self-reported duration of smoking and physical activity to assess risk of undergoing primary total joint replacement. Short- and long-term adverse outcomes following this elective procedure were also assessed. As the aged population grows and obesity becomes more prevalent, the caseload from elective primary TJR will increase and the need for a better understanding of its predictors and outcomes will become more urgent. Identifying high-risk patients and resolving some of the controversies related to modifiable risk factors for undergoing TJR and for experiencing postoperative adverse outcomes are needed. The findings of the studies presented in this thesis could help provide insight into better selection and management of patients who need to undergo this procedure.

Chapter 5

Methods

The longitudinal observational studies presented in this thesis integrated minimal clinical data (actual weight and height of patients, self-reported duration of smoking, and self-reported physical activity) with administrative datasets including HMD and mortality records. Exposures to risk factors such as smoking, obesity, and physical activity were ascertained during HIMS baseline screening (1996-9) - as in a historical cohort study. Study outcomes such as TJR or adverse outcomes following TJR were followed into the future after baseline screening. Morbidities and complications registered in HMD were identified using a combination of diagnosis and procedure codes of the ICD-9-CM and the ICD-10-AM. For each participant, any significant morbidity or health-related outcome was retrieved from the linked data in the period 1970 through to 2007.

5.1 Descriptive analyses

Baseline characteristics were summarised using descriptive statistics. Pearson chi-square tests were used to compare categorical groups on outcomes of interest. For continuous variables with a normal distribution, the mean differences among the various groups were evaluated using Student's t-test. Normality of distribution was assessed by standard diagnostic tools such as normal probability plots and histograms. Statistical significance was set at a P-value of <0.05 (two-sided).

Kaplan-Meier (K-M) analysis was used to plot the probability of staying free of an event of interest (e.g. readmission, death, hospital discharge) over time, and differences in categorical sub-groups (e.g. survival in different BMI categories) were compared using the

log-rank test. In the presence of competing risks, the cumulative incidence function (CIF) was used to estimate the overall risks of the event of interest in the study population. (194,195) The K-M approach assumes that censoring is non-informative and independent of the event of interest, whereas the cumulative incidence function accounts for competing risks which may lead to informative censoring. In the cumulative incidence function approach the probability of experiencing an event was calculated provided that the individual did not develop the event of interest or any other competing risk event in prior time intervals. An example of a competing risk event for, say, primary TJR, is death which may not be uncommon in an elderly population. Death reduces the number of individuals at risk of the event of interest as it intervenes and precludes the onset of the event of interest.

5.2 Multivariable analyses

Time to event models were used to estimate the risks of developing a nominated event (e.g. TJR, THR, TKR, post-operative complication, death), adjusted for risk factors. Attending men who had had a lower limb TJR before baseline screening were excluded from the analyses. Follow-up (person-time) for primary joint replacement started at HIMS baseline (1996-9) and ended as the participants experienced their first joint replacement or died or were right censored at the end of follow-up (March, 2007). Follow-up for length of stay in hospital, readmission or death following TJR started on the day of surgery. Under the assumption of non-informative censoring, the Cox proportional hazards regression model was used to estimate the hazard ratios of the recorded events. A modified proportional hazards model developed by Fine and Gray (196) was applied in the presence of competing risk events.

Some basic assumptions of the Cox proportional model are that: 1) censored cases have the same time to outcome as non-censored cases; and 2) the relative hazard over time is constant.

In practical terms, it is assumed that, given two observations with different values for the independent variables, the ratio of the hazard functions for those two observations does not depend on time. This is known as the proportional hazards assumption. This assumption in both Cox and competing risk regression (CRR) models was tested using Schoenfeld residuals. This approach diagnoses the nature of non-proportional hazards in these models by assessing estimates of time-varying coefficients. (197)

Risk of developing a major in-hospital complication following TJR was assessed using multivariable logistic regression.

5.3 Other methods

5.3.1 Validity analysis

The validity of the hospital morbidity data was defined as the ability of HMD to distinguish between those who have a condition (e.g. past myocardial infarction) and those who do not. The validity was tested by calculating the sensitivity, specificity and positive predictive values (PPV) for each condition of interest. The sensitivity is the ability of HMD to identify correctly those who have a condition. The specificity of HMD is the ability of HMD to identify correctly those who do not have the condition. The PPV or the yield is the proportion of subjects identified by HMD that do actually have a condition. It is a critical measure of the performance of HMD, as it reflects the probability that presence of a recorded co-morbid condition in HMD reflects the underlying condition being assessed. These three measures were based on a 2x2 tables (for example, respiratory system cancer (in HMD) yes/no versus respiratory system cancer (in "Criterion Standard") yes/no).

5.3.2 Performance of co-morbidity adjustment methods

Models were estimated for each of the three co-morbidity adjustment methods, controlling for the same potential confounding factors. The predictive performance of each of the models was measured by the Harrell's C statistic (198,199) which takes values from 0 to 1, with 1 indicating a perfect prediction and 0.5 a chance prediction. The difference in statistical performance between all three co-morbidity adjustment methods was assessed by measuring the difference in the Harrell's C estimates between pairs of models applied to the same patient data. The methods were compared using information on co-morbidity derived only from the index TJR-hospitalization and information drawn from the index together with all prior hospitalizations. Bootstrap analysis (with up to 100 replications) was used to compare Harrell's C estimates produced from different constructed models. (200)

5.3.3 Classification of complications into major or minor

Incident complications as recorded in HMD from index TJR-admission were clinically classified as major or minor based on a questionnaire survey of expert opinion of independent orthopaedic surgeons. A total of 13 experienced orthopaedic surgeons were approached by mail and were asked to classify the complications into major or minor. The assessors were blinded to the outcome of the complications. The only information that was provided was overall mean age and gender of the study population. A complication that was potentially life-threatening was defined as major, while a complication that did not threaten life but did demand medical intervention was defined as minor. (23)

Inter-rater agreement was calculated using Cohen's kappa coefficient (201) and the final decision to classify a condition into major or minor followed a majority rule.

Chapter 6

Accuracy of hospital morbidity data and the performance of comorbidity scores as predictors of mortality

6.1 Preface

This chapter contains the first manuscript contributing to this thesis. The paper has been published in *Journal of Clinical Epidemiology*. The study it describes addresses the first two objectives of this thesis presented in Chapter 1.

The main objectives of this study were:

1. To validate the hospital morbidity data of Western Australia.

2. To assess the performance of three HMD-based co-morbidity adjusting methods in predicting mortality.

The specific objectives of the study were:

a) To assess the accuracy of selected diagnoses and procedures as recorded in WA HMD.

b) To compare the performance of three HMD-based co-morbidity adjusting methods: Enhanced-Charlson Index, Deyo adaptation of Charlson Index, and Elixhauser method, in predicting 1-year and 5-year all-cause mortality in a male elderly general hospital population.

c) To compare levels of model discrimination and performance of the three co-morbidity adjusting methods using information derived from a single index hospitalization with that derived from all past hospital admissions.

d) To assess the association of HMD-based co-morbidity adjusting methods with all-cause hospital readmission following baseline screening of the original abdominal aortic aneurysm study.

e) To assess the associations of HMD-recorded repeated episodes of selected co-morbid conditions with 5-year mortality.

Rationale of study objectives

The validation of WA HMD is crucial for its use in future research. The study findings could help provide empirical evidence for choosing an appropriate HMD-based co-morbidity adjustment method in health services and epidemiological research involving elderly patients.

6.2 Statement of Authorship

Mnatzaganian G, Ryan P, Norman PE, Hiller JE. Accuracy of hospital morbidity data and the performance of comorbidity scores as predictors of mortality. *Journal of Clinical Epidemiology* 2011; DOI: 10.1016/j.jclinepi.2011.03.014. © 2011 Elsevier Inc.

George Mnatzaganian (Candidate)

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

Signed: Date: 21 /12/ 2011

Philip Ryan

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

Signed: Date: 21 – 12 – 2011

Paul E Norman

Contributed to the acquisition of data, and reviewed the manuscript. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 19/12/11

Janet E Hiller

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

Signed: Date: 19/12/11

6.3 Article

Abstract

Objective: The main objectives of this study were to validate the hospital morbidity data (HMD) and to compare the performance of three co-morbidity adjusting methods in predicting 1-year and 5-year all-cause mortality in a male general hospital population in Western Australia (WA).

Design: Population-based data were integrated with WA linked-data-system. Deyo-Charlson Index, Enhanced-Charlson Index and Elixhauser's method measured co-morbidity. Mortality was modeled using Cox regression and model discrimination was assessed by Harrell's C statistics.

Results: The HMD were most likely to identify major co-morbidities such as cancer, myocardial infarction, diabetes mellitus and major operations. The presence of co-morbidity was independently associated with an increased risk of adverse outcomes. All models achieved acceptable levels of discrimination (Harrell's C: 0.70-0.76). The Enhanced-Charlson Index matched the Deyo-Charlson Index in predicting mortality. Elixhauser's method outperformed the other two. Including information from past admissions achieved non-significant improvement in model discrimination. A dose-response effect was observed in the effect of repeated episodes on risk of 5-year mortality.

Conclusion: Co-morbidities diagnosed at different points in time may have different associations with the risk of adverse outcomes. More research is required to integrate the effect of repeated episodes in currently used methods that measure and adjust for co-morbidity.

Introduction

Monitoring systems often use administrative data (e.g. hospital morbidity data) to predict, at the time of hospital admission, each patient's probability of developing an adverse outcome if average care were given. (129,202) Differences in outcome among patients may or may not indicate differences in the quality of care that the patients received because these differences may be attributed to many factors including differences in age, severity of illness, co-morbid conditions, but also differences in methods of data collection and data quality. (68,89,90,203-205)

The power of any model to predict an adverse outcome depends on the extent and accuracy of the data on each patient's clinical condition when care began. (60) While clinical data retrieved from patients' files (or chart review) are considered the gold standard for accurate clinical information, these are costly and time consuming to obtain and often large clinical databases for comparative purposes are not easily available. Therefore, administrative data or claims data are being increasingly used to assess clinical outcomes and monitor, evaluate and improve the quality of care. (71,206) These data have many advantages over the clinical data derived from chart review including their availability and coverage of large populations. However, research based on administrative data such as hospital morbidity data (HMD), requires a rigorous assessment of their quality, so considerable effort must be invested in data validation. (62,65,130,204) This is particularly true given that HMD were not originally collected for the purpose of health research. Another major disadvantage of HMD is the difficulty of differentiating complications from co-existing conditions, (69) particularly if a single hospital admission (or index admission) rather than all previous hospital admissions is used to derive the medical information. Extraction of co-morbidity information that relies on a single hospital admission may underestimate a patient's co-morbid status. (116,123) This becomes evident when an attending physician who summarizes the discharge document chooses to document more serious clinical conditions, while leaving out "less serious"

diagnoses like chronic conditions. (60) This is especially true in administrative datasets that have limited coding spaces. (59) Incomplete coding of secondary diagnoses may result in inadequate adjustment for illness-severity due to differences in case-mix reporting which may bias assessments of patient risks of poor outcomes, as demonstrated in a large study on in-hospital mortality among elderly patients. (60) Iezzoni et al found that chronic conditions such as adult-onset diabetes mellitus, hypertension, angina pectoris, heart valve disease and previous myocardial infarction significantly lowered the risk of in-hospital mortality. Since on a clinical basis, these conditions were expected to increase the risk of death, the researchers concluded that their findings were probably due to under-coding of chronic conditions for more severely ill patients. (60)

In hospitalized populations, co-morbidity is one of the main factors associated with adverse outcomes. (89,90-94) Studies have consistently shown that co-morbidity (either acute or chronic illness) predicts higher in-hospital mortality, longer length of hospital stay, higher hospital costs and readmissions. (91-94) Thus, many researchers have developed coding algorithms that suit administrative data to account for patients' co-morbidity conditions. (102-111) Among the International Statistical Classification of Disease (ICD) coding algorithms, Charlson's Co-morbidity Index (CCI) (103) with its many adaptations (105-109) and Elixhauser's co-morbidities (111) are the most widely used in administrative datasets to measure and control for the effects of co-morbid illness. Initially developed in 1987, (103) the Charlson Co-morbidity Index predicts major outcomes (mainly 1-year-all-cause mortality) for patients who may have up to 19 co-morbid conditions. Each condition is assigned a score of 1, 2, 3 or 6 depending on the risk of dying associated with the condition. The scores are summed to give a total score that predicts the event of interest. In contrast, Elixhauser's 30 co-morbidities do not sum to an index but are retained as separate and independent measures, thus allowing the assessment of the association of different co-morbid conditions with different outcomes. (111)

The objectives of this study that integrated longitudinal data from a large population-based cohort of men with WA hospital morbidity data, Cancer Registry, Mental Health Services System, and mortality records were: 1) to validate the hospital morbidity data of Western Australia (WA), 2) to compare the performance of three co-morbidity adjusting methods in predicting 1-year and 5-year all-cause mortality in a male elderly general hospital population in WA, 3) to compare levels of model discrimination using information derived from a single index hospitalization with that derived from all past hospital admissions, 4) to assess the association of co-morbidity with 1-year and 5-year mortality and with any hospitalization after baseline screening, 5) and to assess the associations of past repeated conditions with mortality.

Methods

Data sources and study population:

The study population comes from the Health In Men Study (HIMS) cohort (45,46) which was originally established via a randomized population-based trial of ultrasound screening for abdominal aortic aneurysms (AAA) in men aged 65-83 living in Perth, Western Australia (WA) in 1996-9. A total of 41,000 men was identified via the electoral roll (voting is compulsory in Australia) and was randomized into invited and control groups of equal size. Of the 19,352 men who were invited, 12,203 attended the baseline screening (Appendix 1). At baseline these 12,203 participants provided detailed health and other information including self-reported history of major co-morbidities, detailed smoking history, alcohol consumption and medications for chronic illnesses. During 2001-04 the surviving men of the 12,203 initial participants were invited to a follow-up survey and 5,571 subjects agreed to participate providing detailed health information including smoking, medical history, and medications used.

Electronic record linkage to population based named identified records was used for deaths and admissions to hospital (HMD) in Western Australia to identify end points in the target

population. (47) Significant morbidity was retrieved from the HMD in the period 1979-2007. Linkage was also performed to obtain information on cancer status and mental health as reported to the WA Cancer Registry and WA Mental Health Services System, respectively. The HMD allows the inclusion of up to 21 diagnoses and 11 procedure codes for each hospitalization in every hospital department. Patients may move among different hospital departments in a single hospitalization episode and the HMD consider each of the departmental moves as a separate hospitalization.

Statistical analysis

Co-morbidity adjustment methods

Since its first introduction in 1987, (103) the original Charlson Co-morbidity Index has undergone many adaptations including those introduced by Deyo et al., (105) Romano et al., (108) D'Hoore et al., (106) and Ghali et al.. (107) The Deyo Charlson Index was further modified by Quan et al (109) producing the Enhanced Charlson Co-morbidity Index.

In this study, we chose to use three co-morbidity adjustment methods: the Deyo, (105) the Enhanced (109) and Elizhauser co-morbidities, (111) to measure and control for the effect of co-morbid illness. For all three methods, we used the corresponding sets of five-digit International Statistical Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses, as delineated in these authors' original publications. The original Charlson weights (103) were applied to the Deyo and Enhanced methods.

Elixhauser et al. (111) made clear distinctions between co-morbidities and secondary diagnoses that were related to the diagnosis-related group (DRG). This was not accounted for in this study since all the hospitalizations were historic and a patient was considered as having a condition (e.g. heart failure) if it was identified in the hospital morbidity data (see Appendices I and II for codes used to form co-morbidity adjustment scores pages 214-218).

The presence of co-morbid conditions was obtained from both the patient's last hospital admission prior to baseline screening (considered here as the index admission) and from all past hospitalizations.

Endpoints

The Kaplan-Meier method was used to estimate the probability of remaining free of an event of interest (death at 5 years or any hospital admission after baseline screening) and differences in survivorship between various Charlson Index Score categories were evaluated by the Log Rank test.

Cox proportional hazards regression models were fitted to the data by modeling 1-year or 5-year mortality as a function of age, emergency or unplanned hospital admission, admission due to injury or trauma, hospital sector, number of previous admissions, years of past smoking, socioeconomic status as measured by the Socio-Economic Index For Areas (SEIFA), (207) and a co-morbidity adjusting measure. SEIFA indices indicate relative social disadvantage of populations living in different geographic areas with low scores reflecting disadvantage. Since most of the participants were recruited before 1999 (Table 1), we used the 1996 census to calculate the index. At baseline screening the participants provided their residential postcode which lowered the chances of misclassification of SEIFA due to incorrect postcode.

Univariate Cox proportional hazards modeling was used to examine the association between 1-year or 5-year survival with the co-morbidities that comprise Elixhauser's method. All Elixhauser's co-morbidities that were significant at P-value of less than 0.1 were considered for the multivariate analysis. The Cox proportional hazard assumptions were tested using Schoenfeld residuals.

Performance of co-morbidity adjusting methods

Models were estimated for each of the three co-morbidity adjustment methods, controlling for the same potential confounding factors. The predictive performance of each of the twelve

models was measured by the Harrell's C statistic (198,199) which takes values from 0 to 1, with 1 indicating a perfect prediction and 0.5 a chance prediction. The difference in statistical performance between all three co-morbidity adjustment methods was assessed by measuring the difference in the Harrell's C estimates between pairs of models applied to the same patient data. The methods were compared using information on co-morbidity derived only from the index hospitalization and information drawn from the index together with all prior hospitalizations. Bootstrap analysis was used to compare Harrell's C estimates produced from all 12 models. (200)

Further, the effect of repeated episodes of two major co-morbidities on 5-year survival was assessed using Cox proportional hazards models while controlling for age. The models were also adjusted for the number of past admissions to account for possible reporting bias.

Validity analysis

Validation of the diagnoses recorded in the WA hospital morbidity data was performed using Cancer Registry data, Mental Health Services data, and self-reported data from both the baseline and follow-up HIMS studies. (46) Cancer diagnoses reported in the HMD were validated against diagnoses reported to the Cancer Registry which records all results of pathology tests indicating a malignant disease (other than non-melanotic skin cancer). Since reporting of such results is mandatory, the Cancer Registry data constitute the "Criterion Standard". (250) Cancer that was diagnosed after the patient's last hospitalization episode was not included in the validation tests. Psychiatric diagnoses registered in the Mental Health Services System (MHSS) were used to validate the reported psychiatric diagnoses in the HMD. The MHSS included all psychiatric diagnoses of patients who were admitted to a mental health institution. Since not all patients with a mental illness are hospitalized in a mental institution, some of the psychiatric conditions reported in the HMD may not be known to the MHSS. Despite this limitation, the MHSS was considered the "Criterion Standard".

A selected number of major co-morbidities as reported in the HMD was validated against the self-reported history of these co-morbidities as provided by the study participants during their baseline screening (1996-9) and follow-up study (2001-4). In each of the validation analyses that relied on self-reported data, all hospital admissions that came after baseline screening or follow-up study were excluded.

Moreover, the newly diagnosed AAA among the attending men who were screened at baseline for its presence, was used to validate this diagnosis as reported in the HMD. The AAA was also detected if the condition was asymptomatic. The sensitivity, specificity and positive predictive values (PPV) for each condition of interest were based on a 2x2 tables (for example, respiratory system cancer (in HMD) yes/no versus respiratory system cancer (in Cancer Registry) yes/no).

The ICD-9-CM and ICD-10-AM (Australian Modification) coding algorithms used to identify the conditions were revised and checked by a professional clinical coder.

Ethical approval was obtained from the Human Research Ethics Committees of Health Department of Western Australia and The University of Adelaide prior to commencement of study. All analyses used de-identified data.

All analyses were performed using Stata statistical program (version 11, Stata-Corp.).

Results

Study population

A total of 12,203 men (mean age + SD 72.1 + 4.4 years) participated in the baseline AAA screening study (Table 1), of whom 12,013 (98.4%) had at least one hospital admission during 1970-2007. Of these, 10,950 men (91.1%) had already been hospitalized at least once before baseline screening. The hospital morbidity data for these 10,950 men contained 66,344 hospitalizations with a median of four hospitalizations per person.

Validation

The hospital morbidity data were most likely to identify cancer for any site except for melanoma, when the Cancer Register indicated it was present (sensitivity ranging from 0.77 to 1.00) (Table 2). The HMD detected major operations such as coronary artery bypass or hip or knee replacement, as self-reported by the study participants. The HMD database also identified past myocardial infarction and diabetes mellitus with acceptable sensitivities (>0.65). When validation was restricted to insulin-treated diabetes mellitus, the sensitivity rose to 0.93. However, not all co-morbid conditions were necessarily detected by the HMD. The database was less likely to detect mental illness (sensitivity of 0.55-0.59), AAA (sensitivity of 0.55), asthma (sensitivity of 0.31-0.36) and dyslipidaemia (sensitivity of 0.22-0.31) (Table 3). Similarly, smoking was underreported in the HMD (sensitivity of 0.26-0.48). The high specificity for all the diagnoses implies that those without the recorded HMD codes were actually free of that condition. The relatively high positive predictive values for most of the conditions (except for depression) indicate that the coded conditions in the HMD convey a true presence of the condition and that few patients were mistakenly coded as having these conditions.

Risk of an adverse outcome

The presence of co-morbidity, irrespective of method used to measure it (Deyo, Enhanced, or Elixhauser) was independently associated with an increased risk of short- and long-term mortality. Given age, urgency status at the time of the index admission, admission due to injury or trauma, number of past admissions, hospital sector, years of smoking and socioeconomic status, it was found that a 1-point increase in the Deyo Charlson Index would increase the hazard of death at 1 and 5 years by 29% and 27% respectively (Table 4). Significant determinants of increased death rates at 1 and 5 years, besides co-morbidity, were age, an emergency or unplanned admission, and number of past admissions. Given age and other risk factors, years of smoking significantly increased mortality within 5 years after screening, while admission to the private hospital sector had a significant protective effect.

The Kaplan-Meier estimates of 5-year survival were lower for patients with a co-morbid condition as measured by the Deyo Charlson Index compared with those without a reported co-morbidity (Figure 1). Survival was lowest in patients with an index of 3 or more. Similarly, the risk of a hospitalization after baseline screening was increased in patients with higher Charlson Index scores (Figure 2).

Overall model performance

We compared the overall predictive performance of the adjusting co-morbidity methods in models predicting 1-year and 5-year all-cause mortality in the adult male general hospital population. Table 5 depicts the Harrell's C estimates calculated using 12 different Cox proportional hazards regression models. All the models achieved acceptable levels of discrimination (Harrell's C estimates ranging from 0.70 to 0.76) but better discrimination was noted when the Elixhauser method was applied. In predicting 1-year mortality, models that used Elixhauser's co-morbidities significantly outperformed those that used the Deyo or the Enhanced method, ($P<0.008$ for each of the comparisons). In predicting 5-year mortality, all three methods provided similar levels of discrimination when the information was drawn only from the index admission but when the co-morbidity was based also on all prior admissions, the Elixhauser method achieved better discrimination than the other two methods ($P<0.001$). Drawing information on co-morbid conditions from all prior hospital admissions substantially increased the prevalence of most co-morbid categories (Appendix 2). However, this added information for all three methods produced slight improvements in model discrimination over that produced using diagnoses reported from only the index hospitalization. The differences in levels of discrimination (index versus index together with all prior admissions) in each of the three adjustment methods were not statistically significant. Similar findings were demonstrated when the analyses were done on a randomly selected hospital admission (results not shown). These findings suggest that information from any index hospitalization may be sufficient to measure and adjust for co-morbidity.

