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Epidemiology of Fracture in Adults with Kidney Disease

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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(Thesis format: Integrated Article)

by

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ABSTRACT

Fractures are a global health concern, leading to morbidity and mortality. Individuals with reduced kidney function experience bone mineral metabolism changes which can increase fracture risk. Yet, there is little consensus on the fundamentals: prediction, incidence, risk factors, and screening of fractures in kidney disease patients. This thesis addressed these critical areas helping decrease the health burden of fracture in this unique population.

This research used data from the Canadian Multicentre Osteoporosis Study (CaMos) to examine individuals with chronic kidney disease (CKD) (n=320). CaMos is a national longitudinal study designed to collect information on fractures. To examine kidney transplant recipients data from Ontario administrative healthcare databases was used (n=4821). The predictive ability of the Fracture Risk Assessment Tool (FRAX) in individuals with CKD was evaluated using area under the receiver operator characteristic curves and survival analyses. The incidence and risk factors for fracture in kidney transplant recipients were assessed using incidence rates and Cox hazard regression analysis.

The first manuscript systematically summarized the incidence and risk factors for fracture in kidney transplant recipients; fracture incidence and risk factors were variable across studies.

The second manuscript examined the predictive value of FRAX in individuals with CKD compared to individuals with normal kidney function. The discriminative ability of FRAX for fracture prediction was comparable in both groups.

The third manuscript examined the incidence of fracture in kidney transplant recipients. The cumulative incidence of fracture was low with approximately 2% sustaining a hip fracture over 10-years.

The fourth manuscript examined risk factors for fracture in kidney transplant recipients. Transplant-specific risk factors (i.e., diabetes or cystic kidney disease as the cause of end-stage renal disease and donor age) and general risk factors (i.e., older recipient age and female sex) were significantly associated with fractures.

The fifth manuscript examined the frequency and variability in bone mineral density (BMD) testing across Ontario transplant centres. Over half of kidney transplant

recipients received at least one BMD and the ordering of BMD tests varied widely by centre – from 15% to 92%.

Results can be used to improve prognostication, advance clinical guidelines, clarify fracture incidence, and guide informed consent.

Keywords: fracture, kidney disease, chronic kidney disease, kidney transplant recipient, epidemiology, bone

CO-AUTHORSHIP STATEMENT

All manuscripts contained in this document were primarily conceived, designed, and analysed by Kyla Lynn Naylor for her PhD thesis. The data for the manuscript in Chapter 3 was obtained from the Canadian Multicentre Osteoporosis Study. The data for the manuscripts in Chapters 4, 5, and 6 was obtained from the data holdings at the Institute for Clinical Evaluative Sciences. Support for each manuscript was provided by members of the supervisory committee, Drs. Amit Garg, Guangyong Zou, and Sophie Jamal. Specifically, feedback and methodological and statistical advice was provided by the members throughout the course of this research as needed. For Chapters 2, 3, 4, 5, and 6 there were multiple authors who assisted with editing the manuscripts; their contributions have been recognized at the beginning of each chapter in footnotes. Kyla Lynn Naylor's contributions to each manuscript are detailed below:

Chapter 2: For this study Kyla Lynn Naylor developed the study idea, designed the study, created the data abstraction tool, abstracted the data, analyzed the results, drafted the manuscript, and incorporated co-author comments for revisions. Kyla Lynn Naylor was the primary and corresponding author for this manuscript.

Chapter 3: For this study Kyla Lynn Naylor developed the study idea, designed the study, performed the statistical analysis, analyzed the results, drafted the manuscript, and incorporated co-author comments for revisions. Kyla Lynn Naylor was the primary and corresponding author for this manuscript.

Chapter 4: For this study Kyla Lynn Naylor developed the study idea, designed the study, performed the statistical analysis, analyzed the results, drafted the manuscript, and incorporated co-author comments for revisions. Kyla Lynn Naylor was the primary and corresponding author for this manuscript.

Chapter 5: For this study Kyla Lynn Naylor developed the study idea, designed the study, performed the statistical analysis, analyzed the results, drafted the manuscript, and incorporated co-author comments for revisions. Kyla Lynn Naylor was the primary and corresponding author for this manuscript.

Chapter 6: For this study Kyla Lynn Naylor developed the study idea, designed the study, performed the statistical analysis, analyzed the results, drafted the manuscript,

and incorporated co-author comments for revisions. Kyla Lynn Naylor was the primary and corresponding author for this manuscript.

DEDICATION

To my husband Joel and my parents, who have always provided me with endless support and encouragement.

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Canadian Multicentre Osteoporosis Study (CaMos)

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LIST OF ABBREVIATIONS

aHR	Adjusted Hazard Ratio
AUC	Area Under the Curve
BMD	Bone Mineral Density
BMI	Body Mass Index
CaMOS	Canadian Multicentre Osteoporosis Study
CCI	Canadian Classification of Health Interventions
CCI	Charlson Comorbidity Index
CCP	Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures
CI	Confidence Interval
CIHI-DAD	Canadian Institute for Health Information Discharge Abstract Database
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease-Mineral and Bone Disorder
CORR	Canadian Organ Replacement Register
DX	Diagnostic Code
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-stage Renal Disease
FRAX	Fracture Risk Assessment Tool
GPNPF	General Population No Previous Non-vertebral Fracture
GPPF	General Population Previous Non-vertebral Fracture
HLA-DR	Human Leukocyte Antigen-DR Mismatch
HR	Hazard Ratio
ICD	International Classification of Diseases
ICD-9	9^{th} version of the International Classification of Disease system
ICD-10	10^{th} version of the International Classification of Disease system
ICES	Institute of Clinical Evaluative Sciences
IKN	Institute of Clinical Evaluative Sciences Key Number
KDIGO	Kidney Disease Improving Global Outcomes
MAR	Missing At Random
MCAR	Missing Completely At Random

MNAR	Missing Not At Random
NACRS	National Ambulatory Care Reporting System
NPV	Negative Predictive Value
NR	Not Reported
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PPV	Positive Predictive Value
RR	Relative Risk
SAS	Statistical Analysis Software
SD	Standard Deviation
SF-36	Short Form (36) Health Survey
TGLN	Trillium Gift of Life Network
USRDS	United States Renal Data System
UTD	Unable To Determine
WHO	World Health Organization

GLOSSARY

Bisphosphonate: A drug given to help prevent fracture.

Bone Mineral Density (BMD): The quantity of minerals present in a specific volume of the bone (1). In the general population as BMD decreases fracture risk has been shown to increase (2, 3).

Bone Mineral Density Test: A tool used to measure bone mineral density which provides information on bone mass.

Chronic Kidney Disease (CKD): Estimated glomerular filtration rate (eGFR) (measure of kidney function) less than 60 ml/min/1.73 m^2 for at least 3 months or the presence of kidney damage (4). In this thesis CKD was defined by evidence of one eGFR measurement <60 mL/min/1.73 m^2 (Chapter 3) or using diagnostic codes for CKD (Chapter 4).

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD): A disorder caused by chronic kidney disease that affects bone and mineral metabolism and is characterized by at least one of the following:

- Abnormal metabolism of calcium, phosphorous, parathyroid hormone, or vitamin D
- Abnormal bone mineralization, bone volume, bone turnover, bone strength, or bone growth
- Calcification of the soft tissue or calcification of vasculature (5).

Dialysis: A process that removes wastes and excess water from the body when an individual has kidney failure (eGFR <15 mL/min/1.73 m^2) (6).

End Stage Renal Disease: A loss in kidney function so severe that the kidneys cannot function at a level required in day to day life and at which point dialysis is required (7). Generally this occurs with an eGFR <15 mL/min/1.73 m^2.

Estimated glomerular filtration rate: A measure of kidney function quantified by the amount of blood that travels through the glomeruli per minute (8).

Fracture Risk Assessment Tool (FRAX): A tool developed and validated in the general population that predicts the ten-year probability of hip or major osteoporotic fracture (hip, proximal humerus, forearm, or clinical vertebral) through the use of the following variables: age, sex, clinical risk factors, and with or without bone mineral density (9).

Kidney Disease: A range of diseases that adversely affect the kidney (8). In this thesis kidney disease refers to chronic kidney disease without transplantation and chronic kidney disease with kidney transplantation.

Non-vertebral Fracture: For the purposes of this thesis includes: forearm (radius and ulna), proximal humerus, and hip fractures.

Osteoporosis: A bone disease that increases an individual's susceptibility to fracture (10).

Osteoporotic Fracture: Fractures that occur due to a bone disease (osteoporosis) that causes reduced bone mass and a weakening of the bone microarchitecture, resulting in diminished bone strength (10). Hip, forearm, vertebral, and humerus fractures are considered major osteoporotic fracture locations.

T-score: Bone density compared to white females aged 20-29 years and is expressed in the number of standard deviations above normal (normal defined as $\geq$ -1) (11, 12).

United States Renal Data System (USRDS): An American national dataset that contains information on end-stage renal disease patients (13).

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CHAPTER 1: Introduction

1.1 Background and Overview

The number of individuals in Canada living with kidney disease is increasing with a 40% increase in the number of Canadians living with kidney failure from 2003-2012 (1). The reasons for this increase are multifactorial, including an aging population and an increase in type II diabetes and hypertension (two of the most common causes of kidney disease) (1). There is a desire for the 3 million Canadians living with chronic kidney disease and over 17,000 living with a kidney transplant to live long and healthy lives (2, 3). One often overlooked complication of kidney disease is fracture. When kidney function declines changes in bone mineral metabolism occur which adversely affects the skeleton and increases fracture risk (4). Specifically, many individuals with kidney disease have a complex bone disorder called chronic kidney disease-mineral and bone disorder which is characterized by increased phosphate levels, decreased vitamin D and calcium levels, and secondary hyperparathyroidism (4). Although kidney transplantation improves kidney function many recipients continue to have chronic kidney disease-mineral and bone disorder post-transplant (4). Therefore, fracture risk is thought to be high, relative to the non-kidney disease general population, across the spectrum of kidney disease (mild kidney dysfunction to kidney failure to kidney transplantation) (5-8). Fractures are a concern as they are associated with mortality, morbidity, and economic costs (9-11). Yet, there is little consensus on the fundamentals: prediction, incidence, risk factors, and frequency of preventative screening for fractures in kidney disease patients (defined in this thesis as chronic kidney disease without kidney transplantation and kidney transplantation). This thesis will address this critical area, and will inform future interventional strategies to reduce the health burden of fracture in the kidney disease population.

1.2 Overall Aim

The overall aim of this thesis is to better understand the epidemiology of fracture in adults with kidney disease and to use this information in the care of this unique patient population. Despite the health and economic impact of fractures, there is currently a gap in knowledge about the epidemiology of fracture in patients with kidney disease. Addressing the objectives outlined in this thesis will inform future strategies to reduce the

incidence of fracture in this growing patient population. This thesis is part of a larger body of research I developed throughout my PhD studying bone health in individuals with kidney disease. The five objectives described below will address this overall objective.

1.3 Study Objectives

Objective 1: To efficiently and systematically summarize the incidence and risk factors for fracture in kidney transplant recipients.

Objective 2a: To determine if kidney function modifies the predictive model performance of the Fracture Risk Assessment tool (FRAX). This will be done by assessing the discrimination and calibration of FRAX in individuals who have reduced kidney function compared to individuals with normal kidney function.
Objective 2b: To assess the discrimination and calibration of FRAX (without bone mineral density) after the addition of chronic kidney disease as a variable in the model.
Objective 2c: To assess the ability of the following variables to predict fracture in individuals with normal kidney function and reduced kidney function: age, T-score, and T-score with a history of fall.

Objective 3a: To estimate the age- and sex- specific three-year incidence of non-vertebral fractures (proximal humerus, forearm, hip) in kidney transplant recipients.

Secondary Objectives

i) To estimate the age- and sex-specific three-year incidence of fracture (including all fracture locations) in kidney transplant recipients.

ii) To estimate the age- and sex-specific five-year incidence of non-vertebral fractures in kidney transplant recipients.

iii) To estimate the age- and sex-specific ten-year incidence of non-vertebral fractures in kidney transplant recipients.

iv) To estimate the age- and sex-specific three-year incidence of non-vertebral fractures in kidney transplant recipients who received a transplant in more recent years (2002-2009).

v) To estimate the age- and sex-specific three-year incidence of falls with hospitalization among kidney transplant recipients.

Objective 3b: To assess whether kidney transplant recipients have a higher incidence of non-vertebral fractures compared to the following age-, sex-, and cohort entry date matched reference groups: healthy segment of the general population with no bone disease and no kidney disease, healthy segment of the general population with no evidence of kidney disease and a history of a non-vertebral fracture, individuals with chronic kidney disease (excluding individuals on dialysis), and individuals with rheumatoid arthritis.

Objective 3c: To assess whether kidney transplant recipients have a higher incidence of non-vertebral fractures compared to patients receiving dialysis controlling for age, sex, cohort entry date, and comorbidities in the analysis.

Objective 4: To determine the transplant specific (e.g. type of donor [living vs. deceased]) and general risk factors (e.g. age) for major fractures (proximal humerus, forearm, hip, and clinical vertebral) and other fractures (excluding major fractures, and those of the skull, fingers, and toes) in kidney transplant recipients.

Objective 5a: To determine the frequency, total cost, and the variability in bone mineral density testing across the six Ontario transplant centres in the first three years after kidney transplantation.

Objective 5b: To compare the frequency of bone mineral density testing in kidney transplant recipients to two non-transplant reference groups matching on age-, sex-, and cohort entry date (individuals with no evidence of kidney disease and with no prior non-vertebral fracture; individuals with no evidence of kidney disease and a history of a non-vertebral fracture).

1.4 Structure of the Thesis Document

An integrated manuscript style will be used to present the work of this thesis in a series of five manuscripts. A brief description of each manuscript is provided below. An in-depth description of the methods and additional results are provided in several

appendices (Appendix A for Chapter 2, Appendix C for Chapter 3, Appendix D for Chapter 4, and Appendix E for Chapter 5). Appendix B contains information on the ethics approval, consent form, and questionnaire for Chapter 3. Appendix F provides documentation for the privacy impact assessment approval for Chapters 4, 5, and 6. Appendix G provides copyright information.

The second chapter of this thesis contains the literature review, conceptual model, and a version of the first manuscript entitled "Fracture Risk in Kidney Transplant Recipients: A Systematic Review" which was published in *Transplantation.* This manuscript addresses objective 1 of this thesis and systematically summarizes the incidence and risk factors for fracture in kidney transplant recipients.

The second manuscript entitled "Comparison of fracture risk prediction among individuals with reduced and normal kidney function" was published in the *Clinical Journal of the American Society of Nephrology* and represents a version of Chapter 3. This manuscript addresses objective 2 of this thesis and assesses the prognostic value of the Fracture Risk Assessment Tool (FRAX) in adults with reduced and normal kidney function.

The third manuscript entitled "Fracture incidence in adult kidney transplant recipients" was published in *Transplantation* and represents a version of Chapter 4. This manuscript addresses objective 3 of this thesis and provides a comprehensive examination of the incidence of fracture in adult kidney transplant recipients.

The fourth manuscript entitled "Risk factors for fracture in adult kidney transplant recipients" is being prepared for submission to the *Canadian Journal of Kidney Health and Disease*. This manuscript addresses objective 4 of this thesis and provides information on risk factors for fracture in adult kidney transplant recipients.

The fifth manuscript entitled "Frequency of bone mineral density testing in adult kidney transplant recipients" has been submitted to the *Canadian Journal of Kidney Health and Disease.* This manuscript addresses objective 5 of this thesis and examines the frequency, total cost, and the variability in bone mineral density testing in kidney transplant recipients across the six Ontario transplant centres. This manuscript was initially a secondary objective in Chapter 4; however, given the importance of the

findings and the additional analyses that were performed, a chapter dedicated to these findings was warranted.

The last chapter of this thesis is the Discussion (Chapter 7). This chapter summarizes the major findings of this thesis and links all chapters of the thesis together. Information on implications for clinical practice, strengths and limitations, future directions, and conclusions are also discussed.

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measured by the Health Utilities Index in the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int* 2003;14:895-904.

CHAPTER 2: Literature Review[a]

[a]A version of this chapter, in particular Sections 2.5 and 2.6, was published elsewhere as, Naylor KL, Li AH, Lam NN, Hodsman BA, Jamal SA and Garg AX. Fracture Risk in Kidney Transplant Recipients: A Systematic Review. *Transplantation 2013;* 95:1461-1470. Wolters Kluwer Health Lippincott Williams & Wilkins© No modifications will be permitted.

An extensive literature review was performed through searching PubMed, Embase, Medline, and Google Scholar for all objectives. For objectives 3 and 4 there was a large amount of literature assessing the incidence and risk factors for fracture in kidney transplant recipients, therefore, a systematic review was performed and is highlighted in part of this chapter.

2.1 Osteoporotic Fracture

Osteoporotic fractures are fractures that occur due to a bone disease (osteoporosis) that causes reduced bone mass and a weakening of the bone microarchitecture, resulting in diminished bone strength (1). The most common osteoporotic fracture sites include hip, vertebrae, forearm, and proximal humerus (2). These fractures are a global health concern for several reasons (3-7). First, these fractures are associated with morbidity (7, 8). For example, hip fractures have been found to be associated with chronic pain and loss of mobility (9). Second, these fractures can adversely impact quality of life (10, 11), with Adachi *et al.,* finding women with a prior hip fracture had a significantly lower health-related quality of life score with particularly low scores in self-care (4). Last, these fractures increase mortality (12, 13). For example, compared to women and men without a major osteoporotic fracture individuals with a fracture had a significantly higher age-standardized mortality ratio (proximal femur: 2.18, 95% [confidence interval] CI 2.03-2.32; vertebral 1.66, 95% CI 1.51-1.80) (6). The adverse effects of these fracture are troublesome as from 1985-2005 there were over 570,000 hip fractures in Canada, with more than 145,000 hip fractures from 2001 to 2005 (14). The monetary cost of these fractures can also place a large economic burden on the healthcare system. The direct healthcare costs of osteoporotic fractures in Canada currently exceed $2 billion each year with the cost of hip fracture alone estimated to reach $2.4 billion / year in the next three decades (3, 15).

2.2 Kidney Disease

The kidneys are important organs in our body that are needed to remove waste and filter blood (16). When the kidneys are not functioning properly an individual can develop kidney disease which is a broad term used to describe a range of diseases that

adversely affect the kidney (16). A permanent and meaningful decrement in kidney function is called chronic kidney disease (CKD) (16). Chronic kidney disease can progress to kidney failure (end-stage renal disease) at which point an individual requires either dialysis or a kidney transplant to survive (16). An in-depth description of CKD and kidney transplantation, which are the exposures of interest in this thesis, is provided below.

2.2.1 Chronic Kidney Disease

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define CKD as an estimated glomerular filtration rate [eGFR] <60mL/min/1.73 m^2 (lower eGFR indicative of worse kidney function) for at least three months or a higher eGFR with the presence of kidney damage (17). The KDIGO guidelines further categorize CKD into 5 stages (Table 2.1) (17). The number of Canadians with CKD is increasing with approximately 3 million adult Canadians living with CKD (18, 19). This increase is partially attributable to the aging population and an increase in the number of Canadians with type II diabetes and hypertension (20, 21). CKD can advance to kidney failure, at which point an individual would require dialysis or a kidney transplant to sustain life. From 2003 to 2012, there has been an approximate 40% increase in the number of Canadians living with kidney failure (n=40,000) (20). The large number of Canadians with CKD is concerning given the large number of comorbidities, increased mortality, and high economic costs (dialysis costs over $1 billion per year in Canada) associated with the disease (22-25).

Table 2. 1. Description of the stages of chronic kidney disease (17)

Stage	Estimated Glomerular Filtration Rate (eGFR) and Description
Stage 1:	Estimated glomerular filtration rate (eGFR) is normal (≥ 90 mL/min/1.73m^2) or increased with evidence of kidney damage
Stage 2:	Mild decrease in kidney function (eGFR 60-80 mL/min/1.73m^2) with evidence of kidney damage
Stage 3a:	Moderate decrease in kidney function (eGFR 45-59 mL/min/1.73m^2)
Stage 3b:	Moderate to severe declines in kidney function (eGFR 30-44mL/min /1.73m^2)

Stage 4: Severe decline in kidney function (eGFR 15-29 mL/min/1.73m^2)

Stage 5: Kidney failure (eGFR <15 ml/min/1.73m^2)

2.2.2 Kidney Transplantation

While dialysis can be used to maintain life, kidney transplantation is considered the best treatment for kidney failure as it improves survival and decreases costs to the healthcare system (26, 27). The number of kidney transplants performed in Canada, as in most countries, has increased over the last decade (with 1,193 kidney transplants performed in 2003 and 1,358 in 2012) (20, 28). As of 2012, over 17,000 Canadians were living with a functioning kidney transplant (20). With over 90% of kidney transplant recipients surviving one-year post-transplant and over 80% of kidney transplant recipients surviving five-years post-transplant, the focus is now on maximizing long-term recipient health (27).

2.3 Changes in Bone Mineral Metabolism in Kidney Disease

It is well established that individuals with CKD are at an increased fracture risk (29-38). For example, Naylor *et al.,* found women aged 40-65 years with an eGFR of 15-29 mL/min/1.73 m^2 had approximately a two-time higher fracture risk compared to similarly aged women with normal kidney function (rate ratio 2.4, 95% CI 1.5-4.0) (29). Conversely, in kidney transplant recipients the risk of fracture has not been well quantified but many studies suggest that the fracture risk is higher than the non-kidney disease population (39-41). For example, Ramsey-Goldman *et al.* reported that the risk of fracture in female kidney transplant recipients aged 45-64 years was 34 times higher than their counterparts in the general population (41). Similar to the non-kidney disease population, these fractures are concerning in individuals with kidney disease as they are associated with mortality and morbidity (32, 39, 42). Nitsch *et al.,* reported that compared to individuals with an eGFR $\geq$ 60 mL/min/1.73 m^2 (normal kidney function) individuals with an eGFR < 45 mL/min/1.73 m^2 had almost a two-fold higher age- and sex-adjusted hazard ratio of death related to hip fracture (hazard ratio 1.98, 95% CI 1.12-3.50) (43). Abbott *et al.,* found that the 1-year mortality for kidney transplant recipients after hip fracture was 14% compared to 7% in recipients who did not fracture (P <0.01) (39).

The reasons for the higher fracture risk amongst individuals with kidney disease are not fully understood but are likely multifactorial. Figure 2.1 provides a schematic on the pathways that lead to fracture. As kidney function declines individuals may develop a complex disorder of bone and mineral metabolism called chronic kidney disease-mineral and bone disorder (CKD-MBD). CKD-MBD is characterized by at least one of the following 1) abnormal metabolism of calcium, phosphorous, parathyroid hormone or vitamin D; 2) abnormal bone mineralization, bone volume, bone turnover, bone strength or bone growth; and 3) calcification of the soft tissue or calcification of vasculature (44). In summary, changes in bone mineral metabolism occur when kidney function declines and often continues after kidney transplantation. Specifically, these changes include declining levels of serum calcium and calcitriol (active form of vitamin D), and increasing levels of serum phosphate, and fibroblast growth factor 23 (44-46). Many individuals on dialysis develop secondary hyperparathyroidism which increases bone turnover, thereby weakening the bone (47). Post-transplant, after some of the kidney function has been restored, serum calcium levels and phosphate levels may normalize (48, 49); however, secondary hyperparathyroidism often persists (47, 50-52). Drugs administered to kidney transplant recipients may also play a role in fracture. Specifically, corticosteroids used to prevent transplant rejection have been found to promote bone loss (apoptosis of osteoblasts; decrease in gonadal function; decrease in intestinal calcium absorption) (53, 54). The role of cyclosporine (an immunosuppressant) in bone loss is controversial with in vivo studies finding cyclosporine increases bone resorption and in vitro studies finding it impedes bone resorption (55-61). In summary, individuals with kidney disease experience numerous bone mineral metabolism changes that are detrimental to the skeletal system raising a concern about fracture risk.

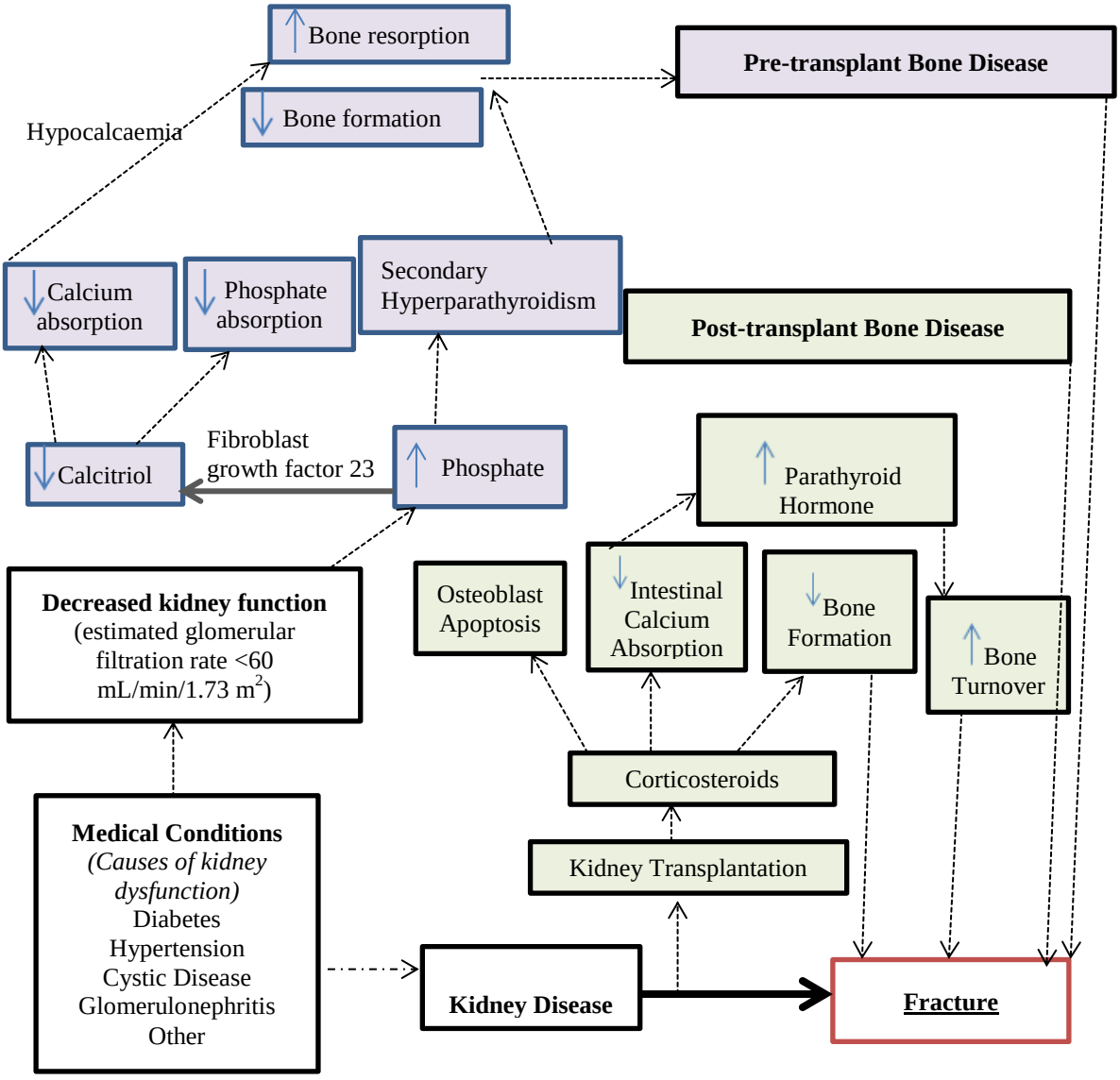

Figure 2. 1. Mechanisms for increased fracture risk in individuals with kidney disease

2.4 Fracture Risk Prediction in Chronic Kidney Disease

As previously discussed, it is well established that individuals with chronic kidney disease (CKD) have a higher risk of fracture compared to individuals with normal kidney function (29-38). Even individuals with a more moderate decline in kidney function experience a high fracture risk with risk increasing in a graded manner as kidney function declines (P for trend <0.0001; Figure 2.2) (29). For example, Naylor *et al.*, found women aged > 65 years with an estimated glomerular filtration rate (eGFR) 45-59 mL/min/1.73 m^2 had a significantly higher fracture rate (proximal humerus, forearm, hip, and pelvis)

compared to individuals with normal kidney function (defined as an eGFR ≥ 60 mL/min/1.73 m^2) (rate ratio 1.4, 95% CI 1.3-1.5) (29). However, the best technique to identify individuals with CKD who are at a high fracture risk is not known. This is concerning as to decrease the economic costs, morbidity, and mortality associated with fractures we must identify those at high risk and target treatments to these individuals. Moreover, early therapeutic intervention is particularly important in individuals with reduced kidney function as there is a concern about the safety and efficacy of bisphosphonates (fracture prevention therapy) in individuals with an eGFR < 30ml/min/1.73 m^2 (17, 62).

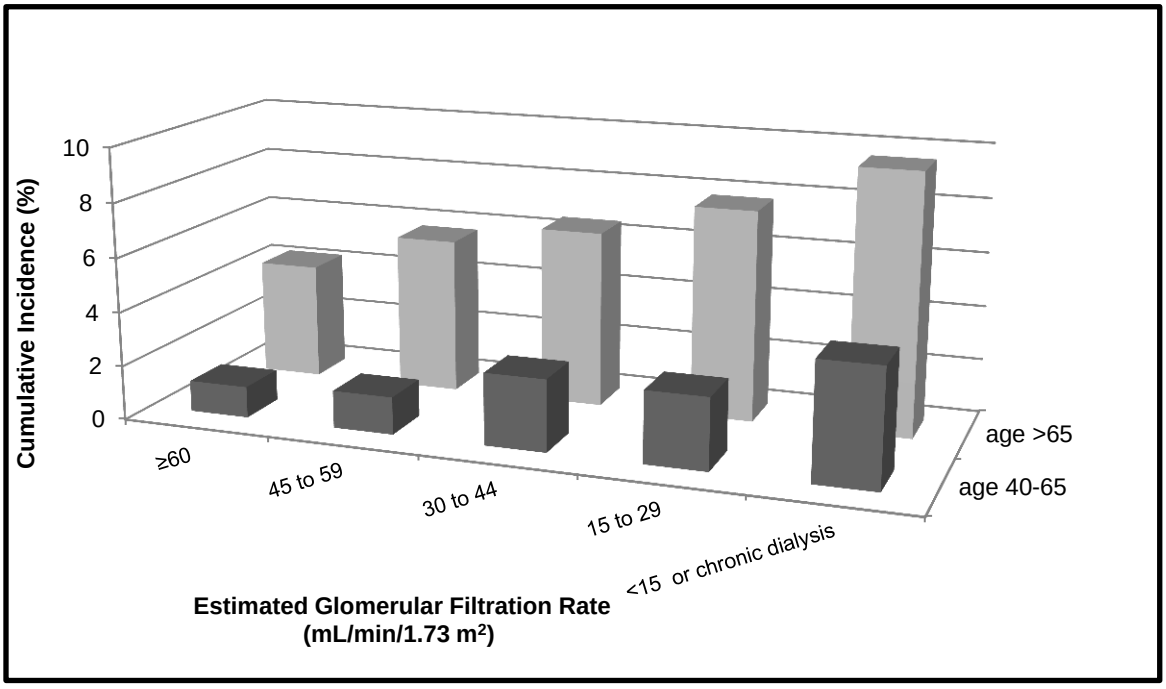

Figure 2. 2. Three-year cumulative incidence of fracture in women (29)
Source: Naylor KL, McArthur E, Leslie WD, Fraser LA, Jamal SA et al. The three-year incidence of fracture in chronic kidney disease. *Kidney International* 2014;86 :810-818.

2.4.1 Fracture Risk Assessment Tool (FRAX)

The fracture risk assessment tool (FRAX) is widely used in clinical practice to predict fracture and to help guide treatment decisions in individuals with normal kidney function (63). FRAX was developed by the World Health Organization and can be described as a computer-based algorithm which can be easily used by physicians to predict a patient's fracture risk (Figure 2.3) (63, 64). It has been validated in the general

population using eleven validation cohorts and has been found to be accurate (average area under the receiver operating characteristic curve >0.6) (65). Specifically, FRAX predicts the 10-year probability of major osteoporotic fracture (hip, humerus, forearm or clinical spine) or hip fracture alone through the use of the following variables: age, sex, and clinical risk factors (with or without bone mineral density [BMD]) (66).These clinical risk factors were identified through meta-analyses assessing risk factors for fracture and include: high alcohol intake (defined as ≥3 units per day), previous fracture, current smoking, parental hip fracture, secondary osteoporosis, rheumatoid arthritis, low body mass index (defined as <19 kg/m^2), and extended glucocorticoid use (defined as exposure for ≥3 months at a dose of 5mg/day) (63, 64, 67-69) (Table 2.2). However, given the complex pathophysiology of bone disease in CKD this patient population may have unique risk factors for fracture. For example, Nickolas *et al.*, found low BMD, older age, and female sex, common risk factors in the non-kidney disease population, were not associated with an increased hip fracture risk in individuals with CKD (36).

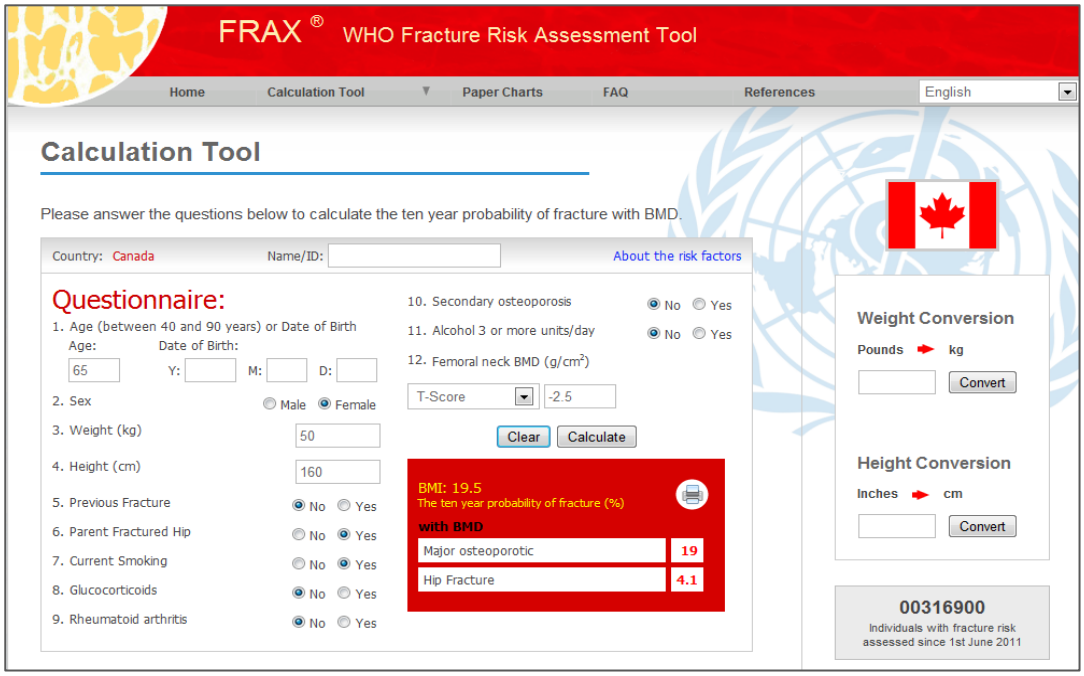

Figure 2. 3. Screen shot of the Canadian FRAX input page and the results (67)

Table 2. 2. FRAX variables (67, 69)

Variables
Age
Sex
Body mass index (kg/m^2)
Previous fracture
Parental hip fracture
Current smoking
Prolonged use of glucocorticoids
Rheumatoid arthritis
Secondary osteoporosis *(chronic liver disease, type I diabetes, hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition/malabsorption and osteogenesis imperfect)*
Alcohol use ≥3 units/day
Femoral neck BMD (g/cm^2 or T-score) is optional

2.4.2 Fracture Risk Assessment Tool (FRAX) in Chronic Kidney Disease

One previous study has assessed the ability of FRAX to predict fracture in individuals with CKD, finding that FRAX was able to discriminate between individuals with and without a clinical non-spine fracture (area under the receiver operating characteristic curve 0.72, 95% CI 0.65-0.78) (70). However, this study had limitations. First, the study was cross-sectional preventing the calibration (comparison between the observed and FRAX predicted fracture risk) of the tool to be assessed. Second, CKD was defined as an eGFR <90 mL/min/1.73 m^2. The KDIGO guidelines define CKD as an eGFR < 60 mL/min/1.73 m^2 and an eGFR ≥ 60 mL/min/1.73 m^2 requires other evidence of kidney disease (e.g. proteinuria) (17). Third, there was no comparison group of individuals with normal kidney function to determine how the tool's performance in individuals with CKD compares (70). Fourth, the study did not assess several other potential predictors of fracture in addition to FRAX. For example, T-score and previous falls may be accurate predictors of fracture in the CKD population; in the general population a lower T-score and a previous fall have been found to increase fracture risk

(71-73). Fifth, all the FRAX variables were not able to be included in the FRAX model; information on previous fracture was not available (70). Last, the study included both Canadian and American CKD patients (70); this is problematic as FRAX needs to be calibrated for each country given the variability in fracture rates across countries (74). Therefore, the best way to identify individuals with CKD who are at a high fracture risk is unknown.

2.5 Kidney Transplantation and Fracture Risk

2.5.1 Fracture Incidence

As previously discussed, literature suggests that fracture risk remains high in kidney transplant recipients relative to the non-kidney disease population despite improvements in kidney function after transplantation (39-41). However, there remains poor consensus on the incidence of fracture in kidney transplant recipients with values varying widely in the literature.

Ten studies published between 1996 and 2012 reported on the incidence of fracture in kidney transplant recipients (39, 41, 75-82). The incidence rate of fractures across studies varied from 3.3 to 99.6 fractures per 1000 person-years (Tables 2.3 and 2.4). Similarly, the cumulative incidence was highly variable. There are several potential reasons for this variation. First, recipient characteristics varied across studies. For example, Kalker *et al.* only included diabetic recipients which likely resulted in a high cumulative incidence of fracture (diabetes has been found to increase fracture risk (83)) (79). Specifically, Kalker *et al.* found that the 5-year cumulative incidence of ankle fracture was 27% (79). In contrast, other studies that included both diabetic and non-diabetic recipients found that the 5-year cumulative incidence of fracture ranged from 5% to 22% (76, 80). Second, studies included different fracture sites. Ball *et al.* only included hip fractures and found an incidence rate of 3.3 fractures per 1000 person-years (77). In contrast, Conley *et al.*, included multiple fracture locations and found a fracture incidence rate of 99.6 fractures per 1000 person-years (78). Last, previous studies had variable methodological quality, with study methods' quality scores ranging from 8 to 13 (with higher quality studies receiving a higher score, range 0 to 17) (Table 2.4); methodological quality was assessed using a modified version of the Downs and Black checklist for

nonrandomized studies which assesses the completeness and clarity of reporting, bias, and external validity (84) (Appendix A).

Table 2. 3. Study characteristics of kidney transplant recipients

Study, First Author, Country	**Number of patients**	**Age,** years (mean ± SD)	**Women,** percent	**Time zero**	**Year transplanted**	**Mean follow-up,** years (mean ± SD)	**Diabetic,** percent
Prospective Cohort							
de Sévaux *et al.*, (2003) Netherlands	61	42.0 ± 13.0	37.7%	Transplant date	1995-1996	2.0 [€]	3.3%
Rizzari *et al.*, (2012) United States	Living Donor: 791	NR	38%	Transplant date	1999-2010	5.3*	Type 1 Diabetes 27% , Type 2 Diabetes 11%
	Deceased Donor: 450	NR	41%	Transplant date	1999-2010	3.0*	Type 1 Diabetes 22%, Type 2 Diabetes 20%
Retrospective Cohort							
Abbott *et al.*, (2001) United States	Fracture: 379	47.7 ± 14.0	48.5%	Transplant date	1994- 1997	1.7 ± 1.1	49.9%[†]
	No Fracture: 33 100	42.8 ± 14.6	39.7%	Transplant date	1994- 1997	1.7 ± 1.1	26.4%[†]
Ball *et al.*, (2002) United States	59 944	NR	39.2%	Transplant date	1990-1999	NR	26.1%[‡]
Conley *et al.*, (2008) United States	No Bisphosphonate: 239	46.9 ± 0.2	46%	1.2 ± 0.05 years after transplant	1998-2006	2.5 ± 0.05	Type 1 Diabetes 17%, Type 2 Diabetes 12%;
	Bisphosphonate: 315	45.9 ± 0.7	40%	1.2 ± 0.05 years after transplant	1998-2006	2.5 ± 0.05	Type 1 Diabetes 32%, Type 2 Diabetes 9%
Kalker *et al.*, (1996) United States	214	39[ß]	38%	6 months after transplant	1985-1992	3.8	100%
Nikkel *et al.*, (2009) United States	No Fracture: 53 344	43.3	38%	Transplant date	1988-1998	5 [€]	22.9%[†]
	Fracture: 15 470	44.2	45.5%	Transplant date	1988-1998	5 [€]	36%[†]

Table 2.3. Study characteristics of kidney transplant recipients (continued)

Study, First Author, Country	**Number of patients**	**Age,** years (mean ± SD)	**Women,** percent	**Time zero**	**Year transplanted**	**Mean follow-up,** years (mean ± SD)	**Diabetic,** percent
Retrospective Cohort							
Nikkel *et al.*, (2012) United States	Early Corticosteroid Withdrawal : 11 164	49.9 ± 13.4	38%	Transplant date	2000 to 2006	4.1	26%[†]
	Corticosteroid-base immunosuppression: 66 266	48.9 ± 13.4	40%	Transplant date	2000 to 2006	2.5*	24.1%[†]
Opelz *et al.*, (2011) Multinational	20 509	47.9 ± 13.0	38.4%	1 year after transplant	1995 to 2008	5[€]	8.6%[‡]
Ramsey-Goldman *et al.*, (1999) United States	432	41.3 ± 12.3	40%	30 days after transplant	1992 to 1996	2.1 ± 1.5	40%[¥]

NR - not reported
[ß] reported as an average
[€] reported as total time since transplant
[*] reported as median
[†] type 1 and type 2 diabetes are combined
[‡] reported as diabetic neuropathy
[¥] combined diabetes and hypertension

Table 2.4. Fracture incidence in kidney transplant recipients

Study	Incidence/Cumulative incidence	Most common fracture location	Time to fracture	Quality score
Incidence				
Abbott *et al.*	Males: 6.90 fractures per 1000 person-years Females: 9.93 fractures per 1000 person-years	Femur (34.8%)	Linear increase in cumulative hazard of fracture after transplant.	13
Ball *et al.*	3.3 fractures per 1000 person-years	Hip† (100%)	Shortly after transplant hip fracture risk was higher in transplant recipients compared to dialysis patients on the transplant wait list (RR 1.34 , 95% CI 1.12-1.61); 630 days after transplant, patients who were on dialysis had a similar fracture risk as recipients (RR 1.00, 95% CI 0.87-1.15)	12
Conley *et al.*	*No bisphosphonate* 36.7 fracture per 1000 patient years; *Bisphosphonate* 99.6 fractures per 1000 patient years	Fractures other than vertebral and femoral neck (91.7%)	Fracture free survival was over 90% at 2 years and decreased to approximately 40% at 6 years	12
Nikkel *et al.*	*Early corticosteroid withdrawal* :5.8 fractures per 1000 patient years*; Corticosteroid-based immunosuppression:*8.0 fractures per 1000 patient years	Femur (29%)	Fracture incidence was significantly less than those with early corticosteroid withdrawal compared to corticosteroid-based immunosuppression 24 months after fracture	13
Ramsey-Goldman *et al.*	39 fractures per 1000 person-years	Foot (42.4%)	Mean time to first fracture after transplant was 1.64±1.18 years	8
de Sévaux *et al.*	34 fractures per 1000 person-years	Hip (50%)	NR	10
Cumulative Incidence				
Kalker *et al.*	~10% at 2 years ~27% at 5 years	Foot¶ (100%)	Incidence increased from 0- 2 years post-transplant, plateaued from 2-3 years and increased up until 5 years	8
Nikkel *et al.*	22.5% in 5 years	Foot/ankle(28.2%)	Mean time to first fracture 2.5 years	12
Opelz *et al.*	0.85% over 5 years	Hip† (100%)	Cumulative rate of fracture increases over 5 years	12
Rizzari *et al.*	**Living Donor:** *Recipients w/ Diabetes*: 4% 1 year; 16% 5 years; 33% 10 years *w/o Diabetes:*1% 1 year; 5% years; 10% 10 years **Deceased Donor:** *Recipients w/ Diabetes:* 6%1 year; 15% 5 years; 23% 10 years *w/o Diabetes:*3% 1 year; 7% 5 years; 9% 10 years	NR	NR	11

NR-not reported; RR, relative risk; CI, confidence interval.
† hip only location assessed;¶ foot only region assessed

The aforementioned studies have several limitations worth noting. First, none of the studies included Canadian kidney transplant recipients and therefore may not accurately reflect Canadian recipients' fracture rate. In the general population fracture rates have been found to vary as much as 15-fold across countries (74). For example, Leslie *et al.* found that proximal femoral fracture rates were significantly lower in Canadian women compared to women from the U.S. with Canadian women having a 30% lower fracture rate (85). Additionally, differences in transplant outcomes and transplant characteristics exist across countries (86). For example, there are differences in mortality in recipients from the United States and Canada (e.g. 29.8 deaths per 1000 person-years, Canada: 40.9 deaths per 1000 person-years, United States) and differences in recipient characteristics (e.g. Canadians have more male kidney transplant recipients [63.8% versus 60.0%]) (86). Previous work supports that Canadian kidney transplant recipients may have a different fracture rate compared to recipients from other countries. For example, in a study which included kidney transplant recipients (n=458) from Manitoba, Canada, Naylor *et al.* found the 10-year observed major osteoporotic fracture risk was only 6.3% (defined as a composite of hip, forearm, proximal humeurs, and clinical vertebral fractures) (87); clinical guidelines define high fracture risk as a 10-year major osteoporotic risk $\geq$ 20% and low fracture risk < 10% (2, 88, 89). However, the low observed fracture risk in the Naylor *et al.* study may not accurately reflect the fracture rate of Canadian recipients as recipients were approximately 5 years younger (mean age 45 years) than the average age of a Canadian recipient (87). Moreover, cohort entry was an average of 1-year post-transplant (87); recipients may have a rapid loss in bone mineral density and a higher fracture risk in the first year post-transplant, consequently fracture events may have been missed (77, 90-93). Second, previous studies did not have long-term follow-up. The largest studies to assess fracture risk in kidney transplant recipients have all used the United States Renal Data System (USRDS) (19, 41-43); a major limitation of this data source is that after 3 years all data is censored for recipients less than 65 years of age, preventing long-term follow-up. Specifically, the average follow-up of previous studies was less than 6 years, limiting discussion on long term fracture risk. With over 80% of recipients surviving 5 years post-transplant long-term follow-up is crucial (27). Third, close to half of studies included only one fracture

location (e.g. foot fractures) preventing a precise estimate of fracture incidence (63). Fourth, studies may not be representative of the current recipient population. Only four out of ten studies included recipients of kidney transplants after the year 2000 (63); the characteristics of recipients (e.g. comorbidities) and clinical practice patterns have changed in the last 10 years, potentially impacting fracture rates (20, 94). Specifically, the age of Canadian recipients has increased with approximately 27% over the age of 60 years in 2003 and 35% in 2012 (increasing age is a risk factor for fracture (68, 73, 95)) (20); there has also been a trend towards decreasing corticosteroid dose (81, 96). This hypothesis is supported by a study which found hip fracture rates in kidney transplant recipients from the United States have decreased from 1997 to 2010 ($P<0.001$); they hypothesized that potential reasons for this decrease were decreased corticosteroid dose, decrease in acute rejection episodes, increase in tacrolimus (may decrease bone loss compared to cyclosporine) (97), and lifestyle changes (e.g. physical activity) (93). Last, only one study reported on loss to follow-up and reasons for losses (63). This is a serious concern that threatens the validity of most prior studies, particularly if there were differential losses to follow-up (80). Therefore, the true incidence of fracture in kidney transplant recipients is unknown.

2.5.2 Fracture Risk in Kidney Transplant Recipients Compared to Several Referent Groups

Previous studies have compared fracture rates in kidney transplant recipients to the non-kidney disease population and to the dialysis population (39, 77, 87, 98). However, no previous studies have compared fracture rates in kidney transplant recipients to other referent groups. The use of referent groups is crucial to help quantify fracture risk among kidney transplant recipients. One group that is defined by Osteoporosis Canada as low fracture risk and four groups that are defined as having an increased fracture risk are described in detail below (99).

2.5.2a Healthy Segment of the General Population with No Kidney Disease and No Previous Non-vertebral Fracture (Low fracture risk)

Three previous studies have compared fracture risk in kidney transplant recipients to the general population (39-41). However, no previous studies have compared fracture rates in kidney transplant recipients to individuals without kidney disease excluding

individuals who have had a prior non-vertebral fracture and/or an osteoporosis diagnosis. The benefit of the aforementioned exclusion criteria is it helps ensure this is truly a low risk referent group. Studies that have compared kidney transplant recipients to individuals from the general population have suggested that kidney transplant recipients are at an increased risk of fracture, with Abbott *et al.* describing an incidence ratio of 4.59 (95% CI 3.29-6.31) (39). Similarly, Ramsey-Goldman *et al.* found that male kidney transplant recipients ages 25-44 and 45-64 years had a five-time higher fracture risk compared to the general male population of a similar age (41). Particularly concerning is the potentially high hip fracture rate in kidney transplant recipients compared to the general population (39, 81). Ball *et al.* found an incidence rate of 3.3 hip fractures per 1000 person-years (approximately 80% of the sample was ≤ 54 years) (77). In contrast, hip fracture rates in the general Canadian population (age <54 years) are less than 0.1 fractures per 1000 person-years (14).

2.5.2b Healthy Segment of the General Population with No Kidney Disease and a History of Non-vertebral Fracture (Increased fracture risk)

No previous studies have compared fracture rates in kidney transplant recipients to individuals without kidney disease who have previously sustained a non-vertebral fracture. In the non-transplant population, one of the strongest risk factors for a future fracture is sustaining a previous osteoporotic fracture (100). A meta-analysis conducted in the non-transplant population found that individuals who had sustained a previous fracture had an 86% relative increase in fracture compared to individuals who had not sustained a previous fracture (relative risk [RR] 1.86, 95% CI 1.75-1.98) (100).

2.5.2c Non-dialysis Chronic Kidney Disease (CKD) (Increased fracture risk)

No previous studies have compared fracture rates in kidney transplant recipients to individuals with CKD (excluding patients on dialysis). As described in section 2.4, previous literature has found that individuals with CKD are at an increased risk of fracture compared to individuals with normal kidney function (35-37). For example, Dooley *et al*. found that there was a 439% relative increase in hip fracture risk in individuals with stage 4 CKD compared to individuals with normal kidney function (RR 5.39, 95% CI 2.86 to 10.15) (37).

2.5.2d Rheumatoid Arthritis (*Increased fracture risk)*

No previous studies have compared fracture rates in kidney transplant recipients to individuals with rheumatoid arthritis. Rheumatoid arthritis is a well-established risk factor for fracture due to the use of steroids and the disease itself (101, 102). Van Staa *et al.* found that individuals with rheumatoid arthritis have a 100% relative increase in hip fracture (RR 2.0, 95% CI 1.8-2.3) compared to age- and sex-matched individuals without rheumatoid arthritis (102).

2.5.2e Dialysis (Increased fracture risk)

It is well established that dialysis patients have a high fracture risk with 1 in 10 (9.6%) women aged ≥ 65 years sustaining a fracture (defined as proximal humerus, forearm, hip, or pelvis) in the first 3 years of end-stage renal disease (29). Two previous studies have compared fracture risk in kidney transplant recipients to the dialysis population (77, 87). Ball *et al.* found that shortly after transplant hip fracture risk was higher in recipients compared to the dialysis population on the transplant waitlist (RR 1.34, 95% CI 1.12-1.61). However, this study only assessed hip fracture and included recipients who received a transplant over 10 years ago; as previously discussed changes in recipient characteristics and practice patterns may have affected fracture rates (7, 77). In contrast, Stehman-Breen *et al.* found that kidney transplant recipients and the hemodialysis population had a comparable hip fracture risk with kidney transplant recipients having a slightly higher risk, but this did not reach statistical significance (RR 1.1, 95% CI 0.4-2.9) (87). However, this study included all end-stage renal disease patients instead of restricting to individuals on the transplant waitlist; to make health status comparable previous literature recommends comparing recipients to individuals on the transplant waitlist (77, 103).

2.6 Risk Factors for Fracture in Kidney Transplant Recipients

Six previous studies reported on risk factors for fracture in kidney transplant recipients and their associated effect measures (39, 77, 78, 80-82) (Table 2.5). Risk factors for fracture in kidney transplant recipients were variable across studies. The most common factors found to be associated with an increased risk of fracture included: older age, female sex, diabetes, and dialysis prior to transplant. Other risk factors associated

with fracture in recipients included previous history of fracture, the induction regimen used to immunosuppress the recipient, type of donor (living *versus* deceased), and year of transplant. Potential reasons for the variation in risk factors across studies include inclusion of different recipient populations, inclusion of different fracture locations, and the use of different statistical models (i.e., backward elimination versus forward selection) with different p-values to determine which variables should be included in the multivariable model (104).

Unlike the transplant population, risk factors for fracture in the general population are well-established and include: older age, female sex, low body mass index (BMI), history of fracture, family history of a parent fracturing a hip, glucocorticoid use, rheumatoid arthritis, smoking, low bone mineral density (BMD [g/cm^2]), secondary osteoporosis (e.g. type 1 diabetes), previous fall and drinking ≥ 3 units of alcohol a day (2). Kidney transplant recipients may have different risk factors for fracture given the unique pathophysiology that underlies their bone disease (105). For example, many of the common risk factors for fracture in the general population (e.g. age, sex, BMI) are not consistently associated with fracture in kidney transplant recipients (Table 2.5). In a study conducted by Naylor *et al.* it was found that the only common risk factor for major osteoporotic fracture in the general population that reached statistical significance in kidney transplant recipients was high alcohol use (87). However, this study had a small sample size (n=326) and therefore may have had inadequate statistical power (87). Moreover, a recent study found that a parathyroid hormone level >130 ng/L was a unique and independent risk factor for fracture (adjusted hazard ratio 7.5, 95% CI 2.2 -25.5) in kidney transplant recipients while age, sex, and BMI did not reach statistical significance; however, this may have been due to limited power (106).

The aforementioned studies had a few limitations. Previous studies failed to assess potentially relevant risk factors of fracture. In the kidney transplant population no previous studies have assessed fall in the year prior to transplant as a risk factor for fracture. Falls have been found to be associated with an increased fracture risk in the general population (72, 107). Previous studies have also failed to assess risk factors specific to different fracture locations; in the general population different fractures sites

have been found to have unique risk factors (108, 109). For example, increasing age may not be associated with an increased risk of ankle fracture (110).

Table 2. 5. Fracture risk factors in kidney transplant recipients

Risk factor	Number of studies that assessed risk factor	Number of studies with significance	Author, Effect measures* (95% Confidence Interval)
Older age	**4**	**3**	
45-65	1	1	Nikkel (2012), HR 1.14 (1.10-1.18) Reference (<45 years)
50-65	1	1	Nikkel (2009), HR 1.76 (1.59-1.94) Reference 18-50
>65 years	2	2	Nikkel (2009), HR 3.27 (2.91-3.67) Reference 18-50 Nikkel (2012), HR 1.69 (1.58-1.81) Reference (<45 years)
Continuous (per year)	2	1	Abbott, OR 1.02 (1.03-1.04)
Female sex	**4**	**3**	Nikkel (2012), HR 1.36 (1.32-1.40) Reference male Nikkel (2009), HR 1.42 (1.31-1.55) Reference male Abbott, OR 1.29 (1.02-1.64) Reference male
Combined age gender interaction	**1**	**1**	*Opelz*
Female aged 40 to 59	1	1	HR 2.26 (1.09-4.68)
Female recipients ≥ 60 years of age	1	1	HR 5.14 (2.43-10.9)
Male recipients ≥ 60 years of age	1	1	HR 2.39 (1.10-5.20)
Diabetes	**5**	**4**	
Diabetes (Type 1 and Type2)		3	Abbott, OR 1.97 (1.46-2.66) Reference no diabetes Nikkel (2009), HR 1.39 (1.18-1.64) Reference hypertension Nikkel (2012), HR 1.41 (1.25-1.59) Reference no diabetes
Type 1 diabetes		1	Conley, HR 2.02 (1.18-3.48) Reference no diabetes
Pre-transplant dialysis	**6**	**4**	
Per year of dialysis prior to transplantation		2	Abbott, OR 1.74 (1.02-2.96) Nikkel (2009), HR 1.04 (1.03–1.06)
Dialysis treatment 3 to 12 months before transplantation		1	Ball, RR 1.67 (1.22- 2.29) Reference recipients on dialysis for less than 3 months
Administration of pre-transplant dialysis		1	Nikkel (2012), HR 1.08 (1.04-1.13) Reference no pre-transplant dialysis
Prior Fracture	**2**	**2**	
Hospitalization for fracture prior to transplant		1	Abbott, OR 2.82 (1.06-5.14) Reference no prior fracture
Fracture between ESRD and transplant		1	Nikkel (2009), HR 2.82 (2.33-3.43) Reference no prior fracture
Donor type	4	**2**	
Deceased		2	Nikkel (2012), HR 1.30 (1.19-1.42) Reference living donor Nikkel (2009), HR 1.36 (1.24-1.49) Reference living donor

Table 2.5. Fracture risk factors in kidney transplant recipients (continued)

Risk factor	**Number of studies that assessed risk factor**	**Number of studies with significance**	**Author, Effect measures**[*] (95% Confidence Interval)
Race	**5**	**3**	
White	1	1	Abbott, OR 1.66 (1.24-2.24) Reference black
Asian	1	1	Nikkel (2012), HR 0.34 (0.26-0.47) Reference white
Black	2	2	Nikkel (2009), HR 0.81 (0.78-0.85) Reference white Nikkel (2012), HR 0.63 (0.56- 0.7) Reference white
Other	2	1	Nikkel (2009), HR 0.54 other (0.48-0 .61) Reference white
Donor Age	**1**	**1**	
Donor age ≥ 60 years of age		1	Opelz, HR 1.75 (1.15 -2.66) reference donors < 60 years of age
Body Mass Index (Kg/m^2)	**5**	**1**	*Nikkel* (2012)
<18		1	OR 1.39 (1.08-1.78) Reference BMI 18-25
25-30		1	OR 0.87 (0.78-0.96) Reference BMI 18-25
>30		1	OR 0.83 (0.75-0.93) Reference BMI 18-25
Weight	**1**	**1**	*Abbott*
< 48.6 kg		1	OR 2.01 (1.38-2.94) Reference Weight >95.9 kg
48.6–72.3 kg		1	OR 1.86 (1.32-2.63) Reference Weight >95.9 kg
72.4–95.9 kg		1	OR 1.77 (1.26-2.49) Reference Weight >95.9 kg
Glomerulonephritis (as cause of kidney failure)	**4**	**2**	Abbott, OR 0.51 (0.32-0.82) Reference no glomerulonephritis Nikkel (2009), HR 0.53 (0.51-0.56) Reference diabetes
Hypertension (as cause of kidney failure)	**3**	**1**	Nikkel (2009), HR 0.56 (0.53-0.59) Reference diabetes
Femoral neck T-score at baseline[†] (lower T-score indicative of greater risk) (continuous: SD)	**1**	**1**	Conley, HR 0.69 (0.57 -0.86)
Interleukin-2 receptor blockade	**1**	**1**	Conley, HR 0.40 (0.25-0.66) Reference no Interleukin-2 receptor blockade
y-GT, gamma-glutamyltransferase (continuous: units/litre)	**1**	**1**	Conley, HR 1.005 (1.0034-1.0076)
urine protein to creatinine ratio (continuous: gram/gram)	**1**	**1**	Conley, HR 1.23 (1.05-1.45)
Human leukocyte antigen mismatches	**3**	**1**	
1 HLA-DR mismatch		1	Opelz, HR 1.85 (1.18 -2.89) Reference zero HLA-DR mismatch
2 HLA-DR mismatch		1	Opelz, HR 2.24 (1.25-4.02) Reference zero HLA-DR mismatch

Table 2.5. Fracture risk factors in kidney transplant recipients (continued)

Risk factor	Number of studies that assessed risk factor	Number of studies with significance	Author, Effect measures* (95% Confidence Interval)
Induction regimen	**5**	**2**	
Early steroid withdrawal		1	Nikkel (2012), HR 0.69 (0.59-0.81) Reference steroid-based regimen
Dual induction¥ vs no induction		1	Nikkel (2012), HR 1.14 (1.08-1.20) Reference no induction
Transplant date	**3**	**1**	
Quartiles of transplant date (continuous: per increase in quartile)‡		1	Abbott, OR 0.82 (0.72-0.92)

Note: Nikkel (09), Nikkel (12), Abbott and Ball all provided adjusted effect measures. We excluded four studies from the risk factor analysis that did not use multivariable methods to ascertain risk factors. Therefore, five studies is the highest number of studies assessed for this risk factor. One additional study was included for pre-transplant dialysis resulting in six studies as the maximum number of studies assessed for this risk factor

*A value greater than 1 indicates that the group of patients with the factor had a higher risk of fracture compared to the reference group and a value lower than 1 indicates that the group of patients with the factor had a lower risk of fracture compared to the reference group.

Abbreviations: ESRD, end stage renal disease; HLA-DR mismatch, human leukocyte antigen-DR mismatch

†t-score measured as the number of standard deviations below the average peak bone density of a young adult

¥ Dual induction is defined as a combination of methylprednisolone and an antibody-based induction agent

‡ Quartiles of transplant date defined as July 1, 1994-Apriil 12, 1995, April 13, 1995- January 9, 1996, January 10, 1996 –October 3, 1996, October 4, 1996 –June 30, 1997

2.7 Bone Mineral Density Testing in Kidney Transplant Recipients

Kidney transplant recipients may be a high risk group for fracture and as a result assessing bone health may be beneficial. One way to assess bone health is to perform a bone mineral density (BMD) test; the results of the test are used to guide treatment decisions for fracture prevention and to monitor the effectiveness of treatment (2, 111, 112). In the general population a lower BMD associates with a higher fracture risk and higher mortality risk (113-116). Osteoporosis Canada guidelines recommend that in the general population all individuals ≥ 65 years of age have a BMD test (2). Conversely, in the kidney transplant population the KDIGO guidelines for CKD-MBD recommend testing in the first three months after transplantation when kidney function is adequate (defined as an eGFR > 30 mL/min/1.73 m^2) and there is evidence of osteoporosis risk factors or corticosteroid administration (44). However, this guideline received a weak recommendation given the lack of evidence that BMD can accurately predict fracture in kidney transplant recipients (44). Moreover, it is suggested by the KDIGO guidelines that given the high prevalence of adynamic bone disease (i.e., low turnover bone disease) it is reasonable to use a bone biopsy to guide treatment decisions instead of the result of the BMD test; however, this recommendation was not graded (44).

Despite the lack of evidence in the literature demonstrating the benefit of BMD testing in kidney transplant recipients, previous single centre studies describe a large number of BMD tests in this population (117, 118). For example, Naylor *et al.* reported more than 1000 BMD tests over an 8 year period in kidney transplant recipients (n=326) from Manitoba, Canada (117). Similarly, Akaberi *et al.*, reported more than 600 BMD tests over a 12 year period in kidney transplant recipients (n=238) from Sweden (118). However, both of these studies were performed at a single centre which mandated routine BMD testing. No studies have assessed the frequency of BMD testing in Ontario, where many transplant centers have no fixed protocol for BMD testing post-transplant (personal communication with the centres). Given the negative impact of unwarranted screening and the financial costs to the healthcare system this deserves further investigation (119, 120).

2.8 Conclusion

Despite the health and economic impact of fractures, there is currently a gap in knowledge about the epidemiology of fracture in adults with kidney disease. As highlighted in this literature review, many questions remain unanswered and several limitations of previous studies need to be addressed. As the kidney disease population continues to increase and survival continues to improve the economic burden this population may place on the healthcare system due to fracture events may increase. In the non-kidney disease population fracture prevention therapies (e.g. bisphosphonates) have proven successful (121-123); however, in the kidney disease population the efficacy and safety of such therapies has not been determined (44, 124). Furthermore, many of the KDIGO guideline's for the evaluation and treatment of bone disease in kidney disease patients received a weak grade of evidence or are ungraded (44). Therefore, it is crucial that a paradigm shift in bone disease research occurs towards understudied populations who have not experienced success in fracture prevention. This research will provide a better understanding of the epidemiology of fracture in kidney disease patients which is required before much needed well designed clinical trials and prospective cohort studies can be conducted. Moreover, an improved understanding of fracture will provide the information needed for an in-depth discussion of fracture in kidney disease patients in future kidney disease guidelines and osteoporosis guidelines.

2.9 Conceptual Model

Figure 2.4 demonstrates the hypothesized relationship between kidney disease and fracture.

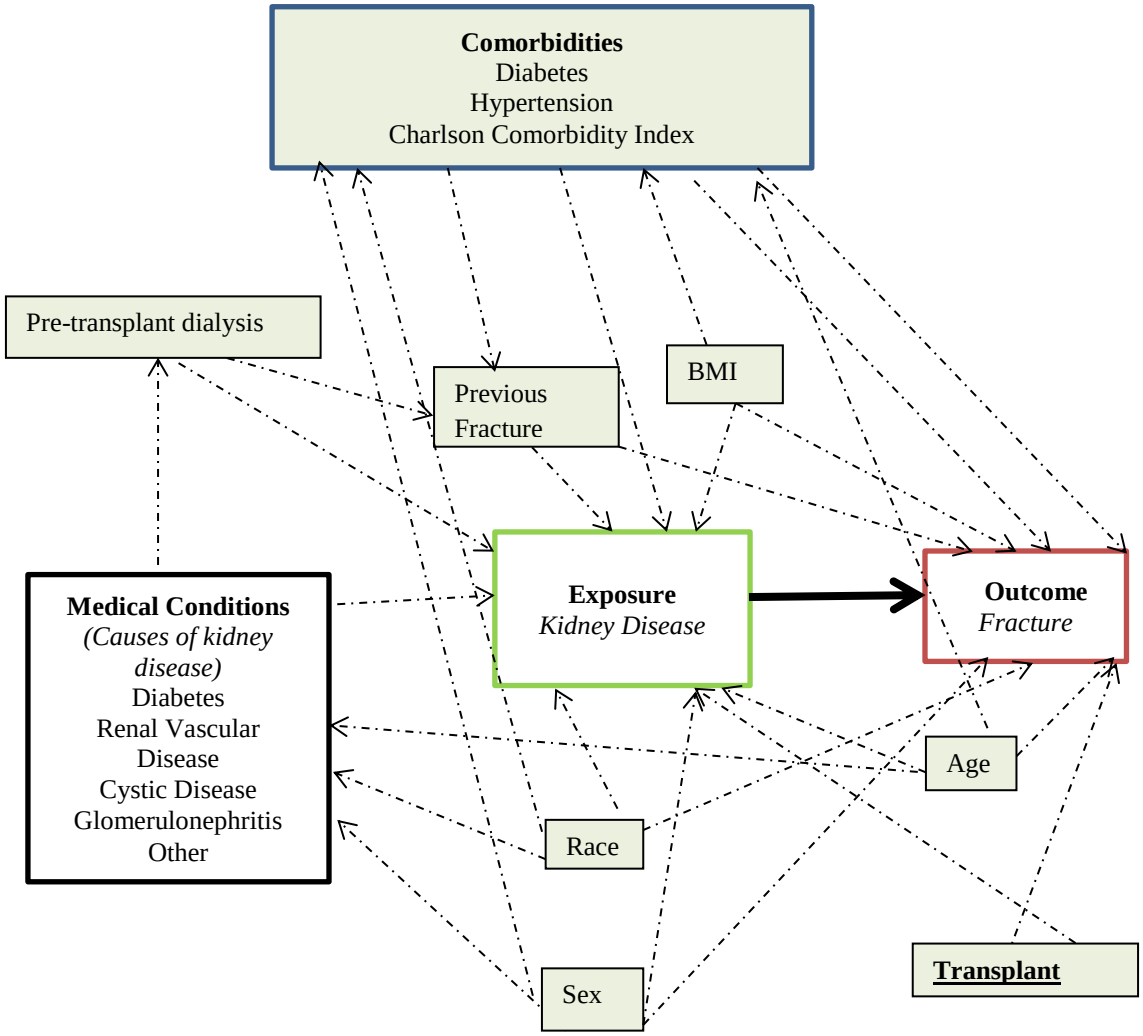

Figure 2. 4. Conceptual model of the hypothesized relationship between kidney disease and fracture.