Repeated episodes of co-morbid conditions

We assessed the associations of repeated myocardial infarctions and cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) as reported in the HMD with the risk of dying within 5 years after screening. Controlling for age and number of past hospitalizations, repeated episodes of these two major co-morbid conditions significantly increased the risk of dying, showing a dose response effect (Table 6).

Discussion

This study linked longitudinal clinical data from a large population-based cohort with routinely collected datasets including hospital morbidity data, Cancer Registry, Mental Health Services System and Mortality Records. For each participant, any significant morbidity or health-related outcome was retrieved from the linked data in the period 1979 through to 2007. The linkage with clinical data enabled us to validate lifetime co-morbidities as listed in the WA hospital morbidity data. Several studies have attempted to validate diagnoses reported in routinely collected datasets against various data sources, including patients' medical charts, [80,81] discharge summaries [82] or patient-self-reported conditions. [83-85] In this study we validated the HMD against mandatory information reported to two registries and self-reported clinical conditions. Our validation study demonstrated that the WA HMD system was most likely to identify major co-morbid conditions such as cancer, myocardial infarction (MI), diabetes mellitus (DM) and major operations. In a previous, smaller WA HMD validation study, using patients' chart review as the criterion standard, Preen et al found a high proportion of false negatives in the WA HMD in many co-morbid conditions such as any malignancy (sensitivity of 0.53), and MI (sensitivity of 0.26). [80] Our corresponding sensitivities for these conditions were 0.90 and 0.67, respectively. Preen et al retrieved information on co-morbid conditions as reported in the HMD from admissions that occurred within 5 years from the index hospitalization. This most probably led to an underestimation of the prevalence of many diagnoses as demonstrated in our and other study. [85] In a validation

study, Robinson et al. (85) showed how using additional years of routinely collected data would increase the agreement between data sources. Similarly, our study showed that including all lifetime admissions doubled to trebled the prevalence of most conditions. Moreover, Preen et al. (80) did not report proportions of patients who actually had an admission prior to the index hospitalization. Unlike our study, Preen et al study design may have limited their data collection to a time period that did not include all relevant or all complete information on the patients' co-morbid conditions.

Findings from validity studies of routinely collected databases may significantly vary with the condition studied. (68) Agreement for inpatient principal diagnosis based on three-digit ICD-9-CM codes was found in 78.2% of cases with the National DRG Validation Study (65) and in 92% of cases with the California Office of Statewide Health Planning and Development. (63) Jollis et al (68) assessed agreement between clinical and claims data in 12,937 patients undergoing cardiac catheterization and found that the kappa agreement estimates ranged from 0.83 for the diagnosis of diabetes to 0.09 for the diagnosis of unstable angina with an overall agreement of 0.75. Consistent with other research, (63,68) our study showed significant differences in the validity tests of different conditions, suggesting that the HMD may be more likely to report diagnoses of a more serious nature. In contrast, self-reported asthma, smoking or dyslipidaemia were less likely to be detected by the HMD. The relatively low positive predictive values for psychiatric conditions (ranging from 0.57 to 0.62) may not necessarily imply false positives in the HMD but rather would suggest that these patients were not known to the Mental Health Services System, as their condition may not have necessitated hospitalization in a mental institution. The relatively low sensitivity of serious conditions such as melanoma or AAA may indicate underreporting by medical staff. In contrast, some sensitivities may have been underestimated if the diagnosed condition that was known to the patient did not necessitate hospital admission (e.g. angina pectoris, or diet-controlled non-insulin dependent diabetes mellitus).

The current study evaluated the comparative statistical performance of three methods of adjusting for co-morbidity by applying all three methods to the same study population. The enhanced Charlson Index (109) performed similarly to the original Deyo adaptation of Charlson Index, (105) while Elixhauser adjusting method (111) outperformed them both with models showing better discrimination, as found by another study. (116) Further, we examined whether including diagnoses from prior hospitalizations would improve model discrimination in predicting 1-year and 5-year survival. The diagnoses detected from prior lifetime admissions increased the prevalence of co-morbid conditions when compared to those detected from a single index admission. However, this additional information on co-morbidity achieved minimal improvement in model discrimination. Our findings suggest that co-morbid conditions diagnosed at different points in time may have different associations with the risk of dying. It is possible that conditions such as myocardial infarctions that were diagnosed a long time ago (e.g. 10 years ago) will not have a similar effect on mortality as a more recent myocardial infarction (e.g. 1 or 2 years ago). Thus merging long-diagnosed conditions together with recently-diagnosed conditions may have resulted in antagonistic combinations that have weakened their independent effect. This could explain why Elixhauser et al did not find any significant associations between some major conditions (e.g. past myocardial infarction, leukemia) and in-hospital mortality. (111) Another major drawback in currently used methods to adjust for co-morbidity is the lack of adjustment for repeated episodes of co-morbid conditions. The risk of an adverse event may be significantly higher after a second or third episode of the same condition as supported by our detecting a dose-response effect of number of past myocardial infarctions or cerebrovascular accidents on risk of dying within 5 years after screening.

Our population-based study has several strengths including its longitudinal follow-up design, and linkage of participants' records to the WA linked data system which enabled us to account for major co-morbidities for each individual. However, the study has some limitations. Our

study used self-reported information to validate co-morbid conditions. Self report has been criticized as underestimating the accuracy of the diagnostic codes in administrative data since patients are not necessarily aware of all the diagnoses recorded by their physicians. (83) Besides information bias, self report can also be affected by recall bias. However, one study found high agreement levels between self reported co-morbid conditions and those reported in administrative datasets. (85) Furthermore, it has been shown that self-reported Charlson indices predicted 1-year mortality comparable to that predicted using indices based on administrative data. (84) The validation analysis refers to the WA HMD and the results may not be generalizable to other hospital morbidity databases whose data collection and data quality differ from the WA HMD. Another limitation concerns the use of SEIFA to adjust for socioeconomic status. The SEIFA indices used to rank areas reflect the socio-economic well-being of the populations within those areas rather than that of individuals themselves. Any area can include both relatively advantaged and disadvantaged people. Using the postcode may have introduced some misclassifications, (208) however, since the postcode was provided by the participants, this misclassification was less likely to occur.

Conclusion

Our study shows that the hospital morbidity data can be a valid tool to assess major outcomes among the general hospitalized population. The presence of co-morbidity as noted in these data significantly and independently predicts short- and long-term major outcomes. Co-morbidities diagnosed at different points in time may have different associations with the risk of adverse outcomes. More research is required to integrate the effect of repeated episodes in currently used methods that measure and adjust for co-morbidity.

Acknowledgement

Tables and Figures

Table 1: Baseline characteristics of the 12,203 men who participated in study

Variable	
Age, mean $\pm$ SD, (range)	72.1 $\pm$ 4.4 (65 - 84)
Marital status, %	
Married	80.5
Never married	4.2
Divorced / widowed	12.6
Other	2.7
Place of birth, %	
Oceania / Australia	56.0
Europe	36.2
Asia / Africa	5.8
Americas	0.5
Unknown	1.5
BMI, mean $\pm$ SD, (range)	26.8 $\pm$ 3.7 (14.0 - 67.1)
Deyo Charlson Index, mean $\pm$ SD, (range)	0.88 $\pm$ 1.4 (0 - 11)
Ever smoked, %	70.8
Years of smoking, mean $\pm$ SD, (range)	24.5 $\pm$ 20.5 (0 - 73)
SEIFA, mean $\pm$ SD, (range)	1025.5 $\pm$ 89.9 (531.7 - 1220.8)
Year of recruitment into study, %	
1996	14.9
1997	52.4
1998	32.6
1999	0.05

Abbreviations: BMI (body mass index); SEIFA (Socio-Economic Index For Areas)

Table 2: Validation[*] of cancer by site in HMD using the Cancer Registry and psychiatric diagnoses reported in HMD using the Mental Health Register (N=11,984)

	Sensitivity	Specificity	Positive Predictive Value
Site of cancer			
Upper GI including stomach	0.82	0.99	0.83
Lower GI	0.98	0.99	0.92
Liver/Pancreas/Bile ducts/other GI	0.90	0.99	0.68
Respiratory system / intrathoracic	0.97	0.99	0.89
Genital and urinary systems	0.88	0.99	0.95
Melanoma	0.38	0.99	0.87
Bone/cartilage/soft tissue	0.77	0.99	0.69
Central nervous system	1.00	0.99	0.69
Lymphatic/ Haematopoietic systems	0.92	0.99	0.92
Any cancer	0.90	0.85	0.78
Type of psychiatric disorder			
Uni-polar depression	0.55	0.83	0.57
Bi-polar depression	0.59	0.97	0.59
Psychosis	0.55	0.97	0.62

Abbreviations: HMD (hospital morbidity data), GI (gastrointestinal)

Sensitivity= TP/ (TP+FN); Specificity= TN/ (TN+FP); Positive predictive value= TP/ (TP+FP)

* All validation analyses (sensitivity, specificity, and positive predictive values) were statistically significant with *P*-values of <0.001

Table 3: Validation[*] of selected co-morbidities in hospital morbidity data using self-reported co-morbidities and clinically diagnosed abdominal aortic aneurysm (AAA)

Co-morbidity	Based on AAA baseline screening N=10,950			Based on follow-up study N=5392		
	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
Myocardial infarction	0.67	0.98	0.87	0.69	0.96	0.80
Diabetes Mellitus	0.62	0.99	0.93	0.68	0.98	0.88
Asthma	0.36	0.99	0.89	0.31	0.99	0.88
Stroke	0.59	0.97	0.65	0.51	0.96	0.66
Angina pectoris	0.50	0.96	0.78	0.51	0.92	0.65
Hypertension / treat	0.56	0.93	0.86	0.60	0.88	0.83
Ever smoking	0.26	0.97	0.96	0.48	0.97	0.98
Dyslipidaemia	0.22	0.97	0.83	0.31	0.97	0.90
Coronary angioplasty	0.78	0.97	0.62	-	-	-
Coronary artery bypass	0.95	0.99	0.97	0.91	0.99	0.93
Hip or knee replacement	-	-	-	0.92	0.98	0.92
AAA	0.55	0.99	0.88	-	-	-

Sensitivity= TP/ (TP+FN); Specificity= TN/ (TN+FP); Positive predictive value= TP/ (TP+FP);

* All validation analyses (sensitivity, specificity, and positive predictive values) were statistically significant with *P*-values of <0.001

Table 4: The association of co-morbidity with death after adjusting for selected hospital and patient characteristics: Cox proportional hazards regression models[!]

Variable	Category	One-year mortality HR	95% CI	Five-year mortality HR	95% CI
Age	Continuous	1.10	1.06 -1.15 [*]	1.10	1.08 - 1.11 [*]
Deyo Charlson Index[!!]	Continuous	1.29	1.18 - 1.41 [*]	1.27	1.23 - 1.31 [*]
Unplanned admission	Yes	1.78	1.17 - 2.73 [**]	1.18	1.01 - 1.39 [**]

! Each of the models was adjusted for hospital sector, admission due to injury or trauma, number of past hospital admissions, years of smoking and SEIFA
!! The Deyo Charlson Index was based on all prior admissions including index hospitalization
* P-value < 0.001; ** 0.001 < *P*-value < 0.05

Table 5: Harrell's C statistics from Cox proportional hazards 1-year and 5-year models - performance of co-morbidity scores based on three different coding algorithms

	Deyo's coding algorithm[24]	Enhanced coding algorithm[27]	Elixhauser co-morbidities[29]
One-year mortality[*]			
Information from index[#] only	0.7238	0.7236	0.7470
Information from all past admissions	0.7280	0.7269	0.7595
Five-year mortality[*]			
Information from index[#] only	0.7034	0.7032	0.7077
Information from all past admissions	0.7108	0.7122	0.7246

Index admission was the last hospital admission just before baseline screening
*All the models were adjusted for age, unplanned or emergency admission, number of past admissions, hospital sector, admission due to injury or trauma, years of smoking and SEIFA

Table 6: Association of number of past myocardial infarction and cerebrovascular accident (CVA) or transient ischemic attack (TIA) with risk of dying within 5 years after screening: Cox proportional hazards regression

	Categories	Hazard Ratios	95% CI
Model a[^]			
Age	Continuous	1.10	1.09 - 1.11 [*]
Past myocardial infarction	Yes	1.56	1.26 - 1.93 [*]
Past CVA or TIA	Yes	1.67	1.31 - 2.11 [*]
Model b[^]			
Age	Continuous	1.10	1.09 - 1.11 [*]
Number of past myocardial infarctions	1	1.39	1.16 - 1.67 [*]
	2 - 3	1.46	1.19 - 1.78 [*]
	4 +	1.82	1.39 - 2.39 [*]
Number of past CVAs or TAIs	1-2	1.51	1.27 - 1.79 [*]
	3 +	1.72	1.29 - 2.28 [*]

^ Both models were also adjusted for the number of past hospitalizations
* P-value < 0.001

Figure 1: Kaplan Meier estimates of 5-year survival by the Deyo Charlson Co-morbidity Index (CCI) based on all past hospital admissions
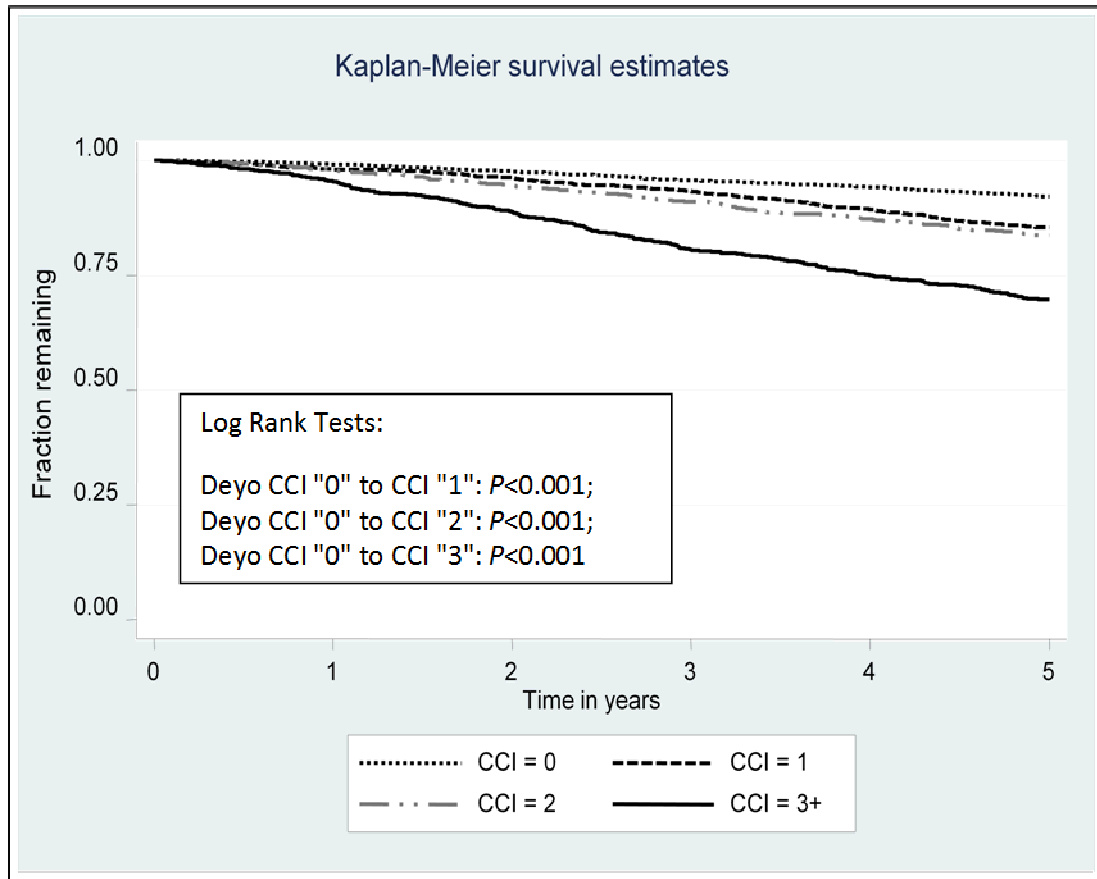
Figure 2: Kaplan Meier estimates of remaining free of any hospital admission after baseline screening by the Deyo Charlson Co-morbidity Index (CCI) based on all past hospital admissions
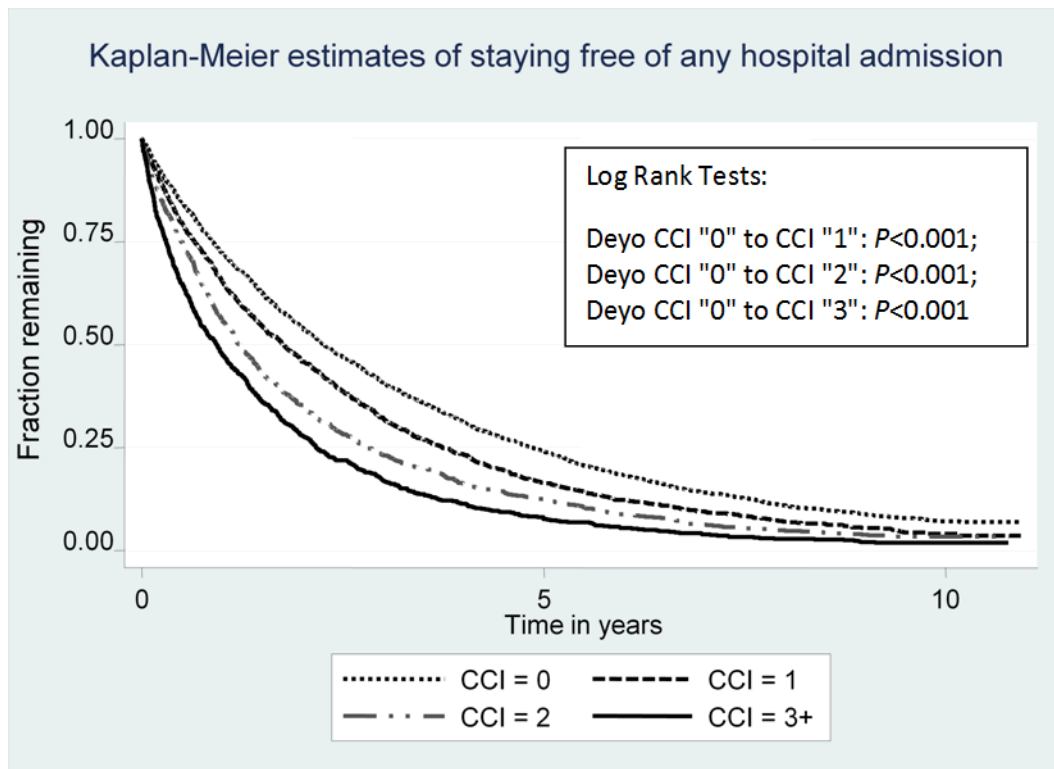
Appendix1 : Proportions of the Health In Men Study sub-groups captured in Perth during baseline (1996-1999)

HIMS cohort sub-groups	N	%
Participated in AAA trial	12,203	29.8
Invited but refused to participate	7,149	17.4
Died before invitation - initially belonged to potential participants	1,148	2.8
Controls, not invited	19,352	47.2
Died before invitation - initially belonged to the control group	1,148	2.8
Total	**41,000**	**100.0**

Abbreviation: AAA (abdominal aortic aneurysm)

Appendix 2: Five-year crude mortality and prevalence of co-morbid conditions as defined by Elixhauser, by hospital admission

| Condition | Prevalence of conditions at baseline screening | | Five-year crude mortality[+] % |
	Retrieved from the last admission	Retrieved from all previous admissions[#]	
Congestive heart failure	1.56	4.20	35.7
Cardiac arrhythmias	4.51	8.89	22.9
Valvular disease	1.36	3.10	19.3
Pulmonary circulation disorders	0.06	0.24	(35.3)*
Peripheral vascular disorders	1.76	4.59	28.3
Hypertension	16.10	27.31	16.8
Paralysis	0.69	1.60	19.6
Other neurological disorders	0.96	1.77	33.1
Chronic pulmonary disease	5.44	10.20	26.0
Diabetes, uncomplicated	5.34	6.63	23.9
Diabetes, complicated	0.34	0.83	43.1
Hypothyroidism	0.36	0.63	20.4
Renal failure	0.49	1.14	43.7
Liver failure	0.29	0.74	28.8
Peptic disease excluding bleeding	2.31	6.27	15.9
AIDS	0.00	0.04	(0.0)*
Lymphoma	0.41	0.54	36.8
Metastatic cancer	0.53	1.49	36.5
Solid tumour without metastasis	7.10	12.83	20.0
Rheumatoid arthritis / collagen vascular diseases	0.51	1.37	19.8
Coagulopathy	0.51	1.47	29.1
Obesity	0.81	3.83	22.8
Weight loss	0.01	0.01	(100.0)*
Fluid and electrolyte disorders	0.53	1.89	27.3
Blood loss anaemia	0.06	0.46	12.5
Deficiency anaemia	0.63	2.59	28.7
Alcohol abuse	0.61	1.51	27.4
Drug abuse	0.03	0.07	(20.0)*
Psychoses	0.19	0.67	29.8
Depression	0.37	1.34	26.6

+Five-year crude mortality was estimated on subjects with conditions retrieved from all previous admissions
*Less than 20 patients having the condition
All previous admissions including the last admission

Chapter 7

Smoking, body weight, physical exercise, and risk of lower limb total joint replacement in a population-based cohort of men

7.1 Preface

This chapter contains the second manuscript contributing to this thesis. The paper has been published in *Arthritis & Rheumatism*. In the previous analysis (see Chapter 6), elements of the WA HMD were validated showing that HMD-based co-morbidity scores perform well in predicting mortality in elderly men. In this analysis, data on actual weight and height of HIMS 11,388 participants, their self-reported duration of smoking and physical activity were integrated with HMD and mortality records. The study described in this paper addresses the third objective of this thesis presented in Chapter 1.

The main objective of this study was:

1. To assess risk of undergoing an elective primary total joint replacement in elderly men.

The specific objectives of the study were:

a) To assess the associations of modifiable risk factors of body weight, duration of smoking, and vigorous and non-vigorous physical exercise with risk of undergoing an elective: 1) total joint replacement (TJR), 2) total hip replacement (THR), and 3) total knee replacement (TKR), after controlling for age, Deyo-Charlson co-morbidity

adjustment method or Elixhauser method, height, hospital type, and socio-economic status.

b) To verify whether more deaths occurred among the smokers compared to never-smokers and whether this "selective mortality" (209) contributed to the inverse association of smoking with risk of undergoing a TJR.

c) To assess the risk of undergoing TJR while accounting for the competing risk of mortality.

Rationale of study objectives

Much of the research that has evaluated risk of undergoing TJR has disregarded co-morbidities and concentrated mainly on a selected number of risk factors. Therefore, an important aspect of this study was to verify the relationship between important modifiable factors with risk of undergoing lower limb joint replacement while controlling for the confounding effect of co-morbidities. The study findings could help provide insight into future research for better understanding the pathogenesis of osteoarthritis.

7.2 Statement of Authorship

Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Smoking, body weight, physical exercise, and risk of lower limb total joint replacement in a population-based cohort of men. *Arthritis & Rheumatism* 2011;63(8):2523-2530. DOI 10.1002/art.30400. © 2011, American College of Rheumatology.

George Mnatzaganian (Candidate)

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

Signed: Date: 21/12/2011

Philip Ryan

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

Signed: Date: 21 - 12 - 2011

Paul E Norman

Contributed to the acquisition of data, and reviewed the manuscript. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 19/12/11

David C Davidson

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

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Janet E Hiller

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

Signed: Date: _19/12/11_

7.3 Article

Abstract

Objective: To assess the associations of smoking, body weight and physical activity with risk of undergoing total joint replacement (TJR) in a population-based cohort of men.