**It is important to note that the word that is bolded and underlined is only specific to kidney transplant recipients.*

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CHAPTER 3: Comparison of fracture risk prediction among individuals with reduced and normal kidney function[a]

[a]A version of this chapter has been published elsewhere as: Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WD, Fraser LA, Adachi JD, Morin S, Goltzman D, Lentle B, Jackson SA, Josse RG, Jamal SA. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *CJASN* 2015; 10:646-653.

3.1 Introduction

The World Health Organization's Fracture Risk Assessment Tool (FRAX) is used commonly in the general population to predict the 10-year probability of a major osteoporotic fracture (defined as hip, forearm, clinical vertebral, and humerus fractures) using an algorithm that includes age, sex, and several clinical risk factors for fracture (bone mineral density optional) (1, 2). The clinical risk factors for fracture incorporated in the FRAX algorithm include: parental hip fracture, previous fragility fracture, rheumatoid arthritis, current smoking, secondary osteoporosis (which does not include chronic kidney disease), low body mass index (<19 kg/m^2), prolonged glucocorticoid use, and excessive alcohol intake (3-7).

Men and women with chronic kidney disease (CKD) have a high fracture risk (8-11). For example, women with moderate declines in kidney function (estimated glomerular filtrate rate 45-59 mL/min/1.73 m^2) are at almost a 4-fold increased risk of fracture compared to women with normal kidney function (11). The clinical utility of FRAX in predicting fracture risk in patients with reduced kidney function is uncertain. CKD is associated with disturbances in mineral metabolism including changes in calcium, phosphate, and parathyroid hormone which likely alter bone volume, turnover, and mineralization increasing fracture risk (12). Therefore, factors in the FRAX algorithm that are associated with fracture risk in the general population may not accurately predict fracture in individuals with reduced kidney function. One prior study has reported on the prognostic value of FRAX in individuals with reduced kidney function, however, this study was cross-sectional and did not include a comparison group of individuals with normal kidney function (13). The current study addresses these limitations. We utilized data from a multicentre cohort study (Canadian Multicentre Osteoporosis Study – CaMos) to characterize the predictive ability of FRAX in patients with reduced kidney function, and to determine if the predictive ability differs from individuals with normal kidney function. As a secondary analysis we examined the ability of FRAX to predict fracture when adding CKD as a secondary cause of osteoporosis in individuals with reduced kidney function. We also assessed the ability of age, T-score, and T-score with a history of fall to predict fractures in both groups.

3.2 Methods

3.2.1 Canadian Multicentre Osteoporosis Study (CaMos)

CaMos is a prospective observational study that began in January 1996 (14). Detailed methods concerning CaMos have been published elsewhere (14, 15) (Appendix C). Briefly, non-institutionalized individuals were eligible to participate in CaMos if they were ≥ 25 years of age at the start of the study, lived within a 50 kilometer radius of 1 of 9 major Canadian cities (St. John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Calgary, Vancouver, and Saskatoon) and could speak English, French or Chinese (14). Residential phone numbers were used to randomly select households and within households one member who met eligibility criteria was randomly selected; at baseline interview 42% of participants contacted agreed to participate (14). In January 1996 participants completed a standardized interviewer-administered questionnaire; the questionnaire was subsequently administered every 5 years. The questionnaire assessed demographics, medication use, nutrition, general health, medical history, fracture risk factors, and fracture events (14). Bone mineral density, weight and height were also assessed at baseline and every five years (14). In year 10 blood samples were obtained and serum stored from participants in 8 out of the 9 study centres. Serum creatinine was analyzed by CDL Labs, Montreal. In agreement with the Helsinki Declaration, written informed consent was provided by study participants. Ethics approval was obtained from McGill University and from each study centre's applicable ethic review board.

3.2.2 Cohort

The beginning date of our present study (cohort entry) was the CaMos study year 10 – the first time 8 out of the 9 centres assessed blood work. For this analysis, we included individuals who met the following criteria at cohort entry: 1) men and women who were ≥40 years of age, 2) those who had a creatinine value, 3) femoral neck bone mineral density (BMD) measurement, and 4) no prior organ transplant. Creatinine values were missing in those who did not sign the consent form for blood and in those who were from Hamilton (centre that did not collect blood work). We calculated the estimated glomerular filtration rate (eGFR) using the CKD epidemiology collaboration equation (16). We defined kidney function at cohort entry using thresholds defined in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines (17); an eGFR <60

mL/min/1.73 m^2 was defined as reduced kidney function and an eGFR ≥60 mL/min/1.73 m^2 was defined as normal kidney function. We used this classification for our primary analysis. To characterize the degree of renal impairment we further stratified kidney function in individuals with an eGFR <60 mL/min/1.73 m^2 according to the 2012 KDIGO guidelines: 45–59 (stage 3a), 30–44 (stage 3b), 15–29 (stage 4), and <15 mL/min/1.73 m^2 (stage 5) (17).

3.2.3 Bone Mineral Density

Bone mineral density (BMD) was measured at the femoral neck using the Hologic QDR dual energy x-ray absorptiometry scanner (Marlborough, MA, USA) at four centres and the Lunar scanner (Piscataway, NJ, USA) at 5 centres. Each centre used a spine phantom to monitor longitudinal stability. Standard methods were used to convert lunar data to corresponding Hologic values (18-21). The Bio-Imaging Bona Fide Phantom (Bio-Imaging Technologies, Newtown, PA, USA) was used to calibrate densitometers at all centres and the coordinating centre re-analyzed measurements from each centre. Details on the BMD quality assurance-quality control program and cross-calibration have been published elsewhere (22). As recommended by the World Health Organization we calculated femoral neck T-scores for both genders by comparing each individual's BMD to the Third National Health and Nutrition Examination Survey reference range for white females aged 20-29 years (23).

3.2.4 Fracture Ascertainment

Data on incident clinical fractures were collected over 5 years after cohort entry by self-report from a yearly postal questionnaire or in-person assessment (year 15 of the CaMos study) (15). Fractures were confirmed by: structured interview to determine further information (date, fracture location, medical treatment, and cause of fracture [i.e., fall]) and/or verification from the treating physician or hospital (15). We defined fracture as a composite of incident clinical spine, hip, forearm/wrist, and humerus fractures (major osteoporotic fractures) that resulted from low trauma.

3.2.5 Fracture Risk Assessment using FRAX

We used the Canadian FRAX tool (FRAX® Desktop Multi-Patient Entry, version 3.7) to calculate the 10-year probability of a major osteoporotic fracture (with and without BMD).(3) The US and Canadian versions of FRAX are derived using identical

methodology and give similar results with regards to fracture prediction (24, 25). A complete list of the variables we used to calculate the FRAX score is provided in Table 3.1. Body mass index (BMI) was calculated at cohort entry by dividing weight (kg) by height squared (m^2). When BMI (kg/m^2) was missing at year 10 we carried forward values from year 5 of the CaMos study (<0.5% missing). We defined rheumatoid arthritis as a self-report of a diagnosis of rheumatoid arthritis combined with evidence of treatment (prednisone, betamethasone, methotrexate, hydroxychloroquine, leflunomide, etanercept, infliximab, sulfasalazine, adalimumab). Prior corticosteroid use was defined as use of intravenous or oral glucocorticoids for ≥ 3 months from baseline to cohort entry. Previous fracture was defined as any low trauma fracture (excluding hands, feet, head, and ankle) occurring prior to cohort entry. History of parental hip fracture was defined using self-report at year 5 of CaMos. All other clinical risk factors were based on self-report at cohort entry or before.

Table 3. 1. Variables used in FRAX Tool

Variable
Age
Sex
Weight (kg)
Height (cm)
Parental hip fracture
Previous fracture
Prolonged use of glucocorticoids
Current smoking
Alcohol use ≥ 3 units/day
Secondary osteoporosis *(Defined as: chronic liver disease, type I diabetes, hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition/malabsorption and osteogenesis imperfect)*
Rheumatoid arthritis
Femoral neck BMD (T-score) is optional

Sources: 1. FRAX World Health Organization Fracture Risk Assessment Tool [Internet]. World Health Organization; 2011. Available from http://www.shef.ac.uk/FRAX/index.aspx. 2. Kanis JA, McCloskey EV, Johansson H, Strom O, Borgstrom F, Oden A. How to decide who to treat. *Best Pract Res Clin Rheumatol* 2009; 23: 711.

3.2.6 Statistical Analysis

We described continuous variables as means (±SD) or median (interquartile range) and categorical variables as proportions. To compare baseline characteristics between adults with an eGFR <60 versus ≥60 mL/min/ 1.73 m^2 we used the Student *t* test or Mann-Whitney U for continuous variables and chi-square test or the Fisher's Exact tests where appropriate for categorical variables. We used area under the receiver operator characteristic curve to determine how well FRAX could discriminate between individuals with a fracture and without a fracture (null value was defined as an area under the curve value of 0.5 which indicates that the ability of FRAX to discriminate fracture is no better than chance) (26). To assess differences in fracture discrimination between individuals with an eGFR <60 and ≥60 mL/min/1.73 m^2 we calculated mean differences (95% confidence interval) using the two-tailed z test. In an additional analysis we assessed the predictive discrimination of FRAX (without BMD) including CKD as a cause of secondary osteoporosis in all individuals with an eGFR <60 mL/min/1.73 m^2. The rationale for this was that we wanted to capture some of the unique risk factors for fracture in CKD patients that are currently not included in the FRAX algorithm (12). It is important to note that only FRAX without BMD can be assessed when including CKD as a secondary cause of osteoporosis because FRAX assumes that secondary causes of osteoporosis effect fracture risk through lowering BMD. We had a maximum of 5 years of follow up. As a result, to calculate the estimated fracture risk in the cohort using FRAX we divided the FRAX 10-year risk by two. The 5-year observed fracture probabilities and 95% confidence intervals were calculated using a survival analysis method that adjusts for the competing risk of death (27). To assess calibration (defined as the agreement between observed and predicted values) we compared the 5-year FRAX estimated fracture risk with the 5-year observed fracture risk. We performed all statistical analysis using the Statistical Analysis System (SAS version 9.3, SAS Institute, Cary, NC, USA). We considered two-sided p-values <0.05 as statistically significant.

3.3 Results

3.3.1 Baseline Characteristics

We included 320 adults with an eGFR <60 mL/min/1.73 m^2 and 1787 adults with an eGFR ≥60 mL/min/1.73 m^2 (Figure 3.1). During follow-up, 3.3% (n=69) died (5.9% [n=19] with an eGFR <60 and 2.8% [n=50] with an eGFR ≥60 mL/min/ 1.73 m^2) and 3.8% (n=81) were lost to follow-up (8.4% [n=27] with an eGFR <60 and 3.0% [n=54] with an eGFR ≥60 mL/min/ 1.73 m^2). Of the adults with an eGFR <60 mL/min/1.73 m^2 72.2% (n=231) had stage 3a CKD, 23.8% stage 3b (n=76), and 4.0% (n=13) had stage 4 or stage 5. Compared to individuals with an eGFR ≥60 individuals with an eGFR <60 mL/min/1.73 m^2 were older (75.9 vs. 65.6 years; P<0.001) (Table 3.2). When comparing individuals with an eGFR <60 to individuals with an eGFR ≥60 mL/min/1.73 m^2 individuals with reduced kidney function were more likely to have type 2 diabetes (13.1% vs. 6.6%; P<0.001), more likely to have sustained a previous fracture (25.3% vs. 17.1%; P<0.001), were less likely to report good, very good or excellent health (87.5% vs. 93.6%; P<0.001), and self-reported bisphosphonate use was similar between the two groups (26.9% vs. 23.5%; P=0.19).

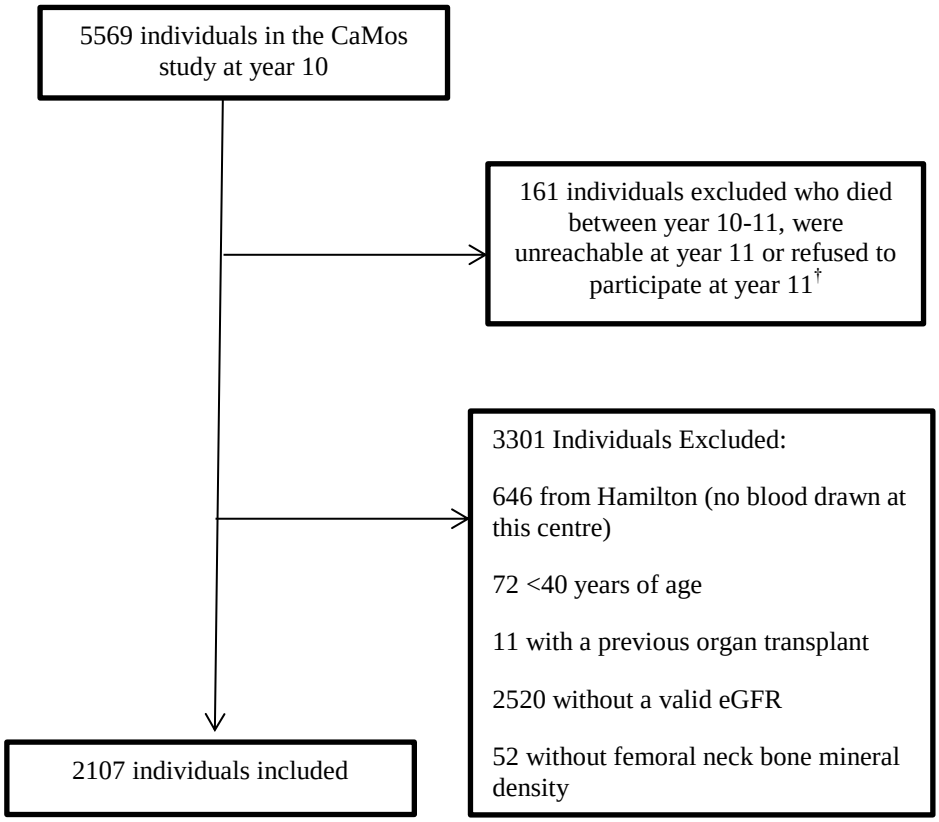

Figure 3. 1. Study Cohort

†Individuals who died or were not reachable at year 11 were excluded as we would not able to obtain fracture data from these individuals.

Table 3. 2. Baseline characteristics by estimated glomerular filtration rate[¥]

Characteristic	*Estimated glomerular filtration rate (eGFR)*		
	<60 mL/min/1.73 m^{2}[‡] (n=320)	**≥60** mL/min/1.73 m^{2} (n=1787)	***P* Value**
FRAX Variables			
Women	227 (70.9%)	1258 (70.4%)	0.85
Age (yrs)	75.9 ± 7.2	65.6 ± 9.9	<0.001
Body mass index (kg/m^{2})	27.6 ± 4.6	27.1 ± 4.7	0.09
<18.5	1 (0.3%)	23 (1.3%)	
18.5-24.9	102 (31.9%)	595 (33.3%)	
25-29.9	134 (41.9%)	737 (41.2%)	
≥30	83 (25.9%)	432 (24.2%)	
Previous fracture	81 (25.3%)	306 (17.1%)	<0.001
Parent fractured hip	35 (10.9%)	232 (13.0%)	0.31
Current smoking	24 (7.5%)	156 (8.7%)	0.47
Corticosteroid use for >3 months	11 (3.4%)	22 (1.2%)	0.003
Rheumatoid arthritis	3 (0.94%)	13 (0.7%)	0.72
Secondary osteoporosis[¶]	22 (6.9%)	66 (3.7%)	0.009
≥ 3 alcoholic beverages per day	0 (0%)	21 (1.2%)	0.06
Femoral neck T-score	-1.27 ± 0.96	-1.01 ± 1.02	<0.001
Comorbidities			
Estimated glomerular filtration rate[†]	49.5 ± 9.0	81.3 ± 11.5	<0.001
Stage 3a	231 (72.2%)		
Stage 3b	76 (23.8%)		
Stage 4/5	13 (4.0%)		
Fall in the past 12 months	77 (24.1%)	465 (26.0%)	0.46
Bisphosphonate use[€]	86 (26.9%)	420 (23.5%)	0.19
Hypertension	186 (58.1%)	577 (32.3%)	<0.001
Type 2 Diabetes	42 (13.1%)	117 (6.6%)	<0.001
Kidney stones	37 (11.6%)	140 (7.8%)	0.03

Excellent, very good or good self-reported current health	280 (87.5%)	1673 (93.6%)	<0.001
≥ Post-secondary education	154 (48.1%)	1067 (59.7%)	<0.001
Lab Values			
Albumin (g/L)	43.7 ± 2.7	44.6 ± 2.5	<0.001
Parathyroid hormone[*] (pg/mL)	62.6 (48.0-85.4)	56.1 (44.2-71.1)	<0.001
Missing	36 (11.3%)	293 (16.4%)	
Hyperparathyroidism (*defined as >65 pg/mL*)	126 (44.4%)	491 (32.9%)	<0.001
Serum 25(OH)D (ng/mL)	28.2± 10.6	28.3± 9.7	0.89
Missing	30 (9.4%)	262 (14.7%)	
Low serum 25(OH)D *(defined as <30 ng/mL)*	172 (59.3%)	914 (60.1%)	0.84
Serum calcium (mg/dL)	9.6 ± 0.5	9.5 ± 0.4	0.02
Serum phosphate (mg/dL)	3.7 ± 0.5	3.4 ± 0.5	0.007
Total vitamin D (includes supplements, mcg/day)	6.7 (0-16.3)	6.7 (0-15.0)	0.61
Total Calcium (includes food and supplements, mg/day)	1249.5 (782.9-1697.2)	1211.6 (764.5-1719.8)	0.94

Data are Mean ± SD, median (interquartile range), or N (%).
Abbreviations: BMD, bone mineral density; FRAX, Fracture Risk Assessment tool
[¥]Baseline characteristics were taken at year 10 of the study.
[†]eGFR calculated using the chronic kidney disease epidemiology collaboration equation
[‡] Estimated glomerular filtration rate <60 mL/min/ 1.73 m^2 encompasses stages 3a, 3b, 4, and 5 chronic kidney disease as defined by the Kidney Disease Improving Global Outcomes Guidelines.
[€] Defined as a composite of alendronate, clodronate, etidronate, risedronate, ibandronate, pamidronate, zoledronate at cohort entry.
[¶]Defined as any of the following: chronic liver disease, type I diabetes, hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition/malabsorption and osteogenesis imperfecta. Source: *World Health Organization: FRAX World Health Organization Fracture Risk Assessment Tool, 2011. Available at: http://www.shef.ac.uk/FRAX/index.aspx. Accessed May 20, 2014.*
[*] Reference range for the PTH assay was 21.8-104.5 pg/mL and was measured by the Liaison (Diasorin Incorporated) assay.

3.3.2 Fracture Risk Prediction and Discrimination

Over an average of 4.8 years of follow-up, there were a total of 64 (3.0%) major osteoporotic fractures events (16 [5.0%] with an eGFR <60 mL/min/1.73 m^2 [2.5% stage 3a, 2.2% stage 3b, and 0.3% stage 4/5] and 48 [2.7%] with an eGFR ≥60 mL/min/1.73 m^2). The area under the curve (AUC) values for the FRAX models, femoral neck T-score alone, age alone, and T-score with a previous fall are presented in Table 3.3. We found

that all AUC values were statistically significant (greater than 0.5) regardless of renal function. The major osteoporotic fracture FRAX AUC values were higher in individuals with an eGFR ≥60 mL/min/1.73 m^2 compared to individuals with an eGFR <60 mL/min/1.73 m^2. However, these differences did not reach statistical significance (Table 3.3). Moreover, there were no statistically significant differences in the predictive discrimination of T-scores alone, age alone, and T-scores with previous falls between individuals with an eGFR <60 versus ≥60 mL/min/1.73 m^2 for major osteoporotic fractures (Table 3.3).

Table 3. 3. Area under the curve for incident fracture prediction for major osteoporotic fracture according to estimated glomerular filtration rate

	<60 mL/min/1.73 m^2		**≥60 mL/min/1.73 m^2**			
Risk Factor	**AUC**	**95% CI**	**AUC**	**95% CI**	**AUC Difference, 95% CI**	***P* Value**
FRAX with BMD	0.69	0.54 to 0.83	0.76	0.70 to 0.82	-0.07 (-0.23 to 0.09)	0.38
FRAX without BMD	0.65	0.52 to 0.79	0.74	0.67 to 0.81	-0.09 (-0.24 to 0.06)	0.25
FRAX without BMD and with secondary osteoporosis	0.65	0.51 to 0.80				
Femoral neck T-score	0.65	0.52 to 0.80	0.72	0.65 to 0.79	-0.07 (-0.23 to 0.09)	0.39
Femoral neck T-score and prior history of fall	0.71	0.58 to 0.84	0.75	0.68 to 0.82	-0.04 (-0.19 to 0.11)	0.59
Age	0.70	0.56 to 0.83	0.69	0.62 to 0.77	0.01 (-0.14 to 0.16)	0.90

Abbreviations: AUC, area under the curve; BMD, bone mineral density; CI, confidence interval; FRAX, Fracture Risk Assessment tool

3.3.3 Fracture Events and Fracture Risk Calibration

In individuals with an eGFR <60 mL/min/1.73 m^2 the observed major osteoporotic fracture risk (5.3%, 95% CI 3.3 to 8.6%), calculated using a survival analysis method that adjusts for the competing risk of death (27), was slightly lower than the FRAX predicted major osteoporotic fracture risk with BMD (6.4%, 95% CI 6.0 to 6.9%) and also slightly lower than the FRAX predicted major osteoporotic fracture risk without BMD (8.2%, 95% CI 7.6 to 8.7%) (Figure 3.2); however, the observed and

FRAX predicted fracture risks were concordant with the FRAX predicted fracture risk within the observed fracture risk 95% CI. In individuals with an eGFR ≥60 mL/min/1.73 m^2 the observed major osteoporotic fracture risk (2.7%, 95% CI, 2.1 to 3.6%) was lower than the FRAX predicted major osteoporotic fracture risk with BMD (4.6%, 95% CI 4.5 to 4.8%) and lower than the FRAX predicted major osteoporotic fracture risk without BMD (5.3%, 95% CI, 5.0 to 5.4%). When including CKD as a cause of secondary osteoporosis in individuals with an eGFR <60 mL/min/1.73 m^2 the calibration of FRAX without BMD did not improve; the FRAX predicted risk in our cohort was 11.0% (95% CI 10.3 to 11.7%) compared to an observed major osteoporotic fracture risk of 5.3% (95% CI, 3.3 to 8.6%).

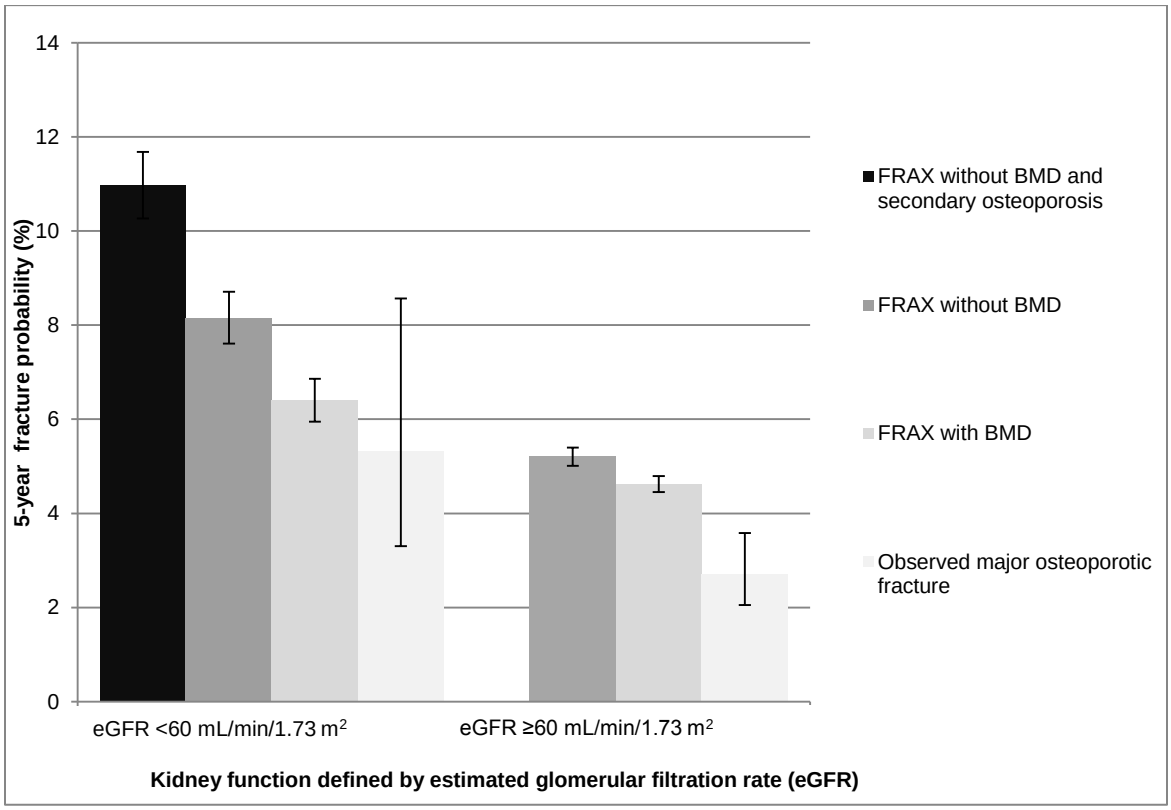

Figure 3. 2. Mean predicted 5-year fracture risk from the Canadian FRAX tool (with and without bone mineral density [BMD]) and observed 5-year major osteoporotic fracture risk (Kaplan-Meier) according to estimated glomerular filtration rate. Error bars are 95% confidence intervals.

3.4 Discussion

We found that the discriminative ability of FRAX to predict major osteoporotic fractures was similar and independent of renal function. Further, in individuals with an eGFR <60 mL/min/1.73 m^2 the FRAX predicted probabilities were comparable to the observed major osteoporotic fracture probabilities. Our finding suggests that FRAX may be a valuable tool for clinicians to accurately assess fracture risk in individuals with reduced kidney function.

Area under the curve values in individuals with an eGFR <60 mL/min/1.73 m^2 that we found were similar, although slightly lower, to the values found in a cross-sectional study assessing the ability of FRAX to discriminate fracture status in individuals with reduced kidney function (13). Jamal *et al.* included individuals with an eGFR <90 mL/min/1.73 m^2 and found an AUC of 0.72 (95% CI, 0.65 to 0.78) for FRAX with BMD while we found an AUC of 0.69 (95% CI, 0.54 to 0.83) (13). The AUC values in our study were also similar to average AUC values found in 11 international FRAX validation cohorts (n= 230,486) performed in the general population for both FRAX with BMD (AUC 0.62) and FRAX without BMD (AUC 0.60) (2).

In individuals with an eGFR <60 mL/min/1.73 m^2 the AUC values for FRAX with (0.69) and without BMD (0.65) were lower than the AUC value for age alone (0.70) which might suggest that FRAX performs no better than age alone; however, similar results have been found in studies conducted in the general population (28-30) and comparison of AUC values has been criticized as insensitive (31-33). Moreover, due to the small number of fractures in our study we were not able to test whether these results reached statistical significance as thousands of individuals are required to test whether a statistically significant difference occurs in correlated receiver operator characteristic curves (2, 34, 35).

In individuals with an eGFR <60 mL/min/1.73 m^2 the observed major osteoporotic fracture risk (5.3%) and FRAX predicted probability of major osteoporotic fracture risk were similar (6.4% with BMD and 8.2% without BMD). We found that the calibration of FRAX without BMD did not improve when adding CKD as a cause of secondary osteoporosis in individuals with an eGFR <60 mL/min/1.73 m^2; we calculated the FRAX predicted fracture risk to be 11.0% and the observed major osteoporotic

fracture risk was 5.3%. It may be that adding CKD as a cause of secondary osteoporosis does not accurately capture all the complexities of CKD-mineral and bone disorder (12). In the future, large prospective studies that incorporate CKD specific fracture risk factors (e.g. fibroblast growth factor 23) and include more individuals with advanced CKD are needed.

Our study has several strengths. The prospective design enabled us to compare observed and FRAX predicted fracture risks. Moreover, in accordance with FRAX, which includes the death hazard, we accounted for the competing risk of death by using a modified Kaplan-Meier method (27). To our knowledge this is the first study to assess the discrimination and calibration of FRAX in predicting risk of incident fractures comparing individuals with reduced kidney function to individuals with normal kidney function. Our study had some limitations. The small number of fractures limited our statistical power. Thus, we were unable to assess the prognostic value of FRAX for hip fracture alone, compare different FRAX models (i.e., assess the performance of FRAX versus age alone), and we were unable to further stratify kidney function into additional eGFR categories. This last point is of particular clinical relevance because as eGFR decreases the fracture rate increases which may be largely attributable to changes in bone and mineral metabolism (8, 12); therefore, it may be valuable to assess the performance of FRAX at each stage of CKD. However, even given the small number of fracture events all of the AUC values for major osteoporotic fracture prediction were statistically significant. The generalizability of our findings may be limited; the majority of our sample was white ($\geq$ 99%) and individuals with reduced kidney function were largely community dwelling adults who were unaware they had decreased kidney function. Therefore, these results may not be generalizable to individuals with more severe stages of CKD and diagnosed CKD-mineral and bone disorder. Moreover, we were only able to include Canadians which may limit the generalizability of the results to different countries; due to the wide variability of fracture rates across countries FRAX needs to be calibrated separately for each country (36). Additionally, a high proportion of individuals with normal kidney function had hyperparathyroidism (> 30%) which may limit generalizability to other populations; one potential explanation for this is previous research has found individuals with moderate declines in kidney function (i.e., eGFR 60-

69 mL/min/1.73 m^2) are more likely to have hyperparathyroidism (> 20%) (37); moreover, many individuals in our study had low vitamin D levels (approximately 60%); as vitamin D levels decrease parathyroid hormone levels increase (38).

In summary, FRAX was able to accurately predict fracture risk in this cohort of individuals with an eGFR <60 mL/min/1.73 m^2 which was demonstrated by the similar observed and FRAX predicted fracture rates. Moreover, FRAX demonstrated major osteoporotic fracture predictive discrimination in individuals with an eGFR <60 mL/min/1.73 m^2 which was similar to individuals with an eGFR ≥60 mL/min/1.73 m^2. Therefore, FRAX may be a useful tool for clinicians to use to assess fracture risk in patients with reduced kidney function. However, given the limited sample size results should be interpreted with caution and large prospective studies are needed before FRAX can be recommended to be used routinely for fracture risk assessment in individuals with reduced kidney function.

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CHAPTER 4: Fracture incidence in adult kidney transplant recipients[a]

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4.1 Introduction

Declining kidney function is associated with changes in mineral metabolism that contribute to an increased fracture risk (1). Of note, changes in mineral metabolism can persist after a kidney transplant despite improvements in kidney function (1-3) and fracture risk may be further increased due to the use of glucocorticoids (4, 5). Moreover, kidney transplant recipients may be frail potentially predisposing them to falls, thereby increasing fracture risk (6-11). However, it remains uncertain whether kidney transplant recipients are a high risk group for fracture, defined in most clinical guidelines as a 10-year hip fracture risk $\geq$ 3% (12, 13). Prior studies suggest recipients may have a higher risk of fracture compared to the general population (14-22), with males aged 25-44 years experiencing a five-time higher fracture risk compared to their counterparts in the general population (18).

Current data concerning fracture risk post-transplant has several limitations. First, few prior studies included kidney transplant recipients who received a transplant after the year 2000 (this is important because characteristics of recipients [e.g. comorbidities] and clinical practice patterns [e.g. trend towards decreased steroid use] have changed over time (22-25)). Second, many previous studies had a short follow-up time, with median follow-up times less than 6 years, which limits our ability to comment on the long term risks of fracture post-transplant (26). Third, these studies did not compare fracture rates in transplant recipients to a reference population which limits our ability to understand the specific burden of fracture post-transplant. Moreover, large between-study variability in fracture rates in recipients is recognized (incidence rates ranging from 3.3 to 99.6 fractures per 1000 person-years), with studies varying in their fracture locations (26).

A better understanding of fracture incidence remains important for estimating sample size requirements for future fracture prevention trials, obtaining informed consent, and clinical prognostication. Given the variability in fracture incidence across the literature, limitations of previous studies, and because fracture rates can widely vary across countries (27, 28) we conducted this study to provide a precise estimate of the 3-year incidence of non-vertebral fracture according to age and sex in a cohort of adult Canadian kidney transplant recipients. To provide a comprehensive examination of fracture in a secondary analysis we examined the following: 3-year incidence of all

fractures (excluding skull, toe, and fingers) and falls with hospitalization according to age and sex; 5- and 10-year incidence of non-vertebral fracture according to age and sex; 10-year incidence of hip fracture alone according to age and sex; and non-vertebral fracture incidence in adult Canadian kidney recipients compared to several matched non-transplant reference groups (one group at a low fracture risk; two groups at increased fracture risk).

4.2 Methods

4.2.1 Design and Setting

We used healthcare databases at the Institute for Clinical Evaluative Sciences in Ontario, Canada to conduct a population-based cohort study. All residents of Ontario are provided with universal access to physician and hospital services. We conducted this study using a protocol approved by the Research Ethics Board at Sunnybrook Health Sciences Centre (Ontario, Canada).

4.2.2. Data Sources

We used several linked databases to ascertain the study population, patient characteristics, and outcome data. The Canadian Organ Replacement Register (CORR) provided information on all kidney transplant recipients in Ontario. The Ontario Health Insurance Plan reported information on Ontario physicians' billing claims for inpatient and outpatient services. Information on diagnostic and procedural codes for Ontario hospitalizations were provided by the Canadian Institute for Health Information. The National Ambulatory Care Reporting System provided information on emergency room visits. Information on demographics and vital status was obtained from the Ontario Registered Persons Database. The Ontario Drug Benefit Plan, a universal drug plan for individuals aged ≥ 65 years, provided information on outpatient prescription drug usage. Since April 1997 information was also provided for special populations < 65 years. Data was complete except for race (10% missing), primary cause of end-stage renal disease (11%), and donor type (1%).

4.2.3 Primary Cohort

4.2.3.1 Kidney transplant recipients

We reviewed the CORR database from July 1st, 1994 to December 31st, 2009 for evidence of a first kidney-only transplant. We excluded recipients who previously received another organ transplant (including simultaneous transplants [e.g. kidney-pancreas]), recipients who were < 18 years of age on the date of transplant, and recipients who were non-Ontario residents at the time of transplant (defined by postal code). The date of cohort entry (index date) was defined as the date of the kidney transplant.

4.2.4 Reference Cohorts

To help put the burden of fracture into context we matched a kidney transplant recipient to three different reference cohorts (one group at a low fracture risk; two groups at increased fracture risk) on age (± 1 year), sex, and index date (± 1 year). To increase statistical power we matched one recipient to four non-transplant persons in two of the three reference cohorts, and in the last cohort we matched one recipient to one non-transplant person due to a smaller sample size. Cohort creation for the reference groups is described below.

4.2.4.1 Healthy segment of the population with no bone disease and no kidney disease (low fracture risk)

We randomly assigned an index date to the entire adult (≥ 18 years) Ontario population (n=18,184,929 from 1994 to 2009) based on the index date distribution of the recipient cohort. We looked back to the initiation of the databases (July 1, 1991) and excluded individuals with chronic kidney disease (including prior receipt of a kidney transplant or dialysis), osteoporosis (defined as an osteoporosis diagnostic code within 1 year after a dual-energy x-ray absorptiometry examination) (29), or a previous non-vertebral fracture (proximal humerus, forearm, hip).

4.2.4.2 Healthy segment of the general population with no kidney disease and a previous non-vertebral fracture (increased fracture risk)

As in the previous cohort we randomly assigned an index date based on the index date distribution of the recipient cohort; however, in this cohort we only included individuals who had a non-vertebral fracture (proximal humerus, forearm, hip) within the

5 years prior to index date. We excluded individuals with chronic kidney disease (including prior receipt of a kidney transplant or dialysis).

4.2.4.3 Non-dialysis chronic kidney disease (CKD) (increased fracture risk)

We reviewed the databases from July 1st, 1994 to December 31st, 2009 for first evidence of a CKD diagnostic code (date of the first CKD diagnosis defined as index date); a CKD diagnostic code identifies Ontario individuals who have a median estimated glomerular filtration rate of 38 mL/min/1.73 m^2 (30).We excluded individuals who received chronic dialysis or a previous transplant.

4.2.5 Outcomes

In the primary analysis we followed kidney transplant recipients for 3 years after the date of transplant or until evidence of a non-vertebral fracture (including multiple fractures on the same day) or death; if an individual had multiple fractures on the same day we only counted one fracture as an event. We continued to follow recipients even if they experienced graft failure (defined as return to chronic dialysis or re-transplant). The last possible date of follow-up was December 31st, 2012. Our primary outcome was non-vertebral fracture with hospital presentation (emergency room visit or hospital admission) which was defined as a composite of proximal humerus, forearm, and hip fracture. We selected these locations as they are considered major osteoporotic fracture locations and are associated with morbidity and mortality (31-33). Moreover, fracture codes for these sites have been validated and have high accuracy (> 90% sensitivity, ≥ 85% specificity, > 80% positive predictive value) (34-38). All analyses were performed including fractures accompanied by trauma codes; in addition to low-trauma fractures, fractures associated with high-trauma are more likely to occur in individuals with reduced bone strength (39). Although vertebral fractures are considered a major osteoporotic fracture, they were excluded from the primary analysis because merely one-third are clinically detected (40). In an additional analysis, we included the following fracture locations along with non-vertebral fractures: lower leg (ankle, tibia, fibula, patella), femoral shaft, rib/sternum/trunk, scapula, clavicle, clinical vertebral, and pelvis fractures. We used the 9th version of the Canadian Modified International Classification of Disease (ICD) system prior to April 1st, 2002 and the 10th version thereafter to ascertain fracture events.

Diagnosis codes for hip, forearm, and femoral shaft fractures also had to have evidence of associated procedural codes to increase fracture definition accuracy (37, 41, 42). We identified procedural codes from hospital encounters and physician billing codes. Given falls are associated with an increased fracture risk and are associated with significant morbidity and economic costs we also assessed falls with hospital presentation using the 9th and 10th version of the Canadian Modified International Classification of Disease system codes (9, 10, 43-45).

4.2.6 Statistical Analyses

We used median (interquartile range) to summarize baseline characteristics for continuous data and percentages to summarize categorical data. We defined the 3-year cumulative incidence of fracture as the proportion of recipients who sustained a fracture in the 3 year follow-up period; no fracture could occur in follow-up if the recipient died before fracture. We similarly calculated the 3-year cumulative incidence of falls. We also calculated the 3-year incidence rate of fracture (rate per 1000 person-years) and censored at death or fracture during the follow-up period. We presented the results for fracture and falls by sex (male versus female) and age (< 50 versus ≥ 50 years) at date of transplant. The age dichotomization was chosen for several reasons, including: based on previous research we expected that the median age of kidney transplant recipients would be 50 years (46), average age of menopause is roughly 50 years (47, 48) (fracture risk increases with menopause) (49, 50), and previous research has found kidney transplant recipients $\geq$ 50 years have an increased fracture risk (22). To test the hypothesis that there was no difference in non-vertebral fracture incidence between recipients and each reference group we used the log-rank test stratifying on matched pairs; we also used Cox proportional hazard analysis to assess the effect of transplant status (transplant versus no transplant) on the hazard of fracture; we stratified on matched sets and tested for the proportional hazard assumption (proportional hazard was met). In addition to matching on age ($\pm$ 1 year), sex, and index date ($\pm$ 1 year) we performed an analysis adjusting for diabetes (given diabetes is a strong risk factor for fracture (51)). We also examined the 5- and 10-year cumulative incidence and incidence rate of non-vertebral fracture and the 10-year incidence of hip fracture alone. We considered a two-tailed p-value < 0.05 as

statistically significant for all tests. We conducted all analyses with SAS (Statistical Analysis Software), version 9.3 (www.sas.com).

4.2.7 Additional Analyses

In a sensitivity analysis we only included kidney transplant recipients who received a transplant between April 1st, 2002 and December 31st, 2009, providing a more current representation of fracture rates and accounting for potential changes in coding (Ontario switched to ICD-10 coding April 1st, 2002). To take into account graft failure we performed an additional sensitivity analysis to determine the 3-year cumulative incidence of non-vertebral fracture censoring at the time of graft failure (defined as return to chronic dialysis or re-transplant).

4.3 Results

4.3.1 Baseline Characteristics

We studied 4821 kidney transplant recipients who received a transplant from 1994 to 2009. Baseline characteristics for the recipient cohort are described in Tables 4.1 and 4.2. The median age of recipients was 50 years (interquartile range, 38-59) and 36.9% were women. When known, the most common cause of end-stage renal disease was glomerulonephritis, 74.1% had hypertension, and the median time on dialysis prior to transplant was 2.4 years (interquartile range, 1.0-4.5). Baseline characteristics for the reference groups (healthy segment of the general population with no previous non-vertebral fracture [n=19,284]; healthy segment of the general population with a previous non-vertebral fracture [n=4821]; and non-dialysis CKD [n=19,284]) are described in Table 4.1.

Table 4. 1. Baseline characteristics of kidney transplant recipients compared to several reference groups

		Reference Groups		
Characteristic	**Kidney transplant recipients** (n=4821)	**Healthy segment of the general population with no bone disease and no kidney disease** (n=19,284)	**Healthy segment of the general population with no kidney disease and a previous non-vertebral fracture** (n=4821)	**Non-dialysis Chronic kidney disease** (n=19,284)
Age, years	50 (38-59)	50 (38-59)	49 (38-59)	50 (38-59)
Women	1781 (36.9%)	7124 (36.9%)	1781 (36.9%)	7124 (36.9%)
Era				
1994-1997	914 (18.9%)	3655 (19.0%)	906 (18.8%)	3643(18.9%)
1998-2001	1111 (23.1%)	4424 (22.9%)	1083 (22.4%)	4441 (23.0%)
2002-2005	1182 (24.5%)	4776 (24.8%)	1214 (25.2%)	4736 (24.6%)
2006-2009	1614 (33.5%)	6429 (33.3%)	1618 (33.6%)	6464 (33.5%)
Hypertension	3572 (74.1%)	3829 (19.9%)	1040 (21.5%)	9050 (46.9%)
Diabetes	1255 (26.0%)	1527 (7.9%)	503 (10.4%)	6371 (33.0%)
Cardiovascular disease[¶]	2068 (42.9%)	1424 (7.4%)	490 (10.2%)	4486 (23.3%)
Prior non-vertebral fracture[‡]	106 (2.2%)			296 (1.5%)

Data are medians (interquartile range) or n(%).

[¶]Cardiovascular disease was defined as the presence of peripheral vascular disease, congestive heart failure or coronary artery disease.

[‡]Prior non-vertebral fracture defined as a composite of proximal humerus, forearm, hip fractures from 1991 to cohort entry. The median number of years (interquartile range) of baseline records prior to cohort entry is as follows: kidney transplant recipients, 11.9 years (7.5-15.6); non-dialysis chronic kidney disease, 11.9 years (7.6-15.6).

Note: The reference group general population with no previous non-vertebral osteoporotic fracture has no previous fracture as this was a requirement to enter the cohort. The reference group general population with a previous non-vertebral osteoporotic fracture has 100% sustaining a fracture prior to cohort entry as this was requirement for cohort entry.

Table 4. 2. Additional characteristics of kidney transplant recipients

Characteristic	Kidney transplant recipients (n=4821)
Race	
White	3277 (68.0%)
Black	272 (5.6%)
Asian	309 (6.4%)
Other‡	485 (10.1%)
Missing	479 (9.9%)
Cause of end-stage renal disease	
Glomerulonephritis	1710 (35.4%)
Cystic kidney disease	620 (12.9%)
Diabetes	843 (17.5%)
Renal vascular disease	448 (9.3%)
Other	665 (13.8%)
Unknown/missing	535 (11.1%)
Pre-transplant dialysis	
Peritoneal dialysis	1441 (29.9%)
Hemodialysis	2880 (59.7%)
Pre-emptive†	500 (10.4%)
Donor Type	
Living	2007 (41.6%)
Deceased	2755 (57.2%)
Missing	59 (1.2%)
Dialysis (years prior to transplant)ǀ	2.4 (1.0-4.5)
Delayed graft functionϵ	899 (18.6%)
Primary non-functionβ	143 (3.0%)
Pretransplant Parathyroidectomy	257 (5.3%)
Medications£	
Glucocorticoids¶	22.5 (12.5-30)
Cyclosporine⁑	367 (13.6%)
Tacrolimus¥	1417 (52.6%)

Bisphosphonates[**]	646 (18.2%)

Data are median (interquartile range) or n (%).
[‡]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial.
[†]If there was no evidence of hemodialysis or peritoneal dialysis prior to transplant the recipient was coded as having a pre-emptive transplant.
[l]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years.
[€] Delayed graft function was defined as presence of one dialysis code contained in administrative databases in the first 7 days after transplant.
[β] Primary non-function was defined as at least three codes for dialysis on three different days with at least one code appearing in the first 7 days after the transplant date, one in the 8- 30 days after the transplant date, and one in the 31-60 days after the transplant date.
[£] Medication information was obtained in the first 90 days *after* transplantation for glucocorticoids, cyclosporine and tacrolimus. Medication information was obtained in the first 3 years *after* transplantation for bisphosphonates.
[¶] Glucocorticoid information was available for 1896 kidney transplant recipients and was presented as the median dose in the first 90 days after transplant (mg/day).
[*]Denominator was n=2695 (number of recipients eligible for prescription drug coverage in the first 90 days after transplantation).
[¥] Denominator was n=2695 (number of recipients eligible for prescription drug coverage in the first 90 days after transplantation).
[**]Denominator was n=3540 (number of recipients eligible for prescription drug coverage in the first 3-years after transplantation).

Over 3 years of follow-up (13,850 person-years) 298 (6.2%) recipients died and 77 (1.6%) sustained a non-vertebral fracture. For the reference groups, during the 3 year follow-up, 260 (1.3%) individuals from the healthy segment of the general population with no previous non-vertebral fracture died and 98 (0.5%) sustained a non-vertebral fracture, 170 (3.5%) from the healthy segment of the general population with a previous non-vertebral fracture died and 113 (2.3%) sustained a non-vertebral fracture, and 2637 (13.7%) individuals with non-dialysis CKD died and 207 (1.1%) sustained a non-vertebral fracture.

4.3.2 Fracture Risk

The 3-year cumulative incidence and incidence rate of non-vertebral fracture (proximal humerus, forearm, hip) according to age and sex is presented in Table 4.3.The overall 3-year cumulative incidence of non-vertebral fracture in recipients was 1.6% (95% CI 1.3-2.0%). In recipients, the number of non-vertebral fracture events increased linearly over the 3 years after transplant (Figure 4.1). For hip fracture alone the overall 3-year cumulative incidence in recipients was 0.4% (95% CI, 0.3-0.7%).The overall 5- and 10-year cumulative incidence of non-vertebral fracture in recipients was 2.7% (95% CI, 2.2-3.2%) and 5.5% (95% CI 4.6-6.5%), respectively (Table 4.4). For hip fracture alone the overall 10-year cumulative incidence in recipients was 1.7% (1.2-2.3%) (Table 4.5). For

all analyses women recipients aged ≥ 50 years had the highest cumulative incidence of fracture (Tables 4.3, 4.4, 4.5).

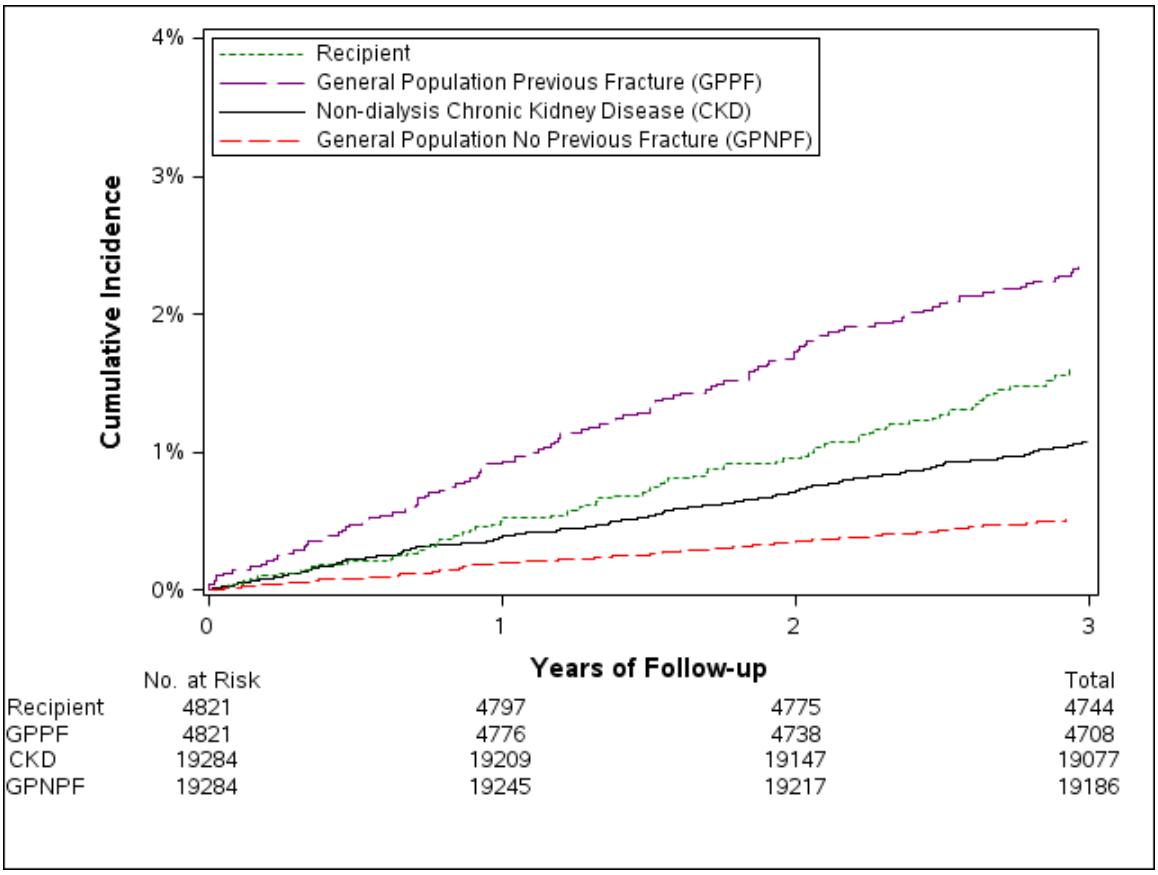

Figure 4. 1. Cumulative incidence of non-vertebral fracture (proximal humerus, forearm, or hip) in recipients and non-transplant reference populations. Kidney transplant recipients had a significantly higher fracture rate compared to the non-dialysis chronic kidney disease population (P=0.03 by the log-rank test) and the healthy segment of the general population with no bone disease and no kidney disease (P<0.0001 by the log-rank test). Kidney transplant recipients had a significantly lower fracture rate compared to the healthy segment of the general population with no kidney disease and a previous non-vertebral fracture (P=0.007 by the log-rank test).

Table 4. 3. 3-year cumulative incidence and incidence rate of non-vertebral fracture (proximal humerus, forearm, or hip) stratified by sex and age in kidney transplant recipients[¶]

	3-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)
Overall (n=4821)	1.6 (1.3-2.0)	5.6 (4.4-7.0)
Women < 50 years (n=944)	0.6 (0.3-1.4)	2.2 (0.8-4.7)
Women ≥ 50 years (n=837)	3.1 (2.1-4.5)	11.1 (7.3-16.3)
Men < 50 years (n=1463)	0.7 (0.4-1.3)	2.3 (1.1-4.1)
Men ≥ 50 years (n=1577)	2.2 (1.6-3.1)	7.9 (5.5-11.0)

Abbreviation: CI, confidence interval

[¶]3-year cumulative incidence defined as the proportion of kidney transplant recipients who sustained a non-vertebral fracture within the 3 years of follow-up; no fracture could occur in follow-up if the kidney transplant recipient died before fracture. Incidence rate defined as the rate per 1000 person years; censoring occurred at death or at the time of a fracture event during the follow-up period.

Table 4. 4. 5- and 10-year cumulative incidence and incidence rate of non-vertebral fracture in kidney transplant recipients stratified by sex and age

	5-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)		10-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)
Overall (n=4070)	2.7 (2.2-3.2)	5.8 (4.8-7.0)	***Overall*** (n=2385)	5.5 (4.6-6.5)	6.4 (5.3-7.6)
Women < 50 years (n=817)	1.5 (0.8-2.6)	3.1 (1.6-5.3)	***Women < 50 years*** (n=536)	3.7 (2.4-5.6)	4.1 (2.5-6.3)
Women ≥ 50 years (n=682)	5.7 (4.2-7.7)	12.8 (9.1-17.5)	***Women ≥ 50 years*** (n=354)	13.3 (10.1-17.2)	17.3 (12.7-23.0)
Men <50 years (n=817)	1.3 (0.8-2.0)	2.6 (1.5-4.2)	***Men <50 years*** (n=817)	2.6 (1.7-3.9)	2.7 (1.7-4.2)
Men ≥ 50 years (n=1291)	3.3 (2.5-4.5)	4.8 (2.9-7.5)	***Men ≥ 50 years*** (n=678)	6.3 (4.7-8.4)	8.1 (5.9-10.9)

Note: For the 5-year cumulative incidence/incidence rate we only included kidney transplant recipients who received a transplant before April 1, 2008 and for the 10-year cumulative incidence/incidence rate we only included kidney transplant recipients who received a transplant before April 1, 2003. To increase the number of kidney transplant recipients for this additional analysis we defined the maximum follow-up as March 31, 2013.

Table 4. 5. 10-year cumulative incidence and incidence rate of hip fracture in kidney transplant recipients stratified by sex and age

	10-year cumulative incidence, % (95% CI)	**Incidence rate per 1000 person years (95% CI)**
Overall (n=2385)	1.7 (1.2-2.3)	1.9 (1.4-2.6)
Women ≥ 50 years (n=354)	5.6 (3.7-8.6)	7.1 (4.3-10.9)
Men ≥ 50 years (n=678)	2.5 (1.6-4.0)	3.2 (1.8-5.0)

Note: For the 10-year cumulative incidence/incidence rate we only included kidney transplant recipients who received a transplant before April 1, 2003. To increase the number of kidney transplant recipients for this additional analysis we defined the maximum follow-up as March 31, 2013.
We were not able to report the 10-year cumulative incidence of hip fracture for women and men <50 years for reasons of privacy (cell size, 1-5).

Recipients had a higher 3-year cumulative incidence of non-vertebral fracture (1.6%, 95% CI 1.3-2.0%) compared to the healthy segment of the general population (matched on age, sex, and index date) with no previous non-vertebral fracture (0.5%, 95% CI 0.4-0.6%; P<0.0001) and compared to the non-dialysis CKD population (1.1%, 95% CI 0.9-1.2%; P=0.03) (Table 4.6) (Figure 4.1). However, recipients had a lower 3-year cumulative incidence of non-vertebral fracture compared to the healthy segment of the general population with a previous non-vertebral fracture (2.3%, 95% CI 1.9-2.8%; P=0.007). After adjusting for diabetes in addition to matching all results remained statistically significant (Table 4.6).

Table 4. 6. 3-year cumulative incidence, incidence rate, and hazard ratios of non-vertebral fracture (proximal humerus, forearm, or hip) in several reference groups compared to kidney transplant recipients matched on age, sex, and index date[¥]

Population	3-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)	Hazard Ratio[¥] (95% CI)	Hazard Ratio[‡] (95% CI)
Kidney transplant recipients (n=4821)	1.6 (1.3-2.0)	5.6 (4.4-6.9)	1.00 (reference)	1.00 (reference)
Healthy segment of the general population with no bone disease and no kidney disease (n=19,284)	0.5 (0.4-0.6)	1.7 (1.4-2.1)	0.3 (0.2- 0.4)	0.3 (0.2-0.4)
Healthy segment of the general population with no kidney disease and a previous non-vertebral fracture (n=4821)	2.3 (2.0-2.8)	8.1 (6.6-9.7)	1.4 (1.1-1.9)	1.6 (1.1-2.2)
Non-dialysis chronic kidney disease (n=19,284)	1.1 (0.9-1.2)	4.0 (3.5-4.6)	0.8 (0.6-0.98)	0.7 (0.6-0.9)

[¥] Matched on age (±1 year), sex, and index date (±1 year)
[‡]Matched on age (±1 year), sex, and index date (±1 year) and adjusting for diabetes.

When including all fracture locations, the overall 3-year cumulative incidence in recipients was 3.5% (95% CI 3.0-4.1%); amongst the four age and sex strata, the 3-year cumulative incidence was highest in women recipients aged ≥ 50 years (5.7%, 95% CI 4.3-7.5%) (Table 4.7). The most common location of first clinically diagnosed fracture in recipients was the lower leg (defined as a composite of tibia, fibula, patella, and ankle) (32.5% of all fractures) and a similar result was found in the healthy segment of the general population with a previous non-vertebral fracture (27.9% of all fractures) (Table 4.8).

Table 4. 7. 3-year cumulative incidence and incidence rate of all fracture in kidney transplant recipients stratified by sex and age[‡]

	3-year cumulative incidence, % (95% CI)	**Incidence rate per 1000 person years (95% CI)**
Overall (n=4821)	3.5 (3.0-4.1)	12.3 (10.5-14.3)
Women < 50 years (n=944)	2.1 (1.4-3.3)	7.3 (4.5-11.3)
Women ≥ 50 years (n=837)	5.7 (4.4- 7.5)	20.8 (15.3-27.5)
Men < 50 years (n=1463)	2.4 (1.7- 3.3)	8.2 (5.7-11.4)
Men ≥ 50 years (n=1577)	4.2 (3.3- 5.3)	15.0 (11.6-19.1)

[‡] All fracture locations defined as a composite of hip, forearm, proximal humerus, lower leg (ankle, tibia, fibula, patella), femoral shaft, rib/sternum/trunk, scapula, clavicle, vertebral, and pelvis fractures

Table 4. 8. Location of the first fracture in follow-up[‡]

Fracture location	**Kidney transplant recipients** (n=4821)	**Healthy segment of the general population with no kidney disease and a previous non-vertebral fracture** (n=4821)
Hip	17 (10.6%)	24 (10.6%)
Forearm	43 (26.9%)	60 (26.6%)
Proximal humerus	12 (7.5%)	24 (10.6%)
Lower leg[†]	**52 (32.5%)**	**63 (27.9%)**
Ribs/sternum/trunk	12 (7.5%)	33 (14.6%)
Pelvis	10 (6.2%)	7 (3.1%)
Other[¥]	14 (8.8%)	15 (6.6%)

[‡]Multiple fracture events that occurred on the same day were excluded from this table; therefore, for kidney transplant recipients there were a total of 160 events (n=9 excluded) and 226 (n=12 excluded) in the general population with a previous non-vertebral fracture.
[†]Lower leg includes a composite of tibia, fibula, patella and ankle fractures
[¥] Other includes a composite of fracture locations that had ≤5 events including: vertebral, clavicle, femoral shaft, scapula fractures
Note: The most common fracture location for each group is denoted in bold.

4.3.3 Additional Analyses

When we limited the analysis to recipients who received a transplant in recent years (transplant received from 2002 to 2009) the overall 3-year cumulative incidence of non-vertebral fracture was similar to when we included all transplant years (1.8%, 95% CI 1.4-2.4%) and again was highest amongst women recipients aged ≥ 50 years (3.0%, 95% CI 1.9-4.8%) (Table 4.9). When we censored after graft failure (308 returned to dialysis [6.4%] and 14 re-transplanted [0.3%]) the overall 3-year cumulative incidence in recipients decreased slightly (1.5%, 95% CI 1.2-1.9%) (Table 4.10). With respect to falls, the overall 3-year cumulative incidence in recipients was 7.9% (95% CI 7.1-8.7%); amongst the four age and sex strata, women recipients aged ≥50 years had the highest 3-year cumulative incidence of falls (11.1%, 95% CI 9.1-13.4%) (Table 4.11).

Table 4. 9. 3-year cumulative incidence and incidence rate of fracture stratified by sex and age only including kidney transplant recipients who received a transplant from 2002-2009

Fracture location	**3-year cumulative incidence, % (95% CI)**	**Incidence rate per 1000 person years (95% CI)**	**Fracture location**	**3-year cumulative incidence, % (95% CI)**	**Incidence rate per 1000 person years (95% CI)**
Proximal humerus, forearm, or hip			***All fracture locations*** ‡		
Overall (n=2723)	1.8 (1.4-2.4)	6.3 (4.6-8.3)	***Overall*** (n=2723)	3.9 (3.2-4.7)	13.7 (11.2-16.6)
Women < 50 years (n=461)	<1.5%	3.0 (0.8-7.6)	***Women < 50 years*** (n=461)	1.7 (0.9- 3.4)	6.0 (2.6-11.7)
Women ≥ 50 years (n=531)	3.0 (1.9-4.8)	10.7 (6.1-17.4)	***Women ≥ 50 years*** (n=531)	5.5 (3.8- 7.6)	19.6 (13.2-28.2)
Men < 50 years (n=721)	<1.5%	3.3 (1.3-6.8)	***Men < 50 years*** (n=721)	3.2 (2.1- 4.7)	11.0 (6.9-16.4)
Men ≥ 50 years (n=1010)	2.2 (1.4-3.3)	7.8 (4.9-11.7)	***Men ≥ 50 years*** (n=1010)	4.6 (3.4- 6.0)	16.4 (12.0-21.8)

‡ All fracture locations defined as a composite of hip, forearm, proximal humerus, lower leg (ankle, tibia, fibula, patella), femoral shaft, rib/sternum/trunk, scapula, clavicle, vertebral, and pelvis fractures.

Table 4. 10. 3-year cumulative incidence and incidence rate of non-vertebral fracture (proximal humerus, forearm, or hip) stratified by sex and age and censoring after graft failure

	3-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)
Overall (n=4821)	1.5 (1.2-1.9)	5.4 (4.2-6.8)
Women < 50 years (n=944)	0.6 (0.3-1.4)	2.3 (0.8-5.0)
Women ≥ 50 years (n=837)	2.9 (1.9-4.2)	10.7 (6.9-15.9)
Men < 50 years (n=1463)	0.7 (0.4-1.3)	2.4 (1.2-4.5)
Men ≥ 50 years (n=1577)	2.0 (1.4-2.9)	7.5 (5.1-10.5)

Abbreviation: CI, confidence interval

¶ 3-year cumulative incidence defined as the proportion of kidney transplant recipients who sustained a non-vertebral fracture within the 3 years of follow-up; no fracture could occur in follow-up if the kidney transplant recipients died or experienced graft failure before fracture. Incidence rate defined as the rate per 1000 person years of follow-up; censoring at the time of death, graft failure, or fracture in follow-up

Table 4. 11. 3-year cumulative incidence, incidence rate of falls stratified by sex and age

	3-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)
Overall (n=4821)	7.9 (7.1- 8.7)	28.3 (25.5-31.3)
Women < 50 years (n=944)	6.4 (5.0- 8.1)	22.3 (17.0-28.7)
Women ≥ 50 years (n=837)	11.1 (9.2- 13.4)	41.4 (33.4-50.8)
Men < 50 years (n=1463)	5.2 (4.2-6.5)	18.1 (14.2-22.6)
Men ≥ 50 years (n=1577)	9.5 (8.2-11.1)	35.1 (29.7-41.2)

Abbreviation: CI, confidence interval

4.4 Discussion

The cumulative incidence of fracture in kidney transplant recipients was lower than previously reported with approximately 1 in 50 sustaining a non-vertebral fracture in the 3 years after transplant, approximately 1 in 20 sustaining a non-vertebral fracture in the 10 years after transplant, and approximately 2% sustaining a hip fracture in the 10-year follow-up (≥ 3% defines high risk). Among women recipients aged ≥ 50 years only 1 in 30 sustained a non-vertebral fracture in the 3 years after transplant. Further, recipients had a lower fracture incidence compared to the healthy segment of the general population with a previous non-vertebral fracture. Our results suggest that despite the changes in mineral metabolism and use of steroids after kidney transplantation, recipients may not be a high risk group for fracture.

The fracture incidence in our study is lower than many prior studies (15-21, 52); however, it is important to note that a variety of locations are included across studies making comparisons difficult. For example, Ball *et al.* found an incidence rate of 3.3 hip fractures per 1000 person-years in kidney transplant recipients (20); in contrast, we found an incidence rate of 1.9 hip fractures per 1000 person-years. However, not all previous studies have found a high fracture incidence. For example, Opelz *et al.* conducted a study including recipients from 32 countries and found a 5-year cumulative incidence of hip fracture of 0.85%, similar to our study 3-year cumulative incidence estimate of 0.4% and a 10-year cumulative incidence of 1.9% (53). Moreover, a recent Canadian study suggests kidney transplant recipients are not a high risk fracture group (10-year major osteoporotic fracture risk 6.3%) (54), but follow-up time for this analysis began an average of one-year after kidney transplant (54); previous studies have suggested that an accelerated loss in bone mineral density happens in the first one-year post-transplant therefore early fractures may have been missed (55-57).