Methods: A cohort study of 11,388 men that integrated clinical data with hospital morbidity data and mortality records. In three separate age groups we modelled the risk of TJR on baseline weight, height, co-morbidity, socioeconomic status, years of smoking and exercise, using Cox proportional hazards regressions and competing risk regressions (CRR).

Results: A dose-response relationship between both weight and smoking, and risk of TJR was observed. Being overweight independently increased the risk of TJR, while smoking lowered the risk. The decreased risk among smokers was demonstrated in both Cox and CRR models and became apparent after 23 years of exposure. Men who were in the highest quartile (48+ years of smoking) were 42% to 51% less likely to undergo TJR than never-smokers. Tests for trend in the log hazard-ratios across both smoking and weight quantiles yielded $P<0.05$. Vigorous exercise increased the hazard of TJR, however, the association reached statistical significance only in the 70-74 year-old age-group (adjusted-hazard ratio: 1.64, 95% CI: 1.19 - 2.24). Adjusting for Deyo-Charlson Index or Elixhauser's co-morbidities did not eliminate these associations.

Conclusion: Being overweight and reporting vigorous physical activity increased the risk of TJR. This study is the first to demonstrate a strong inverse dose-response relationship of duration of smoking and TJR. More research is needed to better understand the role of smoking in the pathogenesis of osteoarthritis.

Introduction

Total hip replacement (THR) and total knee replacement (TKR) are among the most common elective surgical procedures performed in developed countries. (1-4) The most common indicator for total joint replacement (TJR) is severe osteoarthritis (OA); (8,35) TJR is often considered an acceptable surrogate indicator of severe OA. (31-33) Factors associated with OA (e.g., age, female gender, obesity) are predictors of TJR. (32,34)

In the ageing population, OA is the most common form of arthritis, (35) causing much disability and impairing quality of life. (24) Independent risk factors for this disorder include older age, (151) female gender, (139) obesity, (36,139-141) physical activity, (139,141,151) and never-smoking. (31,139,140) However, the reported association of some of these factors with an increased risk of OA or subsequent TJR has not been consistent. Being overweight shows the most consistent association with OA (31,36,139,140) and with TJR (32,33,141) while the results for physical activity and smoking have been the most inconsistent. (31,32,139-152) Smoking has variously shown a negative association with OA (31,139,140, 144,145,152) or TJR, (146) a positive association with OA (147,148) or TJR (32), and no significant association with OA. (142,149,151) Similarly, the association of physical activity with the risk of OA is unclear. An example of contradictory findings was demonstrated in two studies based on the population-based Framingham cohort. In the first publication on this topic, based on a sub-population from the first cohort enrolled, patients in the highest quartile of physical activity had 3.3 times the odds of developing OA compared with those in the lowest quartile of physical activity. (139) However, in a second publication, based on a sub-population of the first cohort's children and their spouses, the association between physical activity and radiographic OA was weaker and did not reach statistical significance (Adjusted OR=1.20, 95% CI 0.65 - 2.21). (143) Inconsistencies in the findings of these and other studies reflect: sampling biases or unrepresentative cases; a lack of, or incomplete adjustment for, co-

morbidities and other confounders; inconsistencies in definitions of disease; or inaccuracies in definition of exposure. (32,36,148,151) Some studies did not make appropriate distinction between current and past smoking, (36,148) while others disregarded duration of smoking. (32,151)

The purpose of this study was to assess the predictors of undergoing a lower limb total joint replacement in a large population-based cohort of elderly men while focusing on the modifiable factors of body weight, duration of smoking, and physical activity.

Methods

Data sources and study population

The study population is drawn from the Health In Men Study (HIMS) (45,46) which arose from a randomized population-based trial of ultrasound screening for abdominal aortic aneurysm (AAA) in men aged 65-83 living in Perth, Western Australia (WA). A total of 41,000 men was identified via the electoral roll (voting is compulsory in Australia) and was randomized into invited and control groups of equal size. Of the 19,352 men who were invited, 12,203 attended the baseline screening in 1996-9. At baseline the participants provided detailed health and other information including a comprehensive smoking history, and details of vigorous exercise activity (defined in the questionnaire as 'exercise that makes you breathe harder - e.g. jogging, aerobics, tennis, football, squash, etc.') a yes/no question or non-vigorous exercise (defined as 'exercise that does not make you breathe harder - e.g. slow walking or cycling, yoga, Tai Chi etc.') a yes/no question in a usual week. In addition, study nurses recorded weight, height, and waist and hip circumferences. Electronic record linkage was used to identify admissions to hospital (hospital morbidity data) for TJR in the target population. All-cause mortality was ascertained through linkage to WA Health Department mortality records. Follow-up for study end points started at baseline screening and ended in March, 2007.

The hospital morbidity data (HMD) system is a core part of the WA Linked Data System (47) and includes demographic, diagnostic, and procedural information on all patients discharged from all public and private hospitals in WA. The HMD, which has been validated, (210) allows the inclusion of up to 21 diagnoses and 11 procedure codes for each hospitalization in every hospital department. The validation analysis of the HMD showed good to acceptable sensitivities and positive predictive values (PPV) for major operations (e.g., TJR: sensitivity and PPV of 0.92), and major morbidity (e.g., any cancer: sensitivity of 0.90 and PPV of 0.78; past myocardial infarction: sensitivity of 0.69 and PPV of 0.80; diabetes mellitus: sensitivity of 0.68 and PPV of 0.88). (210)

Definitions

The Deyo-Charlson Co-morbidity Index (105) and Elixhauser's co-morbidities (111) which were used to adjust for co-morbidity were based on all reported conditions in admissions that preceded baseline screening. The Deyo-Charlson Index was built using the original Charlson weights, (103) and the corresponding International Statistical Classification of Disease, 9th Revision, ICD-9-CM (Clinical Modification) algorithms were used as delineated in the authors' original publication. (105) We further used an ICD-10-AM (Australian Modification) adaptation of the Deyo-Charlson Index as developed and validated using population-based hospital data from Australia. (110) The coding algorithms defining Elixhauser co-morbidities were based on definitions by Quan et al. (109)

The Socio-Economic Index For Areas (SEIFA) (207) was used to define the participants' socioeconomic status. SEIFA indices indicate relative social disadvantage of populations living in different geographic areas with low scores reflecting disadvantage. Since most of the participants were recruited before 1999, (210) we used the 1996 census to calculate the index. At baseline screening the participants provided their residential postcode, thus lowering the chances of misclassification of SEIFA due to incorrect postcode. Presence of traumatic

fracture of the lower limb on day of surgery was also identified from the HMD. Body mass index (BMI) was defined as body weight in kilograms divided by height in meters squared.

The ICD codes used to detect primary total hip or total knee replacement (Appendix 1) were checked by a professional clinical coder.

Statistical analysis

Attending men who had had a lower limb TJR before baseline screening were excluded from this analysis. The remaining eligible participants were followed from baseline screening until they experienced their first TJR or died or were right censored at the end of follow-up (March, 2007). Since the focus of the study was elective TJR, all patients who experienced a fracture of the lower limb (among those who had and did not have a TJR) were excluded from the analysis.

In three separate age groups (65-69 years, 70-74 years, and 75+ years), we modelled time to TJR on weight, height, socioeconomic status, Deyo-Charlson Co-morbidity Index (or Elixhauser's co-morbidities), vigorous or non-vigorous physical exercise and years of smoking using Cox proportional hazards regressions and competing risk regressions (CRR) as defined by Fine and Gray. (196) The latter analyses assessed the effect of predictors on the hazard of the subdistribution for TJR (the "subhazard") while accounting for the competing risk of death, since the study population was elderly and death represented a competing risk that reduced the number of individuals at risk of the event of interest, TJR. (194,195) We also used the cumulative incidence function (CIF), (195) to estimate the overall risks of TJR and of death in the study population.

Tests for trend in the log hazard ratios across quantiles of duration of smoking and body weight were performed by introducing each of the ordered variables in the multivariable Cox models. The Cox proportional hazard assumptions were tested in each of the age groups using Schoenfeld residuals.

The crude attributable risk of dying among heavy-smokers (48+ years of smoking) was defined as incidence of death among the heavy-smokers minus incidence of death among the never-smokers divided by the incidence of death among the heavy-smokers. (211)

All analyses were performed using Stata statistical program (version 11, Stata-Corp.).

Ethical approval was obtained from the Human Research Ethics Committees of Health Department of Western Australia and The University of Adelaide prior to commencement of study. All analyses used de-identified data.

Results

Of the total 12,203 men (mean age $\pm$ SD 72.1 $\pm$ 4.4 years, range 65 to 84 years) who participated in the baseline AAA screening study, 815 men (6.7%) were excluded as they already had undergone a TJR prior to baseline screening leaving a total of 11,388 participants for the current analysis. Of these remaining eligible participants, a total of 857 men (7.5%) had a TJR after screening, with 510 (59.5%) having a TKR and 347 (40.5%) a THR. The baseline characteristics of these 857 men differed significantly from participants who never had a TJR. The former were significantly younger, had less co-morbidity (defined by Deyo-Charlson Index), had higher mean BMI, belonged to a higher socioeconomic status, and smoked less years than those who did not undergo TJR after baseline (Table 1). A total of 486 men (with fracture of lower limb) were excluded, thus leaving 10,902 men for the study analysis.

To meet the proportionality assumptions of time-to-event models, the cohort was divided into three age groups (based on the actual age distribution in the cohort: 65-69 years, 70-74 years, and 75+ years) and the subsequent analyses were done separately on each of the age-groups.

We stratified TJR by weight quintiles and found that within each age category, the crude proportion of men undergoing TJR increased with weight, while within quintiles of weight the proportion was relatively constant across age groups (Table 2).

We further stratified TJR by years of smoking, age and BMI categories and found an inverse association of duration of smoking and TJR (Table 3). To verify whether more deaths occurred among the smokers compared to never-smokers and whether this "selective mortality" (209) contributed to the inverse association of smoking and TJR, we assessed the crude and age-adjusted death rates as shown in Table 4. The crude mortality rate in each of the age-groups increased as the years of smoking increased. In the younger men (65-69 age-group), 72.4% of the crude mortality among the heavy smokers (48+ years of smoking) was attributable to smoking. This attributable risk fell to 40.5% in the 75+ age-group. The overall age-adjusted and crude mortality rates were similar, showing an increased risk of death as years of smoking increased (Table 4).

To investigate the etiological associations of the study covariates with TJR, we calculated the cause-specific relative hazards (212) using multivariable Cox proportional hazards regressions (Table 5). After adjustment for other covariates in the models, being overweight was significantly associated with an increased hazard of TJR, showing a dose-response relationship across quintiles of the distribution of weight (P<0.001) in all three age strata. In the middle age group (70-74 years), men weighing > 87.9 kg were 4.4 times more likely to undergo TJR compared to men weighing <68.4 kg (HR= 4.36, CI 95% 2.58-7.36). Vigorous exercise reported at baseline increased the hazard of undergoing TJR but this association was only statistically significant in the 70-74 age-group, (HR:1.64, CI 95% 1.19-2.24). Belonging to a higher socioeconomic status was positively associated with TJR in the 70-74 age-group, (HR:1.50, CI 95% 1.14-1.97). Smoking had an inverse association with TJR, showing a dose-response relationship across quartiles of the distribution of years of smoking in all three age strata (65-69 age-group P<0.001, 70-74 age-group P=0.002, 75+ age-group P=0.05). Compared to never-smokers, men who had smoked 48 years or more were 42% to 51% less likely to undergo TJR (HR= 0.49, CI 95% 0.32-0.74 in the 65-69 age-group; HR= 0.58, CI 95% 0.41-0.82 in the 70-74 age-group; HR= 0.51, CI 95% 0.30-0.85 in the 75+ age-group).

Similar results were found after modelling time to TJR using competing risk regression (CRR) to account for the competing risk of death. However, the CRR modelling strengthened the significant associations of weight and of smoking with TJR (results not shown).

To control for potential confounding from other co-morbidities not accounted for in the Deyo-Charlson Index, the CRR models were run using Elixhauser's method (instead of Deyo-Charlson Index) and this produced findings almost identical to those of the first models (results not shown).

To assess the association of weight with different joints, we further modelled THR and TKR separately and found that the association of weight was stronger with TKR than with THR; however the dose-response relationship across quintiles of the distribution of weight was maintained in both TKR and THR. Patients weighing ≥87.9 kg were 5.7 times more likely to have a TKR (adjusted HR=5.72, CI 95% 3.74-8.75), and 2.7 times more likely to have a THR (adjusted HR=2.74, CI 95% 1.75-4.29), compared with patients who weighed 68.4 kg and less.

No statistically significant interactions were found between body weight and smoking or physical activity, nor with smoking and physical activity.

Discussion

This study, involving a large population-based cohort of men, is the first to report an independent dose-response relationship of duration of smoking on the reduction of the risk of undergoing subsequent TJR.

In addition and consistent with other studies, we also demonstrated that being overweight (32,33,141) and engaging in vigorous exercise (141) (latter shown only in the age category 70-74 years old) significantly increased the risk of TJR.

Smoking and TJR

The association of smoking with decreased risk of OA, (31,139,140,144,145,152) or subsequent TJR, (146) has been reported previously. One of the earliest reports came from the

cross sectional population-based first Health and Nutrition Examination Survey (HANES I) in the United States (157) which found an age-adjusted significant inverse association of number of cigarettes smoked per day and radiographic knee OA among both men and women. To test for confounding, researchers from the Framingham Study controlled for age, sex, BMI, physical activity and past knee injury and found a similar negative association in two separate studies. (139,140) In the first prevalence analysis of 1,424 participants, the adjusted OR for knee OA was 0.74 (P<0.05) among the smokers. (140) The second analysis investigated the incidence of radiographic knee OA and showed that heavy smokers had significantly lower risk of developing new knee OA among a cohort of 598 participants initially free of OA (OR=0.4; 95% CI: 0.2-0.8). (139) A similar decrease in risk was reported in a large longitudinal population-based cohort of construction workers. (31) Never-smokers had an increased relative risk of about 40% of undergoing hip replacement due to OA, while ex-smokers had an increased risk of 20% compared with smokers. (31) Our study confirms the inverse association of smoking with risk of TJR. However, smokers were more likely to die than never-smokers, but even accounting for this competing risk of death, men who smoked for more years were less likely to undergo TJR compared to never-smokers.

The mechanisms behind this decrease in risk are not clear. There is some evidence that smoking may directly reduce the severity of OA. An in vitro study found a relationship between nicotine and stimulation of the anabolic activity of the chondrocytes (cells found in joint cartilage). (158) This was supported by a population-based prospective cohort study that showed a positive dose-response between pack-years of smoking and knee cartilage volume among healthy individuals. (152)

The decrease in risk may have other explanations. Our study retrieved co-morbid conditions from the HMD and since this dataset was not originally formed for the purpose of health research, some co-morbid conditions may have been under-reported. If co-morbidity were underestimated, the risk of TJR among never-smokers could have been overestimated (given

that the ever-smokers had more co-morbidities than the never-smokers). However, we have shown that the HMD is a valid tool to assess major health-care outcomes. (210) The validation analysis showed good to acceptable sensitivities and positive predictive values for serious conditions such as major co-morbidities and major surgical procedures. Another explanation is the possibility of confounding by factors not accounted for in this analysis or by selection biases prior to surgery. A survey that sought to find indications for THR or TKR as perceived by orthopedic surgeons showed that the decision against surgery was mainly affected by patient age, co-morbidity, obesity, alcohol use, technical difficulties and lack of motivation among the patients. Smoking was not indicated as a factor that would sway the decision against TKR or THR. (101)

Being overweight and TJR

Body weight is one of the most investigated factors in the study of OA or TJR. In many studies, being overweight and measures of relative body mass have been associated with an increased risk of OA (31,36,139,140,155) and TJR, (32,33,141) with some showing a stronger association in knee OA, (36) suggesting a biomechanical component in the relationship between body weight and OA. However, more studies are showing a positive relationship between being overweight and OA at different body sites including knee and hip, (33,36) and non-weight bearing joints such as small joints of the hands (153,154) suggesting a connection between OA and metabolically active adipose tissue.

After controlling for physical activity, smoking, socioeconomic status, height, and co-morbidities, our study found a dose-response relationship of body weight on the risk of undergoing THR and TKR. However, the association of weight with TKR was stronger than that with THR.

Furthermore, we found that in the older age groups, the probability of undergoing TJR was similar in the highest body weight quintiles. A possible explanation could be selection prior to

surgery. Morbid obesity in these advanced ages may have swayed the decision against surgery, (101) thus lowering the HR in the highest weight categories.

Vigorous exercise and TJR

This study found a positive association between vigorous exercise and TJR. (141) This association could have been underestimated since the participants were relatively old when asked about their weekly exercise habits and one would assume that old age might have naturally limited their physical activity. Nevertheless, these findings suggest that those who were physically active in their younger ages stayed active as they got older and this activity was positively related to an increased risk of TJR.

This study has several strengths including its longitudinal follow-up design, accurate clinical data on body weight and many years of past exposure to smoking. Moreover, the linkage of participants' records to the HMD allowed us to account for major co-morbidities for each individual. However, the study has limitations. Although we considered TJR a surrogate indicator of severe OA, we did not directly ascertain OA status among study participants. The SEIFA indices ranked socio-economic well-being of the populations within areas rather than individuals themselves. Any area can include both relatively advantaged and disadvantaged people. Using the postcode may have introduced some misclassifications, (208) however, since the postcode was provided by the participants, any misclassifications were minimized. Information on the physical activity of the participants was self-reported and not validated and the case definition was too broad. Also, case definitions of physical activity may vary among studies thus making comparisons among studies less applicable. The clinical data presented in the study were collected at baseline screening and, except for age, the study did not account for changes in patient characteristics (e.g., change in body weight, physical activity) that could have occurred over time. However, the mean time from baseline screening to TJR was not long (4.6 ± 2.7 years) and one may assume that in this relatively elderly cohort, OA (a degenerative disease that takes long to develop) was probably present at baseline but this was

not assessed in this study. Finally, our longitudinal study is observational and a causal relationship between smoking and OA cannot necessarily be inferred.

Conclusion

This population-based cohort study has shown an increased risk for TJR with body weight and vigorous exercise, and an inverse association with smoking. Our study is the first to report a strong, inverse, dose-response relationship between duration of smoking and risk of TJR. More research is needed to better understand the role of smoking in the pathogenesis of OA, but also into the selection pathways for patients for whom TJR is indicated. Notwithstanding the findings, this study reinforces the overwhelming excess risk of premature mortality associated with smoking.

Acknowledgement

Tables

Table 1: Baseline characteristics of study population by TJR status after baseline screening

Characteristics	Had TJR N=857	Did not have TJR N=10,531	*P*-value
Age, mean $\pm$ SD, (range)	71.6 $\pm$ 4.2 (65 - 84)	72.0 $\pm$ 4.4 (65 - 84)	0.026
Deyo Charlson Index, mean $\pm$ SD, (range)	0.69 $\pm$ 1.2 (0 - 8)	0.89 $\pm$ 1.4 (0 - 11)	<0.001
BMI, mean $\pm$ SD, (range)	28.1 $\pm$ 3.5 (19.3 - 41.0)	26.7 $\pm$ 3.7 (14.0 - 67.1)	<0.001
Vigorous exercise (during a usual week), %	27.4	25.3	0.175
Ever smoked, %	67.8	71.3	0.030
Years of smoking, mean $\pm$ SD, (range)	21.8 $\pm$ 19.8 (0 - 70)	24.7 $\pm$ 20.6 (0 - 73)	<0.001
Socioeconomic status as SEIFA distribution, % Lower tertile (Low SES) Middle tertile Higher tertile (High SES)	29.9 32.1 38.0	33.3 33.0 33.7	0.024
Fracture of lower limb, %	4.4	4.2	0.802

Abbreviations: TJR (total joint replacement), BMI (body mass index)

Table 2: Crude [1] rate of TJR by age and body weight categories [2]

Age categories, years	1st quintile (weight $\leq$68.4 kg) N=2,181	2nd quintile N=2,240	3rd quintile N=2,186	4th quintile N=2,118	5th quintile (weight 87.9+ kg) N=2,177	Total N=10,902
65-69	3.2%	5.9%	6.8%	8.2%	11.6%	**7.5%**
70-74	2.6%	7.3%	8.9%	11.9%	10.7%	**8.3%**
75-84	2.2%	6.0%	7.6%	9.6%	9.8%	**6.4%**
Total	**2.6%**	**6.4%**	**7.8%**	**9.9%**	**10.9%**	**7.5%**

[1] Not accounting for censoring
[2] Excluding those who had fracture of lower limb
Abbreviation: TJR (total joint replacement)

Table 3: Crude [1] rate of TJR by age, BMI, and years of smoking categories[2]

	BMI <30				BMI 30+			
	Never smoking	1st tertile of smoking 1-28yrs	2nd tertile of smoking 29-43 yrs	3rd tertile of smoking 44+ yrs	Never smoking	1st tertile of smoking 1-28yrs	2nd tertile of smoking 29-43 yrs	3rd tertile of smoking 44+ yrs
65-69 years	7.4%	7.6%	6.5%	4.6%	15.2%	11.4%	8.6%	9.0%
70-74 years	8.8%	7.5%	8.1%	6.2%	10.2%	12.9%	8.8%	12.9%
75+ years	5.8%	6.6%	6.7%	3.8%	13.5%	10.0%	8.6%	9.3%

[1] Not accounting for censoring
[2] Excluding those who had fracture of lower limb
Abbreviations: TJR (total joint replacement), BMI (body mass index)

Table 4: Crude and age-adjusted death[1] rates by years of smoking categories

	Never smoked	**1st quartile 1-23 yrs of smoking**	**2nd quartile 24-36 yrs of smoking**	**3rd quartile 37-47 yrs of smoking**	**4th quartile 48+ yrs of smoking**
65-69	64/1281= 5.0%	40/632= 6.3%	60/701= 8.6%	71/669= 10.6%	103/569= 18.1%
70-74	111/1119= 9.9%	80/731= 10.9%	113/721= 15.7%	130/693= 18.8%	186/765= 24.3%
75-84	191/896= 21.3%	123/570= 21.6%	137/503= 27.2%	136/507= 26.8%	195/545= 35.8%
Crude total death rate	366/3296= **11.1%**	243/1933= **12.6%**	310/1925= **16.1%**	337/1869= **18.0%**	484/1879= **25.8%**
Age-standardized death rates[2]	**11.3%**	**12.2%**	**16.4%**	**18.1%**	**25.3%**

[1] Deaths that preceded TJR
[2] Adjusted for age by direct standardisation method (using total population as standard)

Table 5: Hazard ratios for TJR by age categories: Multivariable Cox proportional hazards model[1]

	Age group: 65-69 years N=3852 Had TJR, N=290 (7.5%)		Age group: 70-74 years N=4029 Had TJR, N=336 (8.3%)		Age group: 75-84 years N=3021 Had TJR, N=193 (6.4%)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
DC Index, (cont)	0.69 (0.61-0.78)	0.000	0.77 (0.70-0.85)	0.000	0.67 (0.59-0.76)	0.000
SEIFA distribution, %						
Lower tertile (Low SES) ref	1.00		1.00		1.00	
Middle tertile	0.94 (0.69-1.27)	0.696	1.19 (0.89-1.59)	0.244	1.01 (0.70-1.46)	0.952
Higher tertile (High SES)	1.00 (0.74-1.37)	0.951	1.50 (1.14-1.97)	0.004	0.81 (0.56-1.17)	0.269
Height, cm (cont)	1.00 (0.98-1.02)	0.760	0.98 (0.97-1.00)	0.111	0.98 (0.96-1.00)	0.207
Weight, kg						
1st quintile (≤68.4kg), ref	1.00		1.00		1.00	
2nd quintile (68.5-74.8 kg)	1.69 (0.97-2.95)	0.061	2.98 (1.78-4.99)	0.000	2.98 (1.69-5.27)	0.000
3rd quintile (74.9-80.6 kg)	2.23 (1.29-3.85)	0.004	4.65 (2.79-7.75)	0.000	3.34 (1.90-5.86)	0.000
4th quintile (80.7-87.8 kg)	2.68 (1.56-4.60)	0.000	5.09 (3.08-8.42)	0.000	4.53 (2.56-7.98)	0.000
5th quintile (87.9+ kg)	3.17 (1.88-5.35)	0.000	4.36 (2.58-7.36)	0.000	4.09 (2.26-7.40)	0.000
Exercise						
None, ref	1.00		1.00		1.00	
Non-vigorous exercise	1.33 (0.97-1.81)	0.078	1.04 (0.79-1.38)	0.763	1.27 (0.89-1.81)	0.191
Vigorous exercise	1.29 (0.91-1.82)	0.145	1.64 (1.19-2.24)	0.002	1.29 (0.82-2.03)	0.261
Years of smoking						
Never smoked, ref	1.00		1.00		1.00	
1st quartile (1-23 yrs)	1.06 (0.75-1.49)	0.756	0.88 (0.64-1.22)	0.453	0.89 (0.59-1.35)	0.587
2nd quartile (24-36 yrs)	0.79 (0.56-1.11)	0.177	0.76 (0.54-1.07)	0.123	1.10 (0.72-1.69)	0.653
3rd quartile (37-47 yrs)	0.52 (0.35-0.76)	0.001	0.65 (0.45-0.95)	0.024	1.11 (0.72-1.71)	0.637
4th quartile (48+ yrs)	0.49 (0.32-0.74)	0.001	0.58 (0.41-0.82)	0.002	0.51 (0.30-0.85)	0.009

[1] The Cox model in each age group represents a multivariable analysis that assesses the association of each covariate with TJR while controlling for all other covariates listed in table.