There are several explanations for the lower than expected fracture incidence. First, 6 out of the 10 previous studies assessing fracture risk in kidney transplant recipients did not include recipients who transplanted after the year 2000 (26). In recent years there have been changes in maintenance immunosuppressive regimens. Specifically, tacrolimus is now used more commonly than cyclosporine which may result in less bone loss (58). In our study, of recipients eligible for prescription drug coverage,

8.7% were on cyclosporine and 63.6% were on tacrolimus. There has also been a trend towards decreasing prednisone dose after kidney transplantation; corticosteroids are well known to promote bone loss (4, 5). In our study the median steroid dose in the first 90 days after transplant in 1997 was 27.6 mg/day compared to 20.2 mg/day in 2009. In recent years there may be an increase in the number of recipients prescribed fracture prevention therapy (bisphosphonates and vitamin D); the Kidney Disease Improving Global Outcomes for Chronic Kidney Disease-Mineral and Bone Disorder guidelines recommend that bisphosphonates and vitamin D are prescribed to recipients who have an estimated glomerular filtration rate >30 mL/min/1.73 m^2 and low bone mineral density (1). In our study, of recipients eligible for prescription drug use, 5.5% of recipients who received their transplant in 1997 were prescribed bisphosphonates in the first three years after transplant compared to 11.5% in 2009, but the number of fracture events was too small to detect any impacts from these interventions. Therefore, including recipients who more recently transplanted may have decreased the overall incidence rate. Second, to increase the accuracy of our fracture definition it was necessary that hip and forearm fracture diagnostic codes were accompanied by associated procedural codes (37, 41, 42); failure to include procedural codes may lead to over-ascertainment of fractures. Therefore, previous transplant studies may have been overestimating fractures at these locations. Last, the majority of previous studies have been conducted in the US (26); fracture rates and patient characteristics may vary across countries. For example, Leslie *et al.* found that in the general population proximal femoral fracture rates were 30% lower in Canadian women compared to women from the US (28). Moreover, differences in transplant characteristics have been found between the US and Canada, potentially affecting fracture rates (e.g. more obese individuals in the US) (59).

The low fracture incidence provides an explanation for why previous clinical trials assessing the efficacy of bisphosphonates in kidney transplant recipients have been underpowered (60). To conduct a 2-arm parallel randomized control trial (80% power) and to obtain a 60% relative risk reduction we would need a total of 9900 recipients (based on 1.6% of recipients sustaining a non-vertebral fracture). However, we did not include vertebral fractures; smaller sample sizes would likely be required if these fracture

locations were included. Nevertheless, to conduct a fracture prevention trial with adequate statistical power there would still need to be participation of multiple centres.

We found recipients had a significantly lower 3-year cumulative incidence of non-vertebral fracture compared to the healthy segment of the general population with a previous non-vertebral fracture, matching on age, sex, and index date. Although one of the strongest risk factors for a future fracture is a previous fracture (61), we expected that recipients would have a higher fracture incidence due to bone mineral metabolism changes associated with CKD and steroid administration (1). Despite these factors, based on clinical practice guidelines recipients would not be considered a high risk fracture group with only 1.7% sustaining a hip fracture in the 10 years after transplant (high risk defined as $\geq 3\%$). Only women recipients ≥ 50 years would be defined as a high risk fracture group with 5.6% sustaining a hip fracture in the 10-years after transplant. However, recipients did have a 3 time higher fracture risk compared to a healthy segment of the general population (no kidney disease and no bone disease); previous studies comparing recipients to the general population have found an even higher relative fracture risk (14, 18, 19). For example, Ramsey-Goldman *et al.* found female recipients between the ages of 45-64 years had almost a 35 times higher fracture risk compared to similarly aged individuals from the general population (18). However, previous studies comparing recipients to the general population did not include recipients who received a transplant more recently (after the year 2000), therefore, potentially overestimating fracture risk in more contemporary recipients.

Several strengths of our study deserve mention. No other study, to our knowledge, has compared fracture rates in recipients to several matched reference groups to better quantify incremental fracture risk. Moreover, our study's large sample size and long-term follow-up allowed us to meaningfully examine long-term fracture risk (10-year follow-up). We are also the first study to report the incidence of falls stratifying by age and sex. Finally, to account for changes in recipient characteristics and changes in clinical practice, we performed an additional analysis restricted to recipients who received a transplant after the year 2002.

Limitations of this study should be recognized. First, we may not have captured all fracture events; we did not include vertebral fracture in our primary fracture definition

with merely one-third of these fractures being recognized in a clinical setting (40); this may have underestimated fracture risk. However, using only hip fracture codes kidney transplant recipients were not considered to have a high fracture risk (10-year risk <3%); all hip fractures should be treated in the hospital and therefore will not be missed using administrative databases. Moreover, even the upper bound of the 95% confidence interval for non-vertebral fracture was low with only 2.0% of recipients fracturing. Second, we were only able to capture fractures and falls that presented at the hospital or in the emergency room. However, the majority of fractures are managed through the emergency room or hospital; additionally, we used the same databases and codes to capture fracture events in recipients and the reference groups. Third, we were not able to compare fracture incidence in recipients to individuals on the transplant waitlist; our administrative databases do not provide information on individuals on dialysis who were on the transplant waitlist; therefore, we did not think individuals on dialysis would make an accurate comparison given many of these individuals would have greater comorbidities and not qualify for transplantation. However, one previous study has compared fracture rates in waitlist patients to transplant recipients finding hip fracture risk was higher in the first 600 days after transplant, however, it decreased after this time point (20). Fourth, these results may not readily generalize to all races; 68% of recipients in our study were white (whites have a higher fracture risk compared to blacks) (62). Moreover, these results may not generalize to other countries given the large global variation in fracture rates (27). Fifth, due to the small number of non-vertebral fracture events (n=77) we were not able to assess trends in fracture incidence over time and delineate reasons for changes in fracture rates. Sixth, we were only able to obtain drug information for a subset of recipients eligible for prescription drug coverage. Finally, we were unable to obtain serum creatinine values to define CKD and as a result some individuals with CKD may have been misclassified; however, the specificity for the CKD codes was high (>90%) (30).

In conclusion, although kidney transplant recipients had a higher relative fracture risk compared to other populations they had a low absolute fracture risk with few recipients sustaining a fracture after transplantation. Further research is needed to identify reasons for this lower than expected fracture risk.

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CHAPTER 5: Risk factors for fracture in adult kidney transplant recipients[a]

[a]A version of this chapter is being prepared for submission at *Canadian Journal of kidney health and diseases* as, Naylor KL, Jamal SA, Zou GY, McArthur E, Lam NN, Leslie WD, Hodsman AB, Kim SJ, Knoll GA, Fraser LA, Adachi JD, Garg AX. Risk factors for fracture in adult kidney transplant recipients.

5.1 Introduction

Kidney transplant recipients have an increased risk of fracture compared to the general population (1-3). Reasons for the increased fracture risk are multifactorial, and may include perturbations in bone and mineral metabolism that occur in renal bone disease, and the administration of glucocorticoids after transplantation (4). However, we remain uncertain of the risk factors for fracture after transplant; in a recent systematic review many classical risk factors for fracture in the general population (e.g. older age, female sex) were inconsistently associated with fractures in kidney transplant recipients (5). Unlike the transplant population, risk factors for fracture in the general population are well-established and are included in the World Health Organization's (WHO) Fracture Risk Assessment tool (FRAX). FRAX is used to guide treatment decisions in the general population through incorporating age, sex, clinical risk factors (body mass index, parental hip fracture, glucocorticoid use, rheumatoid arthritis, smoking, high alcohol intake [$\geq$ 3 units of alcohol a day]), and bone mineral density (optional) to predict the 10-year hip fracture or major osteoporotic fracture probability (proximal humerus, forearm, hip, or clinical vertebral) (6-8). However, kidney transplant recipients may have different risk factors for fracture given the unique pathophysiology that underlies their bone disease (9). For example, in a recent cohort study the only classical risk factor for fracture that reached statistical significance in kidney transplant recipients was high alcohol use (10); however, this study had only 21 fracture events and may have had inadequate statistical power to identify other risk factors (10). The same study also found that FRAX may be a useful tool to predict fracture in kidney transplant recipients (area under the receiver operating characteristic curve 0.62); however, the authors hypothesized that incorporating transplant-specific risk factors for fracture may improve the accuracy of FRAX (10). FRAX currently does not incorporate kidney transplantation or chronic kidney disease into its algorithm.

The WHO has called for a global strategy on fracture prevention and management (11). Such strategies require an understanding of well-validated fracture risk factors and prediction tools so populations at high risk can be targeted for diagnosis, treatment, and therapeutic trials. Given that risk factors for fracture in kidney transplant recipients have not been well-established, in a modern cohort of Canadian adult kidney transplant

recipients we conducted this study to determine transplant-specific risk factors (e.g. length of time on dialysis prior to transplant) and general risk factors (e.g. age, sex, previous fracture, previous fall) associated with major fractures (proximal humerus, forearm, hip, and clinical vertebral). In a secondary analysis we assessed risk factors for other fracture locations (excluding major fractures, and those of the skull, fingers, and toes).

5.2 Methods

5.2.1 Design and Setting

This was a population-based cohort study using the Institute for Clinical Evaluative Sciences (ICES) healthcare databases in Ontario, Canada. Ontario residents are given universal access to hospital and physician services. Study approval was obtained from Sunnybrook Health Sciences Centre's Research Ethics Board (Toronto, Ontario, Canada).

5.2.2 Data Sources

We utilized several databases to establish our study cohort, patient characteristics, risk factors, and outcome data. Information on all kidney transplant recipients who received their transplant in Ontario was provided by the Canadian Organ Replacement Register (CORR). Information on provincial physicians' billing claims was provided by the Ontario Health Insurance Plan. The Canadian Institute for Health Information database provided information on diagnostic and procedural codes during Ontario hospitalizations and information on emergency room visits was provided by the National Ambulatory Care Reporting System. The Ontario Registered Persons Database provided information on vital status and demographics.

5.2.3 Cohort

We utilized the CORR database from April 1st, 2002 to December 31st, 2009 to identify individuals from Ontario with a first kidney-only transplant who had not previously received another organ transplant and were $\geq$ 18 years of age at the transplant date. We selected April 1st, 2002 as our cohort entry date as this was when the Canadian International Classification of Disease (ICD) system changed from version 9 to 10. The cohort entry date (index date) was the date an individual received their kidney transplant.

5.2.4 Risk Factors

We assessed several general risk factors for fracture (age, sex, and prior major fracture) which are incorporated in the WHO FRAX algorithm. We also assessed other general risk factors found to increase fracture risk in the non-transplant population, including: a fall with hospitalization in the year prior to transplantation, race/ethnicity, and diabetes (only type 1 diabetes is included in FRAX) (12-14). We assessed several transplant-specific risk factors including: length of time on dialysis prior to transplant (years), type of donor (living vs. deceased), cause of end-stage renal disease (ESRD, e.g., diabetes mellitus, glomerulonephritis, renal vascular disease, cystic kidney disease, or other [i.e., any cause of ESRD not included in the aforementioned categories such as pyelonephritis]), pre-transplant dialysis modality (peritoneal, hemodialysis, or pre-emptive), and donor characteristics (age and sex).

5.2.5 Outcomes

We followed kidney transplant recipients from the date of transplant until fracture, death, or end of follow-up (March 31st, 2013). We did not censor kidney transplant recipients if they returned to chronic dialysis or if they had another transplant (graft failure) during follow-up. Our primary outcome was major fractures which were defined as a composite of hip, forearm, proximal humerus, and clinical vertebral fractures. We chose to assess risk factors for major fractures with hospital presentation (emergency room visit or hospital admission) as these fracture locations are associated with excess morbidity and mortality in the general population (15-17). In an additional analysis we assessed other fracture locations, defined as: lower leg (ankle, tibia, fibula, patella), femoral shaft, rib/sternum/trunk, scapula, clavicle, and pelvis fractures. We assessed these fractures as a secondary outcome as they may be more common in kidney transplant recipients (9). For example, in prior studies ankle fractures were common in kidney transplant recipients (1, 18). We included both high and low trauma fractures because, similar to low-trauma fractures, high-trauma fractures occur more commonly when an individual has compromised bone strength (19). We identified fracture events using the 10th version of the ICD system. To increase accuracy, diagnosis codes for hip, forearm, and femoral shaft fractures were accompanied by procedural codes identified from hospital encounters and physician billing codes (20).

5.2.6 Statistical Analysis

We compared differences in baseline characteristics of recipients with a fracture and without a fracture using the Mann Whitney U test for continuous variables and the chi-square test for categorical variables. We calculated the incidence rate of fracture (per 1000 person-years) censoring the observation period on the date of death, first fracture, or end of follow-up (March 31, 2013). We used the Cox proportional hazards model to relate the hazard of the first fracture to risk factors. Prior to obtaining the adjusted hazard ratio (aHR) to quantify the effect of each risk factor model assumptions such as the proportional hazards assumption and linearity of continuous factors (martingale residuals) were assessed with a P-value <0.05 used as criteria for a violation (21-23). We used the backward elimination strategy to select risk factors that would be entered into the final model, with recipient age and sex forced into the model. A priori we chose a p-value of ≤ 0.2 to determine variables that would be included in the final model (24). We chose this p-value to decrease the possibility of missing important risk factors for fracture post-transplant. We assessed multicollinearity among variables prior to entering variables into the backward elimination model. We found limited concern for multicollinearity, since all variance inflation factors were less than 2 (25). We were missing data for the following variables: donor age (2.2%), donor sex (0.9%), cause of ESRD (11.6%), race (10.7%), and donor type (0.8%). We handled missing data by randomly assigning values based on the distribution of variables that were not missing with the exception of donor age for which we supplemented missing values with the median age. We performed all analyses using SAS (Statistical Analysis Software), version 9.4 (www.sas.com).

5.3 Results

5.3.1 Incidence of Fracture

Of the 2723 kidney transplant recipients the total follow-up was 16,274 person-years (average 6 years). Over this time, there were 402 (14.8%) deaths in follow-up and 132 (4.8%) sustained a major fracture (8.1 fractures per 1000 person-years, 95% confidence interval [CI] 6.8-9.6).

5.3.2 Baseline Characteristics

Recipients who sustained a major fracture in follow-up compared to recipients with no major fracture had a significantly higher median age (57 *vs* 51 years), were more likely to be women (48.5% *vs* 35.8%), and were less likely to have glomerulonephritis as their cause of ESRD (29.6% *vs* 36.7%) (Table 5.1).

Table 5. 1. Characteristics of kidney transplant recipients classified by major fracture status[†]

	No fracture (n=2591)	**Major Fracture** (n=132)	**P-value**
General risk factors			
Age, years	50.5 (41-61)	56.5 (45-63)	0.01
Women	928 (35.8%)	66 (48.5%)	0.004
Race			0.40
White	1845 (71.2%)	103 (78%)	
Asian	208 (8.0%)	8 (6.1%)	
Black	198 (7.6%)	7 (5.3%)	
Other[€]	340 (13.1%)	14 (10.6%)	
Diabetes	673 (25.6%)	40 (30.3%)	0.27
Fall with hospitalization in the year prior to the transplant date	92 (3.6%)	8 (6.1%)	0.15
Major fracture prior to the transplant date[‡]			
Transplant specific risk factors			
Length of time on dialysis prior to transplant (measured in years)[¶]	2.8 (1.2-5.4)	2.7 (0.92-5.1)	0.56
Type of donor			0.47
Deceased (vs. Living)	1458 (56.3%)	70 (53.0%)	
Cause of end-stage renal disease[¥]			0.004
Glomerulonephritis	951 (36.7%)	39 (29.6%)	

Cystic kidney disease	385 (14.9%)	31 (23.5%)	
Diabetes	560 (21.6%)	37 (28.0%)	
Other	695 (26.8%)	25 (18.9%)	
Pre-transplant dialysis modality[‖]			0.99
Peritoneal dialysis	701 (27.1%)	35 (26.5%)	
Hemodialysis	1622 (62.6%)	83 (62.9%)	
Pre-emptive	268 (10.3%)	14 (11.6%)	
Donor age, years	46 (36-54)	47.5 (41-55)	0.16
Donor sex			0.73
Women	1295 (50.0%)	68 (51.5%)	

Data are median (interquartile range) or n (%).
[†]Major fracture events were comprised of forearm (n=81), hip (n=22), proximal humerus (n=18), and clinical vertebral fractures (n=13).
[€]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial.
[‡]Due to the small number of recipients with a prior major fracture this risk factor was not able to be assessed.
[¶] Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years.
[¥] Due to the small number of recipients with a major fracture who had renal vascular disease as the cause of their ESRD this category was combined into the other category.
‖We defined hemodialysis and peritoneal dialysis based on the modality the recipient first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant.

5.3.3 Univariable Analysis

We found older recipient age and female recipient sex were the general risk factors associated with an increased risk of major fracture (Table 5.2). For example, female recipients had almost a two-fold greater risk of major fracture (hazard ratio [HR] 1.65, 95% CI 1.18-2.33). Regarding transplant-specific risk factors, cystic kidney disease (HR 1.93, 95% CI 1.20-3.08) and diabetes (HR 1.80, 95% CI 1.15-2.82) as the cause of ESRD (compared to glomerulonephritis as the reference cause) were both associated with a higher risk of major fracture. Each 5-year increase in donor age was also associated with a greater risk of major fracture (HR 1.11, 95% CI 1.04-1.18).

5.3.4 Multivariable Analysis

In the multivariable model, older recipient age (5-year increase) (aHR 1.11, 95% CI 1.03-1.19) and female recipient sex (aHR 1.81, 95% CI 1.28-2.57) were the general risk factors associated with a greater risk of major fracture (Table 5.2). Regarding

transplant-specific risk factors diabetes (aHR 1.72, 95% CI 1.09-2.72) and cystic kidney disease (aHR 1.73, 95% CI 1.08-2.78) as the cause of ESRD (compared to glomerulonephritis as the reference cause), and older donor age (5-year increase) (aHR 1.09, 95% CI 1.02-1.17) were associated with a greater risk of major fracture.

Table 5. 2. Univariable and multivariable analysis of risk factors for major fracture in kidney transplant recipients

	Univariable analysis	**Multivariable analysis**
Risk Factors	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Age *(per 5 year increase)*	1.13 (1.06-1.21)	1.11 (1.03-1.19)
Sex		
Men	Reference	
Women	1.65 (1.18-2.33)	1.81 (1.28-2.57)
Race		
White	Reference	
Asian	0.72 (0.35-1.47)	
Black	0.65 (0.30-1.39)	
Other€	0.78 (0.44-1.36)	
Diabetes *(vs. none)*	1.40 (0.96-2.02)	
Fall with hospitalization in the year prior to the transplant date *(vs. none)*	2.00 (0.98-4.09)	1.72 (0.84-3.50)
Major fracture prior to the transplant date‡ *(vs. none)*		
Length of time on dialysis prior to transplant *(measured in years)*¶	1.06 (0.61-1.84)	
Type of donor		
Living	0.99 (0.70-1.39)	
Deceased	Reference	
Cause of end-stage renal disease¥		

Glomerulonephritis	Reference	Reference
Cystic kidney disease	1.93 (1.20-3.08)	1.73 (1.08-2.78)
Diabetes	1.80 (1.15-2.82)	1.72 (1.09-2.72)
Other	0.92 (0.56-1.53)	0.88 (0.53-1.46)
Pre-transplant dialysis modality[l]		
Hemodialysis	Reference	
Peritoneal dialysis	0.99 (0.67-1.47)	
Pre-emptive	0.96 (0.54-1.68)	
Donor age *(per 5 year increase)*	1.11 (1.04-1.18)	1.09 (1.02-1.17)
Donor sex		
Men	Reference	
Women	1.03 (0.73-1.44)	

[‡] Due to the small number of recipients with a prior major fracture this risk factor was not able to be assessed.
[€]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial.
[¥] Due to the small number of recipients with a major fracture who had renal vascular disease as the cause of their ESRD this category was combined into the other category.
[¶]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years.
[l]We defined hemodialysis and peritoneal dialysis based on the modality the recipient first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant.

5.3.5 Other Fractures

When we assessed other fracture events (excluding the major fractures, and the skull, fingers, and toes) kidney transplant recipients had 141 fractures (8.7 fractures per 1000 person-years, 95% CI 7.3-10.2). Recipients with such fractures compared to those without such fractures were significantly more likely to have diabetes (40.4% *vs* 25.4%) and were more likely to have had a fall with hospitalization in the year prior to transplant (7.1% *vs* 3.5%) (Table 5.3). In the multivariable model we found diabetes and a fall with hospitalization prior to transplantation were the general risk factors associated with an increased risk of fracture, while length of time on dialysis, and renal vascular disease and other causes of ESRD were the transplant-specific risk factors associated with a greater risk of other fractures (Table 5.4).

Table 5. 3. Characteristics of kidney transplant recipients classified by other fractures status[¥]

	No fracture (n=2582)	**Other fracture** (n=141)	**P-value**
General risk factors			
Age, years	52 (42-61)	54 (44-61)	0.18
Women	944 (36.6%)	48 (34.0%)	0.55
Race			0.33
White	1838 (71.2%)	110 (78.0%)	
Asian	208 (8.1%)	8 (5.7%)	
Black	198 (7.8%)	7 (5.0%)	
Other[€]	338 (13.1%)	16 (11.4%)	
Diabetes	656 (25.4%)	57 (40.4%)	<0.001
Fall with hospitalization in the year prior to the transplant index	90 (3.5%)	10 (7.1%)	0.03
Major fracture prior to the transplant date[β]	69 (2.7%)	13 (9.2%)	<0.001
Transplant specific risk factors			
Length of time on dialysis prior to transplant (measured in years)[¶]	2.7 (1.1-5.4)	3.0 (1.7-5.3)	0.068
Type of donor			
Deceased	1439 (55.7%)	89 (63.1%)	0.09
Cause of end-stage renal disease			0.003
Glomerulonephritis	958 (37.1%)	32 (22.7%)	
Cystic kidney disease	397 (15.4%)	19 (13.5%)	
Diabetes	555 (21.5%)	42 (29.8%)	
Renal Vascular Disease	294 (11.4%)	23 (16.3%)	
Other	378 (14.6%)	25 (17.7%)	
Pre-transplant dialysis modality[ł]			0.09
Peritoneal dialysis	694 (26.7%)	42 (29.8%)	

Hemodialysis	1613 (62.5%)	92 (65.3%)	
Pre-emptive	275 (10.7%)	7 (5.0%)	
Donor age, years	46 (36-54)	48 (40-54)	0.13
Donor sex	1298 (50.3%)	65 (46.1%)	0.33
Women			

Data are median (interquartile range) or n (%).
[¥] Other fracture events were comprised of pelvis (n=15), ankle (n=37), patella (n=8), tibia/fibula (n=37), rib/sternum (n=34), and other (femoral shaft, scapula, clavicle; n=16).
[€]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial.
[β]Prior major fracture had to occur from 1991 to cohort entry (date of transplant).
[¶]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years.
‖We defined hemodialysis and peritoneal dialysis based on the modality the recipient first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant.

Table 5. 4. Univariable and multivariable analysis of risk factors for other fracture in kidney transplant recipients

	Univariable analysis	**Multivariable analysis**
Risk Factor	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Age *(per 5 year increase)*	1.09 (1.02-1.17)	1.03 (0.96-1.10)
Sex		
Men	Reference	
Women	0.99 (0.63-1.26)	0.97 (0.68-1.39)
Race		
White	Reference	
Asian	0.67 (0.33-1.37)	0.67 (0.32-1.39)
Black	0.59 (0.27-1.26)	0.47 (0.21-1.02)
Other[€]	0.82 (0.49-1.39)	0.73 (0.43-1.26)
Diabetes *(vs. none)*	2.2 (1.57-3.08)	2.19 (1.38-3.49)
Fall with hospitalization in the year prior to the transplant date *(vs. none)*	2.37 (1.25-4.52)	2.05 (1.07-3.93)
Length of time on dialysis prior to transplant *(measured in years)*[¶]	1.06 (1.00-1.12)	1.07 (1.01-1.14)
Type of donor		

Living	Reference	
Deceased	0.67 (0.47-0.92)	
Cause of end-stage renal disease		
Glomerulonephritis	Reference	Reference
Cystic kidney disease	1.4 (0.8-2.47)	1.35 (0.76-2.39)
Diabetes	2.47 (1.56-3.91)	1.40 (0.78-2.49)
Renal vascular disease	2.40 (1.41-4.10)	2.11 (1.22-3.65)
Other	2.04 (1.21-3.44)	2.03 (1.20-3.45)
Pre-transplant dialysis modality[‖]		
Hemodialysis	Reference	
Peritoneal dialysis	1.06 (0.74-1.53)	
Pre-emptive	0.43 (0.2-0.92)	
Donor age *(per 5 year increase)*	1.07 (1.01-1.14)	1.06 (0.99-1.12)
Donor sex		
Men	Reference	
Women	0.83 (0.6-1.16)	

[€]Other was defined as a composite of: Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial.
[¶]Includes individuals who received a pre-emptive transplant where the time spent on dialysis was defined as 0 years.
‖We defined hemodialysis and peritoneal dialysis based on the modality they first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant.

5.4 Discussion

Of the transplant-specific risk factors available to us in this study, we found only diabetes or cystic kidney disease as the cause of ESRD and increasing age of the kidney donor were associated with a significantly increased major fracture risk; however, the strength of the association for the hazard ratios was only modest. Our results suggest that fracture prediction tools used in the general population may also be suitable to use in the transplant population given few transplant-specific risk factors predicted major fractures.

We previously published a study of 321 kidney transplant recipients from Manitoba, Canada and found that FRAX was able to predict fracture risk; the area under the receiver operating characteristic curve value was 0.62; FRAX also seemed to be

reasonably calibrated with a similar observed and 10-year FRAX predicted major osteoporotic fracture probability (6.3% versus 5.6%) (10). However, the number of major osteoporotic fracture events was small (n=21), with correspondingly wide 95% confidence intervals (10). We hypothesized that a fracture prediction tool incorporating both general and transplant-specific risk factors may improve fracture prediction (10). In the current study only the cause of ESRD (diabetes and cystic kidney disease) and increasing age of the kidney donor reached statistical significance suggesting that a modified fracture prediction tool which includes transplant-specific risk factors may not be needed. Moreover, the low absolute fracture rate, the moderate strength of the transplant-specific risk factors, the large sample size needed to update a model, and the reasonable performance of the original FRAX model in kidney transplant recipients further suggests model updating may not be needed. However, diabetes may be important for clinicians to consider as an independent risk factor for fracture in kidney transplant recipients; similar to our study, previous studies have consistently found diabetes to be associated with an increased fracture risk in kidney transplant recipients (2, 18, 26). Future research should assess other potential transplant-specific risk factors (unavailable in our current analyses), including: change in body mass index after transplantation (weight changes found to increase fracture risk in the general population) and fibroblast growth factor 23 (suppresses mineralization of the bone matrix) (27, 28).

Of concern, several of the risk factors for fracture identified in this study are becoming more common in recent eras of kidney transplant recipients. For example, we found diabetes as the cause of ESRD and older recipient age were significant risk factors for major fractures. The number of recipients with diabetes and the average recipient age has been increasing (29). Similar to results found in a previous study (30), increasing donor age was also associated with an increased risk of major fracture. This is concerning as there has been an increase in the number of recipients receiving a kidney from older donors (31, 32). It is important to note that donor age may only be a surrogate measure for recipient age, with kidneys from older donors often being allocated to older recipients; however, we found that the correlation between these two variables was weak. Nevertheless, the increase in the aforementioned risk factors may have important implications for fracture risk in future recipients.

Unfortunately, none of the risk factors for major fractures found in this study are easily modifiable. However, a hospitalized fall in the year prior to transplant was a significant risk factor for other fractures; falls are potentially modifiable through the use of fall prevention programs (33-35). The paucity of modifiable risk factors is concerning as one of the best ways to prevent fractures in the general population is to provide therapy (e.g. bisphosphonates); the efficacy of these therapies in kidney transplant recipients is unclear (36). However, given that not many recipients sustained a fracture the lack of modifiable risk factors may be less of a concern.

We found that risk factors for fracture may vary across fracture locations. For example, there were different risk factors for fracture between our two fracture classifications (major fracture locations *versus* other fracture locations). A possible explanation for this finding is that in the kidney transplant population risk factors for fractures are site specific. For example, similar to what some studies have found in the general population, in our study increasing recipient age and female recipient sex were both associated with an increased major fracture risk (37-39). However, increasing age and female recipient sex were not associated with an increased risk of other fractures. This provides a potential explanation for the results of a previous systematic review which found risk factors for fracture in kidney transplant recipients were inconsistent; studies in the review included different fracture locations (5). However, we cannot discount the possibility that the differences in risk factors across fracture locations found in this study were the result of a type II error.

Strengths of this research deserve discussion. First, we are the first study to assess transplant-specific and general risk factors for major fractures. Given these fractures are associated with mortality and morbidity it is important to understand their risk factors (15-17). Second, to our knowledge, this is the first study to look at a previous fall with hospitalization as a risk factor for fracture in kidney transplant recipients. Limitations of the study are noted. First, we were unable to assess drug use (e.g. glucocorticoids) as a potential risk factor for fracture; drug information in our databases was only available for a sub-cohort of kidney transplant recipients; therefore, our sample size would have been decreased, limiting statistical power. Second, we were unable to assess several risk factors, such as body mass index, due to a high proportion of missingness (>50%). Third,

the small number of fracture events may have limited statistical power and increased concerns about the validity of the model. However, we selected a liberal p-value in our backward elimination analysis to ensure we were not excluding potentially important variables. Additionally, for risk factors that did not reach statistical significance the confidence intervals were narrow with values gathered around the null value, decreasing our concerns about type II errors (40). Moreover, there were at least 10 events per variable with previous research suggesting type I errors and relative bias are uncommon when there are 5 or more events per variable (41). Finally, due to the small number of fracture events we were also not able to assess several of the other risk factors included in the FRAX algorithm (e.g. rheumatoid arthritis). Last, the generalizability of these results to other races/ethnic groups may be limited as the majority (72%) of our sample was white.

In conclusion, these results provide further support for the use of prediction tools used in the general population to guide prognostication and treatment decisions in kidney transplant recipients. However, future studies with a larger sample size should assess the ability of other transplant-specific risk factors to predict fracture.

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CHAPTER 6: Frequency of bone mineral density testing in adult kidney transplant recipients[a]

[a]A version of this chapter was submitted for publication at *Canadian Journal of Kidney Health and Disease* as, Naylor KL, Jamal SA, Zou GY, McArthur E, Lam NN, Leslie WD, Hodsman AB, Kim SJ, Knoll GA, Fraser LA, Adachi JD, Garg AX. Frequency of bone mineral density testing in adult kidney transplant recipients.

6.1 Introduction

Kidney transplant recipients have a higher risk of fracture compared to the general population (1-3), although recent observations suggest that the absolute incidence is still low (4). The reasons for this higher risk are multifactorial and include pre-existing chronic kidney disease-mineral and bone disorder (CKD-MBD) and glucocorticoid administration after transplantation (5). In the general population Osteoporosis Canada guidelines recommend bone mineral density (BMD) testing be done in individuals at a high risk of fracture, as a decreased BMD can help risk stratify those individuals at a higher risk of fracture (6-8). However, in the kidney transplant population the ability of BMD to predict fracture is unclear (9-11). Limited evidence can lead to substantial practice variability. Therefore, we conducted a population-based study to determine the frequency, total cost, and the variability in BMD testing across all six transplant centres in Ontario, Canada. We also compared the frequency of BMD testing in transplant recipients to non-transplant reference groups (matching on age, sex, and date of cohort entry).

6.2 Methods

6.2.1 Design and Setting

We used healthcare databases form Ontario, Canada contained at the Institute for Clinical Evaluative Sciences (ICES). These data sets were held securely in linkable files without direct personal identifiers, and were analyzed at ICES. In Ontario residents have universal healthcare. Ethics approval was obtained from Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada).

6.2.2 Data Sources

Information on Ontario kidney transplant recipients is provided by the Canadian Organ Replacement Register. Information on Ontario physicians' billing claims for inpatient and outpatient services is reported by the Ontario Health Insurance Plan (OHIP). The Ontario Registered Persons Database provides information on demographics and vital status. Prescription drug utilization data is provided from the Ontario Drug Benefit Plan (individuals who are ≥ 65 years are provided with drug coverage). It also provides information since April 1997 on special populations aged < 65 years who are

eligible for the program. The ICES Physician Database provides information on physician specialty. Emigration from the province was the only reason for loss to follow-up (0.5% per year) (12).

6.2.3 Primary Cohort

6.2.3.1 Kidney Transplant Recipients

We included all Ontario adults (age ≥ 18 years) with a first kidney transplant from July 1st, 1994 to December 31st, 2009 (excluding individuals with a previous transplant). We defined the date of the kidney transplant as the date of cohort entry (also referred to as the index date).

6.2.4 Reference Cohorts

We matched recipients on age (± 1 year), sex, and index date (± 1 year) to two non-transplant reference cohorts (healthy segment of the general population with no previous non-vertebral fracture [defined as proximal humerus, forearm, hip]; and healthy segment of the general population with a previous non-vertebral fracture). When permitted by the available sample, we matched one recipient to four persons from the non-transplant reference cohort.

6.2.4.1 Healthy Segment of the General Population with No Previous Non-vertebral Fracture

Using the index date distribution of the recipient cohort we randomly assigned an index date to the Ontario population (≥ 18 years). We excluded individuals with chronic kidney disease (including evidence of kidney transplantation or dialysis), osteoporosis (defined as a dual-energy x-ray absorptiometry examination followed by an osteoporosis diagnostic code within 1 year) (13), or a previous non-vertebral fracture (proximal humerus, forearm, hip) prior to index date (looked back to July 1, 1991).

6.2.4.2 Healthy Segment of the General Population with a History of Non-vertebral Fracture

As described above, using the index date distribution of the recipient cohort we randomly assigned an index date to the Ontario population; however, to enter the cohort the individual had to have sustained a non-vertebral fracture (proximal humerus, forearm, hip) in the 5 years prior to entering the cohort. Our cohort excluded chronic kidney disease patients (including evidence of kidney transplantation or dialysis).

6.2.5 Outcomes

We used physician fee-for-service billings to identify BMD by dual energy x-ray absorptiometry and, prior to April 1998, dual-photon absorptiometry tests (14). In Ontario, these data are largely complete with approximately 94% of physicians submitting such billing (15). These BMD billing codes have been successfully used in several prior studies (Table 6.1 describes codes utilized) (13, 16). We tabulated the number of BMD tests in the three years following kidney transplantation; multiple billings for a BMD test for a given person on the same day were counted as one test. To calculate the total cost of the BMD tests we included all associated billings, even if there were multiple billings on the same day, and accounted for inflation. We included fee suffixes A, B, and C in the OHIP fee schedule. Fee suffix A was used prior to April 1, 2001 to describe both the technical and physical component of the exam (17). After April 1, 2001 fee suffixes B (technical component of the exam) and C (professional component) were required to be billed separately (17).

Table 6. 1. Database codes for bone mineral density tests

	OHIP Fee Codes
Dual-photon absorptiometry	J654 *Bone mineral density by single proton method* J655 *Total boday calcium proton actiation* J656 *Bone min. content dual-photon absorbtiomet. 2 or more sites* J688 *Bone mineral content by dual photon single site* J854 *Bone mineral density by single photon method* J855 *Total body calcium - neutron activation* J856 *Bone min. content dual-photon absorbtiomet. 2 or more sites* J888 *Bone mineral content by dual photon absorb*
Dual energy x-ray absorptiometry	X145 *Bmd - baseline test, one site* X146 *Bmd - baseline test, two or more sites* X149 *Bone mineral density high risk 1 site* X152 *Bone mineral density low risk 1 site* X153 *Bone mineral density low risk 2+ sites* X155 *Bone mineral density high risk 2+sites* X157 *Diag. rad. bone density (mineral content) measurement*

Abbreviations: OHIP, Ontario Health Insurance Plan

6.2.6 Statistical Analysis

To describe baseline characteristics for continuous data we used medians (interquartile range [IQR]) or means (standard deviation) and we used proportions to describe categorical data. To compare baseline characteristics between recipients with at

least one BMD test to those without a BMD test we used the chi-square test, Mann-Whitney U test, or Student's t-test as appropriate. We stratified the frequency of BMD testing by sex (men versus women) and age at the time of transplantation (< 50 versus ≥ 50 years). We used logistic regression to determine if there was a statistically significant difference across transplant centres in the decision to perform at least one BMD test after transplantation. We adjusted for covariates that may influence a physician's decision to order a BMD test (age, sex, previous fracture, and comorbidities [as measured by the Charlson comorbidity index(18)]). To determine if there were changes over time in the number of BMD tests performed we used the Cochran-Armitage test for trend. To compare the number of recipients who had at least one BMD test to the matched non-transplant reference groups we used the McNemar's test. We considered a two-sided p-value < 0.05 as statistically significant. We conducted the analyses using the Statistical Analysis Software (SAS version 9.3).

6.3 Results

6.3.1 Baseline Characteristics

We included 4821 kidney transplant recipients with a total observation time of 13,943 person-years; 304 (6.3%) recipients died within three years. Comparing recipients who had at least one BMD (n=2786) to recipients who did not (n=2035), recipients with at least one BMD were significantly more likely to be women (66.4 versus 33.6%; P<0.001), to have received a transplant in the later years of cohort entry (2006-2009 versus 1994-1997) (67.9 vs. 32.1%; P<0.001), and were older (50 versus 49 years; P=0.04); there was no significant difference in history of a previous non-vertebral fracture prior to transplant (2.4% vs. 2.0%) (Table 6.2). Matching characteristics were similar between recipients and the non-transplant reference groups (Table 6.3).

Table 6. 2. Characteristics of kidney transplant recipients classified by presence of at least one bone mineral density (BMD) test in the 3 years after transplantation

	Bone Mineral Density Test		
Characteristic	**Yes** (n=2786)	**No** (n=2035)	**P-value**
Age, years	50 (39-59)	49 (38-59)	0.04
Women	1182 (66.4%)	599 (33.6%)	<0.001
Transplant era			<0.001
1994-1997	290 (31.7%)	624 (68.3%)	
1998-2001	631 (56.8%)	480 (43.2%)	
2002-2005	769 (65.1%)	413 (34.9%)	
2006-2009	1096 (67.9%)	518 (32.1%)	
Diabetes	690 (24.8%)	565 (27.8%)	0.02
Previous non-vertebral fracture‡	68 (2.4%)	41 (2.0%)	0.33
Charlson Comorbidity Index¥	2.6 ± 1.0	2.7 ± 1.2	0.002

Data are median (interquartile range), mean (± SD) or n (%)
Abbreviation: BMD, bone mineral density; SD, standard deviation
‡Prior non-vertebral fracture was defined as a composite of proximal humerus, forearm, hip fractures from 1991 to transplant date (cohort entry).
¥All recipients with a Charlson Comorbidity Index (CCI) of 0 were given a score of 2 and those with a score of 1 were given a score of 3; one of the variables in the CCI is presence of end-stage renal disease which automatically results in recipients receiving a score of 2.

Table 6. 3. Baseline characteristics of reference groups[¥]

Characteristic	Kidney transplant recipients (n=4821)	Healthy segment of the general population with no previous non-vertebral fracture (n=19,284)	Healthy segment of the general population with a previous non-vertebral fracture (n=4821)
Age, years	50 (38-59)	50 (38-59)	49 (38-59)
Women	1781 (36.9%)	7124 (36.9%)	1781 (36.9%)
Era			
1994-1997	914 (18.9%)	3655 (19.0%)	906 (18.8%)
1998-2001	1111 (23.1%)	4424 (22.9%)	1083 (22.4%)
2002-2005	1182 (24.5%)	4776 (24.8%)	1214 (25.2%)
2006-2009	1614 (33.5%)	6429 (33.3%)	1618 (33.6%)
Diabetes	1255 (26.0%)	1527 (7.9%)	503 (10.4%)
Prior non-vertebral fracture[‡]	109 (2.3%)		

Data are median (interquartile range) or n (%)
[¥] Matched on age (±1 year), sex, and index date (±1 year)
[‡] Prior non-vertebral fracture defined as a composite of proximal humerus, forearm, hip fractures from 1991 to cohort entry.
Note: The reference group healthy segment of the general population with no previous non-vertebral fracture has no previous fracture as this was a requirement to enter the cohort. The reference group healthy segment of the general population with a previous non-vertebral fracture has 100% sustaining a fracture prior to cohort entry as this was a requirement for cohort entry.

6.3.2 Bone Mineral Density (BMD)

Approximately 58% (n=2786) of kidney transplant recipients had at least one BMD test within three years of receiving their transplant and 22% (n=1047) of recipients had received a BMD test in the three months following transplant. Among those with at least one BMD test, the median time after transplant to first BMD was 133 days (interquartile range 62-372 days). A total of 68.1% of female recipients aged ≥ 50 years received a BMD test, a higher proportion than the other three age and sex strata ($P<0.005$) (Table 6.4). There were a total of 4802 BMD tests (median 1, range 0-6 tests per recipient) and almost one-third (31.7%) of recipients received more than one BMD test in the three years after transplant (Table 6.5). The total cost of these tests was $614,997 (CAD 2014 equivalent dollars) (approximately $128 per recipient) across the 18-year study period.

Table 6. 4. Number (proportion) of kidney transplant recipients with at least one bone mineral density test in the 3 years after transplantation by age and sex

	Kidney transplant recipients (n=4821)
Overall	2786 (57.8%)
Women < 50 years (n=944)	612 (64.8%)
Women ≥ 50 years (n=837)	570 (68.1%)
Men < 50 years (n=1463)	741 (50.7%)
Men ≥ 50 years (n=1577)	863 (54.7%)

Table 6. 5. Frequency of bone mineral density tests performed in kidney transplant recipients (n=4821)

Number of BMD tests per recipient	**N (%)**
0	2035 (42.2%)
1	1259 (26.1%)
2	1081 (22.4%)
3	412 (8.5%)
4	27 (0.6%)
≥5	7 (0.1%)

Abbreviation: BMD, bone mineral density

The proportion of recipients who received at least one BMD test in follow-up varied from 15.6 to 92.1% (P<0.001) across the six Ontario transplant centres. The variation across transplant centres persisted after adjustment for recipient age, sex, history of a previous non-vertebral fracture, and comorbidities (logistic regression model, P<0.001). When information on the ordering physician was available (96% of tests), BMD tests for recipients were most commonly ordered by nephrologists (67.8%) and family physicians (16.5%), followed by general internists (5.0%), rheumatologists (3.4%), and endocrinologists (2.4%).

6.3.3 Non-transplant Reference Groups

In the healthy segment of the general population with a previous non-vertebral fracture (n=4821), there were 863 BMD tests (range 0-4) in the three years after the index date compared to 4802 BMD tests in the recipient population. In the healthy segment of the general population with no previous non-vertebral fracture (n=19,284), there were 1936 BMD tests (range 0-4). There were a significantly higher number of kidney transplant recipients with at least one BMD (58%) in the three year follow-up versus both matched reference groups (13.8 % healthy segment of the general population with a previous non-vertebral fracture and 8.5% healthy segment of the general population with no previous non-vertebral fracture, respectively, P value < 0.001 for each paired comparison) (Table 6.6). The proportion of individuals who received at least one BMD test in follow-up significantly increased over time in all three groups (recipients, 20.9% in 1994 and 66.4% in 2009; healthy segment of the general population with a previous non-vertebral fracture, 3.5% in 1994 and 15.6% in 2009; healthy segment of the general population with no previous non-vertebral fracture, 2.6% in 1994 and 8.5% in 2009; P for trend < 0.001) (Figure 6.1).

Table 6. 6. Number (proportion) of kidney transplant recipients with at least one bone mineral density test in the 3 years of follow-up compared to reference groups matched on age, sex, and index date[¥]

Population	N (%)	P-value[‡]
Kidney transplant recipients (n=4821)	2786 (57.8%)	Reference
Healthy segment of the general population with no previous non-vertebral fracture (n=19,284)	1645 (8.5%)	<0.001
Healthy segment of the general population with a previous non-vertebral fracture (n=4821)	665 (13.8%)	<0.001

[¥] Matched on age (±1 year), sex, and index date (±1 year)
[‡]Paired P-value

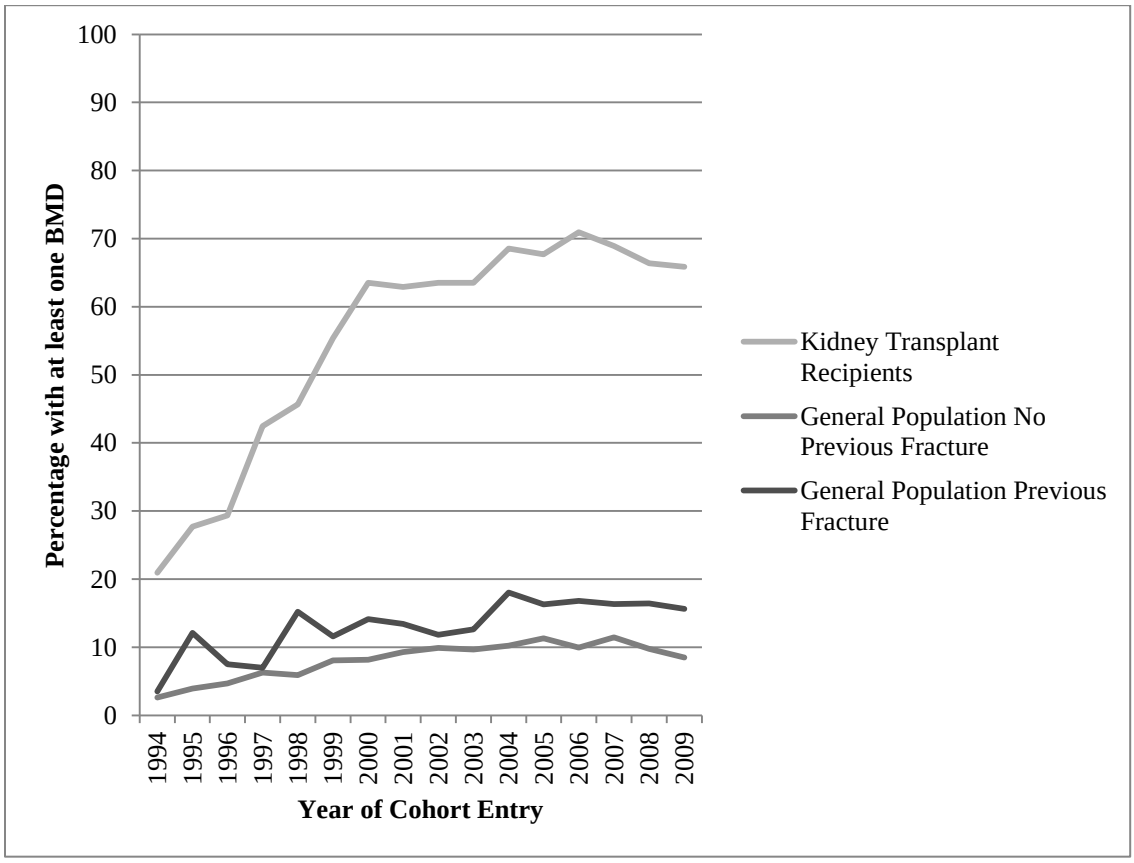

Figure 6. 1. Kidney transplant recipients, individuals from the healthy segment of the general population with a previous non-vertebral fracture (GPPF), and individuals from the healthy segment of the general population with no previous non-vertebral fracture (GPNPF) with at least one bone mineral density test in the 3 years after cohort entry, presented by year of cohort entry (P for trend <0.001 for all 3 cohorts).

6.3.4 Bisphosphonates

Of the 3540 recipients who had prescription drug coverage through universal healthcare benefits, 646 (18.2%) were prescribed bisphosphonates in the first 3 years after transplant. Of recipients prescribed bisphosphonates, 548 (84.8%) of these prescriptions were filled at a median of 57 days (IQR 21 to 175 days) after the BMD test, with 417 receiving a bisphosphonate prescription in the first six months after a BMD test.

6.4 Discussion

In Ontario, Canada we found that over half of the kidney transplant recipients received at least one BMD test in the subsequent three years after transplant and many

recipients received multiple tests. The frequency of BMD testing varied widely by centre – from as few as 15% of recipients receiving a BMD test to as many as 92%, and this variability was not explained by recipient characteristics. Kidney transplant recipients were significantly more likely to receive a BMD compared to two matched non-transplant reference groups. Our results suggest that BMD testing is commonly performed in kidney transplant recipients despite conflicting evidence in the literature supporting its widespread use.

The results of our population-based multicentre study extend the findings of two prior single centre reports with smaller sample sizes. In the first study of kidney transplant recipients (n=326) from Manitoba, Canada, almost 60% of recipients were found to have had at least two BMD tests within approximately eight years of their transplant (19). The second study from Akaberi *et al.* found that 670 BMD tests were performed in 238 kidney transplant recipients (75% had at least two BMD tests) from Sweden over 12 years (9). The centres in these two prior studies had protocols in place for routine BMD testing, and so the frequency of BMD testing would be expected to be high. In contrast, in our study only a few of the transplant programs had a protocol for BMD testing (information provided by the six Ontario transplant centres, personal communication).

Particularly striking are the high number of kidney transplant recipients who had multiple BMD tests in the three years after transplantation, at a high cost to the healthcare system. For example, almost one-third of kidney transplant recipients received two or more BMD tests within three years of their transplant; in the non-transplant population the benefits of performing multiple BMD tests over several years has been questioned (20, 21), especially given the increasing knowledge of unwarranted screening harms (22, 23).

The variability in BMD testing we observed across transplant centres was in the setting of universal healthcare benefits. It is possible BMD testing variability across transplant centres might be even greater in jurisdictions without such healthcare benefits, as economic factors may also influence testing.

The benefit of BMD tests in kidney transplant recipients remains uncertain. First, the utility of BMD in predicting fracture in kidney transplant recipients is unclear (9-11). For example, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for

Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) suggest that patients with an estimated glomerular filtration rate > 30 mL/min/1.73 m^2 have their BMD assessed in the first three months after kidney transplant if they received glucocorticoids or have other risk factors for osteoporosis (5); given the limited evidence, this suggestion was given the weakest grade of evidence (5). It is important to note that this recommendation is being reassessed in the revised version of the guidelines in light of recent evidence finding that BMD may be predictive of fracture in individuals with CKD, including dialysis (24-26); however, there is still conflicting evidence in kidney transplant recipients (9-11). Second, given the high incidence of adynamic bone disease (i.e., low turnover) in kidney transplant recipients, the KDIGO guidelines suggest that a bone biopsy may be needed to guide treatment decisions; this limits the clinical usefulness of BMD testing post-transplant (5). Last, and perhaps most relevant, recent research suggests in contrast to what has been previously reported, most kidney transplant recipients will not fracture and have an average mean BMD for age and sex (4, 9, 19, 27). Note, however, that the lower than expected fracture incidence and normal BMD may be the result of increased monitoring of bone health after transplant. Taken together this suggests there may be little need to perform BMD tests routinely. New high-quality information from prospective observational studies and clinical trials is needed to guide the optimal recommended timing and frequency of BMD testing. Such studies should also assess the ability of BMD to predict fracture and its cost-effectiveness.

It is important to note that BMD testing may alter clinical practice. Many kidney transplant recipients were prescribed a bisphosphonate in the first six months after receiving a BMD test. However, the efficacy of this and other fracture prevention strategies in kidney transplant recipients remains uncertain (28).

Strengths of this study should be recognized. To our knowledge we are the first multicentre study and largest study (n=4821) to assess BMD testing practices across several kidney transplant centres. Moreover, to help put the frequency of BMD testing into context we are the first study to compare BMD frequency in recipients to matched non-transplant reference groups.

Study limitations are worth noting. We did not have drug dispensing information for the entire transplant cohort (only those who were covered by provincial drug

benefits). While we were unable to characterize immunosuppression use at the patient level, during the time frame of this study steroids were nearly universally prescribed at the Ontario transplant centres. Additionally, we only knew if a BMD was done, without information on the BMD value. However, the former supported the primary objective of this study - to determine the frequency of BMD testing in the first three years after transplant across several kidney transplant centres. Finally, we did not assess the impact of the KDIGO CKD-MBD guidelines on BMD testing. However, this guideline received the weakest grade of evidence; therefore, its uptake would likely be variable across transplant centres as demonstrated in this study.

In conclusion, many kidney transplant recipients receive a BMD test in the three years after transplantation but there was wide practice pattern variation. These results highlight the need for further studies to investigate the utility, frequency, timing, and cost-effectiveness of BMD testing in kidney transplant recipients.

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CHAPTER 7: Discussion and Conclusions

7.1 Introduction

The overall goal of this thesis was to better understand the epidemiology of fracture in adults with kidney disease and to use this information in the care of this unique patient population. The specific objectives were 1) to summarize the incidence and risk factors for fracture in kidney transplant recipients; 2) to determine the predictive ability of FRAX in individuals with reduced kidney function compared to individuals with normal kidney function; 3) to estimate the incidence of fracture in kidney transplant recipients; 4) to determine risk factors for fracture in kidney transplant recipients; and 5) to examine the frequency, total cost, and the variability in bone mineral density (BMD) testing in kidney transplant recipients across Ontario transplant centres. Data sources utilized in this thesis allowed for a comprehensive examination of the epidemiology of fracture in a Canadian context, addressing many limitations of previous research.

7.2 Summary of Key Findings

7.2.1 Systematic Review of Fracture Risk in Kidney Transplant Recipients

Chapter 2 systematically summarized cohort studies that provided information on fracture incidence and risk factors in kidney transplant recipients.

The incidence and risk factors for fracture in kidney transplant recipients were variable across studies. Potential reasons for this variability across studies included differences in study methodological quality, inclusion of different fracture locations, and differences in recipient characteristics. The results of this study allowed for the identification of several knowledge gaps in the literature. Specifically, previous studies had a short follow-up time; given recipients are surviving longer there is a need for studies with an increased follow-up time (1). Moreover, few previous studies included recipients who recently received a transplant; given changes in clinical practice (2-4) and changes in recipient characteristics there was a need for studies that included recently transplanted kidney transplant recipients (4, 5). With respect to risk factors there was a need to assess other potentially relevant risk factors (e.g. falls) and a need to assess risk factors specific to different fracture locations. Therefore, these results provided the information required to design high quality studies in chapters 4 and 5 of this thesis.

7.2.2 Comparison of Fracture Prediction among Individuals with Reduced and Normal Kidney Function

Chapter 3 examined the predictive ability of FRAX in individuals with reduced kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2) compared to individuals with normal kidney function (eGFR ≥ 60 mL/min/1.73 m^2) using data from the Canadian Multicentre Osteoporosis Study (CaMos).

FRAX was able to predict major osteoporotic fractures in individuals with reduced kidney function with similar accuracy to individuals with normal kidney function. Specifically, the 5-year observed major osteoporotic fracture risk in individuals with reduced kidney function was comparable to the FRAX predicted fracture risk. Moreover, there were no significant differences in the area under the curve (AUC) values for FRAX when comparing individuals with reduced and normal kidney function. These results paralleled findings from a study conducted by Jamal *et al.* which found FRAX may be an accurate tool for clinicians to use to predict fractures in individuals with reduced kidney function (6). Similarly, these results are consistent with findings from a study conducted by Naylor *et al.* in kidney transplant recipients (a group that experiences similar changes in bone mineral metabolism to those with non-transplant chronic kidney disease [CKD]) which found observed and FRAX predicted fracture risks were concordant and AUC values were statistically significant (7).

Taken together the results of chapter 3 suggest that FRAX may be a useful tool for clinicians to use to predict fracture and help guide treatment decisions in individuals with reduced kidney function. However, validation of FRAX with a different data source is needed before it can be routinely used in clinical practice. In particular, the discrimination and calibration of FRAX should be assessed across different levels of kidney dysfunction (i.e., stage 3a, stage 3b, stage 4 and stage 5 CKD). Moreover, given the limited sample size in this study, larger studies are also needed before its use is implemented into routine clinical practice.

7.2.3 Fracture Incidence in Kidney Transplant Recipients

Chapter 4 used several of Ontario's large healthcare databases held at the Institute for Clinical Evaluative Sciences (ICES) to examine the incidence of fracture and falls in kidney transplant recipients.

In contrast to previous studies which found kidney transplant recipients have a high fracture risk (3, 8-15) in this study the 10-year cumulative incidence of hip fracture was 1.7% (where a high risk is defined as ≥ 3% in clinical guidelines) (16, 17). These findings are consistent with a previous Canadian study conducted by Naylor *et al.* where the 10-year incidence of major osteoporotic fracture in kidney transplant recipients from Manitoba, Canada was approximately 6% (where a low risk is defined as <10%) (7, 17, 18); however, cohort entry was an average of 1-year post-transplant preventing an accurate estimation of fracture (7). These findings are also consistent with another study conducted by Naylor *et al.* which found that bone mineral density (BMD) in kidney transplant recipients from Manitoba, Canada was not below the average for age and sex (19).

Kidney transplant recipients had a significantly higher incidence of non-vertebral fracture compared to a healthy segment of the general population (no kidney disease and no bone disease; low fracture risk group) and the non-dialysis CKD population (group with an increased fracture risk), but had a significantly lower incidence of non-vertebral fracture compared to a healthy segment of the general population with no kidney disease and a previous non-vertebral fracture (group with an increased fracture risk). Therefore, although kidney transplant recipients had a low absolute fracture risk they still had a high relative fracture risk.

Many kidney transplant recipients experienced a fall with hospitalization with a 3-year cumulative incidence of 11.1% in women aged ≥ 50 years. These findings are comparable to a Canadian study conducted by Naylor *et al.* where the 3-year cumulative incidence of falls with hospitalization in the non-transplant CKD population was 9.1% in women aged ≥65 years with stage 4 CKD and 13.1% in individuals with stage 5 CKD (end-stage renal disease) (20). The high incidence of falls highlights the need for further study assessing the effectiveness of interventions to prevent falls in kidney transplant recipients.

Despite bone mineral metabolism changes and administration of steroids after transplantation results from chapter 4 suggest that bone health in kidney transplant recipients is better than previous research has suggested. However, it is important to emphasize that these encouraging results may be unique to Canadian recipients due to

variability in fracture rates across countries (21, 22), differences in recipient comorbidities (23), and potential practice pattern differences. Moreover, it is important to note that even though a low absolute fracture risk was observed in this study, fracture rates in this population should be continually monitored due to several factors which could potentially increase fracture rates, including: an increasing average recipient age (5), an increase in recipients with comorbidities (e.g. diabetes) (5), and an increase in suboptimal quality kidneys (24, 25).

7.2.4 Risk Factors for Fracture in Kidney Transplant Recipients

Chapter 5 used healthcare administrative databases to examine transplant specific (e.g. donor age) and general (e.g. sex) risk factors for major fractures (hip, forearm, proximal humerus, and clinical vertebral) and other fractures (excluding the major fractures, and the skull, fingers, and toes).

The multivariable analysis revealed that the general risk factors associated with a greater risk of major fracture were older recipient age and female sex. Transplant-specific risk factors associated with a greater risk of major fracture included diabetes or cystic kidney disease as the cause of end-stage renal disease (ESRD) (compared to glomerulonephritis as the reference cause) and older donor age. General risk factors associated with a greater risk of other fractures were diabetes and a prior fall with hospitalization. The transplant-specific risk factors associated with an increased risk of other fractures were length of time on dialysis prior to transplant and renal vascular disease or other as the cause of ESRD (compared to glomerulonephritis as the reference cause).

Few of the transplant-specific risk factors that were available to assess in chapter 5 predicted major fractures in the post-transplant period with any significance. Therefore, there may not be a need to create a modified FRAX tool that incorporates transplant-specific risk factors; as previously discussed, Naylor *et al.* found FRAX may be a useful tool for fracture prediction in kidney transplant recipients with an area under the receiver operating characteristic curve value of 0.62 and a comparable observed and FRAX predicted fracture risk (7). Rather, fracture prediction tools used in the general population in combination with the use of a few independent transplant-specific risk factors could be used for prognostication. For example, clinicians could use the FRAX score in

combination with information on whether the recipient had diabetes as the cause of their ESRD to guide treatment decisions. Unfortunately, risk factors for fracture identified in chapter 5 are not easy to modify; this is concerning given that the efficacy of fracture prevention therapy (e.g. bisphosphonates) in kidney transplant recipients is uncertain (26).

7.2.5 Bone Mineral Density Testing in Kidney Transplant Recipients

Chapter 6 examined the frequency, total cost, and variability in bone mineral density (BMD) testing in kidney transplant recipients across the six transplant centres in Ontario, Canada, from 1994 to 2009 using ICES databases.

There were a total of 4802 BMD tests performed in 4821 kidney transplant recipients in the first three years after transplant (range 0 to 6), costing approximately $600,000 (2014 CAD equivalent dollars). The proportion of recipients who received at least one BMD test varied widely across the six transplant centres (15.6 to 92.1%). This finding is similar to a study conducted in the general population which examined BMD testing patterns in Ontario from 1992-1998, a time period when there was a lack of consensus on BMD guidelines, finding there was significant regional variation across Ontario in the number of BMD tests performed (range 0.2 to 47.1 tests per 1000 women) (27).

Overall the results of chapter 6 demonstrate that a large number of BMD tests were performed in kidney transplant recipients with many recipients receiving multiple tests, despite conflicting evidence to support their ability to predict fracture (28-30). Even in the general population, where the utility of BMD has been well established, the frequency and timing of BMD tests has been questioned with recent studies finding there is little benefit of repeating BMD tests within several years (31, 32). This is an important finding as the harms of unwarranted screening have become increasingly recognized, and many guidelines now recommend less frequent screening (33, 34). Given how frequently these tests are being performed, prospective studies are needed to determine the optimal timing and frequency of BMD testing and the ability of BMD to predict fracture.

7.3 Implications

7.3.1 Clinical Practice Guidelines

Currently kidney disease patients are not discussed in the Osteoporosis Canada Clinical Practice guidelines and are minimally discussed in the United States National Osteoporosis Foundation guidelines (35, 36). Given greater than 30% of adults over the age of 60 years have CKD these guidelines are failing to provide advice for a large segment of the population who are at an increased fracture risk (37). The results in chapter 3 combined with results from a study conducted by Jamal *et al.* (6) provide some evidence to support the use of FRAX in the non-transplant CKD population; currently, Osteoporosis Canada and the National Osteoporosis Foundation only support the use of FRAX in the non-kidney disease general population (35, 38). Results from chapter 4 suggest guidelines should highlight that kidney transplant recipients have a significantly higher relative fracture risk compared to the healthy general population; therefore, these individuals should be monitored more closely by clinicians and counseled on potential preventative actions for fracture (e.g. weight bearing exercise, bisphosphonates).

The results of this thesis also indicate that a discussion on falls is needed in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) (43). Chapter 4 found falls were common in recipients and chapter 5 found falls were a significant risk factor for other fractures (excluding the major fractures, and the skull, fingers, and toes). However, currently the guidelines provide no discussion of falls in the context of kidney transplant recipients. Regarding the non-transplant CKD population falls were minimally discussed with the guidelines simply stating that these individuals may experience more falls which may impact fracture risk (43). In chapter 3 a previous fall in combination with T-scores was found to discriminate between individuals who did and did not fracture providing support that kidney disease patients who fall should be given a fracture risk assessment. Recognizing the important relationship between falls and fractures (39), in the general population Osteoporosis Canada guidelines provide an in-depth discussion of falls and strategies to prevent falls (e.g. exercise programs); the guidelines also state that management of falls is integral to reducing the number of fracture events in Canada (18).

7.3.2 Clinical Prognostication

Accurately identifying kidney disease patients who are at a high fracture risk is important to appropriately target high risk groups for fracture prevention, diagnosis, and therapeutic trials. Chapter 3 revealed FRAX may be an accurate tool to predict fractures in individuals with reduced kidney function and guide treatment decisions. Given concerns about the safety and efficacy of bisphosphonates in individuals with more severe decrements in kidney function applying early therapeutic intervention could conceivably prevent fractures later on when bisphosphonates are contraindicated (40, 41); research in the general population has found that due to bisphosphonates long half-life (40) residual effects of the drug may occur years after discontinuation (42-44). With 1 in 10 women > 65 years of age with ESRD sustaining a fracture over three years (20) and over 60% of dialysis patients dying after sustaining a hip fracture, early preventative therapy could be particularly important (45). Regarding kidney transplant recipients, Naylor *et al.* previously concluded that the discrimination and calibration of FRAX in kidney transplant recipients may be improved by adding transplant specific risk factors (7). However, chapter 5 found few transplant-specific risk factors reached statistical significance suggesting a modified version of FRAX may not need to be developed for kidney transplant recipients. However, diabetes might be an additional risk factor for clinicians to use to help identify recipients who have a high fracture risk, and who may benefit from fracture prevention strategies such as a lower dose of steroids.

7.3.3 Clinical Trials

Therapies are needed to safely prevent fractures in individuals with advanced kidney disease (26, 46, 47). Clinical trials that assess these therapies need to enroll individuals who have a high risk of the outcome to ensure adequate power (48). The results of chapter 3 demonstrate that FRAX may be useful to identify non-transplant CKD patients who have a high fracture risk and would benefit from the inclusion in clinical trials. Regarding kidney transplant recipients, chapter 4 found that due to the low number of fracture events thousands of recipients would need to be enrolled in clinical trials to ensure adequate power. As a result, multicentre collaboration would be required to obtain an adequate sample size. However, given the low absolute fracture risk in kidney transplant recipients there may not be a need for these trials.

7.3.4 Informed Consent

Previous research suggests that in the early post-transplant period recipients have a higher fracture risk compared to individuals on dialysis (14); however, chapter 4 revealed that post-transplant the absolute fracture risk is low. This is reassuring as individuals who receive a transplant not only have improved survival and quality of life compared to dialysis patients but also have a low absolute fracture risk (1, 49, 50). Given fractures are associated with morbidity, mortality, and a decreased quality of life this information is important to provide to potential kidney transplant recipients as part of the informed consent process (51-53).

7.4 Strengths and Limitations

7.4.1 Study Strengths

Strengths of this thesis have been highlighted in the discussion section of each chapter; however, several key strengths of this thesis deserve mention. First, this thesis provided a comprehensive examination of fracture in Canadian kidney disease patients. It was crucial that Canadian studies were conducted as several factors may result in differential fracture rates across countries, including: Canadians have lower vitamin D levels (low vitamin D is a risk factor for fracture) (54, 55); universal healthcare access (Americans less likely to regularly see a doctor and be on needed medications) (56); different patient population (e.g. different racial distribution in the US) (23); and potential differences in immunosuppressant protocols. Indeed, the results of chapter 4 confirmed that fracture rates in recipients were lower than fracture rates found in the United States.

Second, in this thesis several methods were employed to ensure fracture events were accurately captured. In chapter 3 self-reported fractures were required to be verified by structured interviews to obtain more detailed information about the fracture event and/or by the treating physician or hospital (57). The fracture codes used in chapters 4 and 5 were valid (>90% sensitivity, ≥ 85% specificity, > 80% positive predictive value) (58-65). Moreover, procedural codes were required to accompany hip, forearm, and femoral shaft diagnostic codes to increase their accuracy (58, 64, 66); previous literature has found this combination increases accuracy compared to diagnostic or procedural codes alone (58, 64, 66) . For example, Hudson *et al.,* conducted a systematic review and

found that when using diagnostic codes alone the positive predictive value for hip fracture was 63-96% but increased to 86-98% when including both diagnostic and procedural codes (58); therefore, previous studies may have been overestimating the number of fractures in recipients.

Third, loss to follow-up was minimal. In chapter 3 multiple methods were employed to retain over 96% of participants, including: sending a yearly birthday card, sending a yearly non-denominational Christmas card (67), and obtaining contact information from next of kin (57). For chapters 4, 5, and 6 loss to follow-up was also minimal as data from Ontario healthcare administrative databases was utilized where all residents of Ontario are provided with universal access to physician and hospital services. We also only included permanent residents from Ontario with less than 0.5% emigrating from the province each year (68).