Abbreviations: TJR (total joint replacement); DC Index (Deyo Charlson Index); SEIFA (Socio Economic Index For Areas); SES (Socioeconomic Status)

Appendix 1: ICD-9 and ICD-10 codes used to detect primary total hip or total knee replacement

ICD version	Code	Description of procedure
ICD-9-CM	81.51	Total hip replacement
	81.54	Total knee replacement
ICD-10-AM*	49318-00	Total arthroplasty of hip, unilateral
	49319-00	Total arthroplasty of hip, bilateral
	49518-00	Total arthroplasty of knee, unilateral
	49519-00	Total arthroplasty of knee, bilateral
	49521-00	Total arthroplasty of knee with bone graft to femur, unilateral
	49521-01	Total arthroplasty of knee with bone graft to femur, bilateral
	49521-02	Total arthroplasty of knee with bone graft to tibia, unilateral
	49521-03	Total arthroplasty of knee with bone graft to tibia, bilateral
	49524-00	Total arthroplasty of knee with bone graft to femur and tibia, unilateral
	49524-01	Total arthroplasty of knee with bone graft to femur and tibia, bilateral
	49534-01	Total replacement arthroplasty of patellofemoral joint of knee

*The ICD-10 codes were based on those listed in the database

7.4 Additional comments: Reply to Letter-to-Editor

7.4 Preface

In response to the published manuscript presented in Chapter 7, Gill TK and Hill CL addressed a letter to the Editor of the journal *Arthritis & Rheumatism* arguing that the strong inverse dose-response relationship we found between duration of smoking and risk of undergoing elective total joint replacement may be confounded by socioeconomic factors. In response to an invitation from this journal, I submitted a reply, as written in section 7.4.2, which has been accepted for publication in *Arthritis & Rheumatism* (date of acceptance: 1 December, 2011).

7.4.1 Letter-to-Editor

The following section includes the Letter-to-Editor that Gill TK and Hill CL have submitted to *Arthritis & Rheumatism*. The Editor of this journal agreed to include Gill et al. document in my thesis (approval granted on 1 December, 2011).

Gill TK, Hill CL. Smoking, body weight, physical activity and risk of lower limb total joint replacement in a population-based cohort of men: comment on the article by Mnatzaganian et al. *Arthritis & Rheumatism* 2011; DOI 10.1002/art.34325. © 2011, American College of Rheumatology.

To the Editor:

We read with interest the article by Mnatzaganian et al (1), who reported that being overweight and reporting physical activity increased the risk of total joint replacement (TJR) but a strong inverse dose-response relationship of duration of smoking and TJR existed, although the mechanisms behind this were unclear. We acknowledge that the association between smoking and arthritis is unclear and the authors highlight that more research is

needed to understand the pathways for selection of patients for TJR, however we believe that the authors have not discussed other relevant issues that may have impacted on the number of TJRs.

Recently, Hui et al (2) demonstrated in a meta-analysis that the protective effect of smoking in OA which has been observed in epidemiological studies is likely to be false as a result of selection bias. Their results suggested that the use of a hospital setting was a source of study bias. Previous work has also demonstrated the willingness to consider TJA is a strong predictor of when a TJA is undertaken. Willingness has been shown to be associated with patient perceptions of the risks of TJA and the perception of the indications for a TJA (3). However when willingness is removed from the model, education level was the primary factor influencing undergoing a TJA (3). It has also been shown that those with lower education and/or income were less likely to have TJR and that there are racial and ethnic disparities in the receipt of a TJR (4,5). While these studies were undertaken in North America, it is also likely that similar conditions exist in Australia.

Variability in physicians relating to the indications for TJR has been shown to exist (6). While the authors highlighted a survey of orthopaedic surgeons which demonstrated that smoking did not influence the decision to conduct a joint replacement, it has been shown by Singh et al (7) that smoking at the time of elective TJR was associated with an increased level of postoperative complications. Thus initial referral of patients to orthopaedic surgeons may not occur, particularly if patients are known to be smokers. There is also evidence to suggest that appropriate candidates for joint surgery do not have the procedure done. This may be due to health system restraints such as waiting lists and access to surgical resources, or a lack of postoperative assistance and support (8). Smokers may be impacted by long waiting lists which would then limit the number of smokers undertaking a TJR.

The authors indicate that the data includes arthroplasties from both public and private hospitals in Australia. Data from the Australian Orthopaedic Association National Joint

Replacement Registry demonstrates that, despite the presence of universal health care in Australia, the majority (over 60%) of TJR are performed in private hospitals (requiring patients to have access to private health insurance (9). Generally, it is considered that those of higher socioeconomic status have access to private hospital care; these are also the patients with lower levels of co-morbidities and lower levels of smoking.

Smokers are more likely to be from lower socioeconomic groups (10) and these are also groups which have a lower level of health literacy (11). It may be that those who smoke are less willing to undertake a TJR and are impacted more strongly by factors highlighted by Hawker (12) such as sociodemographic factors, health beliefs, lack of community and family support, lack of resources and clinician characteristics.

Thus we would argue that there is not a direct dose-response relationship between smoking and TJR.

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12. Hawker GA. The quest for explanations for race/ethnic disparity in rates of use of total joint arthroplasty. J Rheumatol 2004;31;1683-1685.

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7.4.2 Reply to Letter-To-Editor

The following section includes the reply to Letter-to-Editor.

Statement of Authorship

Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Smoking, body weight, physical exercise, and risk of lower limb total joint replacement in a population-based cohort of men: reply to Letter to Editor. *Arthritis & Rheumatism* 2011; DOI 10.1002/art.34324. © 2011, American College of Rheumatology.

George Mnatzaganian (Candidate)

Designed the study, performed all analyses, interpreted the results, drafted the reply and acted as corresponding author.

Signed: Date: 21/12/2011

Philip Ryan

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 21-12-2011

Paul E Norman

Contributed to the acquisition of data, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 19/12/11

David C Davidson

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: _21/12/2011_

Janet E Hiller

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

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In Reply:

Gill and Hill argue that the strong inverse dose-response relationship we found between duration of smoking and risk of undergoing elective total joint replacement (TJR) may be confounded by socioeconomic factors. Although our cohort study did not account for the health beliefs of the 11,388 study participants or their willingness to undergo TJR, we nevertheless considered various socioeconomic and socio-demographic factors. These included level of education, marital status, country of birth (COB), operating hospital (insurance type) and socioeconomic status (SES) measured by the Socioeconomic Indices for Areas (SEIFA). Having TJR was not associated with either level of education (P=0.88) or marital status (P=0.34), whereas a gradient of increasing rates of TJR with decreasing socioeconomic disadvantage (measured by SEIFA) was seen (P=0.03). Similarly, men born in Australia / New Zealand, Europe and Americas were significantly more likely to undergo TJR compared with those born in Asia or Africa (P<0.00). However, after adjusting for age and comorbidities the association of TJR with COB became statistically insignificant. In the final model, SEIFA and insurance type were included as the measures of SES. (213) To assess for possible confounding, we also controlled for COB, level of education, and alcohol consumption and found similar results (Table 1). Of the 819 men who had elective TJR, 643 (78.5%) were operated in a private hospital while the remaining 176 men were treated in a public hospital. No statistically significant differences were observed in the characteristics of private and public patients in terms of patients' age, comorbidity, BMI, and type of TJR. However, patients treated in the public hospital were more likely to be socioeconomically disadvantaged and to smoke more years. In our analysis, these differences were taken into account.

In a publication in 2004, Hawker et al. (214) reported that the number of comorbidities was independently and inversely associated with willingness to undergo TJR (HR=0.74, 95% CI 0.61-0.89). In a later publication, these authors reported that patients' willingness to

undergo TJR was independently associated with the procedure. (215) However, their final multivariable model did not account for important risk factors including comorbidities, obesity, and smoking, and therefore residual confounding cannot be excluded.

The meta-analysis that Gill and Hill have cited included 8 cohort studies that assessed the association of smoking with osteoarthritis (OA). (216) However, these studies were heterogeneous in design. Five of the eight did not make proper distinction between past and never smokers and disregarded duration of smoking. Comparing current smokers with past and never smokers is not valid when the objective is to assess the association of duration of exposure to smoking with OA. Moreover, seven of the eight studies did not adjust for comorbidities and residual confounding cannot be excluded.

The studies that assessed the association between smoking and worse outcomes following TJR report conflicting findings. In another analysis, we assessed the association between smoking (duration or ever smoking) and risk of postoperative in-hospital complications with results similar to other studies, (217,218) in that we did not find any significant independent association. Lavernia et al. (218) found that smokers had more comorbidities, longer surgical times, and higher hospital charges with no difference in the proportion of complications following TJR. Similarly, we found that smoking was associated with increased comorbidity and when the latter was adjusted for, smoking ceased to be an independent risk factor for in-hospital complications. A possible explanation is that heavy smokers may, in general, be underrepresented in elderly patients who undergo elective TJR since duration of smoking is independently and inversely associated with risk of undergoing an elective TJR, thus the overall effect of smoking with adverse outcomes may become weakened and less apparent.

Controlling for age, comorbidity, weight, height, physical exercise and various socioeconomic factors, we have found a strong inverse dose-response relationship between duration of smoking and TJR. This was also observed when total knee and total hip

replacements were modelled separately. Our significant findings also persisted after accounting for the competing risk of death.

Mnatzaganian G, Ryan P, Norman PE, Davidson DC, and Hiller JE

Table

Table 1: Hazard ratios for undergoing an elective TJR: Cox multivariable regression[!]

Covariate	Hazard ratio (95% CI)	P value
Weight, kg		
First quintile (≤68.4 kg) (reference)	1.00	
Second quintile (68.5-74.8 kg)	2.60 (1.88 - 3.56)	0.000
Third quintile (74.9-80.6 kg)	3.17 (2.31 - 4.35)	0.000
Fourth quintile (80.7-87.8 kg)	4.12 (3.01 - 5.63)	0.000
Fifth quintile (≥87.9 kg)	4.27 (3.10 - 5.87)	0.000
Duration of smoking		
Never smoking (reference)	1.00	
First quintile (1-23 years)	1.04 (0.84 - 1.29)	0.720
Second quintile (24-36 years)	0.72 (0.58 - 0.90)	0.004
Third quintile (37-47 years)	0.70 (0.56 - 0.89)	0.003
Fourth quintile (≥48 years)	0.59 (0.46 - 0.75)	0.000
Physical exercise		
None (reference)	1.00	
Non-vigorous	1.14 (0.94 - 1.37)	0.184
Vigorous	1.27 (1.03 - 1.58)	0.028

[!] Also adjusted for age, Charlson comorbidity index, height, Socioeconomic Indices for Areas, level of education, country of birth, hospital type and alcohol consumption

Chapter 8

Total joint replacement in men: old age, obesity and in-hospital complications

8.1 Preface

This chapter contains the third manuscript contributing to this thesis. The paper has been accepted for publication in ***ANZ Journal of Surgery***. In manuscript 2 (see Chapter 7), I identified 819 men who had had an elective primary total joint replacement. The study described in this paper addresses the fourth objective of this thesis presented in Chapter 1.

The main objective of this study was:

1. To assess risks of in-hospital complications and 1-year and 5-year mortality following elective primary total joint replacement, focusing on the modifiable factor of body weight.

The specific objectives of the study were:

a) To describe rates of incident in-hospital complications following an elective TJR as recorded in the HMD during the index TJR-admission.

b) To classify the incident complications into major or minor.

c) To assess risk of developing a major incident complication following TJR after controlling for age, weight, height, Deyo-Charlson Co-morbidity Index, socio-economic status, duration of smoking or ever smoking, history of alcohol consumption, number of past hospitalizations, insurance payer type (public versus private hospitals), and type of TJR (THR or TKR).

d) To assess risk of dying 1 year and 5 years following an elective TJR after controlling for major or minor complications and the above listed covariates.

<u>Rationale of study objectives:</u>

Identification of patients who are at increased risk for developing postoperative complications and dying following TJR may assist hospitals in assessing case-mix, quality of care, as well as assist clinicians in selecting patients for surgery, and informing patients about their individual risk level.

8.2 Statement of Authorship

Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Total joint replacement in men: old age, obesity and in-hospital complications. *ANZ Journal of Surgery*, 2012; In press

George Mnatzaganian (Candidate)

Designed the study, performed all analyses, interpreted the results, drafted the reply and acted as corresponding author.

Signed: Date: 21/12/2011

Philip Ryan

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Janet E Hiller

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: _19/12/11_

8.3 Article

Abstract

Background: We assessed risks of incident in-hospital complications and 1-year and 5-year mortality following elective primary total joint replacement (TJR), focusing on obesity.

Methods: Data from a population-based cohort of 819 men who had had TJR were integrated with validated hospital morbidity data and mortality records. Complications recorded in the index admission were classified as major or minor by 13 independent orthopaedic surgeons.

Results: Of 819 men (mean age 76.3 (SD 4.5) years), 331 patients (40.4%) had an in-hospital complication from whom 155 (18.9%) had at least one major complication that was classified as potentially life threatening. Obesity and age were independently associated with increased risk of major complications. Compared with patients without complications, those with major complications experienced significantly greater mortality 1 year (5.8% versus 1.2%, P=0.001), and 5 years (16.8% versus 8.0%, P=0.002) following TJR. In Cox regressions, age, Charlson index, and major complications were independently associated with 1-year mortality. Age and Charlson index were also associated with 5-year mortality. Similarly, risk of dying within 5 years of TJR was higher among patients with class II obesity compared with patients with normal weight. The most frequently reported complications were those in the cardio-respiratory and general systems. Complications in the cardio-respiratory system significantly increased hazard of 1- and 5-year mortality.

Conclusion: The elderly and the obese are more likely to develop adverse outcomes following a primary TJR. Our findings may assist clinicians in better selecting elderly patients for surgery, and informing them about their individual level of risk.

Introduction

Total hip replacement (THR) and total knee replacement (TKR) are among the most common elective surgical procedures performed in developed countries. (3) The incidence of these procedures has risen substantially over recent years, reflecting the ageing population, and increases in the prevalence of risk factors such as obesity. Primary total joint replacement (TJR) is considered to be relatively safe with low rates of adverse outcomes. (3) However, there is increasing evidence that elderly patients may be at higher risk for postoperative complications and mortality following the elective procedure. (15,16,18) Besides old age, other independent risk factors for these adverse outcomes include male gender, (15,18) presence of co-morbidity, (15,18,95) and obesity. (7,19) Nonetheless, the reported association of some of these factors with an increased risk of an adverse outcome following TJR has not been consistent. Old age and presence of co-morbidity show the most consistent associations with postoperative complications and mortality (15,16,18,19,95) while the results for being overweight or obese have been the most inconsistent.(7,17,19,170,178,173) Some studies have reported higher rates of postoperative complications among the obese who undergo TJR including higher risk of systemic complications, (19) venous thromboembolic disease,(17) prolonged wound drainage and wound infection,(7) and dislocation,(7) while others did not find any significant increased risk of either short- (170) or long-term (173,178) complications. Inconsistencies in the findings of these and other studies may be attributed to various factors including relatively small sample sizes, differential selection of patients, and lack of, or insufficient, adjustment for the confounding effect of co-morbidity.(170,173,178)

This study integrated longitudinal clinical data from a large population-based cohort of men with validated hospital morbidity data (HMD) and mortality records. The linkage enabled us to retrieve for each participant any significant morbidity, as recorded in HMD, in the period 1970 through to 2007. In an earlier analysis,(213) we identified 819 men who had a primary elective total joint replacement. In this study, 1) we assessed the independent effect

of patient factors (body mass index, socioeconomic status, duration of smoking) and type of TJR on risk of developing an in-hospital complication after adjusting for age and Charlson co-morbidity index, and 2) we evaluated whether these in-hospital complications were independently associated with risk of all-cause short-term (1 year) and long-term (5-year) mortality following the elective procedure.

Methods

[For a more detailed description of Methods, refer to Supplementary Material.]

The study population was drawn from the Health In Men Study (HIMS) which arose from a randomised population-based trial of ultrasound screening for abdominal aortic aneurysm in men aged 65-83 living in Perth, Western Australia (WA).(46) All 12,203 study participants were followed from baseline screening (1996-9) until they experienced their first TJR or died or were right censored at the end of follow-up (March, 2007).(213) Electronic record linkage with WA hospital morbidity data was used to identify admissions to hospital for TJR. All acute in-hospital complications were ascertained from diagnoses that were recorded (for the first time for each patient) in HMD during the index TJR-admission. Thirteen experienced orthopaedic surgeons, who were blinded to the outcome of these conditions, classified the detected conditions into major or minor. A complication that was potentially life-threatening was defined as major, while a complication that did not threaten life but did demand medical intervention was defined as minor as reported by Parvizi et al.(23) Inter-rater agreement was calculated using Kappa coefficient and the final decision to classify a condition into major or minor followed a majority rule.

For mortality, all men having TJR were followed for a mean time of 3.2 (SD 2.6) years or till censoring at the end of follow-up (March 2007). All-cause mortality was ascertained through linkage with WA Health Department mortality records. The occurrence of a major in-hospital complication was modelled using multivariable logistic regression and mortality following TJR was modelled using Cox proportional hazards regression. These multivariable models

were fitted to the data as a function of age, Charlson Co-morbidity Index (CCI),(105) body mass index defined as weight over height squared, years of smoking, socioeconomic status based on Socio-Economic Index For Areas (SEIFA),(207) insurance payer type (public versus private hospitals), and type of TJR (THR or TKR). The mortality models were also adjusted for in-hospital complications. The classification criteria for being overweight or obese were defined according to the World Health Organization.(219)

The proportional hazard assumption of the Cox models was tested using Schoenfeld residuals. All analyses were performed using Stata statistical program (version 11, Stata-Corp.).

Results

Patient characteristics

Of the 819 men (mean age 76.3 (SD 4.6) years) who had had an elective TJR, 498 (60.8%) had a TKR and 321 (39.2%) had a THR. No statistically significant differences were observed in the characteristics of patients who had a TKR or a THR. Of all men, only 147 (17.9%) had a normal weight (body mass index [BMI] 18.5-24.9), while 462 (56.4%) were overweight (BMI 25-29.9), 174 (21.3%) were obese class I (BMI 30-34.9), and 35 (4.3%) were obese class II (BMI 35-40). A single patient had a BMI of $41kg/m^2$ and he was classified with those with class II obesity. Compared with patients with normal weight, patients with class II obesity were significantly younger (P=0.001), belonged to a lower socioeconomic status (P=0.034), and smoked more years (P=0.036) (Table 1).

In-hospital complications

All complications reported during index TJR-admission and classified into major or minor are shown in Appendix 1 in *Supplementary Material*. The overall inter-rater agreement among the surgeons was moderate. A total of 331 patients (40.4%) had an in-hospital complication from whom 155 (18.9%) had at least one major complication that was classified as potentially life threatening. The proportion of complications in patients undergoing a THR was not significantly different from that in patients having a TKR. Furthermore, no statistical

differences were observed between the characteristics of patients with and without a minor complication. However, patients with a major complication were more likely to be older and to be overweight or obese compared with patients without a major complication. Controlling for the factors listed in Table 2, age and obesity continued to be independently associated with increased risk of major complications.

Risk of developing a major complication was significantly high in patients with class I and class II obesity. Compared to those with normal weight, patients with class I obesity were 72% more likely to develop a major complication that was classified as life threatening (adjusted-OR=1.72, 95% CI: 1.0-2.9), whereas this risk was even higher among patients with class II obesity who were 2.5 times more likely to develop such a complication (adjusted-OR=2.5, 95% CI: 1.0-6.0).

The most frequent complications were those in the cardio-respiratory and the general systems and these were more frequently reported in older patients ($\geq$ 77 years, the 50th percentile of study population).

Mortality following TJR

The in-hospital, 1-year, and 5-year crude mortality rates for all patients were 0.5%, 2.4%, and 10.5%, respectively. Compared with patients without complications, those with a major complication experienced significantly greater mortality 1 year (5.8% versus 1.2%, P=0.001), and 5 years (16.8% versus 8.0%, P=0.002) following the procedure (Table 3). Age and higher Charlson co-morbidity indices (CCI) (Figure 1) were also associated with an increased hazard of death. In multivariable models, increasing age, high CCI on admission, and a presence of a major in-hospital complication significantly increased the hazard of 1-year mortality. Age and Charlson co-morbidity index continued to be significantly and independently associated with 5-year mortality. Similarly, risk of dying within 5 years of the procedure was significantly higher among patients with class II obesity compared with patients with normal weight.

To clarify which of the in-hospital complications were associated with increased mortality, we further adjusted for these conditions by body system (instead of major and minor complications) and found that complications in the cardio-respiratory system significantly increased hazard of death in the first year (adjusted-HR= 3.0, 95% CI:1.0-8.8). The complications in the cardio-respiratory system also continued to be independently associated with increased hazard of 5-year mortality (adjusted-HR= 1.7, 95% CI: 1.1-2.7).

The proportional hazards assumption was not violated by any of the covariates in either Cox mortality model.

Discussion

This study, involving a population-based cohort of older men, has found a strong association between body mass index and risk of complications classified as potentially life threatening. Obesity and age were the only independent risk factors for developing a major in-hospital complication. In addition, to our knowledge, this study is the first to report increased risk of 5-year postoperative mortality in class II obese patients who undergo an elective TJR.