Last, the studies in this thesis were the first to understand the epidemiology of fracture in kidney disease patients in the context of several reference groups. In chapter 3 the utility of FRAX in individuals with reduced kidney function was compared to individuals with normal kidney function to determine if kidney function affected FRAX's performance. Similarly, in chapters 4 and 6 fracture risk and the number of BMD tests performed in recipients were compared to several reference groups.

7.4.2 Study Limitations

Limitations of this thesis are recognized and described in the discussion section of each chapter. Overall this research had some limitations. First, some data was missing from both data sources used in this thesis. In chapter 3 many individuals were excluded due to a missing eGFR measurement in the CaMos database. However, in an additional analysis multiple imputation was used to handle missing eGFR values and similar results to the complete case analysis were found (Appendix C). Although many of the data sources contained at ICES are robust, there was a considerable amount of missingness for several transplant variables that would have been of interest to assess as potential risk factors for fracture (e.g. body mass index). Moreover, drug information was missing for individuals who were <65 years and were not covered under the Ontario Special Drug Benefits Plan. However, the many benefits of secondary datasets (large sample size;

generalizability; feasibility) made using ICES datasets the most appropriate option to study kidney transplant recipients in this thesis.

Second, the studies contained in this thesis may have under-captured fracture events. Using ICES databases vertebral fractures were not able to be included in the primary analysis of fracture incidence with only one-third coming to clinical attention (69). To increase the reliability of capturing vertebral fractures a prospective study design that utilizes x-rays (e.g. CaMos) would need to be utilized. However, prospective studies are costly and would take several years to complete. In the CaMos database fracture events were self-reported and therefore, some events may have been missed. However, previous studies comparing self-reported fractures to hospital records have found that the number of false negatives is low (<3%) and self-report of fractures is more accurate compared to many other self-reported items (e.g. myocardial infarction) (70-73). Additionally, CaMos requires individuals to complete a fracture questionnaire each year and if individuals failed to return the questionnaire they were censored at the time of the last questionnaire. Although this could potentially introduce selection bias (individuals who left the study could be sicker and thus might be more likely to fracture), as previously discussed loss to follow-up was minimal.

Third, the low number of fracture events prevented the conduction of some meaningful analyses and decreased statistical power. In chapter 3 it would have been of value to assess the discrimination and calibration of FRAX for hip fracture alone given the significant morbidity and mortality associated with these fractures (74, 75). The small number of fracture events also limited statistical power and as a result it was emphasized in chapter 3 that further studies with larger sample sizes are needed before FRAX should be used regularly in clinical practice. In chapter 4 it would have been of value to stratify the incidence of non-vertebral fracture in kidney transplant recipients by presence of a previous non-vertebral fracture, given a previous fracture is a strong risk factor for a future fracture in the general population (76). Moreover, assessing secular trends in fractures would have provided insight about potential reasons for the low absolute fracture risk in kidney transplant recipients. To account for the small number of fracture events in chapter 4 each recipient was matched to a minimum of one individual from the reference groups to increase statistical power (77, 78). For chapter 5 the small number of

fracture events prevented several risk factors for fracture from being assessed and risk factors were not able to be stratified by sex (risk factors for fracture differ by sex in the general population) (79, 80). Given the low number of fracture events in chapter 5 the issue of power was discussed as a limitation and a recommendation for the conduction of future studies with larger sample sizes was provided.

Lastly, the external generalizability of these results may be limited. The majority of individuals in this thesis were of white race; therefore, results may not be generalizable to non-white races. Fracture rates have been found to be variable across races; for example, white individuals have been found to have a higher fracture risk compared to black individuals (81). Risk factors for fracture have also been found to vary across races (82). Moreover, given the variation in fracture rates across countries these results may only generalize to the Canadian population (83).

7.5 Future Directions

This thesis addressed numerous limitations of previous studies done in the field; however, there are still many unanswered questions regarding the epidemiology of fracture in kidney disease patients which require further research. These knowledge gaps are reflected in the minimal number of recommendations from the KDIGO CKD-MBD guidelines which are currently being reassessed for updating (84).

First, future research should determine reasons for the low observed fracture rate in kidney transplant recipients. Specifically, secular trends in fracture preventative therapy (e.g. bisphosphonates and vitamin D) need to be studied to determine if an increase in bisphosphonate use has decreased fracture rates. Additionally, research needs to examine the effects of increased BMD monitoring, decreased steroid dose, and changes in recipient characteristics (e.g. increasing age, body mass index, and diabetics) on fracture rates.

Second, studies that assess fracture prevention strategies are needed, particularly in individuals with more severe declines in kidney function. For example, the efficacy of fracture prevention therapies, fall prevention programs, and the utility of BMD to predict fracture need to be better understood.

Third, although FRAX may be an accurate tool to use in kidney disease patients, given the complex pathophysiology of bone disease, other risk factors that are unique to the kidney disease population and were not assessed in this thesis may also be useful to use as markers for fracture (6, 7). For example, risk factors that may be unique to the kidney disease population, such as fibroblast growth factor 23, may play an accurate role in fracture prediction (85, 86). Moreover, in the general population a relatively new method to assess bone texture (bone microarchitecture) called the trabecular bone score has been found to accurately predict fracture (87-89) and could be useful at predicting fracture in the kidney disease population.

Fourth, improvements in the data quality of kidney disease information contained in administrative healthcare databases are needed. As previously discussed, drug information for only a sub-cohort of kidney transplant recipients was available in ICES databases and some important kidney transplant recipient variables (e.g. body mass index) had considerable missingness. One method to obtain more detailed information on Ontario kidney transplant recipients is to perform a medical chart abstraction as was done for living kidney donor studies at ICES (90, 91); however, this takes a considerable amount of time and funding. Chart abstraction could also be used to ensure the accuracy of information contained in the recipient database through conducting validation studies.

Last, family physicians are often the primary care providers for individuals with mild to moderate reductions in kidney function (92) and once an individual receives a kidney transplant they are often managed by a family physician in tandem with a nephrologist. Therefore, family physicians can play a critical role in preventing fractures in the kidney disease population. The Canadian Society of Nephrologists recognizes this stating that it is important that fracture prevention guidelines specific to CKD patients be provided to family physicians (93). Survey research should be conducted to determine family physicians' knowledge of bone disease in kidney disease patients and their fracture prevention practices. The results would assist with determining areas for improvement in the medical school curriculum and in determining how to better disseminate this information to family physicians.

7.6 Conclusions

As improvements in survival have been achieved in kidney disease patients (5, 94), associated long-term complications have become an increasing concern. This thesis examined one important complication of kidney disease, fracture. The knowledge gained from this thesis provided information to improve prognostication, advance osteoporosis and transplant guidelines, guide the allocation of healthcare resources, assist with sample size estimations for future fracture prevention trials, clarify fracture incidence, and guide informed consent.

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APPENDIX A: Chapter 2 Details[a]

[a]A version of this appendix was published elsewhere as, Naylor KL, Li AH, Lam NN, Hodsman BA, Jamal SA and Garg AX. Fracture Risk in Kidney Transplant Recipients: A Systematic Review. *Transplantation* 2013; 95:1461-1470. Wolters Kluwer Health Lippincott Williams & Wilkins© No modifications will be permitted.

A.1 Additional Methods

For objectives 3 and 4 a systematic review was performed as part of the literature review. Detailed methods for this systematic review are described below.

A.1.1 Design and Study Selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used in the reporting of this systematic review (1). Inclusion and exclusion criteria were developed a priori. Studies were included if they met the following criteria:1) full-text English articles, 2) cohort study, 3) more than 50 kidney transplant recipients, 4) mean age ≥ 18 years (the mechanisms underlying fracture in children are different than in adults) (2), 5) reported any type of fracture (including low or high trauma), 6) earliest accrual period after 1984 (1984 was the year cyclosporine was introduced into clinical practice) (3), 7) time zero (start of follow-up) the day of kidney transplant or thereafter, and 8) mean follow-up greater than one year. The following studies were excluded from the review: 1) no incidence of fracture reported (i.e., only bone mineral density, which is controversial in kidney transplant recipients) (4, 5), and 2) insufficient information on when the fracture occurred (see Figure A.1 for final study selection).

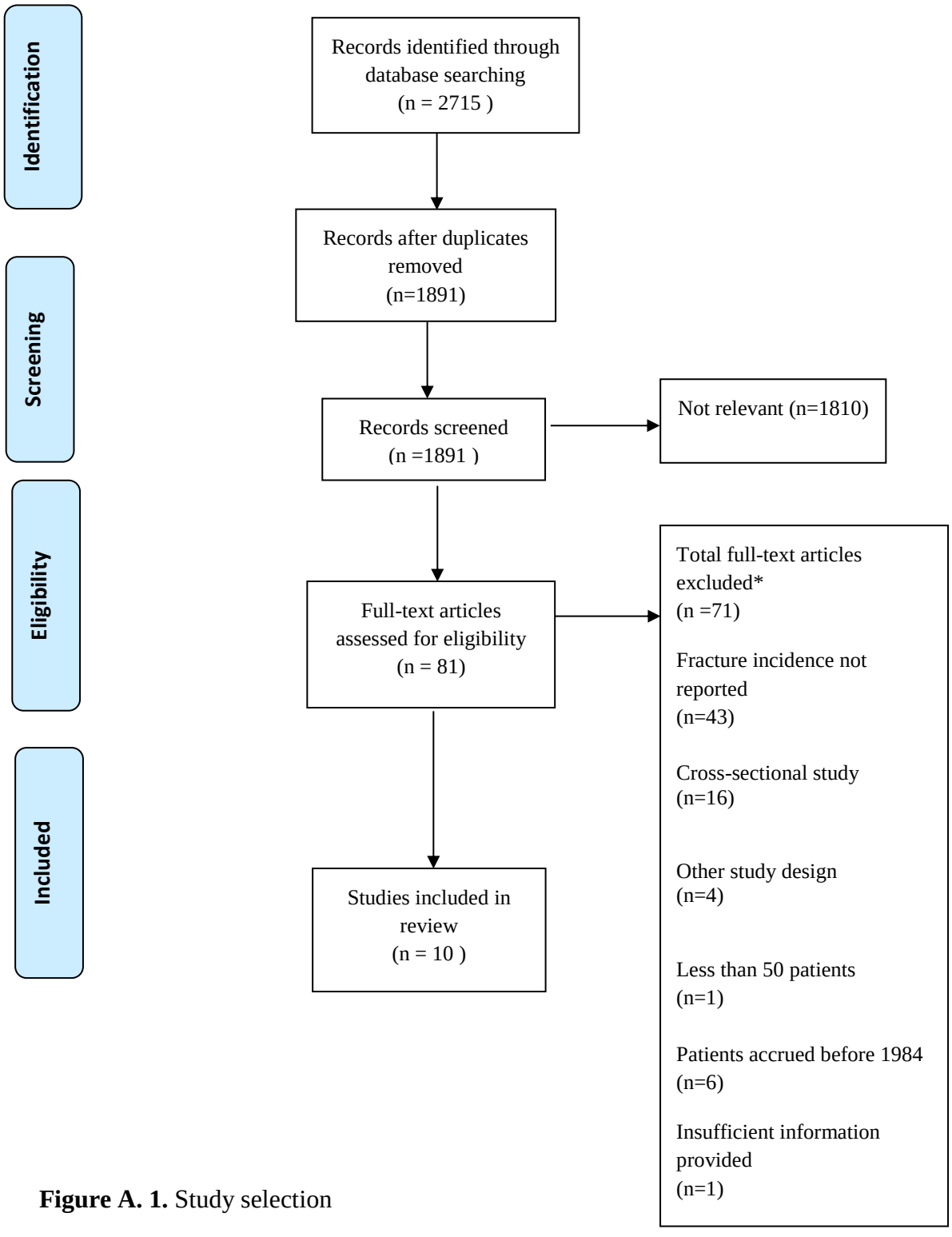

Figure A. 1. Study selection

*Excluded if met first exclusion criteria

A.1.2 Identifying Relevant Studies

Both MEDLINE (1984 to November, 2012) and EMBASE (1984 to December, 2012) were searched. For both databases, the search strategies were pilot tested and modified to ensure known relevant articles were identified. The final search strategy consisted of keywords such as kidney transplantation, renal transplant, fracture, bone, and falls (Tables A.1 and A.2). The search strategy was modified for each database used. The related articles option was also used in Google Scholar to search for additional articles.

Table A. 1. Search strategies: Embase search strategy <1984 to 2012 Week 50>

1 exp kidney transplantation/
2 kidney transplant$.tw.
3 renal transplant$.tw.
4 kidney graft$.tw.
5 renal graft$.tw.
6 kidney allograft$.tw.
7 renal allograft$.tw.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp fracture/
10 exp bone/
11 posttraumatic osteoporosis/ or primary osteoporosis/ or senile osteoporosis/ or involutional
osteoporosis/ or secondary osteoporosis/ or idiopathic osteoporosis/ or osteoporosis/ or corticosteroid
induced osteoporosis/ or osteoporosis.mp. orpostmenopause osteoporosis/
12 osteoporosis$.tw.
13 fracture$.tw.
14 (mineral$ adj2 bone$ adj2 disease$).tw.
15 exp falling/
16 fall$.tw.
17 BMD.tw.
18 exp renal osteodystrophy/co, di, dm, dr, dt, ep, et, pc, si, su, thYOU
19 renal osteodystrophy$.tw.
20 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 8 and 20
22 limit 21 to yr="1984 -Current"
23 limit 22 to english language

Table A. 2. Search strategies: Medline search strategy (1946 to November Week 3 2012)

1. exp Kidney Transplantation/
2. kidney transplant$.tw.
3. renal transplant$.tw.
4. kidney graft$.tw.
5. renal graft$.tw.
6. kidney allograft$.tw.
7. renal allograft$.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. exp Fractures, Bone/
10. fracture$.tw.
11. exp Osteoporosis/
12. osteoporosis$.tw.
13. exp Renal Osteodystrophy/
14. exp Accidental Falls/
15. fall$.tw.
16. 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 8 and 16
18 limit 17 to yr="1984 -Current"
19 limit 18 to English

A.1.3 Article Eligibility Criteria

Two reviewers (K.N. and A.L.) independently screened each citation's title and/or abstract to determine eligibility. Full-text articles were retrieved for citations that were identified by either reviewer as potentially relevant. Both reviewers independently assessed the eligibility of full-text articles. Discrepancies among the two reviewers were resolved through re-evaluation and discussion.

A.1.4 Data Abstraction

The data abstraction form was designed and pilot tested. The following data was abstracted independently by paired reviewers: study design, patient characteristics, fracture incidence, and fracture risk factors. Differences in abstracted data were discussed by two reviewers and were resolved.

The methodological quality was assessed using a modified version of the Downs and Black checklist for nonrandomized studies (Table A.3) (6). The completeness and clarity of reporting, bias, and external validity was assessed. On the modified scale, all included studies were given a score from 0 to 17, with a higher score indicative of greater

quality. Attempts were made to obtain additional study information by contacting corresponding authors.

Table A. 3. Modified Downs and Black checklist for non-randomized studies (Prospective and Retrospective Studies)

ALL CRITERIA	DESCRIPTION OF CRITERIA (with additional explanation as required, determined by consensus raters)	POSSIBLE ANSWERS
1	**Is the hypothesis/aim/objective of the study clearly described?** Must be explicit	Yes/No
2	**Are the main outcomes to be measured clearly described in the Introduction or Methods section?** If the main outcomes are first mentioned in the Results section, the question should be answered no. **ALL** primary outcomes should be described for YES	Yes/No
3	**Are the characteristics of the patients included in the study clearly described?** In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given. Single case studies must state source of patient. *Are baseline characteristics of individuals clearly described.	Yes/No
4	**Are the main findings of the study clearly described?** Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions.	Yes/No
5	**Does the study provide estimates of the random variability in the data for the main outcomes?** In nonnormally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported	Yes/No
6	**Have the characteristics of patients lost to follow-up been described?** If not explicit = NO. RETROSPECTIVE – if not described = UTD; if not explicit re: numbers agreeing to participate = NO. Needs to be >85%	Yes/No
7	**Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?**	Yes/No
8	**Were the subjects asked to participate in the study representative of the entire population from which they were recruited?** The study must identify the source population for patients and describe how the patients were selected.	Yes/No/UTD
9	**Were those subjects who were prepared to participate representative of the entire population from which they were recruited?** The proportion of those asked who agreed should be stated.	Yes/No/UTD
10	**Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?** For	Yes/No/UTD

	the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. Must state type of hospital and country for YES.	
11	**If any of the results of the study were based on "data dredging", was this made clear?** Any analyses that had not been planned at the outset of the study should be clearly indicated. Retrospective = NO. Prospective= YES	Yes/No/UTD
12	**In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?** Where follow-up was the same for all study patients the answer should yes. Studies where differences in follow-up are ignored should be answered no. Acceptable range 1 yr follow up = 1 month each way; 2 years follow up = 2 months; 3 years follow up = 3months.....10years follow up = 10 months	Yes/No/UTD
13	**Were the statistical tests used to assess the main outcomes appropriate?** The statistical techniques used must be appropriate to the data. If no tests done, but would have been appropriate to do = NO	Yes/No/UTD
14	***Were the main outcome measures used accurate (valid and reliable)?** YES=used radiographs, codes, patient records or multiple methods (i.e. questionnaires verified by codes). NO=questionnaires only used to determine if patient fractured. UTD=no method was reported	Yes/No/UTD
15	***Was a case definition of fracture provided?** YES=stated that a fracture was a fall from standing height or less and/or stated that they excluded/included high trauma fractures NO=not reported	YES/NO
16	**Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?** In nonrandomised studies if the effect of the main confounders was not investigated or no adjustment was made in the final analyses the question should be answered as NO. If no significant difference between groups shown then YES	Yes/No/UTD
17	**Were losses of patients to follow-up taken into account?** If the numbers of patients lost to follow-up are not reported = unable to determine.	Yes/No/UTD

YES=1
NO=0
UTD (unable to determine)=0 **Total Score**:____**/17**

*Items that have been added.
Source: Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998; 52: 377.

A.1.5 Data Analysis

Where possible, incidence rates were normalized to 1000 person-years, although in some studies only cumulative incidence was reported. Risk factors were summarized if

they were determined by multivariable analysis and were statistically significant in at least one study. A meta-analysis was not performed because the studies were too heterogeneous.

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APPENDIX B: Ethics Approval, Consent Form, and Questionnaire for the Canadian Multicentre Osteoporosis Study (Chapter 3)

B.1 Ethics Approval

Center for Applied Ethics

November 3, 2014

Comité d'éthique
Génétique et populations
Biomédicale D
a/s Mme Esther Boyle

Research Ethics Board
Genetics/Population Research/
Gen Investigator Initiated
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c/o Ms. Esther Boyle

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Dr. David Goltzman
[redacted]

RE: REC. July 19, 1994 entitled "Canadian Multicenter Osteoporosis Study - CAMOS".

Dear Dr. Goltzman:

We have received an Application for Continuing Review of the GEN-Research Ethics Board for the research study referenced above and the report was found to be acceptable for ongoing conduct at the McGill University Health Centre.

At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

We are pleased to provide you with re-approval, via expedited review by the Co-Chairman on November 3, 2014. It is noted that the study is closed to recruitment and subjects are in long-term follow-up. A total of 10, 424 subjects have been enrolled in the study since study initiation, including 315 minors.

All research involving human subjects requires review at a recurring interval. It is the responsibility of the principal investigator to submit an Application for Continuing Review to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year". However, should the research conclude for any reason prior to the next required review, you are required to submit a Termination Report to the Committee once the data analysis is complete to give an account of the study findings and publication status.

RE-APPROVAL	**NOVEMBER 3, 2014**
EXPIRATION	**NOVEMBER 2, 2015**

Should any revision to the study, or other unanticipated development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

We trust this will prove satisfactory to you.

Sincerely,

[redacted]

Dr. Terry Chow
Chairman
Genetics/Population Research/Gen Investigator Initiated Studies
MUHC-Montreal General Hospital

B.2 Conset Form

Canadian Multicentre Osteoporosis Study (CaMos) **Extension**
CONSENT FORM

PRINCIPAL INVESTIGATOR : Dr. David Goltzman

FUNDING AGENCIES : Representatives of the Pharmaceutical Industry : Merck Frosst, Eli Lilly Canada Inc., Novartis Pharmaceuticals, Amgen Canada.

PROCEDURES OF THE EXTENDED STUDY

Each year for the next five years (year 15 to year 19 follow-up), you will receive a short questionnaire to fill out. Completing the questionnaire will usually take less than five minutes. If you had a fracture, you will also be asked questions about the event and how it affects your life. We will ask your permission to contact the physician who diagnosed and treated you and/or the hospital where you were treated, in order that we may learn the relevant medical details of the event. This is the same procedure that was done in the annual follow-ups. In addition, at the year 16 follow-up you may be asked to be re-interviewed and to have a DXA test, blood sample collection and X-Ray of your spine (if you are 50 years or over at the time of your interview).

OTHER PERTINENT INFORMATION

Confidentiality : When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records will be kept in a file in a locked room.

Sharing of Research data : Over the course of the study, the research data may be shared with other investigators and sponsors. The information that could identify you as a participant will not be transmitted under any circumstances, the shared data will remain anonymous at all times.

Questions and Problems : If any questions arise with regard to the study, please contact :
Dr. David Goltzman
[redacted]

We will inform you of any new information which may affect your decision to remain in this research study.
Consent document : we suggest that you retain a copy of this document for your later reference and personal records.

Participant's Initials _____
Date _____

COMPLETE ITEM BELOW

I have read the explanation about the Canadian Multicentre Osteoporosis Study (CaMos) and have been given the opportunity to discuss it and ask questions. I hereby consent to take part in this study.

Name of Participant _____

Signature of Participant _____ Date Signed _____

Name of Investigator _____

Signature of Investigator _____ Date Signed _____

Name of Witness
(If applicable) _____

Signature of Witness _____ Date Signed _____

Participant's Initials _____
Date _____

B.3 Questionnaire

RESPONDENT I.D. # QID

CAMOS1D10

INTERV10 * *Age at study entry* _____

Age at last interview CAGLINT10

TMLINT10 *Date of last interview* ____ / ____ / ____ (Day / Month / Year)

CaMos

CENTRE IDENTIFICATION ☐☐ HICNUM10

INTERVIEWER I.D. _____ MEDRECN10 NAME _____

LOCATION OF INTERVIEW SITE10 ☐1 HOSPITAL ☐2 HOME ☐3 OTHER ⇢ *(Specify)* SITEOTH10

INTDATE10 INTDAY10 / INTMON10 / INTYR10
YEAR 10 INTERVIEW ____ / ____ / ____ (Day / Month / Year)

ABEGINT10 ABEGINH10 ABEGINM10
TIME BEGAN ☐☐ HRS ☐☐ MIN

AENDT10 AENDH10 AENDM10
TIME ENDED ☐☐ HRS ☐☐ MIN

CLINICAL ASSESSMENT * DEXA	BBDMI10	☐1 Yes	☐2 No	
ULTRASOUND	BULTRAS10	☐1 Yes	☐2 No	
X-RAY *(40 years and over at study entry)*	BXRAY10	☐1 Yes	☐2 No	☐3 N/A
BLOOD	BBLOOD10	☐1 Yes	☐2 No	☐3 N/A
URINE	BURINE10	☐1 Yes	☐2 No	☐3 N/A
HEARING IMPAIRMENT	AHEAR10	☐1 Yes	☐2 No	
VISUAL IMPAIRMENT	AVISUAL10	☐1 Yes	☐2 No	
RESULTS TO BE SENT TO PHYSICIAN	BTESTMD10	☐1 Yes	☐2 No	
RESULTS TO BE SENT TO PARTICIPANT	BTESTPT10	☐1 Yes	☐2 No	

BENTDAT10 BENTDAY10 / BENTMON10 / BENTYR10
CAMOS DATA ENTRY DATE ____ / ____ / ____ (Day / Month / Year) _____ (Initials)

COMMENTS _____

RESPONDENT I.D. # _____

I would like to ask you general questions about yourself.

1. SOCIO-DEMOGRAPHIC INFORMATION

1.1 Sex: *(Answer by observation)* . . . . . HDI_SEX10 ☐ 1 Male ☐ 2 Female

CAGE10

1.2 What is your date of birth? . . . . . CDOBDAT10 CDOBDAY10 / CDOBMON10 / CDOBYR10 _____ / _____ / _____ (Day / Month / Year)

1.3 Have you moved **SINCE YOUR LAST INTERVIEW**? . . . . . BMOVE10 ☐ 1 Yes ☐ 2 No

→ How many times have you moved? BMOVTIM10

→ For your most recent move, where have you moved ? BMOVWHR10

- ☐ 1 Single family home
- ☐ 2 Apartment
- ☐ 3 Condominium
- ☐ 4 Lodge
- ☐ 5 Nursing home
- ☐ 6 Extended care home
- ☐ 7 Chronic care hospital
- ☐ 8 Other *(specify)* BMOVOTH10 _____

1.4 What is your current marital status? *(Indicate only one)* BMARSTA10

- ☐ 1 Married or living with a partner
- ☐ 2 Single
- ☐ 3 Separated
- ☐ 4 Divorced
- ☐ 5 Widowed

1.5 With whom do you currently live? *(Check all that apply)*

- ☐ 1 Spouse / partner BLIVC1_10
- ☐ 2 Sibling BLIVC2_10
- ☐ 3 Children BLIVC3_10
- ☐ 4 Parents BLIVC4_10
- ☐ 5 Lives alone BLIVC5_10
- ☐ 6 Other *(specify)* BLIVC6_10 BLIVCOT10

Go to quest 1.7

RESPONDENT I.D. # _____

1.6* If living with spouse or a partner *(answered in question 1.5)*, which best describes your partner's current or most recent occupation?

Show the list to the respondent. Help interpret if necessary. Mark only one.

COCCP5T10

- ☐ 1 Executive, administrative and or managerial
- ☐ 2 Professional specialty occupation
- ☐ 3 Technician and or related support occupation
- ☐ 4 Marketing and or sales occupation
- ☐ 5 Administrative support occupation
- ☐ 6 Service occupation
- ☐ 7 Agriculture, forestry, fishing and/or related worker
- ☐ 8 Precision production, crafts and/or repair occupation
- ☐ 9 Operator, fabricator and/or laborer
- ☐ 10 Partner does not work

1.7* What is your current employment status?

BSTATUS10

- 1 = 1 ☐ 1 Employed full time
- 2 = 3 ☐ 2 Employed part time *(or semi-retired)*
- 3 = 6 ☐ 3 Retired
  - 4 = 4 Since your last interview?
  - 5 = 2 RETLINT10 ☐ 1 Yes ☐ 2 No
  - 6 = 8
  - 7 = 5 How old were you? CRETAGE10 years
- ☐ 4 Unemployed
- ☐ 5 Homemaker *(full time)*
- ☐ 6 Student
- ☐ 7 Disability

1.8* Which best describes your current or most recent occupation, if currently employed or retired?

Show the list to the respondent. Help interpret if necessary. Mark only one.

CUROCCP10

- ☐ 1 Executive, administrative and or managerial
- ☐ 2 Professional specialty occupation
- ☐ 3 Technician and or related support occupation
- ☐ 4 Marketing and or sales occupation
- ☐ 5 Administrative support occupation
- ☐ 6 Service occupation
- ☐ 7 Agricultural, forestry, fishing and/or related worker
- ☐ 8 Precision production, crafts and/or repair occupation
- ☐ 9 Operator, fabricator and/or laborer

1.9 Do you have a particular doctor or clinic that you would call your regular doctor or clinic? . . . . . CDOCTOR10 ☐ 1 Yes ☐ 2 No

RESPONDENT I.D. # _____

Do not ask question 1.10 if subject did not have a DXA at the last interview ⟶ *Check N/A*

1.10 What were the results of your bone density test, at your last interview? BMDRES10

- ☐ 1 Don't know, I am unsure
- ☐ 2 High or normal bone density
- ☐ 3 Low without osteoporosis *(borderline "osteopenia")*
- ☐ 4 Low or "osteoporosis"
- ☐ 5 N/A *(none at last interview)*

1.11 **SINCE YOUR LAST INTERVIEW**, have you had a bone density measurement other than for this study? . . . . . BMDNREL10 ☐ 1 Yes ☐ 2 No

1.12 **SINCE YOUR LAST INTERVIEW**, have you sought information on osteoporosis:

- ▸ from the Osteoporosis Society of Canada? . . . . . INFOOSC10 ☐ 1 Yes ☐ 2 No
- ▸ from a local public health resource? *(e.g. women's health centre)* . . . INFOPHR10 ☐ 1 Yes ☐ 2 No
- ▸ from a health care professional:
  - Nutritionist . . . . . INFONUT10 ☐ 1 Yes ☐ 2 No
  - Physiotherapist or exercise specialist . . . INFOPES10 ☐ 1 Yes ☐ 2 No
  - Nurse . . . . . INFORN10 ☐ 1 Yes ☐ 2 No
  - Physician . . . . . INFOMD10 ☐ 1 Yes ☐ 2 No
  - Other . . . . . INFOHCP10 ☐ 1 Yes ☐ 2 No
    Specify: _____ INFHCSP10
- ▸ from another source? . . . . . INFOOTH10 ☐ 1 Yes ☐ 2 No
  Specify: _____ INFOTSP10

 * See notes in manual

RESPONDENT I.D. # _____

Now we'll review your past health.

2. MEDICAL HISTORY

2.1 * **SINCE YOUR LAST INTERVIEW**, have you been told by a doctor that you have any of the following conditions?

If YES, at what age was the diagnosis made? Have you received treatment for this condition?

	DIAGNOSIS				TREATMENT			
	Yes	No	DK	Age	Yes	No	DK	N/A
Osteoporosis	OSTEOD10			OSTEOAG10	OSTEOTR10			
Rheumatoid arthritis	RHEUD10			RHEUAG10	RHEUTR10			
Osteoarthritis *(hands, feet, knees, hips, neck)*	OSTEAD10			OSTEAAG10	OSTEATR10			
Lupus *(SLE)*	LUPUSD10			LUPUSAG10	LUPUSTR10			
Thyroid disease: 1 = Hyperthyroidism THYERO10 2 = Hypothyroidism	THYDD10 THY2D10			THYDAG10 THY2AG10	THYDTR10 THY2TR10			
Liver disease	LIVDD10			LIVDAG10	LIVDTR10			
Scoliosis	SCOLD10			SCOLAG10	SCOLTR10			
Eating disorder *(bulemia, anorexia)*	EATDD10			EATDAG10	EATDTR10			
Cancer: Prostate *(for men)*	PRCAD10			PRCAAG10	PRCATR10			
Breast *(for all)*	BRCAD10			BRCAAG10	BRCATR10			
Uterine *(for women)*	UTCAD10			UTCAAG10	UTCATR10			
Multiple myeloma *(bone)*	MLMYD10			MLMYAG10	MLMYTR10			
Other *(specify)* OTHCASP10	OTHCAD10			OTHCAAG10	OTHCATR10			
Inflammatory bowel disease *(Crohn's disease , ulcerative colitis, caeliac disease)*	IBDHD10			IBDAG10	IBDTR10			
Kidney stones	KIDSD10			KIDSAG10	KIDSTR10			
Kidney disease	KIDD10			KIDAG10	KIDTR10			
Hypertension *(high blood pressure)*	HYPD10			HYPAG10	HYPTR10			
Heart attack	HEARTD10			HEARTAG10	HEARTR10			
Stroke, TIA *(Transient Ischemic attack)*	CVTID10			CVTIAG10	CVTITR10			
Neuromuscular disease: Parkinson's	NPRKD10			NPRKAG10	NPRKTR10			
Multiple sclerosis	NMSCD10			NMSCAG10	NMSCTR10			
Other *(specify)* NEUROSP10	NOTHD10			NOTHAG10	NOTHTR10			
Non insulin dependent diabetes *(Type 2)*	DIAB2D10			DIAB2AG10	DIAB2TR10			
Insulin dependent diabetes *(Type I)*	DIAB1D10			DIAB1AG10	DIAB1TR10			
Phlebitis, Thrombophlebitis	PHLED10			PHLEAG10	PHLETR10			
Paget's disease of bone	PAGETD10			PAGETAG10	PAGETTR10			
Lung disease: Asthma	LASTHD10			LASTHAG10	LASTHTR10			
Emphysema	LEMPD10			LEMPAG10	LEMPTR10			
Bronchitis (chronic)	LBRNCD10			LBRNCAG10	LBRNCTR10			
Other *(specify)* LOTHSP10	LOTHD10			LOTHAG10	LOTHTR10			

RESPONDENT I.D. # _____

2.2 **SINCE YOUR LAST INTERVIEW,**
have you had an organ transplant ? . . . . . ORGTRNS10 ☐ 1 Yes ☐ 2 No

Which organ(s) and at what age did the transplant occur?
(Check all that apply)

			Age
TRBONMR10	☐ 1	Bone Marrow	→ TRBMAG10
TRHEART10	☐ 2	Heart	→ TRHRTAG10
TRKIDN10	☐ 3	Kidney	→ TRKDNAG10
TRLIVER10	☐ 4	Liver	→ TRLVRAG10
TRLUNG10	☐ 5	Lung	→ TRLNGAG10
TRPNCRS10	☐ 6	Pancreas	→ TRPNCAG10
TROTH10	☐ 7	Other *(specify)* TROTHSP10 _____	→ TROTHAG10

2.3* **SINCE YOUR LAST INTERVIEW,**
have you been confined to a bed, a wheelchair or by a cast for more than one month at a time? . . . . . IMMOB10 ☐ 1 Yes ☐ 2 No

2.4 **SINCE YOUR LAST INTERVIEW,**
have you had back pain ? . . . . . BCKPAIN10 ☐ 1 Yes ☐ 2 No → Go to question 2.9

Has the back pain lasted continuously for: BPAINDR10
- ☐ 1 more than 1 year
- ☐ 2 less than 1 year, more than 3 months
- ☐ 3 less than 3 months, more than 1 month
- ☐ 4 none of the above

2.5* **SINCE YOUR LAST INTERVIEW,**
have you been bedridden because of back pain for more than 4 continuous hours in a day? . . . . . BEDRIDN10 ☐ 1 Yes ☐ 2 No

→ For how long ? BEDDUR10
- ☐ 1 from 1 to 7 days
- ☐ 2 from 8 to 14 days
- ☐ 3 more than 14 days

→ Were you restricted to bed on the order of a physician? . . . . . BEDPRMD10 ☐ 1 Yes ☐ 2 No

 * See notes in manual

RESPONDENT I.D. # _____

2.6* **SINCE YOUR LAST INTERVIEW**, have you had to limit your activity or miss work because of back pain? . . . . . BPLMACT10 ☐ 1 Yes ☐ 2 No

For how long? BPLMDY10 (1)_____ days - or - BPLMDMN10 (2)_____ months - or - BPLMDYR10 (3)_____ years

2.7 **SINCE YOUR LAST INTERVIEW**, have you had back surgery because of back pain? . . . . . BPSURG10 ☐ 1 Yes ☐ 2 No

SINCE YOUR LAST INTERVIEW,

→ How many times? BPSTIME10

→ How old were you at your first surgery? BPS1AGE10

→ How old were you for the most recent surgery? BPS2AGE10

2.8 **SINCE YOUR LAST INTERVIEW**, have you received or are you receiving disability income or worker's compensation for back pain? BPDIWC10 . . . . . ☐ 1 Yes ☐ 2 No

Are you on permanent disability because of back pain? . . . . . BPPRMD10 ☐ 1 Yes ☐ 2 No

2.9* **SINCE YOUR LAST INTERVIEW**, have you had any of the following surgeries?