Obesity is a major risk factor for undergoing TJR,(213) and compared with those with normal weight, similar to other reports,(7,17,19,23,220,221) we have found that the overweight or obese who undergo this procedure are more likely to develop postoperative complications. Miric et al.(220) assessed postoperative complications in patients undergoing TKR and found higher rates of complications in patients with a BMI above 35 kg/m^2, 38% compared with 25% for patients with BMI of 35 kg/m^2 or lower (P=0.002). Another retrospective study reported high risk of both in-hospital and 1-year complications in the "super-obese" (BMI $\geq$ 45kg/m^2) following TJR.(221) Mantilla et al.(17) found that increased body mass index was associated with a higher likelihood of clinically significant pulmonary embolism and deep vein thrombosis in patients undergoing primary TJR. We further found that patients with class II obesity were significantly more likely to die within the first 5 years following the elective procedure. The mechanism by which morbid obesity may be associated

with increased risk of postoperative death is not clear. This increased mortality may be explained by any late complications (220) that have not been accounted for in this analysis. However, there may be other explanations. Our study retrieved co-morbid conditions from the HMD and since this dataset was not originally formed for the purpose of health research, some co-morbid conditions may have been under-reported. The association of obesity with increased co-morbidity is well documented,(222) and if co-morbidity were underestimated, the risk of death among the morbidly obese could have been overestimated. However, our validation analysis showed good sensitivities and positive predictive values for serious co-morbidities,(210) and there is no evidence to suggest that underreporting of co-morbidities could be disproportionately higher among more obese patients. The lower Charlson indices in the obese patients in our sample (Table 1) may be explained by selection prior to surgery as supported by an expert opinion survey that indicated that obesity and presence of co-morbidities were major factors that could sway the decision against TJR.(101) Fearing worse outcomes in the morbidly obese, the surgeons may have selected the obese with less co-morbidities and who were significantly younger than patients with normal weight as supported by our study. Another explanation is the possibility of confounding by factors not accounted for in this analysis.

Postoperative complications following primary TJR are also not uncommon in the elderly,(16,18) and similar to numerous reports we have found relatively high rates of in-hospital complications in our cohort. Our study results are in accordance with reports that assessed these complications among elderly populations. A retrospective study that assessed perioperative complications in 10,244 patients following TJR found significantly higher frequencies of incident myocardial infarction, pulmonary embolism, deep vein thrombosis, and death in the older patients compared to younger patients in the study.(16) A limitation of studies that report a restricted set of postoperative complications following TJR (7,16,18) is their underestimation of the overall rates of all complications. A prospective study that

reported all incident complications (in-hospital or six weeks following a primary TJR) in 1,636 patients found that 6.4% and 1.0% developed a major systemic or local complication, respectively and 21.6% and 6.1% had a minor systemic or local complication, respectively.(23) Similar to Parvizi et al., we also assessed all reported complications. Our higher incidence of complications may be associated with our much older cohort (mean age 76.2 (SD 4.6) years) compared to patients in Parvizi et al. study whose male population had a mean age of 62 years.

The association of in-hospital complications with postoperative mortality in patients who undergo TJR has been previously reported.(166) Using large US national in-patient data, Memtsoudis et al.(166) showed that major in-hospital complications were the strongest independent risk factors for in-hospital mortality in patients undergoing a TJR. The authors reported that the occurrence of a pulmonary embolism or a cerebrovascular complication increased the odds for death by approximately 40-fold. To our knowledge, our study is the first to assess the associations of these in-hospital complications with 1- and 5-year mortality following primary TJR. We found that major complications following this procedure, and mainly complications in the cardio-respiratory system, independently increased hazard of both short-term and long-term mortality, although the effect of these complications was much stronger on short-term mortality.

Strengths of this study include its population-based provenance, the longitudinal design and the clinical data that were integrated with validated HMD. However, the study has some limitations. HMD may not differentiate complications from co-existing conditions. Our method of retrieving (from the TJR-index admission) only the diagnoses that were reported for the first time for every patient may have misclassified some complications as co-morbidities. We had no access to patients' charts and therefore we could not validate these conditions against these charts and we could not account for the severity of the recorded conditions. Moreover, classification of a complication as major or minor may differ among

studies. Finally, our cohort included only men, and the results may not be generalized for women. Similarly, the study population was relatively old and our findings may not be generalizable to other younger patient populations.

In conclusion, our study found high rates of complications and subsequent mortality in elderly obese men who undergo an elective TJR. The frequencies of cardio-respiratory in-hospital complications and death were higher in patients aged 77 years or more and also in the more obese patients. Given the ageing populations and the increasing prevalence of obesity, TJR procedures are now considered and performed in older patients, in the morbidly obese, and in those with significant co-morbidities.(192) Identification of patients who are at increased risk for developing adverse outcomes following TJR may assist hospitals in assessing casemix, as well as this may help clinicians in informing them about their individual risk level.

Acknowledgements

Tables and Figures

Table 1: Patient characteristics by body mass index (based on weight and height measured by a nurse)

Characteristics	Body mass index (kg/m^2)			
	Normal weight	**Overweight**	**Obese class I**	**Obese class II**[#]
	18.5-24.9	25-24.9	30-34.9	35-40
	N=147 (17.9%)	N=462 (56.4%)	N=174 (21.3%)	N=36 (4.4%)
Age, mean (SD)	77.2 (4.6)	76.3 (4.6)*	75.6 (4.3)*	74.4 (4.7)*
Charlson on admission, mean (SD)	1.3 (1.9)	0.9 (1.4)*	1.2 (1.6)	1.1 (1.5)
Socioeconomic status, %				
Low tertile (low SES)	26.5	28.4	35.1	44.4
Middle tertile	29.3	32.9	32.2	33.3
Higher tertile (SES)	44.2	38.7	32.7	22.2*
Years of smoking, mean (SD)	19.3 (20.2)	21.9 (19.5)	22.9 (19.8)	27.2 (19.7)*
Type of joint replacement, %				
Total knee replacement	53.7	61.9	62.1	69.4
Total hip replacement	46.3	38.1	37.9	30.6

A single patient had a BMI of 41kg/m^2 and was classified as "Obese class II"

* 0.001< P-value <0.05 (comparison with BMI 18.5-24.9)

Abbreviation: SES (socio-economic status as defined according to the distribution of the Socio-Economic Index Areas (SEIFA)

Table 2: Odds ratios for developing a major complication following an elective total joint replacement in men: multivariable logistic regression

Covariate	OR (95% CI)	P value
Age, continuous	**1.04 (1.00 - 1.08)**	**0.046**
Charlson Index on admission, continuous	1.05 (0.95 - 1.17)	0.330
Socioeconomic status (SES)[#]		
Lower tertile (low SES), [reference]	1.00	
Middle tertile	0.93 (0.60 - 1.44)	0.741
Higher tertile (high SES)	0.77 (0.50 - 1.21)	0.265
Years of smoking, continuous	1.00 (0.99 - 1.01)	0.247
Body mass index **kg/m^2**		
Normal weight 18.5-24.9 [reference]	1.00	
Overweight 25.0-29.9	1.57 (0.92 - 2.66)	0.099
Obese class I 30.0-34.9	**1.72 (1.04 - 2.88)**	**0.036**
Obese class II 35.0-40	**2.47 (1.02 - 6.03)**	**0.046**
Hospital type		
Private [reference]	1.00	
Public	1.10 (0.72 - 1.69)	0.649
Type of Joint replacement		
Total hip replacement [reference]	1.00	
Total knee replacement	1.16 (0.80 - 1.67)	0.413

[#] SES (socio-economic status as defined according to the distribution of the Socio Economic Index For Areas (SEIFA)

Table 3: Mortality (%) one and five years following elective total joint replacement in men by presence of an in-hospital complication

| Mortality	Age tertiles[#]	Presence of an in-hospital complication		
		None	**Minor**	**Major**
One year mortality	66-74 yrs	0.0	0.0	2.3*
	75-78 yrs	2.1	1.8	3.4
	79 yrs or more	2.3	4.9	11.3*
	All ages	**1.2**	**2.8**	**5.8***
Five year mortality	66-74 yrs	6.4	4.9	9.3
	75-78 yrs	4.9	11.1	15.3*
	79 yrs or more	14.1	16.1	24.5
	All ages	**8.0**	**11.9**	**16.8***

* $0.001 < P$ value < 0.05 (comparison with patients without any complication); [#] The categories are based on the distribution of age in cohort

Table 4: Hazard ratios and Harrell's C statistics for dying 1 year and 5 years following an elective total joint replacement (TJR) in men: multivariable Cox proportional hazards regressions

Covariates		One year from TJR		Five years from TJR	
		HR (95% CI)	P value	HR (95% CI)	P value
Age, continuous		**1.2 (1.1 - 1.4)**	**<0.001**	**1.1 (1.1 - 1.2)**	**<0.001**
Charlson Index on admission, continuous		**1.5 (1.3 - 1.8)**	**<0.001**	**1.3 (1.2 - 1.5)**	**<0.001**
In-hospital complication					
None, [reference]		1.0		1.0	
Minor		2.6 (0.7 - 9.6)	0.168	1.4 (0.8 - 2.3)	0.262
Major		**6.0 (1.8 - 19.7)**	**0.003**	1.6 (0.9 - 2.7)	0.060
Socioeconomic status (SES)[#]					
Lower tertile (low SES), [reference]		1.0		1.0	
Middle tertile		2.2 (0.6 - 7.6)	0.230	1.0 (0.6 - 1.7)	0.916
Higher tertile (high SES)		1.7 (0.5 - 5.9)	0.426	0.9 (0.5 - 1.5)	0.635
Years of smoking, continuous		1.0 (0.9 - 1.0)	0.733	1.0 (0.9 - 1.0)	0.715
Body mass index kg/m^2					
Normal weight	18.5-24.9 [reference]	1.0		1.0	
Overweight	25.0-29.9	0.5 (0.2 - 1.7)	0.284	1.1 (0.6 - 2.1)	0.658
Obese class I	30.0-34.9	0.9 (0.2 - 3.2)	0.842	1.2 (0.6 - 2.5)	0.577
Obese class II	35.0-40	0.6 (0.1 - 6.7)	0.702	**2.7 (1.1 - 6.6)**	**0.022**
Hospital type					
Private [reference]		1.0		1.0	
Public		1.0 (0.3 - 3.2)	0.941	1.5 (0.9 - 2.4)	0.109
Type of Joint replacement					
Total hip replacement [reference]		1.0		1.0	
Total knee replacement		1.1 (0.4 - 2.9)	0.853	1.4 (0.9 - 2.1)	0.186
Harrell's C statistic		**0.90**		**0.75**	

[#] SES (socio-economic status as defined according to the distribution of the Socio Economic Index For Areas (SEIFA)

Figure 1: Kaplan Meier 5-year survival estimates from elective total joint replacement in men by Charlson Co-morbidity Index (CCI) on admission (log rank tests: CCI=1-2 vs. CCI=0, P=0.02; CI=≥3 vs. CCI=0, P<0.001).
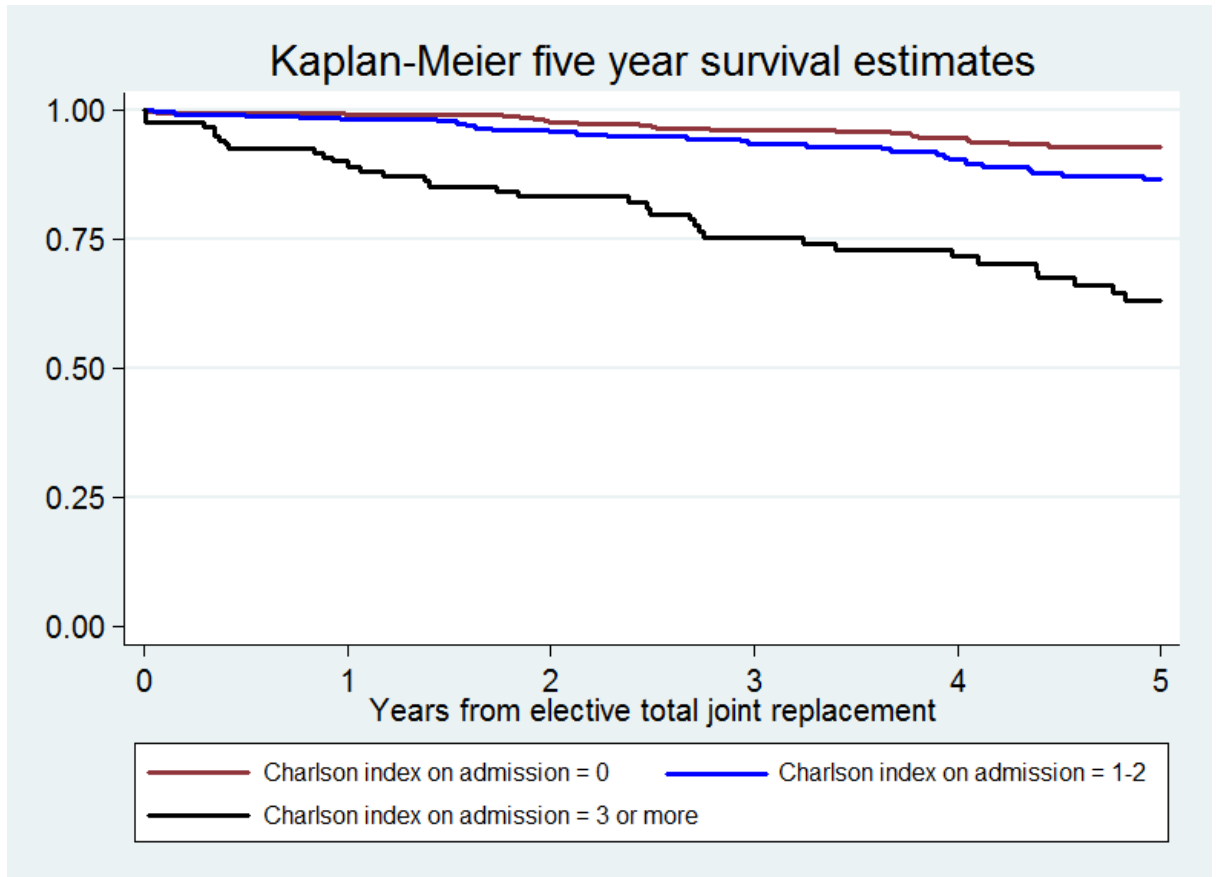
8.4 Supplementary Material as submitted to ANZ J Surg

Methods

Data sources and study population

The study population was drawn from the Health In Men Study (HIMS) which arose from a randomized population-based trial of ultrasound screening for abdominal aortic aneurysm in men aged 65-83 living in Perth, Western Australia (WA).(46) A total of 41,000 men was identified via the WA Electoral Roll and was randomized into invited and control groups of equal size. Of the 19,352 men who were invited, 12,203 attended the baseline screening in 1996-9. At baseline, the participants provided detailed health and other information including a comprehensive smoking history. In addition, study nurses recorded the individuals' weight and height. During 2001-04, the surviving men of the 12,203 initial participants were invited to a follow-up study during which they were weighed a second time. All men were followed from baseline screening until they experienced their first TJR or died or were right censored at the end of follow-up (March, 2007).(213) Electronic record linkage with WA hospital morbidity data was used to identify admissions to hospital for TJR.

In-hospital complications

For the 819 men who had had an elective primary TJR, all incident in-hospital complications (both medical and surgical) were ascertained from diagnoses that were recorded in HMD during the index TJR-admission (Appendix III). If a certain condition was recorded in previous hospital admissions (other than the index admission), it was regarded as a co-morbidity rather than a complication - a method that increased the specificity of the diagnosis rather than its sensitivity. Thirteen experienced orthopaedic surgeons were approached by mail and were asked to classify the detected conditions into major or minor. All 13 surgeons, who were blinded to the outcome of the complications, participated in the survey and provided complete responses. The surgeons were provided with a basic guide to classification: a complication that was potentially life-threatening was defined as major, while

a complication that did not threaten life but did demand medical intervention was defined as minor as reported by Parvizi et al.(23) Inter-rater agreement was calculated using kappa coefficient and the final decision to classify a condition into major or minor followed a majority rule.

The HMD system is a core part of the WA Linked Data System (47) and includes demographic, diagnostic, and procedural information on all patients discharged from all public and private hospitals in WA. A validation study of the HMD showed good to acceptable sensitivities and positive predictive values for major morbidities and major operations.(210)

Body weight

Available data did not permit us to control for weight change over time and therefore we used the body weight of the participants measured at baseline. Time to TJR from baseline (in 1996-1999) was relatively short (mean 4.6 (SD 2.7) years) and so we assumed that weight measured at baseline remained constant up till surgery. To test this assumption, we compared the weights measured at baseline with the corresponding weights measured 5 years later in HIMS follow-up survey in 2001-4. Of the 819 men who had had TJR, 461 (56.3%) participated in both baseline and follow-up HIMS surveys. The mean weight of these men at baseline was 82.6 (SD 10.8) kg, and their corresponding mean weight 5 years later was 82.4 (SD 11.4) kg; paired t-test P=0.454. Agreement between the weights is also demonstrated in the Bland-Altman plot (Figure 1) which supports our assumption of relatively constant weight over time in this cohort of older men. (223)

Statistical analysis

For in-hospital complications, all men were followed till hospital discharge, while for mortality they were followed for a mean time of 3.2 (SD 2.6) years or till censoring at the end of follow-up (March 2007). All-cause mortality was ascertained through linkage with WA Health Department mortality records (WA Heath Department was the custodians of these

data). The Kaplan-Meier method was used to estimate the probabilities of survival. Differences in the Kaplan Meier estimates among the various groups were evaluated by the log rank test. The occurrence of a major in-hospital complication was modelled using a multivariable logistic regression, while mortality following TJR was modelled using Cox proportional hazards regression. These multivariable models were fitted to the data as a function of age, Charlson Co-morbidity Index (CCI),(105) weight, height, years of smoking, socioeconomic status based on Socio-Economic Index For Areas (SEIFA),(207) insurance payer type (public versus private hospitals), and type of TJR (THR or TKR). SEIFA indices indicate relative social disadvantage of populations living in different geographic areas with low scores reflecting disadvantage. The mortality models were also adjusted for in-hospital complications. The proportional hazard assumption of the Cox models was tested using Schoenfeld residuals.

The CCI which was used to adjust for co-morbidity was based on all reported conditions in admissions that preceded the index TJR-admission. The co-morbidity index was built using the original Charlson weights,(103) and the corresponding International Classification of Diseases, 9th Revision, ICD-9-CM (Clinical Modification) algorithms were used as described in the authors' original publication.(105) We further used an ICD-10-AM (Australian Modification) adaptation of the CCI as developed and validated using population-based hospital data from Australia.(110) The ICD codes used to detect primary total hip or total knee replacement were checked by a professional clinical coder.(213)

All analyses were performed using Stata statistical program (version 11, Stata-Corp.).

<u>Ethics</u>

Ethical approval was obtained from the Human Research Ethics Committees of Health Department of Western Australia and The University of Adelaide prior to commencement of study. All analyses used de-identified data.

Figure 1: Bland-Altman comparison of weight (in kilograms) at baseline (1996-9) with weight (in kilograms) at follow-up (2001-4) [N=461]
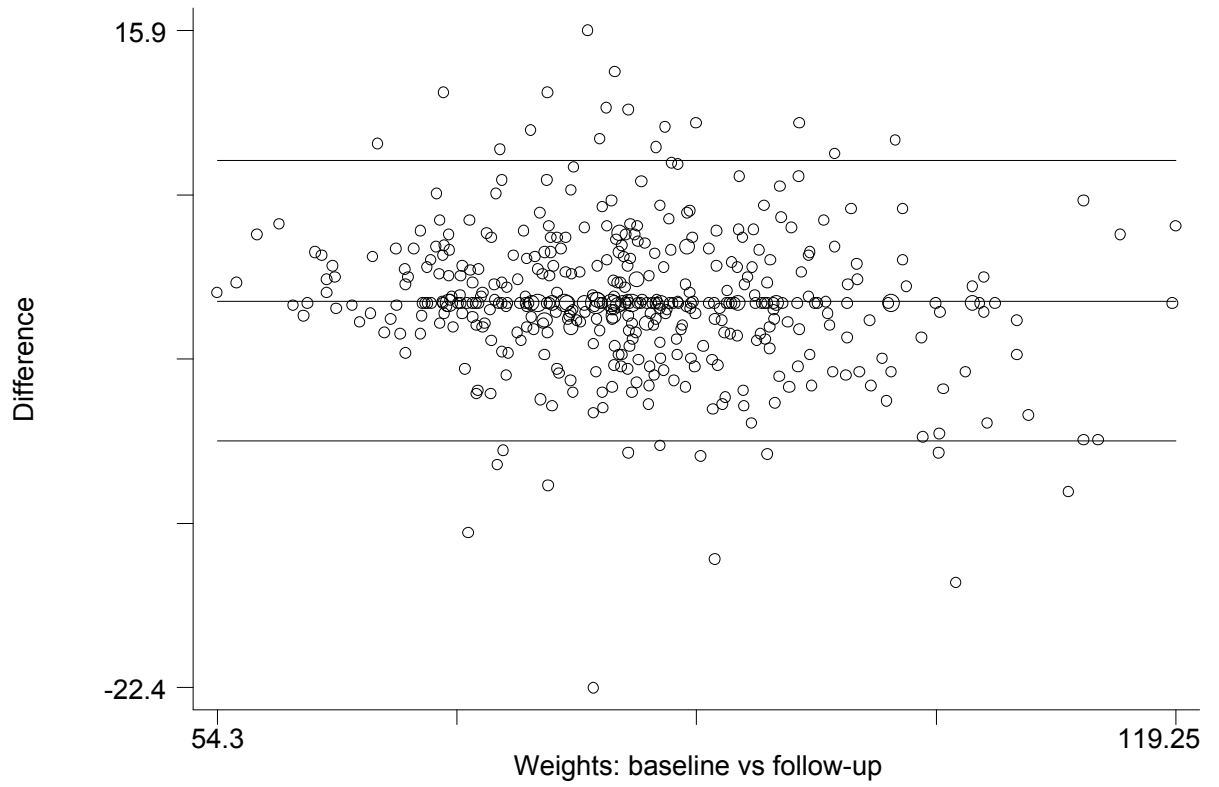
Appendix 1: List of in-hospital complications[1] following an elective total joint replacement (as reported in hospital morbidity data during index admission) by classification[2] into major or minor (N=819)

In-hospital major complications	N	%	In-hospital minor complications	N	%
Cardiovascular system			**Cardiovascular system**		
Acute myocardial infarction	6	0.7	Abnormal ECG	1	0.1
Arterial embolism	1	0.1	Accidental puncture of blood vessel	1	0.1
Cardio respiratory arrest	4	0.5	Atrial fibrillation and other arrhythmias	37	4.5
Angina pectoris / unstable angina	9	1.1	Bradycardia	7	0.8
Complete heart block	1	0.1	Hypovolemia	12	1.5
Congestive heart failure	10	1.2	Iatrogenic hypotension	16	1.9
Post operative shock	1	0.1	Syncope	6	0.7
Supra-ventricular / ventricular tachycardia	6	0.7	Tachycardia	5	0.6
Thromboemboli	17	2.1			
Respiratory system			**Respiratory system**		
Acute pulmonary oedema	3	0.4	Acute laryngitis and tracheitis	1	0.1
Adult respiratory distress syndrome	5	0.6	Atelectasis	20	2.4
Pneumonia / aspiration pneumonia	7	0.8	Dyspnoea	1	0.1
Pulmonary embolism	11	1.3	Pleural effusion	3	0.4
			Respiratory tract bleeding	3	0.4
			Unspecified lower respiratory tract infection	10	1.2
Gastrointestinal system			**Gastrointestinal system**		
Abdominal obstruction	13	1.6	Abnormal liver function test	8	1.0
Acute gastrointestinal bleeding / ulcer	8	1.0	Acute colitis / diarrhoea	6	0.5
Acute hepatic failure	1	0.1	Anal abscess	1	0.1
			Candida esophagitis	1	0.1
			Nausea / vomiting	12	1.5
			Paralytic ileus	4	0.5
Renal system			**Renal system**		
Acute renal failure	13	1.6	Retention of urine / obstruction of bladder	40	4.9
Oliguria / anuria	15	1.8	Urinary tract infection / Orchitis	15	1.8
Musculoskeletal system / skin			**Musculoskeletal system / skin**		
Dehiscence of surgical wound	2	0.2	Cellulitis	4	0.5
Haemorrhage complicating a procedure	19	2.3	Decubitus ulcer	7	0.8
Hip abscess / septic arthritis	2	0.2	Synovial cyst	2	0.2
Mechanical complications due to prosthesis (e.g. fracture of bone)	5	0.6			
Nervous system			**Nervous system**		
			Agitation, restlessness, delirium, confusion	41	5.0
Acute CVA / TIA	3	0.4	Transient paralysis of limb	1	0.1
Convulsions	1	0.1	Transient psychosis , hallucination	14	1.7
Semi coma	1	0.1			
General			**General**		
Bacteraemia	12	1.5	Abnormal coagulation profile	5	0.6
Diabetic hypoglycaemic shock	2	0.2	Acute reaction to medicine	1	0.1
Post operative infection / sepsis	18	2.2	Anaemia	66	8.1
			Electrolyte imbalance / fluid overload	17	2.1
			Generalized oedema / anasarca	2	0.2

[1] Patients may have more than one complication. [2] The classification was based on the expert opinion of 13 orthopaedic surgeons who were blinded to the outcome of the diagnoses. Abbreviations: CVA= cerebrovascular accident; ECG = electrocardiogram; TIA = transient ischemic attack

Chapter 9

Use of routine hospital morbidity data together with weight and height of patients to predict in-hospital complications following elective total joint replacement

9.1 Preface

Obesity is an important risk factor for major adverse health outcomes, particularly among surgical patients; nonetheless, the recording of weight and height of patients is not mandatory in any HMD system. In manuscript 3 (see Chapter 8), I reported that actual weight of patients was independently associated with risk of major in-hospital complications, showing a dose response effect. The study described in this paper addresses objective 8 b of this thesis presented in Chapter 1. The paper is currently under review in the journal ***BMC Health Services Research.***

The main objective of this study was:

1. To assess the role of obesity in predicting major in-hospital complications in men who undergo an elective TJR.

The specific objectives of the study were:

a) To assess the validity of the diagnosis of obesity in WA HMD.

b) To evaluate whether the augmentation of WA HMD with actual weight and height (both measured by clinical staff) could improve its ability to predict major in-hospital complications following TJR.

<u>Rationale of study objectives</u>

Study findings may provide evidence of the importance of routine collection of actual weight and height in any HMD system.

9.2 Statement of Authorship

Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Use of routine hospital morbidity data together with weight and height of patients to predict in-hospital complications following elective total joint replacement. Under review in *BMC Health Services Research*.

George Mnatzaganian (Candidate)

Designed the study, performed all analyses, interpreted the results, drafted the reply and acted as corresponding author.

Signed: Date: 21/12/2011

Philip Ryan

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 21-12-2011

Paul E Norman

Contributed to the acquisition of data, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 19/12/11

David C Davidson

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: _21/12/2011_

Janet E Hiller

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: _19/12/11_

9.3 Article

Background

Routinely collected administrative data such as hospital morbidity data (HMD) are progressively more used in studying clinical outcomes among patients undergoing total joint replacement (TJR). These data are readily available and cover large populations. However, since these databases were not originally collected for the purpose of health research, a rigorous assessment of their quality is required. We assessed the accuracy of the diagnosis of obesity in HMD and evaluated whether the augmentation of HMD with actual weight and height of patients could improve its ability to predict major in-hospital complications following total joint replacement in men.

Methods

The electronic records of 857 participants in the Health In Men Study (HIMS) who had had TJR were linked with Western Australia HMD. HMD-recorded diagnosis of obesity was validated using the actual weight and height obtained from HIMS. In-hospital major complications were modeled using multivariable logistic regressions that either included the weight and height or HMD-recorded obesity. Model discrimination was calculated using area under ROC curve.

Results

The HMD were unlikely to identify obese patients. Only 64 patients (7.5%) were recorded in HMD as obese although 216 (25.2%) were obese [BMI: $\geq$30kg/m^2] (sensitivity: 0.21, positive predictive value: 0.70). Overall 174 patients (20.3%) developed an in-hospital major complication which was significantly higher in the overweight and obese comparing with patients with normal weight. HMD-recorded obesity was not independently associated with major complications, whereas a dose-response relationship between weight and these complications was observed. Using the actual weight and height of the participants instead of

HMD-recorded diagnosis of obesity improved model discrimination by 8.7%, with areas under ROC curve of: 0.69, 95% CI:0.64-0.73 for the model with HMD-recorded obesity compared with 0.75, 95% CI:0.70-0.79 for the model with weight and height, P<0.001.

Conclusion

Body weight is an important risk factor for in-hospital complications in patients undergoing TJR. HMD systems do not include weight and height as variables whose recording is mandatory. Augmenting HMD with patients' weight and height may improve prediction of major complications following TJR. Our study suggests making these variables mandatory in any hospital morbidity data system.

Background

Hospital morbidity data (HMD), or administrative claims data, are increasingly being used to study important clinical outcomes including in-hospital mortality, (129,130) re-admissions, (130,131) and post-operative complications. (62) These routinely collected data are both readily available and cover large populations. However, in comparison with clinical data (usually retrieved from individual patient chart review) these data may lack detail on co-morbidities, severity scores, and timing of diagnoses. (60,65,68) Moreover, administrative datasets that have restricted coding spaces are often limited to a minimum set of data. (59) In addition, HMD do not routinely include important risk factors such as weight and detailed smoking history. Nonetheless, owing to their many advantages, researchers have tried to improve these data, validate them (81,210) and augment them with additional information in order to use them in health care research. (132-135)

Total joint replacement (TJR) is among the most common elective surgical procedures performed in developed countries. (3) The incidence of this procedure has risen over recent years mainly because of the ageing population and increases in the prevalence of risk factors such as obesity. (1,5) It has been estimated that the demand for total joint replacement will continue to grow. (3) Although TJR is considered to be relatively safe with low rates of adverse outcomes, (14) the procedure is nevertheless associated with short- and long-term complications. (15,18) These adverse outcomes are more frequent in older patients, particularly men, (15) and the obese (19,20) and a thorough understanding of potential complications in this group is important for the delivery of the highest quality medical care. To study these outcomes, researchers have used existing large databases including joint registries and hospital morbidity data. The latter have frequently been used to characterize the rates of immediate postoperative outcomes of both primary (15,18,19) and revision total joint replacement. (15,44) Methods to improve existing data sources, such as hospital morbidity data, to predict complications following TJR have never been documented.

In an earlier analysis, we have shown that WA HMD are more likely to identify major co-morbidities and major operations with relatively high sensitivities and positive predictive values compared with co-morbidities of a less serious nature. (210) In this current study we assessed the accuracy and recording of the diagnosis of obesity in this HMD system, and we evaluated whether its augmentation with actual weight and height (both measured by clinical staff) could improve its ability to predict major in-hospital complications following TJR.

Methods

Data sources and study population

The study integrated longitudinal data from a large population-based cohort with WA HMD. The study population is drawn from the Health In Men Study (HIMS) which arose from a randomized trial of ultrasound screening for abdominal aortic aneurysm in men aged 65-83 living in Perth, Western Australia. (46) Of the 19,352 men who were invited, 12,203 attended the baseline screening in 1996-9. At baseline study nurses recorded the participants' weight and height. During 2001-04 the surviving men of the 12,203 initial participants were invited to a follow-up survey and 5,571 subjects agreed to participate and were weighed a second time. Electronic record linkage was used to identify admissions to hospital (hospital morbidity data) for TJR (Appendix 1) and post-operative complications in the target population. Of the total 12,203 men, 857 (7.0%) had a total joint replacement after baseline screening and these constituted the study population of this analysis.

The HMD system is a core part of the WA Linked Data System (47) and includes demographic, diagnostic, and procedural information on all patients discharged from all public and private hospitals in WA. The HMD allow the inclusion of up to 21 diagnoses and 11 procedure codes for each hospitalization. In an earlier validation study we have shown that the sensitivity and positive predictive value of the HMD-recorded TJR were both 0.92 and the specificity was 0.98. (210)

Statistical analysis

Validity analysis

The diagnosis of obesity was retrieved from the HMD using the following codes: the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) "278.0" code and the ICD-10-AM (Australian Modification) "E66" code. Validation of this HMD-recorded diagnosis of obesity was performed using the body mass index (BMI) that was calculated from the actual weight and height of the participants (obtained from HIMS baseline survey). Those who had a BMI of 30 kg/m^2 or more were considered to be obese and this was held as the "Criterion Standard". The sensitivity and positive predictive value (PPV) were based on a 2x2 table (having a recorded diagnosis of obesity in HMD yes/no versus BMI $\geq$ 30kg/m^2 yes/no).

Weight measured at baseline and follow-up

Available data did not permit us to account for weight change over time and therefore we used body weight of the participants that was measured at baseline. Time to TJR was not long (mean 4.6 (SD 2.7) years) and, therefore, we assumed that weight measured at baseline (1996-9) remained constant up till surgery. To test this assumption, we compared the weights measured at baseline with the corresponding weights measured 5 years later in HIMS follow-up survey in 2001-4. Of all men who had had TJR, 56.3% participated in both baseline and follow-up HIMS surveys. The mean weight of these men at baseline was 82.6 (SD 10.8) kg, and their corresponding mean weight 5 years later was 82.4 (SD 11.4) kg; paired t-test P=0.454 which supported our assumption of relatively constant weight over time in this elderly cohort of men.

Classification of complications

All 857 men who had a TJR were followed till hospital discharge. All conditions recorded in HMD were retrieved from index-TJR admission. If a certain condition was recorded in previous hospital admissions (other than the index admission), it was regarded as a co-morbidity rather than a complication - a method that increased the specificity of the diagnosis

rather than its sensitivity. The detected complications were further clinically classified as major or minor based on a survey of 13 experienced orthopedic surgeons. The surgeons were approached by mail and were asked to classify each of the 60 reported conditions into major or minor and all 13 participated and provided complete responses. The surgeons were blinded to the outcome of theses diagnoses. The only information that was provided was the overall mean age and gender of the study population. A complication that was potentially life-threatening was defined as major, while a complication that did not threaten life but did demand medical intervention was defined as minor. (23) Inter-rater agreement was calculated using kappa coefficient and the final decision to classify a condition into major or minor followed a majority rule.

Risk of major complications

The risk of an in-hospital major complication was assessed using multivariable logistic regressions that were fitted to the data as a function of age, Deyo-Charlson Co-morbidity Index (DCCI), (105) fracture of lower limb, obesity diagnosis as recorded in HMD (a dichotomous variable of yes or no), years of smoking, socioeconomic status based on Socio-Economic Index For Areas (SEIFA), (207) number of past hospitalizations, insurance payer type (public versus private hospitals), type of TJR (total hip replacement [THR] or total knee replacement [TKR]) and presence of a minor complication. SEIFA indices indicate relative social disadvantage of populations living in different geographic areas with low scores reflecting disadvantage. A second model was fitted to the same variables as the first model, except for HMD-recorded obesity that was substituted with actual weight and height of study participants (obtained from baseline HIMS study). In the model, weight was categorized into quintiles according to its distribution in the cohort while height was introduced as a continuous variable. Model discrimination for each of the models was calculated using area under ROC curve. All analyses were performed using Stata statistical program (version 11, Stata-Corp.).

The co-morbidities that compose the Deyo-Charlson Co-morbidity Index were detected from HMD using the ICD-9-CM and the ICD-10-AM codes. (109,110) The original Charlson weights (103) were applied to calculate the co-morbidity index.

Ethical approval was obtained from the Human Research Ethics Committees of Health Department of Western Australia (October 12, 2009; AHEC EC00422) and The University of Adelaide (August 10, 2009; H-106-2009) prior to commencement of the study. All analyses used de-identified data.

Results

Validity of HMD-recorded obesity

Of the 857 men (mean age at surgery 76.3 [SD 4.6] years) who had had a TJR, 488 (56.9%) were overweight [BMI: $25-29.9 kg/m^2$] and 216 (25.2%) were obese [BMI $\geq 30 kg/m^2$], although only 64 men (7.5%) were recorded as obese in HMD. The sensitivity of HMD-recorded diagnosis of obesity was 0.21 and its corresponding positive predictive value was 0.70. Compared with patients with normal weight (based on weight and height from HIMS survey), the obese [BMI $\geq 30 kg/m^2$] were significantly younger (P<0.001) and belonged to a lower social economic status (P=0.030) (Table 1). However, these differences in patients' characteristics were not apparent when patients were stratified according to HMD-recorded diagnosis of obesity. The main differences in the characteristics of those with and without an HMD-recorded diagnosis of obesity were the significantly higher Deyo-Charlson co-morbidity indices and higher duration of smoking among those with a recorded diagnosis of obesity.

In-hospital complications

The inter-rater agreement was moderate with kappa coefficient of 0.49. (224) A total of 174 patients (20.3%) developed an in-hospital complication that was classified by the assessors as major (Appendix 2). An increased risk of these complications was detected both in patients with an HMD-recorded diagnosis of obesity and in patients whose actual BMI was 25 or more (Table 2). However, when stratified by Deyo-Charlson index categories, the differences in

these rates between those with and without an HMD-recorded obesity became statistically insignificant. This was not apparent when the stratification was done by the actual BMI categories.

Adjusting for age, Deyo-Charlson co-morbidity index, socio-economic status, duration of smoking, type of joint replacement, fracture of lower limb, number of past hospital admissions, type of hospital and presence of a minor complication, no statistically significant associations were found between HMD-recorded obesity with risk of major complications following TJR as shown in model 1 in Table 3, whereas, a strong dose-response effect between weight and risk of major complications was observed (model 2 in Table 3). A test for trend in the log odds-ratios across weight quintiles yielded P=0.004. Using the actual weight and height of the participants instead of HMD-recorded diagnosis of obesity improved model discrimination by 8.7%, with areas under ROC curve of: 0.69, 95% CI 0.64-0.73 in model 1 compared with 0.75, 95% CI 0.70-0.79 in model 2, P<0.001 (Figure 1).

Discussion

In a cohort of men who had had a primary TJR, we found that actual weight independently predicted major in-hospital complications following the procedure showing a strong dose-response effect, whereas a record of obesity diagnosis in hospital morbidity data did not. Adding actual weight and height to a HMD system makes the latter a better prognostic tool for this major health outcome.

Monitoring systems often use hospital morbidity data to predict, at the time of hospital admission, each patient's probability of developing an adverse outcome if average care were given. (129) Differences in outcome among patients may or may not indicate differences in the quality of care that the patients received because these differences may be attributed to many factors including differences in patients characteristics, but also differences in data quality. (60,65,68) The power of any model to predict adverse outcomes depends on the extent and accuracy of the data on each patient's clinical condition when care began. (60) Since the HMD

were not originally collected for the purpose of research, many researchers have tried to improve and augment them with additional minimal information in order to use them in health care research and to make them a better predictive tool. (132-135) In a retrospective study of 46,769 patients in 30 acute care hospitals, Pine et al. demonstrated how the addition of laboratory data to hospital administrative datasets could provide accurate predictions of inpatient mortality from acute myocardial infarction, cerebrovascular accident, congestive heart failure or pneumonia with significant improvements in models' discrimination. (132) Other studies have shown how models using claims data to predict mortality following cardiac bypass surgery can be improved with the addition of minimal clinical variables. (134,135) Our study focused on TJR - a high-volume orthopedic procedure in which postoperative complications are not uncommon in elderly patients and the obese. (16,19,20) These postoperative complications have been increasingly used as quality indicators to monitor, evaluate and improve the quality of care administered to patients who undergo this procedure. (224) In this study we have linked minimal information including actual weight and height with HMD and have shown that HMD alone produce inferior predictive models when compared with those that also account for the actual weight and height of patients. Adding weight and height to HMD significantly improved model discrimination for major complications by 8.7%. Identification of patients who are at increased risk for developing postoperative complications following TJR may assist hospitals in assessing casemix, quality of care and resource allocation, as well as this may assist clinicians in selecting patients for surgery, and informing patients about their individual risk level.

In an earlier analysis we reported that major comorbidities (such as myocardial infarction and cancer) and major operations (such as TJR and coronary artery bypass graft surgery) are more likely to be recorded in the HMD than conditions of less serious nature such as dyslipedemia. (210) This current analysis supports our previous findings. We have found that obesity is under-reported in HMD and may be selectively recorded for a more severly ill patients.

Therefore, use of HMD-recorded obesity diagnosis within an HMD may lead to biased assessment of associations.

Strengths of this study include its population-based provenance, the longitudinal design and the clinical data that were integrated with validated HMD. For each participant, any significant morbidity or health-related outcome was retrieved from the linked data in the period 1970 through to 2007 and this enabled us to better account for patient co-morbidities. However, the study has some limitations. HMD may not differentiate complications from co-existing conditions. (69) Our method of retrieving (from the TJR-index admission) only the diagnoses that were reported for the first time for every patient may have misclassified some diagnoses as co-morbidity. Furthermore, HMD systems may be disadvantaged by under-coding or over-coding. We had no access to patients' charts and therefore, we could not validate these conditions against these charts. Moreover, classification of a complication as major or minor may differ among studies and our available data did not allow us to assess risk of individual conditions. Model discrimination was done, however, model calibration was not performed. This study also did not account for other surgical and intervention-related factors (such as type of anesthesia) that may also be associated with postoperative complications.

Conclusions

Body weight is an important risk factor for numerous health outcomes and there is increasing evidence to support a correlation between obesity and adverse outcomes in patients undergoing a TJR. (19,20) Nevertheless, HMD systems do not include weight and height of patients as variables whose recording is mandatory. The lack of validity of the HMD-recorded diagnosis of obesity limits its use in health research. The inclusion of actual weight and height in the HMD would make the HMD a better prognostic tool to assess major complications among patients undergoing TJR. Since the standard hospital practice is to measure the weight and height of patients, (225) our study suggests making actual weight and height mandatory variables in any hospital morbidity data system.

Acknowledgements

Tables and Figure

Table 1: Characteristics of patients by obesity diagnosis as recorded in hospital morbidity data and by body mass index based on actual weight and height measured by nurse

Patient characteristic	Diagnosis of obesity as recorded in HMD[1]		Body mass index calculated from weight and height measured by nurses from HIMS survey[2]		
	No obesity diagnosis N=793 (92.5%)	With obesity diagnosis N=64 (7.5%)	BMI 18-24.9 N=153 (17.9%)	BMI 25-29.9 N=488 (56.9%)	BMI $\geq$ 30 N=216 (25.2%)
Age, mean (SD)	76.3 (4.6)	75.3 (4.3)	77.1 (4.8)	76.4 (4.6)	75.4 (4.4)!!
DCCI, mean (SD)	1.2 (1.7)	2.3 (2.0)!	1.4 (2.0)	1.2 (1.6)	1.4 (1.7)
SES, % Low Middle High	30.1% 31.5% 38.3%	26.6% 39.1% 34.4%	26.1% 30.1% 43.8%	28.3% 32.4% 39.3%	36.1% 32.9% 31.0%!
Yrs of smoking, mean (SD)	21.3 (19.8)	28.4 (19.2)!	19.3 (20.2)	21.9 (19.6)	23.4 (19.8)

! 0.001<p<0.05; !! p<0.001
[1] Patients with an obesity diagnosis in HMD were compared with those who had no such diagnosis in HMD.
[2] Patients with BMI 25-29.9 or BMI $\geq$ 30 were compared with those with BMI 18-24.9
Abbreviations: DCCI (Deyo-Charlson co-morbidity index); SES (socioeconomic status according to distribution of Socio Economic indices For Areas (SEFA); Yrs (years))

Table 2: Rates of major in-hospital complications by HMD-recorded obesity and body mass index based on actual weight and height of patients by Charlson co-morbidity index categories

Deyo-Charlson Index categories	Diagnosis of obesity as recorded in HMD[1]		Body mass index calculated from weight and height measured by nurses from HIMS survey[2]		
	No obesity diagnosis N=793	With obesity diagnosis N=64	BMI 18-24.9 N=153	BMI 25-29.9 N=488	BMI $\geq$ 30 N=216
0 n=384	13.7%	33.3%	16.9%	13.0%	17.0%
1-2 n=323	23.4%	32.1%	9.8%	27.8%!	24.7%!
$\geq$ 3 n=150	25.4%	33.3%	6.5%	32.5%!	31.0%!
All n=857	19.2%	33.9%!	12.4%	21.7%!	22.7%!

! 0.001<p<0.05
[1] Patients with an obesity diagnosis in HMD were compared with those who had no such diagnosis in HMD.
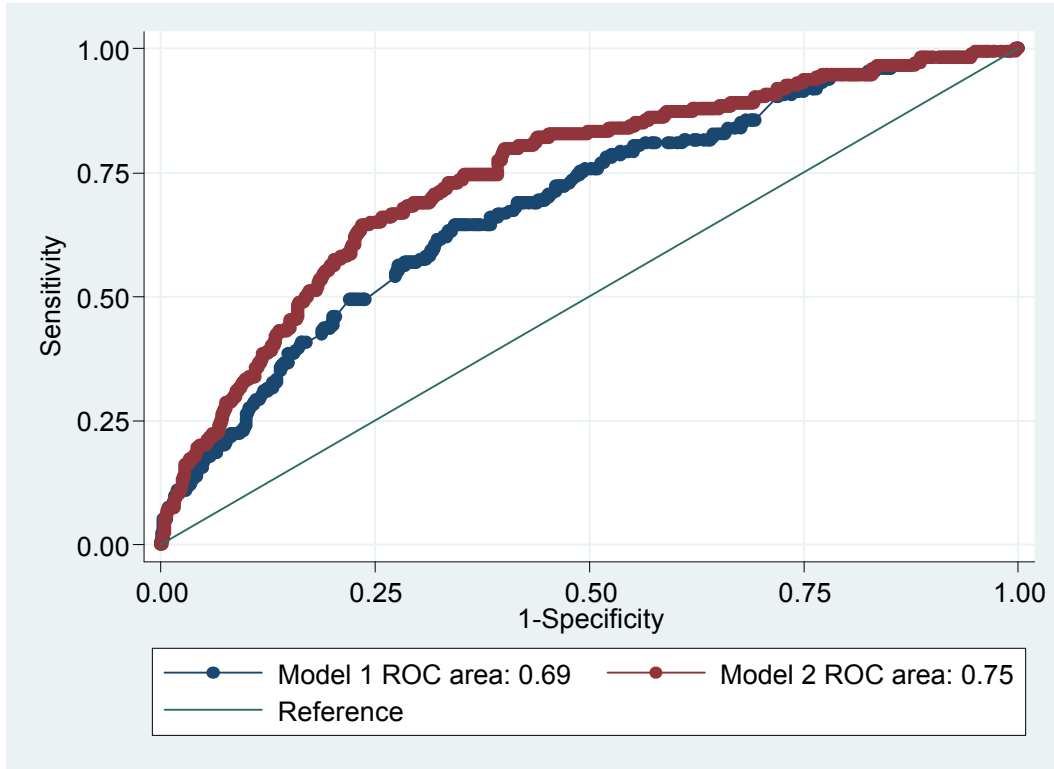[2] Patients with BMI 25-29.9 or BMI $\geq$ 30 were compared with those with BMI 18-24.9

Table 3: Risk of major in-hospital complication following primary TJR: multivariable logistic regressions using either HMD-recorded obesity (model 1) or actual body weight and height (model 2)

	Multivariable analysis Model 1		Multivariable analysis Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
Deyo-Charlson Index	1.10 (1.00 - 1.21)	0.041	1.11 (1.00 - 1.22)	0.040
Obesity as recorded in HMD	1.64 (0.92 - 2.94)	0.100	-	-
Weight quintiles, kg	-	-		
1st quintile: $\leq$ 73.2 (ref)			1.00	
2nd quintile: 73.3-79.6			1.23 (0.67 - 2.26)	0.509
3rd quintile: 79.7-84.4			1.68 (0.91 - 3.09)	0.099
4th quintile: 84.5-91.8			1.87 (1.01 - 3.45)	0.047
5th quintile: $\geq$ 91.9			2.33 (1.23 - 4.41)	0.009
Height	-	-	0.99 (0.96 - 1.02)	0.400
Years of smoking	1.01 (0.99 - 1.02)	0.095	1.01 (0.99 - 1.02)	0.126
Fracture of lower limb				
No	1.00		1.00	
Yes	2.42 (1.18 - 4.93)	0.015	2.40 (1.16 - 4.97)	0.018
Minor in-hospital complication				
No	1.00		1.00	
Yes	2.86 (2.01 - 4.07)	0.000	2.96 (2.45- 7.14)	0.000
Area under ROC curve:	0.69		0.75	

The models also controlled for age, socioeconomic status, type of replacement, private or public hospital, and number of past hospitalizations.

Figure 1: Areas under receiver operating characteristic (ROC) curves of multivariable logistic models that included HMD-recorded diagnosis of obesity (model 1) or actual weight and height of patients (model 2).

Appendix 1: ICD-9 and ICD-10 codes used to detect primary total hip or total knee replacement

ICD version	Code	Description of procedure
ICD-9-CM	81.51	Total hip replacement
	81.54	Total knee replacement
ICD-10-AM*	49318-00	Total arthroplasty of hip, unilateral
	49319-00	Total arthroplasty of hip, bilateral
	49518-00	Total arthroplasty of knee, unilateral
	49519-00	Total arthroplasty of knee, bilateral
	49521-00	Total arthroplasty of knee with bone graft to femur, unilateral
	49521-01	Total arthroplasty of knee with bone graft to femur, bilateral
	49521-02	Total arthroplasty of knee with bone graft to tibia, unilateral
	49521-03	Total arthroplasty of knee with bone graft to tibia, bilateral
	49524-00	Total arthroplasty of knee with bone graft to femur and tibia, unilateral
	49524-01	Total arthroplasty of knee with bone graft to femur and tibia, bilateral
	49534-01	Total replacement arthroplasty of patellofemoral joint of knee

*The ICD-10 codes were based on those listed in the database

9.4 Additional comments

Minimal information added to HMD to better predict primary TJR

This section includes additional analyses that have not been sent to a peer-reviewed journal. Here I assessed whether the augmentation of HMD with actual weight and height of patients and their self-reported duration of smoking could improve the ability of HMD to predict risk of undergoing primary TJR. This analysis addresses objective 8 a of this thesis presented in Chapter 1.

Methods:

Unlike other studies in this thesis, this study followed a nested case-control design. Men who were hospitalized for TJR (cases) were randomly matched to up to three controls hospitalized for reasons other than TJR by age categories at baseline (age categories in years: 65-69, 70-74, 75-79, 80+), high or low socioeconomic status (SES) (above or below the 50th percentile of the distribution of Socio-Economic Index For Areas (SEIFA)), and calendar year of hospitalization. Both cases and controls had similar follow-up times from baseline screening to index admission. Total joint replacement was modelled using multivariable conditional logistic regression adjusting for Deyo-Charlson Co-morbidity Index, fracture of lower limb, recorded diagnosis of arthritis or osteoarthritis, obesity, smoking, and private or public hospital - all derived from the hospital morbidity data. I estimated a second model (the full model) that also included actual weight, height, and self-reported years of smoking as obtained from the HIMS survey. The log likelihood was used to indicate the fit of both models and the likelihood ratio test was used to evaluate which model fits the data better (the reduced model based only on HMD or the full model containing HMD together with minimal additional information). I used Stata 11 software and the procedure "sttocc" to construct a nested case-control study from the cohort. For each case, SES- and age-matched controls are

chosen randomly from those members of the cohort who are at risk at the failure time of the case.

Results:

A total of 857 men underwent primary TJR following baseline screening. Of these, 38 (4.4%) had their procedure following a fracture of the lower limb. All 857 men were randomly matched to 2,246 controls. The cases were similar to their controls in terms of age, socioeconomic status and follow-up time from baseline screening till index hospitalization (Table 1, Figure 1).

Table 1: Characteristics of cases and controls by the matching variables: nested-case-control study, mean (SD)

	Cases (N=857)		Controls (N= 2,246)		P value
Age at baseline	71.6	(4.2)	71.7	(3.9)	0.905
SEIFA[1]	1034.0	(84.4)	1029.2	(92.8)	0.179
Follow up (days)[2]	1679.7	(976.3)	1697.9	(968.7)	0.640

[1] Socio Economic Index For Areas
[2] Follow up from baseline screening till index hospital admission

A total of 524 men had a BMI of 30 kg/m^2 and more, and of these, only 142 (27.1%) were recorded in the HMD as obese. Patients with BMI of $\geq$30kg/m^2 who had a recorded diagnosis of obesity in the HMD were sicker and heavier than those with similar BMI levels but without a record of obesity (Table 2). The mean [SD] of Charlson Co-morbidity Index was significantly higher for obese patients who had a record of obesity (4.1 [SD 3.3]) compared to those without a record of obesity (2.4 [SD 2.7], P<0.001) or non-obese patients (2.7 [SD 2.7], P<0.001). Similarly, recording smoking in the HMD was significantly associated with severity of co-morbidity. Smoking patients who had a record of smoking in the HMD had a mean [SD]

Charlson Co-morbidity Index of 4.2 [SD 3.0] compared to 2.5 [SD 2.6], P<0.001, among

smoking patients who were not recorded as smokers in HMD.

Figure 1: Maximum and minimum differences in days of follow up between cases and
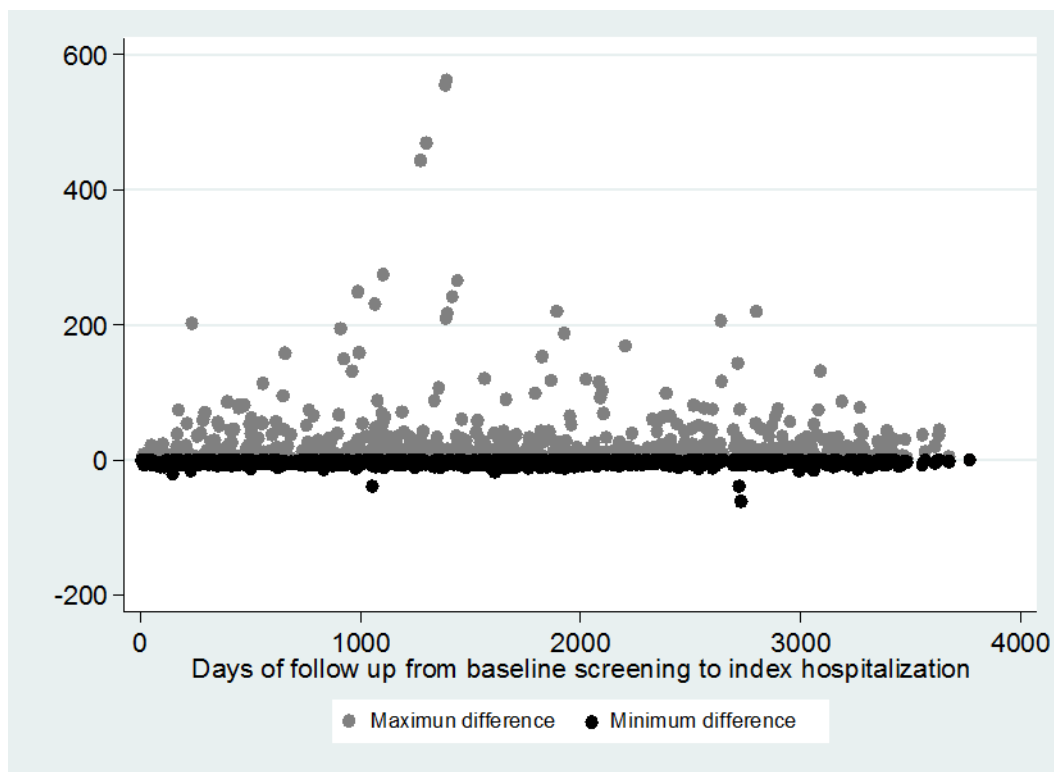their randomly selected controls

Table 2: Characteristics of men with BMI 30+ (known from HIMS survey) who were and were not recorded as obese in the hospital morbidity data (HMD), mean (SD)

	BMI[1] 30+ Recorded as obese in the HMD N=142		BMI[1] 30+ Not recorded as obese in the HMD N=382		*P* value
Weight[1], (kg)	99.5	(12.9)	93.4	(9.1)	0.000
Height[1], (meters)	170.7	(7.4)	170.4	(6.7)	0.606
Charlson Index	4.1	(3.3)	2.4	(2.7)	0.000
Age	71.3	(4.0)	71.5	(4.0)	0.538
SEIFA[2]	1007.6	(86.5)	1021.2	(92.9)	0.131

[1] BMI was calculated based on the actual weight and height obtained from HIMS survey
[2] Socio Economic Index For Areas

No significant associations were found between either HMD-recorded obesity or HMD-recorded smoking with risk of TJR as shown in model 1 in Table 3. Augmenting the HMD with weight, height, and years of smoking significantly improved the model fit when predicting TJR (likelihood ratio P<0.000). In the full model (model 2 Table 3), both weight and years of smoking were significantly associated with risk of TJR as reported in manuscript number 2 in this thesis. No multi co-linearity was observed between HMD-recorded obesity and weight or HMD-recorded smoking with years of smoking.

Table 3: Risk of total joint replacement based on the hospital morbidity data (HMD) with and without additional data: multivariable conditional logistic regression[1]

	HMD alone (reduced model)		HMD with additional data (full model)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
HMD-recorded arthritis /OA	2.85 (2.22 - 3.64)	0.000	2.64 (2.05 - 3.40)	0.000
Fracture of lower limb	1.05 (0.63 - 1.76)	0.845	1.16 (0.68 - 1.98)	0.588
HMD-recorded Charlson Index	0.58 (0.54 - 0.62)	0.000	0.59 (0.55 - 0.63)	0.000
HMD-recorded obesity	0.93 (0.61 - 1.40)	0.719	0.60 (0.38 - 1.04)	0.065
HMD-recorded smoking	0.94 (0.69 - 1.29)	0.719	1.12 (0.80 - 1.57)	0.499
Weight	-	-	1.04 (1.02 - 1.05)	0.000
Height	-	-	0.99 (0.97 - 1.01)	0.217
Self-reported years of smoking	-	-	0.99 (0.98 - 0.99)	0.019
Likelihood ratio test (comparing model 1 to 2): LR chi2=44.3, *P* < 0.000				

[1] The models were also adjusted to the hospital sector (private or public)
All HMD-defined variables were based on all hospital admissions that preceded index hospitalization (admission to perform TJR for the cases or a randomly chosen admission for the controls)
Abbreviations: OA:osteoarthritis

Discussion and Conclusion:

This study has shown that hospital morbidity data alone produce inferior predictive models when compared with those that also include weight, height, and patient-reported years of smoking history. Both obesity and smoking status are under-reported in the HMD and these diagnoses are mainly recorded for a more severely ill subset of patients and so use of these data within an HMD may lead to biased assessment of associations. Both weight and smoking are important risk factors for various health outcomes. This study suggests that including weight, height, and years of smoking history may make the HMD a better tool for research, enabling the researcher to assess risk factors for TJR without the need for linking extra data on these variables from other sources.

Chapter 10

Length of stay in hospital and all-cause readmission following elective total joint replacement in elderly men

10.1 Preface

This chapter contains the fifth manuscript contributing to this thesis. The paper has been published in ***Orthopedic Research and Reviews.*** In manuscript 2 (see Chapter 7), I identified 819 men who had had an elective primary total joint replacement. The study described in this paper addresses objectives 5 to 7 of this thesis presented in Chapter 1.

The main objectives of this study were:

2. To assess risks of prolonged stay in hospital (LOS) and all-cause readmission following elective primary TJR.

3. To assess the association of LOS with readmission and mortality following TJR.

4. To assess the association of readmission following TJR with postoperative mortality.

The specific objectives of this study were:

a. To assess the independent effect of patient factors (age, body weight, socioeconomic status, duration of smoking, insurance type) and clinical factors (presence of co-morbidity, in-hospital postoperative complications, type of TJR) on LOS and all-cause 90-day, 1-year, and 2-year readmission following elective TJR.

b. To determine if LOS was independently associated with all-cause readmission

c. To assess the associations of LOS and readmission with 5-year mortality following this procedure.

<u>Rationale of study objectives:</u>

Identification of patients who are at increased risk for increased consumption of hospital resources including longer stay in hospital and higher short-term readmission may assist hospitals in assessing case-mix, discharge policy, and resource allocation.

10.2 Statement of Authorship

Mnatzaganian G, Ryan P, Norman PE, Davidson DC, Hiller JE. Length of stay in hospital and all-cause readmission following elective total joint replacement in elderly men. *Orthopedic Research and Reviews*. 2012; 4: 43-51.

George Mnatzaganian (Candidate)

Designed the study, performed all analyses, interpreted the results, drafted the reply and acted as corresponding author.

Signed: Date: 21/12/2011

Philip Ryan

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 21-12-2011

Paul E Norman

Contributed to the acquisition of data, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: 19/12/11

David C Davidson

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: _21/12/2011_

Janet E Hiller

Contributed to the design of the study and interpretation of the results, and reviewed the reply. I give consent for George Mnatzaganian to present this paper towards examination for the Doctor of Philosophy.

Signed: Date: _19/12/11_

Mnatzaganian, G., Ryan, P., Norman, P.E., Davidson, D.C. & Hiller, J.E. (2012) Length of stay in hospital and all-cause readmission following elective total joint replacement in elderly men. *Orthopedic Research and Reviews, v. 2012 (4), pp. 43-51.*

Chapter 11

Conclusions and implications

The studies outlined in this thesis used hospital morbidity data (HMD) and mortality records that were linked to minimal clinical data including actual weight and height of 12,203 elderly male study participants and their self-reported duration of smoking and physical activity to assess risks of undergoing primary total joint replacement and postoperative short- and long-term adverse outcomes. The study demonstrates how record linkage improves the predictive power of these routinely collected HMD and stresses the importance of their potential utility in medical outcome research.

11.1 Significance of thesis

Using routinely collected hospital morbidity data to identify patients who are at increased risk for developing in-hospital complications, staying longer in hospital, returning to hospital and dying following elective primary TJR may assist hospitals in assessing case-mix, quality of care and resource allocation, as well as inform clinicians in the selection of appropriate elderly male patients for surgery, and in informing them about their individual level of risk as they undertake this procedure.

11.2 Main findings

This thesis reports the following main findings, linked to the questions posed in Chapter 1:

HMD as a research tool

1. In an elderly population undergoing total joint replacement, HMD-based co-morbidity scores perform well in predicting future morbidity and mortality.

2. HMD-based co-morbidity scores provide significant improvement on age adjustment when predicting postoperative mortality in old men who undergo TJR.

3. In predicting in-hospital complications following TJR, HMD alone produce inferior predictive models than those that also account for the actual weight and height of patients. The inclusion of actual weight and height in the HMD makes the HMD a better prognostic tool to assess major complications among patients undergoing TJR.

4. Both age and HMD-based co-morbidity scores are not strong predictors of all-cause short-term readmission following elective TJR.

5. Co-morbidities diagnosed at different points in time have different associations with the risk of future morbidity or mortality. Repeated HMD-recorded episodes of myocardial infarctions and cerebrovascular accidents (CVA) or transient ischemic attacks (TIA) are positively associated with increased risk of 5-year mortality, showing a dose-response effect.

Risk of undergoing an elective TJR

1. A dose-response relationship between both weight and smoking, and risk of elective TJR was observed. Being overweight independently increased the risk of TJR, while smoking lowered the risk.

2. Reporting vigorous exercise increased risk of TJR.

3. Men coming from disadvantaged socioeconomic backgrounds were less likely to undergo elective TJR.

Major outcomes following elective TJR

1. Postoperative complications following elective TJR are not uncommon in elderly men. Of the 819 men who had had elective TJR, 331 (40.4%) had an incident in-hospital complication and of these, 155 had at least one major complication.

2. Compared with patients without complications, those with any complication experienced significantly greater mortality 1 year and 5 years following the procedure.

3. Obesity was associated with worse outcomes following TJR. Compared with patients with normal weight, the obese were more likely to develop in-hospital major complications, to stay longer in hospital and to be readmitted. Morbidly obese patients were also at more risk to die 5 years following the procedure compared to those with normal weight.

4. Patients undergoing total knee replacement experienced worse outcomes compared with those who had total hip replacement. Length of stay and subsequent readmission were significantly higher among those with TKR.

5. Patients coming from socioeconomic disadvantaged backgrounds were more likely to return to hospital 1 and 2 years following the procedure.

6. All-cause 90-day and 1-year readmission following elective TJR is a major risk marker of long term mortality.

11.3 Topics for discussion

The following section discusses the major topics covered in this thesis starting with the importance of accounting for co-morbidity in observational studies conducted with elderly populations.

11.3.1 Co-morbidity

As the general population ages and obesity becomes more prevalent, the proportion of patients presenting for elective total joint replacement (TJR) will increase. (1-3) The association of age and obesity with increased co-morbidity is well documented (239) and, as a result, surgeons are more likely to confront patients with co-morbid conditions. A study that reviewed hospital discharge, outpatient and primary care patient-files of a random sample of 1,217,103 Americans aged 65 years and older found that 82.0% of the subjects had one or more chronic conditions, while 65.0% had multiple chronic conditions. (240) A case-control

study assessed the presence of co-morbidity in patients with osteoarthritis (OA) matched 11,375 individuals who had consulted general practitioners for OA in 60 sites in England and Wales during a one-year study period with controls without OA. After adjusting for age, sex, and social class, patients who consulted for OA had higher levels of co-morbidity than controls (OR 2.35; 99% CI: 2.16 to 2.55). (241) Some studies have also indicated that patients with OA may have more risk factors for cardiovascular disease, including hypertension, high cholesterol levels, respiratory disease, renal impairment and diabetes than others without OA. (242,243) In the studies contributing to this thesis, TJR was considered a surrogate indicator of severe osteoarthritis, however, OA status was not directly ascertained among study participants, and therefore it was not possible to validate the above cited studies.

The lack of randomisation inherent in observational epidemiological studies presents an important need to account for differences in patients' underlying health status. Co-morbidity, which is one dimension of health status, has long been recognised as a potential confounder in such studies and there is increasing evidence that presence of co-morbidity is independently associated with worse adverse outcomes following TJR including longer hospital stays, higher hospital costs, and higher rates of postoperative complications, readmission and mortality. (15-19,89) For studies that use hospital morbidity data, the primary source of co-morbidity data comprises the diagnosis code fields in which the reason for the hospitalization, as well as any accompanying conditions that required attention, are recorded. Hence, researchers have developed coding algorithms that suit administrative data to account for patients' co-morbidity. (103-111) Among these methods, Charlson co-morbidity index (CCI), together with its many adaptations, is the most widely method used in administrative datasets to measure and control for the effects of co-morbid illness.

Advantages of using a co-morbidity index

Although information may be lost when a single score such as CCI is used to reflect the presence and seriousness of various co-morbidities, using a single index combining

multiple conditions has several advantages over the use of individual conditions. In statistical models, a single summary score enables researchers to adjust for patient co-morbidities with only one variable thus simplifying the process of model building as the number of covariates decreases significantly and this in turn may enhance statistical efficiency. (102,117) Fitting a statistical model to the data as a function of every single co-morbid condition together with other study covariates may result in model over-fitting. (244) Over-fitting generally occurs when a model is excessively complex, such as having too many parameters relative to the number of observations. A model which has been over-fit will generally have poor predictive performance, as it can exaggerate minor fluctuations in the data. (244) Therefore, single co-morbidity adjustment scores may be preferable in research utilizing large databases, where analyses can be conducted on a considerable amount of information. Another advantage is that a validated co-morbidity adjustment method such as Charlson index simplifies the process of variable selection both in the design and analysis of any study, and may increase comparability of findings from different studies.

Age and co-morbidity

Co-morbidity assessment is one means of adjusting for differences in patients' underlying health status, although it is important to recognize that co-morbidity is only one dimension of health status; others include age, gender, functional status, and psychological, cognitive, and psychosocial functioning. (245-247) Of these, age and gender are the most widely used measures of confounding in epidemiological studies. Age - sometimes considered the simplest co-morbidity score - has often been used to also account for co-morbidity. (102,117) Although age may be a poor indicator of co-morbidity, it is recorded accurately and uniformly in all hospital morbidity databases, and methods used to adjust for age are standard. In contrast, co-morbid conditions may be under- or over-reported in HMD, and therefore the predictive performance of HMD-based co-morbidity may largely depend on the accuracy and quality of the routinely collected data. As a result, researchers have often questioned whether

the predictive accuracy of statistical models improves when an HMD-based co-morbidity score is added to a model that initially adjusts for age. (102,112) Melfi et al. used the Deyo adaptation of the Charlson index in assessing 30-day mortality in patients who had undergone total knee replacement. As reported earlier (section 3.5, p 41), these authors found that an increase in the Deyo-CI of one point increased the probability of dying by 17%, however, the addition of this co-morbidity adjusting index showed a marginal and non-significant improvement in model discrimination (C statistic of 0.653 compared with C=0.645 of baseline model). (112) In a much smaller prospective study, Poses et al. used Deyo-CI to predict in-hospital death among 227 patients who were hospitalized for suspected bacteraemia with positive blood cultures. (246) The Deyo-CI was independently associated with increased mortality in a model that also accounted for age and clinical data (OR=1.2, 95% CI: 1.1-1.4). However, the reported area under ROC curve (AUC) for a model that included Deyo-CI was C=0.64, not very different from the AUC for a model that only adjusted for age (C=0.61). In contrast, Holman et al. assessed large cohorts of medical (n=326,456), procedural (n=349,686), and psychiatric (n=16,895) inpatients in Western Australia for 30-day readmission and 1-year mortality and reported that models that included Deyo-CI produced relatively high levels of discrimination with AUC ranging from 0.74 to 0.88 for mortality and 0.61 to 0.64 for 30-day readmission. (119) Using WA HMD and similar to this latter study, we have found that in an elderly population, HMD-based (or ICD-based) co-morbidity scores perform well in predicting future morbidity and mortality. In univariable and multivariable analyses, HMD-based Deyo-CI was strongly associated with risk of various major adverse outcome following TJR including major in-hospital complications, and postoperative 1-year-, and 5-year mortality. This thesis reports that increasing co-morbidity is a stronger predictor than age in all outcomes assessed and the predictive accuracy of all models improve when HMD-based co-morbidity score is added to a model that initially includes age. Consistent with other reports, (78,119) we have shown that the performance of such scores is outcome-

specific. In predicting 1-year mortality following elective primary TJR, model discrimination improved by 12.7% when the Deyo adaptation of the Charlson index was added to a model that included age (C statistic=0.89 for model including Deyo-CI and age versus 0.79 for model that only included age, P=0.01). For the prediction of readmission to hospital, neither age nor co-morbidity showed good model fit. Younger and healthier patients are initially selected for TJR and this may partially explain why age and co-morbidity at the time of the surgery poorly predict readmission. Our study has found that short-term readmission has a stronger association with postoperative (e.g. in-hospital complications) and administrative factors (e.g. hospital type which may indicate hospital policy of readmission threshold) than with age and co-morbidity.

In conclusion, this thesis has shown that HMD-based co-morbidity scores provide significant improvement on age adjustment when predicting mortality in an elderly hospitalized population. This may indicate that adjusting for age alone is insufficient and that co-morbid illnesses can have a substantial influence on patient outcomes, and, without adequate adjustments, their effects can confound observed variations in patient outcomes. (89,93)

11.3.2 Risk of undergoing primary TJR

The main risk factors associated with TJR include age, (248,249) female gender, (1,3,139) obesity, (36,139-141) physical activity (139,141,150) and never smoking. (31,139,140) However, the reported associations of smoking and physical activity with risk of TJR have not been consistent. Inconsistencies in results may be caused by insufficient, or lack of, adjustment for the confounding effect of co-morbidities. Often studies adjust for selected confounding factors based on a-priori assumptions of risk factors for osteoarthritis, disregarding co-morbidities. (32-34,136,141,142,249) The a-priori factors include gender, age, body mass measures, smoking, physical exercise, social class, income, pain and quality

of life measures prior to surgery. One of the objectives of this thesis was to assess risks for undergoing TJR after controlling for the confounding effect of co-morbidity.

Obesity and TJR

After controlling for age, socioeconomic status, smoking, physical activity and co-morbidities, similar to other reports, this study reports that obesity is significantly and independently associated with risk of undergoing both THR and TKR. A dose-response relationship was found between body weight and risks of THR and TKR. However, the association of weight with TKR was stronger than that with THR, suggesting a biomechanical component in the relationship between body weight and severe OA. Furthermore, we found that in the older age groups, the risk of undergoing TJR was similar among patients belonging to the highest body weight quintiles. A possible explanation could be selection prior to surgery. Morbid obesity in these advanced ages may have swayed the decision against surgery, (101) thus lowering the risk in the highest weight categories.

Physical exercise and TJR

Similar to Flugsrud et al., (141) we found that vigorous exercise increased the hazard of TJR, however, the association reached statistical significance only in the 70-74 year-old age-group. This positive association between vigorous exercise and TJR could have been underestimated since the participants were relatively old when asked about their weekly exercise habits and one would assume that old age might have naturally limited their physical activity. Nevertheless, these findings suggest that those who were physically active in their younger ages stayed active as they got older and this activity was positively related to an increased risk of TJR.

Smoking and TJR

The study described in manuscript 2 (see Chapter 7) is the first to report a strong inverse association between duration of smoking and risk of undergoing TJR. This inverse dose-response relationship was also observed when predicting separately THR and TKR. These significant associations remained even after adjusting for the confounding effects of major risk factors including weight, co-morbidity, socioeconomic factors and physical activity and after accounting for the competing risk of death. This decrease in risk may have several explanations. Although the exact mechanisms behind this decrease in risk are not clear, there is some evidence that smoking may directly reduce the severity of OA by increasing cartilage volume. (152,158) However, there may be other explanations for this inverse association. Our study retrieved co-morbid conditions from the HMD and since this dataset was not originally formed for the purpose of health research, some co-morbid conditions may have been under-reported. If co-morbidity were underestimated, the risk of TJR among never-smokers could have been overestimated (given that the ever-smokers had more co-morbidities than the never-smokers). Nonetheless, we have also found that recorded co-morbidity was significantly higher among those who smoked more. Moreover, our validation analysis of WA HMD showed acceptable to good sensitivities and positive predictive values for serious conditions such as major co-morbidities and major surgical procedures. Another explanation is the possibility of confounding by factors not accounted for in this analysis or by selection processes prior to surgery. However, a survey that sought to find indications for THR or TKR as perceived by orthopaedic surgeons showed that the decision against surgery was mainly affected by patient age, co-morbidity, obesity, alcohol use, technical difficulties and lack of motivation among the patients. Smoking was not indicated as a factor that would sway the decision against TKR or THR. (101)

In conclusion, this large population-based cohort study has shown an increased risk for TJR with body weight and vigorous exercise, and an inverse association with smoking.

11.3.3 Outcomes following TJR: vulnerable and high risk patients

Overweight and obese patients

The studies in this thesis report that the overweight or obese who undergo this procedure are more likely to develop postoperative complications, (19,20,22,220) to stay longer in hospital, (19) to return to hospital (221) and die following the procedure. This study is the first to show a dose-response effect of body weight with risks of in-hospital postoperative major complications and longer stay in hospital. This study is also the first to report that weight is independently associated with increased mortality 5 years following an elective TJR. This excess in mortality may be related to long-term complications among the obese (such as higher rates of late infections (232)) that have not been accounted for in this analysis.

Body weight is an important risk factor for various adverse outcomes in patients undergoing TJR, nevertheless HMD systems do not include weight and height as variables whose recording is mandatory. We have found that obesity is under-reported in HMD and is selectively recorded for more severely ill patients. The lack of validity of the HMD-recorded diagnosis of obesity limits its use in health research. When assessing postoperative complications, HMD alone produce inferior predictive models compared with those that also account for the actual weight and height of patients. Adding weight and height to HMD significantly improved model discrimination for major complications by 8.7% with area under ROC curve of: 0.69, 95% CI:0.64-0.73 for the model with HMD-recorded obesity compared with 0.75, 95% CI:0.70-0.79 for the model with weight and height, P<0.001.

The socioeconomically disadvantaged

Our study also reports worse outcomes among men who belong to low socioeconomic groups. The association of socioeconomic disadvantage with worse outcomes in patients who undergo TJR is not new. (234,235) Patients coming from socioeconomic disadvantaged backgrounds often wait longer for surgery, (236) have higher levels of disease severity at the

time of surgery, (237) have lower rates of joint replacement despite their often greater need for surgery (as defined by higher levels of pain, joint functional restrictions), (7,238) and may also experience higher rates of postoperative adverse outcomes. (234) Consistent with other reports, (7,238) we have shown that rates of elective TJR vary by socioeconomic status (SES), with the most deprived experiencing significantly lower rates of this procedure. Hollowell et al. reported a socioeconomic gradient in length of stay in patients undergoing TKR (but not THR), with more socioeconomically advantaged patients having shorter lengths of stays. (234) However, these researchers did not account for the confounding effects of obesity and smoking. In our cohort, compared to the more affluent, the socioeconomically disadvantaged were more likely to be obese and to smoke more years and after we controlled for these factors, no associations were seen between SES and LOS in either THR or TKR. Nonetheless, we found that the socioeconomically deprived patients were significantly more likely to return to hospital 1 and 2 years following the procedure, which may indicate higher rates of late complications in these patients.

Total knee replacement

This study reports that men who undergo TKR have worse outcomes compared with those having THR. In our cohort, no differences were found in the characteristics of patients undergoing either THR or TKR. Moreover, rates of in-hospital complications (either major or minor) were similar between the two procedures. Nevertheless, patients following TKR were significantly more likely to stay longer in hospital, and to be readmitted 1 and 2 years following the procedure. The increased risk of readmission may be related to long-term complications (such as late infections) that have not been accounted for in this analysis. (238)

11.4 Strengths and limitations of study

Strengths of the studies presented in this thesis include their population-based provenance, the longitudinal design, accurate clinical data on body weight and height and the detailed information on past exposure to smoking that were integrated with WA administrative datasets including hospital morbidity data, Cancer Registry, Mental Health Services System and mortality records. For each participant, any significant morbidity or health-related outcome was retrieved from the linked data in the period 1970 through to 2007 and this enabled us to better account for patient co-morbidities. The linkage with clinical data enabled us to validate lifetime co-morbidities as listed in the WA hospital morbidity data. Moreover, since Western Australia Linked Data System links health data of all the inhabitants of Western Australia, all public and private hospital admissions in the period 1970 through to 2007 were included, and loss to follow up was minimal.

Nevertheless, the results from this study should be interpreted in light of the following limitations:

1. HMD systems may be disadvantaged by under-coding or over-coding, and coding practices may be different across hospitals. We had no access to patients' charts and therefore, we could not validate the HMD-recorded co-morbidities and complications against these charts.

2. HMD may not differentiate complications from co-existing conditions. Our method of retrieving (from the TJR-index admission) only the diagnoses that were reported for the first time for every patient may have misclassified some diagnoses as co-morbidities. We chose to increase the specificity of the diagnosis rather than its sensitivity in order not to overestimate the rates of postoperative complications in our elderly cohort of men.

3. Classification of a complication as major or minor may differ among studies, however, unlike other studies, the classification in our study was undertaken by 13 orthopaedic

surgeons who were blinded to the outcome of these conditions. Our available data did not allow us to assess risk of individual conditions.

4. Certain clinical variables such as severity of the complications and type of anaesthesia were not available for this study. These risk factors may be important predictors of some adverse events following TJR including readmission and death.

5. The study results may have been biased toward patients who had been hospitalized. Patients who possibly developed a complication that was treated in the community and that did not result in a readmission to hospital were not captured in this study.

6. Although we considered TJR a surrogate indicator of severe osteoarthritis, we did not directly ascertain OA status among study participants.

7. Information on the physical activity of the participants and their past history of smoking was self-reported and not validated.

8. Available data did not permit us to control for weight change over time and therefore we used the body weight of the participants measured at baseline. However, we have shown that weight over a period of 5 years was relatively constant in this elderly population of men.

9. The SEIFA indices ranked socio-economic well-being of the populations within areas rather than individuals themselves. Any area can include both relatively advantaged and disadvantaged people. Using the postcode may have introduced some misclassifications, however, since the postcode was provided by the participants, any misclassifications were minimized.

10. Besides clinical indications for TJR, other factors might influence the demand for this procedure such as health and insurance policies. However, since the Australian public hospital system provides free medical treatment to all permanent Australian residents under the taxpayer-funded Medicare scheme, this research did not investigate health

system policies that may influence the demand for TJR but rather focused on patient- and disease-related factors.

11. Our cohort included only men, and the results may not be generalized for women. Similarly, the study population was relatively old and our findings may not be generalizable to other younger patient populations.

12. Finally, our study is observational and causal relationships between exposure factors and study outcomes cannot necessarily be inferred.

11.5 Implications for practice and policy making

1. The WA hospital morbidity database is a valid and an important tool for health research.

2. HMD-based co-morbidity scores may be used for different purposes in epidemiological research, to correct for confounding but also to predict outcomes. Although these scores seemed to have limited power to predict some outcomes such as readmission to hospital following TJR, researchers may still consider using these measures to adjust for co-morbidity to better measure the associations between the independent and dependent variables.

3. The inclusion of actual weight and height in the HMD would make the HMD a better prognostic tool to assess major complications among patients undergoing TJR. Since the standard hospital practice is to measure the weight and height of patients, our study suggests making actual weight and height mandatory variables in any hospital morbidity data system.

11.6 Future research

Suggestions for future research include:

a) improving existing co-morbidity adjustment scores by integrating the effect of repeated episodes of serious conditions such as repeated episodes of myocardial infarction or cerebrovascular accidents;

b) assessing the role of smoking in the pathogenesis of osteoarthritis;

c) assessing the independent associations of morbid obesity with long-term mortality following elective TJR and

d) assessing the increased risk of worse outcomes in the socioeconomically disadvantaged patients and those who undergo total knee replacement.

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Appendices

Appendix I: ICD-9-CM and ICD-10 coding algorithms for Charlson Co-morbidities

Condition	Deyo ICD-9-CM [a]	ICD-10 [b]	Enhanced ICD-9-CM [b]
Myocardial infarction	410.x, 412.x	I21.x, I22.x, I25.2	410.x, 412.x
Congestive heart failure	428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	398.91,402.01, 402.11, 402.91,404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Peripheral vascular disease	443.9, 441.x, 785.4, V43.4, Procedure 38.48	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	093.0, 437.3, 440.x, 441.x, 443.1- 443.9, 447.1, 557.1, 557.9, V43.4
Cerebrovascular disease	430.x - 438.x	G45.x, G46.x, H34.0, I60.x - I69.x	362.34, 430.x - 438.x
Dementia	290.x	F00.x - F03.x, F05.1, G30.x, G31.1	290.x, 294.1, 331.2
Chronic pulmonary disease	490.x - 505.x, 506.4	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8
Rheumatic disease	710.0, 710.1, 710.4, 714.0 - 714.2, 714.81, 725.x	M05.x, M06.x, M31.5, M32.x - M34.x, M35.1, M35.3, M36.0	446.5, 710.0 - 710.4, 714.0 - 714.2, 714.8, 725.x
Peptic ulcer disease	531.x - 534.x	K25.x - K28.x	531.x - 534.4
Mild liver disease	571.2, 571.4 - 571.6	B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.x, 571.x, 573.3, 573.4, 573.8, 573.9, V42.7
Diabetes without chronic complications	250.0 - 250.3, 250.7	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	250.0 - 250.3, 250.8, 250.9
Diabetes with chronic complications	250.4 - 250.6	E10.2 - E10.5, E10.7, E11.2, E11.5, E11.7, E12.2 - E12.2, E12.7, E13.2 - E13.5, E13.7, E14.2 - E14.5, E14.7	250.4 - 250.7
Hemiplegia or paraplegia	344.1, 342.x	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.4, G83.9	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9

Renal disease	582.x, 583 - 583.7, 585.x, 586.x, 588.x	I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Any non- metastatic malignancy including lymphoma and leukaemia, except malignancy of skin	140.x - 172.x, 174.x - 195.8, 200.x - 208.x	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, C81.x - C85.x, C88.x, C90.x - C97.x	140.x - 172.x, 174.x - 195.8, 200.x - 208.x, 238.6
Moderate or severe liver disease	456.0 - 456.21, 572.2 - 572.8	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	456.0 - 456.2, 572.2 - 572.8
Metastatic solid tumour	196.x - 199.1	C77.x - C80.x	196.x - 199.x
AIDS / HIV	042.x - 044.x	B20.x - B22.x, B24.x	042.x - 044.x

Source:

a. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45: 613-9.

b. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43: 1130-9.

Appendix II: ICD-9-CM and ICD-10 coding algorithms for Elixhauser Co-morbidities

Condition	Elixhauser's original ICD-9-CM [a]	ICD-10 [b]	Enhanced ICD-9-CM [b]
Congestive heart failure	398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, 428.x	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	398.91,402.01, 402.11, 402.91,404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x
Cardiac arrhythmias	426.10, 426.11, 426.13, 426.2 - 426.53, 426.6-426.8, 427.0, 427.2, 427.31, 427.60, 427.9, 785.0, V45.0, V53.3	I44.1 - I44.3, I45.6, I45.9, I47.x - I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0	426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0 - 427.4, 427.6 - 427.9, 785.0, 996.01, 996.04, V45.0, V53.3
Valvular disease	093.2, 394.0 - 397.1, 424.0 - 424.91, 746.3 - 746.6, V42.2, V43.3	A52.0, I05.x - I08.x, I09.1, I09.8, I34.x - I39.x, Q23.0 - Q23.3, Z95.2, Z95.4	093.2, 394.x - 397.x, 424.x, 746.3-746.6, V42.2
Pulmonary circulation disorders	416.x, 417.9	I26.x, I27.x, I28.0, I28.8, I28.9	415.0, 415.1, 416.x, 417.0, 417.8, 417.9
Peripheral vascular disease	440.x, 441.2, 441.4, 441.7, 441.9, 443.1, 443.9, 447.1, 557.1, 557.9, V43.4	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	093.0, 437.3, 440.x, 441.x, 443.1- 443.9, 447.1, 557.1, 557.9, V43.4
Hypertension, uncomplicated	401.1, 401.9	I10.x	401.x
Hypertension, complicated	402.10, 402.90, 404.10, 404.90, 405.1, 405.9	I11.x - I13.x, I15.x	402.x - 405.x
Paralysis	342.0, 342.1, 342.9-344.x	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.4, G83.9	334.1, 342.x, 343.x, 344.0 - 344.6, 344.9
Other neurological disorders	331.9, 332.0, 333.4, 333.5, 334.x-335.x, 340.x, 341.1- 341.9, 345.0, 345.1, 345.4, 345.5, 345.8, 345.9, 348.1, 348.3, 780.3, 784.3	G10.x - G13.x, G20.x, G22.x, G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x - G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x	334.1, 342.x, 343.x, 344.0, 344.6, 344.9
Chronic pulmonary disease	490.x-492.8, 493.00-493.91, 494.x, 505.x, 506.4	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3	416.8, 416.9, 490.x - 505.x, 506.4, 508.1, 508.8
Diabetes without chronic complications	250.0 - 250.	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9	250.0 - 250.3
Diabetes with chronic complications	250.4 - 250.7, 250.9	E10.2 - E10.8, E11.2 - E11.8, E12.2, E12.8, E13.2 - E13.8, E14.2 - E14.8	250.4 - 250.9

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Hypothyroidism	243 - 244.2, 244.8, 244.9	E00.x - E03.x, E89.0	240.9, 243.x, 244.x, 246.1, 246.8
Renal failure	403.11, 403.91, 404.12, 404.92, 585.x, 586.x, V42.0, V45.1, V56.0, V56.8	I12.0, I13.1, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0 - 583.7, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x
Liver disease	070.32, 070.33, 070.54, 456.0, 456.1, 456.2, 571.0, 571.2 - 571.9, 572.3, 572.8, V42.7	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3, K71.5, K71.7, K72.x - K74.x, K76.0, K76.2 - K76.9, Z94.4	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0 - 456.2, 570.x, 571.x, 572.2 - 572.8, 573.3, 573.4, 573.8, 573.9, V42.7
Peptic ulcer disease excluding bleeding	531.70, 531.90, 532.70, 532.90, 533.70, 533.90, 534.70, 534.90, V12.71	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9
AIDS / HIV	042.x - 044.x	B20.x - B22.x, B24.x	042.x - 044.x
Lymphoma	200.x - 202.3x, 202.5 - 203.0, 203.8, 238.6, 273.3, V10.71, V10.72, V10.79	C81.x - C85.x, C88.x, C96.x, C90.0, C90.2	200.x - 202.x, 203.0, 238.6
Metastatic cancer	196.x - 199.x	C77.x - C80.x	196.x - 199.x
Solid tumour without metastasis	140.x - 172.x, 174.x, 175.x, 179.x - 195.x, V10.x	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, C97.x	140.x - 172.x, 174.x - 195.x
Rheumatoid arthritis/ collagen vascular disease	701.0, 710.x, 714.x, 720.x, 725.x	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0 - M31.3, M32.x - M35.x, M45.x, M46.1, M46.8, M46.9	446.x, 701.0, 710.0 - 710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30
Coagulopathy	286.x, 287.1, 287.3 - 287.5	D65 - D68.x, D69.1, D69.3 - D69.6	286.x, 287.1, 287.3 - 287.5
Obesity	278.0	E66.x	278.0
Weight loss	260.x - 263.x	E40.x - E46.x, R63.4, R64	260.x - 263.x, 783.2, 799.4
Fluid and electrolyte disorder	276.x	E22.2, E86.x, E87.x	253.6, 276.x
Blood loss anaemia	280.0	D50.0	280.0
Deficiency anaemia	280.1 - 281.9, 285.9	280.1 - 281.9, 285.2, 285.9	280.1 - 280.9, 281.x
Alcohol abuse	291.1, 291.2, 291.5 - 291.9, 303.9, 305.0, V11.3,	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1	265.2, 291.1 - 291.3, 291.5, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0 - 571.3, 980.x, V11.3
Drug abuse	292.0, 292.82 - 292.89, 292.9, 304.0, 305.2, 305.9	F11.x - F16.x, F18.x, F19.x, Z71.5, Z72.2	292.x, 304.x, 305.2 - 305.9, V65.42
Psychoses	295.x - 298.x, 299.1	F20.x, F22.x - F25.x,	293.8, 295.x, 296.04,

		F28.x, F29.x, F30.x, F31.2, F31.5	296.14, 296.44, 296.54, 297.x, 298.x
Depression	300.4, 301.12, 309.0, 309.1, 311	F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2	296.2, 296.3, 296.5, 300.4, 309.x, 311

Source:

a. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998; 36: 8-27.

b. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; 43: 1130-9.

Appendix III: ICD codes for in-hospital complications as recorded in HMD during index-TJR admission

ICD-9 codes	"998.2", "998.3", "998.1", "997.5", "996.4", "997.4", "998.9", "998.89", "996.77", "996.78", "996.79", "997.1", "997.0", "997.3", "998.5", "996.6", "999.3", "998.0", "780.09", "997.2", "427.5", "799.1", "799.01", "566", "285.1", "433.", "434.", "436.", "293.", "578.", "570.", "464.", "519.8", "410", "518.4", "584.", "518.81", "995.27", "518.5", "788.5", "444.", "507.0", "250.3", "250.8", "276.0", "276.1", "276.2", "276.3", "276.4", "276.7", "276.8", "276.9", "790.6", "276.6", "785.4", "782.3", "682.6", "485.2", "276.5", "560.39", "787.01", "787.91", "560.1", "567.9", "560.8", "560.9", "511.9", "486.", "518.0", "512.", "415.1", "786.3", "784.7", "041.", "038.", "453.", "435.", "293.9", "599.0", "781.4", "427.8", "427.0", "427.1", "427.2", "785.0", "730.25", "711.0", "790.92", "794.31", "794.8", "285.9", "280.9", "413.", "427.8", "427.9", "427.3", "427.6", "112.84", "682.", "786.5", "428", "293.0", "780.39", "707.", "531.", "532.", "533.", "786.09", "599.70", "286.5", "287.5", "426.", "780.1", "782.4", "604", "458", "799.2", "788.2", "780.2", "727.40", "596.8", "598.9"
ICD-10 codes	"T81.2", "T81.3", "M96.6", "T81.0", "T84.0", "T84.4", "T85.6", "N99.1", "N99.8", "N99.9", "N99.0", "N99.0", "K91.8", "K91.9","K91.3", "T81.8", "T81.9", "T88.8", "T84.8", "T84.9", "I97.1", "I97.8", "G97.", "J95.", "T84.5", "T84.6", "T84.7", "T81.40", "T81.41", "T81.42", "T81.1", "R40.1", "T81.7", "T80.1", "D64.9", "D50.9", "R09.2", "R09.0", "I46.", "K61.", "D62.", "I63.", "I64.", "F05.", "K29.0", "K92.0", "K92.1", "K92.2", "K72.0", "J04.", "J22.", "I21", "I22", "J81.", "N17.", "E11.29", "J96.0", "T88.7", "J80.", "Z06.", "R34.", "I74.", "J69.0", "E10.64", "E87.0", "E87.1", "E87.2", "E87.3", "E87.4", "E87.5", "E87.6", "E87.8", "E87.7", "R02.", "R60.1", "L02.4", "I95.2", "E86.", "K56.4", "R11.", "K52.9", "K56.0", "K56.7", "K56.6", "K65.9", "J90.", "J18.", "J98.1", "J93.", "I26." ,"R04.", "B95.", "B96.", "A40.", "A41.", "I80.", "G45.", "N39.0", "R00.1", "I47.", "R00.0", "J96.9", "M86.9", "M00.", "R94.3", "R94.5", "I20.1", "I20.8", "I20.9", "I48.", "I49.1", "I49.2", "I49.3", "I49.4", "I49.5", "I49.8", "I49.9", "L03.", "L97.", "R07.3", "R07.4","I50", "R41.0", "R56.8", "L89.", "K25.", "K26.", "K27.", "R06.0", "R31.", "D68.3", "D68.8", "D68.9", "D69.6", "I44.", "R44.", "N45.9", "I95.1", "R45.1", "R33", "R55", "M71.2", "N32.0", "N31.9"

"Nothing good ever ends."

The Human Comedy 1943, William Saroyan