If YES, how old were you?

Gall Bladder	SGALL10	☐ 1 Yes	→ Age	SGALLAG10	☐ 2 No
Intestine	SINTES10	☐ 1 Yes	→ Age	SINTAG10	☐ 2 No
Parathyroid	SPARATH10	☐ 1 Yes	→ Age	SPARAG10	☐ 2 No
Thyroid	STHYRD10	☐ 1 Yes	→ Age	STHYAG10	☐ 2 No
Stomach	SSTOMI10	☐ 1 Yes	→ Age	SSTOMAG10	☐ 2 No

RESPONDENT I.D. # _____

Question 2.10 Specify that the following question asks about falls and does not include falls from a sporting or motor vehicle accident.

2.10* Have you fallen **IN THE PAST 12 MONTHS**? . . . . . DFALPY10 ☐ 1 Yes ☐ 2 No

How many times ? **DFALPYT10** _____

DFALREA10

Which of the following was the most important reason for your most serious fall in the last year? *(apart from a sporting or a motor vehicle accident)*

- ☐ 1 I felt dizzy or almost fainted, had a balance problem or a feeling I was spinning
- ☐ 2 I was climbing up onto something *(ladder, chair, stool, etc)* and slipped
- ☐ 3 The footing indoors was slippery
- ☐ 4 The footing outdoors was slippery
- ☐ 5 Didn't see an obstruction
- ☐ 6 I wasn't paying close attention because of alcohol or other substance use or pain tranquilizer or sleeping pill medications
- ☐ 7 I was very ill and felt weak
- ☐ 8 Other *(specify)* . . . . . **DFROTSP10** _____

2.11 Have you stayed overnight in the hospital **IN THE PAST YEAR**? . . . . . **HSPPYR10** ☐ 1 Yes ☐ 2 No

For what reason? *(Check all that apply)*

- **HSPHRT10** ☐ 1 Heart disease
- **HSPPREG10** ☐ 2 Pregnancy
- **HSPBRCN10** ☐ 3 Breast cancer
- **HSPUTCN10** ☐ 4 Cancer of the uterus
- **HSPOTCN10** ☐ 5 Other cancer *(specify)* . . . . . **OTHCNSP10** _____
- **HSPOTSG10** ☐ 6 Other surgery *(specify)* . . . . . **OTSRGSP10** _____
- **HSPOTHA10** ☐ 7 Other hospital admission *(specify)* . . **OTHASP10** _____

* See notes in manual

RESPONDENT I.D. # _____

Now I will ask you about medicines you may have taken SINCE YOUR LAST INTERVIEW

3. DRUGS AND MEDICATIONS

3.1* **SINCE YOUR LAST INTERVIEW**, have you taken any of the following medications regularly or daily?

If YES, for approximately how many months total have you taken it?

				Total # of months taken	
Dilantin / Phenobarbital *(Seizure Pills)*	DILNOW10	☐ 1 Yes	➤ DILMON10		☐ 2 No
Thyroid Pills *(Synthroid®, Eltroxin®)*	THYRNOW10	☐ 1 Yes	➤ THYRMON10		☐ 2 No
Tamoxifen *(Novaldex®)*	TAMXNOW10	☐ 1 Yes	➤ TAMXMON10		☐ 2 No
Alendronate *(Fosamax®)*	ALENNOW10	☐ 1 Yes	➤ ALENMON10		☐ 2 No
Calcitonin *(Calcimar®, Caltine®, Miacalcin nasal spray®)*	CALCNOW10	☐ 1 Yes	➤ CALCMON10		☐ 2 No
Clodronate *(Bonefos®, Ostac®) i.v./p.o.*	CLODNOW10	☐ 1 Yes	➤ CLODMON10		☐ 2 No
Etidronate *(Didronel®, Didrocal®)*	DIDRNOW10	☐ 1 Yes	➤ DIDRMON10		☐ 2 No
Fluoride *(Fluotic®)*	FLURNOW10	☐ 1 Yes	➤ FLURMON10		☐ 2 No
Raloxifene *(Evista®)*	RALXNOW10	☐ 1 Yes	➤ RALXMON10		☐ 2 No
Risedronate *(Actonel®)*	RISENOW10	☐ 1 Yes	➤ RISEMON10		☐ 2 No
Ibandronate *(Bonviva®) i.v./p.o.*	IBANNOW10	☐ 1 Yes	➤ IBANMON10		☐ 2 No
Pamidronate *(Aredia®) i.v.*	PAMDNOW10	☐ 1 Yes	➤ PAMDMON10		☐ 2 No
Zoledronate *i.v.*	ZOLDNOW10	☐ 1 Yes	➤ ZOLDMON10		☐ 2 No
Parathormone or PTH	PARTNOW10	☐ 1 Yes	➤ PARTMON10		☐ 2 No
Diuretics - Thiazide/Other	DIURNOW10	☐ 1 Yes	➤ DIURMON10		☐ 2 No
Laxatives	LAXTNOW10	☐ 1 Yes	➤ LAXTMON10		☐ 2 No
Testosterone :					
Andriol *(testosterone undecanoate)*	ANDRIOL10	☐ 1 Yes	➤ ANDMON10		☐ 2 No
Androgel *(testosterone gel)*	ANDGNOW10	☐ 1 Yes	➤ ANDGMON10		☐ 2 No
Delatestryl *(testosterone enanthate)*	DELATES10	☐ 1 Yes	➤ DELAMON10		☐ 2 No
Depo Testosterone *(testosterone cypionate)*	DEPOTES10	☐ 1 Yes	➤ DEPOMON10		☐ 2 No
Testoderm *(testosterone patch)*	TESTDNOW10	☐ 1 Yes	➤ TESTMON10		☐ 2 No
Climacteron	CLMCNOW10	☐ 1 Yes	➤ CLIMMON10		☐ 2 No
Cortisone / Prednisone :					
Inhaled	CRTINOW10	☐ 1 Yes	➤ CRTIMON10		☐ 2 No
Oral	CRTONOW10	☐ 1 Yes	➤ CRTOMON10		☐ 2 No
Injection:				# of Injection	
Intravenous	CPIVNOW10	☐ 1 Yes	➤ CPIVFRQ10		☐ 2 No
Intramuscular, subcutaneous	CPIMNOW10	☐ 1 Yes	➤ CPIMFRQ10		☐ 2 No

RESPONDENT I.D. # _____

3.2* Have you **EVER** taken any of the following medications regularly or daily?

If YES, for approximately how many months total have you taken it and at what age did you started?

			Total # of months taken	*Age started*	
Testosterone Inhibitors (*Prostate Cancer*)					
Goserelin (*Zoladex®*)	GOSENOW10	☐ 1 Yes →	GOSEMON10	GOSEAGE10	☐ 2 No
Luprelide (*Lupron®*)	LUPRNOW10	☐ 1 Yes →	LUPRMON10	LUPRAGE10	☐ 2 No
Aromatase Inhibitors (*Breast Cancer*)					
Anastasole (*Arimidex®*)	ANASNOW10	☐ 1 Yes →	ANASMON10	ANASAGE10	☐ 2 No
Letrozole (*Femara®*)	LETRNOW10	☐ 1 Yes →	LETRMON10	LETRAGE10	☐ 2 No
Exemestane (*Aromesin®*)	EXENOW10	☐ 1 Yes →	EXEMON10	EXEAGE10	☐ 2 No
Fulvestrant (*Faslodex®*)	FULVNOW10	☐ 1 Yes →	FULVMON10	FULVAGE10	☐ 2 No
Heparin *(daily for at least one month)*	HEPANOW10	☐ 1 Yes →	HEPAMON10	HEPAAGE10	☐ 2 No

3.3* Have you **EVER** taken glucosamine for **arthritis**? . . . . . GLUCOS10 ☐ 1 Yes ☐ 2 No

→ Was it recommended by your physician? . . . . . GLCRMD10 ☐ 1 Yes ☐ 2 No

→ For how many months in total, have you taken glucosamine? . . . . . GLCMON10 _____

→ Please indicate the preparation you took, if you know ?
(ie glucosamine sulphate, glucosamine with chondroitin, etc)

Check all that apply:

GLSUL10 ☐ 1 Glucosamine sulphate
GLCHN10 ☐ 2 Glucosamine with Chondroitin
GLCHM10 ☐ 3 Glucosamine with Chondroitin & MSM
GLCHDC10 ☐ 4 Glucosamine with Chondroitin, Devil's Claw
GLCHDM10 ☐ 5 Glucosamine with Chondroitin, Devil's Claw & MSM
GLCOTH10 ☐ 6 Other : *(specify)* GLOTHSP10 _____
GLCDNK10 ☐ 7 Don't Know

3.4 **SINCE YOUR LAST INTERVIEW**, did you start a medication and/or supplement for the treatment or prevention of osteoporosis? . . . . . OPMEDBG10 ☐ 1 Yes ☐ 2 No

OPMEDSM10 ☐ 1 Supplements *(i.e. vitamins & minerals including calcium)* ☐ 2 Medications ☐ 3 Both

* See notes in manual

RESPONDENT I.D. # _____

VARIABLES IN QST 3.5 ONLY ARE IN FILE MEDS10

3.5* List the current medications and/or supplements taken on a regular basis

Also - include antacids such as Tums and Rolaids

- list medication or supplement taken only a portion of the year

COMPANY NAME *(for vitamins and minerals, herbal and homeopathic products)*	MEDICATION NAME	COMPONENT Calcium /Vit. D	DOSE	FREQUENCY	Since last interview TOTAL # OF MONTHS TAKEN
	CUR1RX10			DRG1FQ10 DRG1DS10 DRG1TM10 DRG1SF10	TOT1MN10
	CUR2RX10			DRG2FQ10 DRG2DS10 DRG2TM10 DRG2SF10	TOT2MN10
	CUR3RX10			DRG3FQ10 DRG3DS10 DRG3TM10 DRG3SF10	TOT3MN10
	CUR4RX10			DRG4FQ10 DRG4DS10 DRG4TM10 DRG4SF10	TOT4MN10
	CUR5RX10			DRG5FQ10 DRG5DS10 DRG5TM10 DRG5SF10	TOT5MN10
	CUR6RX10			DRG6FQ10 DRG6DS10 DRG6TM10 DRG6SF10	TOT6MN10
	CUR7RX10			DRG7FQ10 DRG7DS10 DRG7TM10 DRG7SF10	TOT7MN10
	CUR8RX10			DRG8FQ10 DRG8DS10 DRG8TM10 DRG8SF10	TOT8MN10
	CUR9RX10			DRG9FQ10 DRG9DS10 DRG9TM10 DRG9SF10	TOT9MN10
	CUR10RX10			DRG10FQ10 DRG10DS10 DRG10TM10 DRG10SF10	TOT10MN10
	CUR11RX10			DRG11FQ10 DRG11DS10 DRG11TM10 DRG11SF10	TOT11MN10
	CUR12RX10			DRG12FQ10 DRG12DS10 DRG12TM10 DRG12SF10	TOT12MN10
	CUR13RX10			DRG13FQ10 DRG13DS10 DRG13TM10 DRG13SF10	TOT13MN10
	CUR13RX10			DRG13FQ10 DRG13DS10 DRG13TM10 DRG13SF10	TOT13MN10
	CUR14RX10			DRG14FQ10 DRG14DS10 DRG14TM10 DRG14SF10	TOT14MN10
	CUR15RX10			DRG15FQ10 DRG15DS10 DRG15TM10 DRG15SF10	TOT15MN10
	CUR16RX10			DRG16FQ10 DRG16DS10 DRG16TM10 DRG16SF10	TOT16MN10
	CUR17RX10			DRG17FQ10 DRG17DS10 DRG17TM10 DRG17SF10	TOT17MN10
	CUR18RX10			DRG18FQ10 DRG18DS10 DRG18TM10 DRG18SF10	TOT18MN10
	CUR19RX10			DRG19FQ10 DRG19DS10 DRG19TM10 DRG19SF10	TOT19MN10
	CUR20RX10			DRG20FQ10 DRG20DS10 DRG20TM10 DRG20SF10	TOT20MN10

RESPONDENT I.D. # _____

CAMOS2D10

Now I would like to know about any broken bone you may have had in the past year (since the last follow-up).

4. FRACTURES

4.1* **IN THE PAST YEAR**, have you fractured any bones? . . . . . NOFRACT10 ☐ 1 Yes ☐ 2 No

IN THE LAST YEAR,
how many times have you fractured a bone? . . . . . NUMFRC10 _____

Interviewer: Complete a fracture questionnaire for each incident and each bone fractured.

* See notes in manual

RESPONDENT I.D. # _____

CAMOS3D10

5. REPRODUCTIVE HISTORY

MALE RESPONDENT ..... *Go to page 20 question 5.26*

WOMEN - *In this section, I would like to ask you questions that will help us understand how women's hormones relate to bone structure. We ask everyone these questions.*

1. RESPONDENT WAS 40 TO 60 YEARS OLD AT STUDY ENTRY ..... → *Go to question 5.8*

2. RESPONDENT WAS OVER 60 YEARS OLD AT STUDY ENTRY ..... → *Go to question 5.12*

5.1 Are you currently pregnant? . . . . . **PREGNOW10** ☐ 1 Yes ☐ 2 No ☐ 3 Don't know

5.2 Have you given birth in the last 12 months? . **DPREG12M10** ☐ 1 Yes ☐ 2 No

5.3* **SINCE YOUR LAST INTERVIEW**, how many times have you been pregnant? **DPREGNM10** _____ ..... → *If 0 or currently pregnant* Go to question 5.7

5.4 How many of these pregnancies, resulted in at least one live birth? . . . . . **DBIRTHS10** _____ ..... → *If 0* - Go to question 5.7
(SINCE YOUR LAST INTERVIEW) (Count twins and triplets as 1)

5.5 How old were you at your first live birth, if it occured since your last interview? . . . . . **DAGEBIR10** _____ years ☐ N/A *(if not first live birth)*

5.6 **SINCE YOUR LAST INTERVIEW**, did you breast feed any of your children? . . . . . **DBRSTF10** ☐ 1 Yes ☐ 2 No

For how many months total ? . . . . **DBFMON10** months
(i.e. adding up the months with each child)

RESPONDENT I.D. # _____

5.7* **SINCE YOUR LAST INTERVIEW,**
have you been diagnosed with or treated for infertility or tried for 2 or more years and been unable to get pregnant? . . . . . INFERTL10 ☐ 1 Yes ☐ 2 No

INFRWHY10
What was the reason?
☐ 1 Hormone or ovulation problem
☐ 2 Tubal blockage or abdominal pain
☐ 3 Problem with your partner's fertility
☐ 4 Other *(specify)* INFERSP10 _____

5.8* **SINCE YOUR LAST INTERVIEW,**
have you used hormonal birth control method such as birth control pills, oral contraceptives, contraceptive patch or contraceptive ring? . . . . . CONTRAY10 ☐ 1 Yes ☐ 2 No

→ Go to quest. 5.12

5.9 Was it started for the first time **SINCE YOUR LAST INTERVIEW**? . . . . . CONTSTR10 ☐ 1 Yes ☐ 2 No

→ Go to quest. 5.10

At what age did you start? . . . . . CONTRAG10 _____
(If started for the first time since the last interview)

CONTWHY10
Which of the following was the main reason for which you **FIRST** used hormonal birth control method?
☐ 1 Contraception: to prevent pregnancy
☐ 2 To treat premenstrual symptoms
☐ 3 Treat heavy menstrual flow or abnormal bleeding
☐ 4 To treat severe menstrual cramps *(dysmenorrhea)*
☐ 5 To treat irregular or infrequent periods
☐ 6 To treat acne or unwanted facial or body hair
☐ 7 Other *(specify)* CONTWSP10 _____

5.10* For approximately how long did you use hormonal birth control methods? *(since your last interview)* . . . CONTRLY10 _____ years CONTRLM10 _____ months

* See notes in manual

RESPONDENT I.D. # _____

5.11 Are you still using hormonal birth control methods? . . . CONTRNW10 ☐ 1 Yes ☐ 2 No

At what age did you stop using birth control methods? . CONAGST10 years
(If stopped since the last interview)

5.12 Have you **EVER** used Depo Provera for contraception or other reasons? . . . . . DPROV10 ☐ 1 Yes ☐ 2 No

How many injections in total? _____ DPINJT10
(Make your best guess based on the fact that the usual dose is 4 injections a year)

At what age did you start? _____ DPAGEST10

Have you stopped? DPINJSP10 ☐ 1 Yes ☐ 1 No

At what age did you stop? DPAGESP10

5.13* **SINCE YOUR LAST INTERVIEW**, have you had your uterus removed *(hysterectomy)*? . . . . . DUTER10 ☐ 1 Yes ☐ 2 No

At what age ? DUTERAG10 years

5.14* **SINCE YOUR LAST INTERVIEW**, have you had one or both ovaries removed?

EOVARY10 DOVAGE10

☐ 1 Yes, one ovary removed → at what age? _____

☐ 2 Yes, both ovaries removed → at what age? _____
(If ovaries were removed on separate occasions, write the age at which the second ovary was removed)

☐ 3 Yes, do not know how many → at what age? _____

☐ 4 No

RESPONDENT I.D. # _____

5.15* **SINCE YOUR LAST INTERVIEW**, have you taken estrogen for menopause **OR FOR ANY OTHER REASON?**

ESTROG10 ☐ 1 Yes, currently ☐ 2 Yes, but not now ☐ 3 No

What type(s) ? *(Interviewers to show Ogen®, Estrace, CES, Premarin® etc pills, colors and doses and Estraderm®, Vivelle®, Estracomb®, Climara® etc patches, sizes and doses)*

EPILLUS10 ☐ Pill

Pill N°	Number of days/month	Age started	Age stopped	Total number of months taken *(since last interview)*
(1) EPL1DOS10	EPL1DAY10	EPL1AST10	EPL1ASP10	EPL1TOT10
(2) EPL2DOS10	EPL2DAY10	EPL2AST10	EPL2ASP10	EPL2TOT10
(3) EPL3DOS10	EPL3DAY10	EPL3AST10	EPL3ASP10	EPL3TOT10
(4) EPL4DOS10	EPL4DAY10	EPL4AST10	EPL4ASP10	EPL4TOT10

If # 25 ⇢ specify: (1) EPL1SPC10 (2) EPL2SPC10

(3) EPL3SPC10 (4) EPL4SPC10

EPATUSE10 ☐ Patch

Patch N°	Number of days/month *(patch worn)*	Age started	Age stopped	Total number of months taken *(since last interview)*
(1) EPT1DOS10	EPT1DAY10	EPT1AST10	EPT1ASP10	EPT1TOT10
(2) EPT2DOS10	EPT2DAY10	EPT2AST10	EPT2ASP10	EPT2TOT10
(3) EPT3DOS10	EPT3DAY10	EPT3AST10	EPT3ASP10	EPT3TOT10
(4) EPT4DOS10	EPT4DAY10	EPT4AST10	EPT4ASP10	EPT4TOT10

If # 25 ⇢ specify: (1) EPT1SPC10 (2) EPT2SPC10

(3) EPT3SPC10 (4) EPT4SPC10

EINJUSE10 ☐ Injection How many times/year? EINJTIM10 How many years ? EINJYR10

What dose? EINJDOS10

EVCRUSE10 ☐ Vaginal cream How many times/week? EVCRTIM10

Amount - applicator: EVCRAMT10 ☐ 1 full ☐ 3 ¼ full ☐ 2 ½ full ☐ 4 a little bit on my finger

EPMPUSE10 ☐ Pump applicator How many pumps/day? _____ EPMPFRQ10 - OR - How many pumps/week? _____ EPMPFRW10

ERNGUSE10 ☐ Estring®

ETABUSE10 ☐ Estratab®

 * See notes in manual

RESPONDENT I.D. # _____

5.16* **SINCE YOUR LAST INTERVIEW**,
have you taken progesterone or progestin for menopause **OR FOR ANY OTHER REASON** ?
(Medroxyprogesterone, progesterone, norethindrone, progesterone skin cream, Prometrium etc)

PROGES10 ☐ 1 Yes, currently ☐ 2 Yes, but not now ☐ 3 No

What type(s) ? *(Interviewers to show Micronor®, Provera®, Prometrium® etc pills, colors and doses)*

PROPILL10 ☐ Pill

Pill N°	Number of days/month	Age started	Age stopped	Total number of months taken *(since last interview)*
(1) PRO1DOS10	PRO1DAY10	PRO1AST10	PRO1ASP10	PRO1TOT10
(2) PRO2DOS10	PRO2DAY10	PRO2AST10	PRO2ASP10	PRO2TOT10
(3) PRO3DOS10	PRO3DAY10	PRO3AST10	PRO3ASP10	PRO3TOT10
(4) PRO4DOS10	PRO4DAY10	PRO4AST10	PRO4ASP10	PRO4TOT10

If # 25 ➤ specify: (1) PRO1SPC10 (2) PRO2SPC10

(3) PRO3SPC10 (4) PRO4SPC10

PROINJ10 ☐ Injection How many times/year? PINJTIM10 How many years ? PINJYR10

What dose? PINJDOS10

PROCRM10 ☐ Progesterone cream

RESPONDENT WAS 56 YEARS OLD AND OVER AT STUDY ENTRY ➤ *Go to question 6.1*

5.17* **SINCE YOUR LAST INTERVIEW**, have your
menstrual periods stopped for more than one year? . . PERSTOP10 ☐ 1 Yes ☐ 2 No

Other than due to pregnancy or breastfeeding

At what age ? PERSTAG10 years

Go to question 5.20

RESPONDENT I.D. # _____

Question 5.18 - Ask only if :
- not using birth control methods (refer to question 5.11)
- did not have a hysterectomy (refer to question 5.13 and 5.14)
- not currently on hormone therapy (refer to question 5.15 and 5.16)

5.18 Have you menstruated in the last 3 months? PER3MN10

☐ 1 Yes

What has been your usual cycle interval in the last 10 years?

PEROFTEN10
- ☐ 1 20 days or less
- ☐ 2 21 to 25 days
- ☐ 3 26 to 30 days
- ☐ 4 31 to 36 days
- ☐ 5 37 or more days
- ☐ 6 Don't know

☐ 2 No

How long since your last period?
LASTPER10
- ☐ 1 More than 3 months but less than 6 months — 1 = 3
- ☐ 2 More than 6 months but less than 1 year — 2 = 4
- ☐ 3 N/A *(since before last interview)* — 3 = 6

5.19* *(If menstruating and not using birth control pills or hormones, have not had both ovaries removed)*
Can you tell by the way you feel that your period is coming?

CONTREL10
- ☐ 1 Yes every month
- ☐ 2 Yes, most months
- ☐ 3 Yes, less than half the time
- ☐ 4 Yes, once or twice a year
- ☐ 5 Never
- ☐ 6 N/A

What signs or symptoms indicate to you that your period is coming?
Interviewer record spontaneous, un-prompted comments. ***Do not read the list.***
The interviewer may ask several times "Is there anything else that tells you your period will soon start?"

- ECRAMPS10 ☐ 1 Menstrual cramps or aching back or legs
- EBLOAT10 ☐ 2 Bloating, fluid retention
- EAPPET10 ☐ 3 Increased appetite *(in general or for sweets, salty or spicy foods)*
- EMOOD10 ☐ 4 Moodiness *(frustration, irritability, sadness)*
- EFRONTP10 ☐ 5 Breast tenderness in the front or on the nipple
- ESIDEP10 ☐ 6 Breast tenderness high under the arm
- ESWELL10 ☐ 7 Breast swelling
- EHEADAC10 ☐ 8 Headaches *(migraine or tension)*
- EACNE10 ☐ 9 Acne / pimples / blemishes
- ESYMOTH10 ☐ 10 Other *(specify)* EWHATOT10 _____

 * See notes in manual

RESPONDENT I.D. # _____

5.20* **SINCE YOUR LAST INTERVIEW,**
have you been sufficiently bothered by severe acne, unwanted face or body hair to consult a physician for treatment? . . . . . ACNEHR10 ☐ 1 Yes ☐ 2 No

At what age ? AGESYMD10 ____ years

Introduce the following section by saying that WOMEN in midlife may observe changes in their emotional or physical well being, or in their bodies without any apparent connection to health conditions or diseases. These may simply relate to things such as getting older, or to changing exercise habits or weight"

5.21* There are different stages that women go through in the middle of their lives. Menopause, the completion of the process, means that a year has passed without a period. Where do you believe you are in the process.

MOLSTAT10

☐ 1 No signs of starting yet
☐ 2 Just beginning
☐ 3 In the middle
☐ 4 Near the end
☐ 5 Completed the midlife process

(If the respondent is on hormone therapy, if she has had a hysterectomy, then she should answer that she has completed the process ONLY if she has had no cyclic changes in breasts, fluid, mood, etc. for at least one year)

5.22* **IN THE PAST 3 MONTHS,**
have you noticed any changes in breast tenderness or lumpiness *(nodularity)* ?

CHBR3M10
☐ 1 No changes
☐ 2 Decreasing
☐ 3 Increasing
☐ 4 Never or rarely experience breast tenderness or lumpiness

5.23* **IN THE PAST 3 MONTHS**, have you experienced any changes in how you feel before flow starts, such as breast tenderness or swelling, mood swings, fluid retention or appetite changes?

CHFL3M10
☐ 1 No changes
☐ 2 Decreasing
☐ 3 Increasing
☐ 4 Never or rarely experience
☐ 5 N/A

RESPONDENT I.D. # _____

5.24* **IN THE PAST 3 MONTHS**, have you experienced any changes in the amount of your menstrual flow *(period)*?

CHFLW3M10
- ☐ 1 No changes
- ☐ 2 Decreasing *(flow more like spotting or fewer days of flow)*
- ☐ 3 Increasing *(clots, flooding or more days of flow)*
- ☐ 4 Mixed - sometimes lighter and sometimes heavier flow
- ☐ 5 N/A

5.25* **IN THE PAST 3 MONTHS**, have you experienced any changes in the time interval between the start of one menstrual flow and the start of the next?

CHINTRV10
- ☐ 1 No changes
- ☐ 2 Shorter time *(periods closer together)*
- ☐ 3 Longer time *(periods farther apart)*
- ☐ 4 Mixed - sometimes longer and sometimes shorter *(irregular)*
- ☐ 5 N/A

FEMALE RESPONDENT ..... *Go to question 6.1*

***MEN** - In this section, I would like to ask you questions that will help us understand how men's hormones relate to bone structure. We ask everyone these questions.*

Question 5.26 Include current pregnancies for first child, abortions, extopic pregnancies as a Yes.

5.26 **SINCE YOUR LAST INTERVIEW**, have you fathered any children?

MALECHL10 ☐ 1 Yes

How many? MALENUM10 _____

☐ 2 No

SINCE YOUR LAST INTERVIEW, MALEFRT10
have you been diagnosed with a fertility problem?
☐ 1 Yes ☐ 2 No ☐ 3 Don't know

5.27* **SINCE YOUR LAST INTERVIEW**, which of the following is your usual experience regarding spontaneous erections not related to sex?

MALEERC10
- ☐ 1 One or more times a day *(for example, first thing when I wake up)*
- ☐ 2 Most days
- ☐ 3 Some days
- ☐ 4 Occasionally
- ☐ 5 Rarely
- ☐ 6 Never

RESPONDENT I.D. # _____

In this section, we are interested in knowing about your sleep history

6. SLEEPING HISTORY

6.1 **SINCE YOUR LAST INTERVIEW,** have you ever been repeatedly *(many times)* bothered by the following:

WKEARLY10	Waking early	☐ 1 Yes	☐ 2 No
WKNIGHT10	Nighttime wakening	☐ 1 Yes	☐ 2 No
PRFALSL10	Problems falling asleep	☐ 1 Yes	☐ 2 No
DTMSLP10	Daytime sleepiness	☐ 1 Yes	☐ 2 No

6.2* **IN THE PAST 3 MONTHS**, have you noticed any changes in sleep such as waking early, nighttime wakening or problems falling asleep?

PRSLE3M10
- ☐ 1 No changes
- ☐ 2 Decreasing
- ☐ 3 Increasing
- ☐ 4 Never or rarely experience *(no sleep problem)*

6.3 *Night sweats are hot flushes which occur during sleep*

IN THE LAST 2 WEEKS, how often have you experienced hot flushes during the time when you were sleeping?

NSWT2W10
- ☐ 1 Never → Go to question 7.1
- ☐ 2 Once or twice
- ☐ 3 Three to six times
- ☐ 4 Once a night
- ☐ 5 More than once, most nights

6.4 If you have experienced any night sweats or night time hot flushes **IN THE LAST 2 WEEKS**, please grade their usual severity: *(mark only one)*

NSSEV2W10
- ☐ 1 Mild warm feeling
- ☐ 2 Moderate hot feeling with sweating or flushing
- ☐ 3 Moderately severe hot feeling often with sweating on part of your body
- ☐ 4 A major hot feeling often with sweating on most of your body

RESPONDENT I.D. # _____

Now I am going to ask you about your biological relatives (not those related to you by marriage).

7. FAMILY HISTORY

7.1 Was at least one of your biological parents still living at the time of **YOUR LAST INTERVIEW**? BPARLIV10 ☐ 1 Yes ☐ 2 No ☐ 3 Don't know

Go to question 7.3

7.2* **SINCE YOUR LAST INTERVIEW**, did the following occur in your biological parents?
(Circle appropriate answer for each. If yes, please check the boxes for whom the condition applies)

		Yes	No	DK		
Height Loss	HTLOSS10	1	2	3	HTLOSSN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
Stooping	STOOP10	1	2	3	STOOPN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
Hip Fracture	HIPFRC10	1	2	3	HIPFRCN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
Wrist Fracture	WRIFRC10	1	2	3	WRIFRCN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
Shoulder Fracture *(upper arm)*	SHLDFR10	1	2	3	SHLDFRN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
Pelvic Fracture	PLVFRC10	1	2	3	PLVFRCN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
Ankle Fracture *(lower leg)*	ANKLFR10	1	2	3	ANKLFRN10	☐ 1 Father ☐ 2 Mother ☐ 3 Both

7.3* **SINCE YOUR LAST INTERVIEW**, have any parents, siblings or children been diagnosed with the following?

If YES, please indicate which parent, sibling or child.

NOTE: If no children lived beyond birth then questions relating to children are N/A
If both parents died before last interview then questions relating to parents are N/A (refer to qst 7.1)

***For fractures**, if no siblings or children then indicate N/A*

			Yes	No	DK	N/A		
Fractures EFRAC...								
	Parents	P10	1	2	3	4	PP10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
SIB40_10	Siblings ≥ 40 ☐ 1 Yes ☐ 2 No ☐ 3 N/A	S10	1	2	3		SS10	☐ 1 Brother ☐ 2 Sister ☐ 3 Both
CHL40_10	Children ≥ 40 ☐ 1 Yes ☐ 2 No ☐ 3 N/A	C10	1	2	3		CC10	☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Osteoporosis EOSTO...	Parents	P10	1	2	3	4	PP10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings	S10	1	2	3	4	SS10	☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children	C10	1	2	3	4	CC10	☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Osteoarthritis EOSTA...	Parents	P10	1	2	3	4	PP10	☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings	S10	1	2	3	4	SS10	☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children	C10	1	2	3	4	CC10	☐ 1 Son ☐ 2 Daughter ☐ 3 Both

RESPONDENT I.D. # _____

		Yes	No	DK	N/A	
Paget's disease EPAGT...	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Scoliosis ESCOL...	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both
CVD, ECVD... stroke, aneurysm, hypertension	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Diabetes EDIAB...	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Prostate Cancer EPROCA...	Father P10	1	2	3	4	
	Brother(s) S10	1	2	3	4	
	Son(s) C10	1	2	3	4	
Breast Cancer EBRCA...	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Uterine Cancer EENCA...	Mother P10	1	2	3	4	
	Sister(s) S10	1	2	3	4	
	Daughter(s) .. C10	1	2	3	4	
Ovarian Cancer EOVCA...	Mother P10	1	2	3	4	
	Sister(s) S10	1	2	3	4	
	Daughter(s) .. C10	1	2	3	4	
Colon Cancer ECOLC...	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both
Multiple Myeloma EMLMY...	Parents P10	1	2	3	4	PP10 ☐ 1 Father ☐ 2 Mother ☐ 3 Both
	Siblings S10	1	2	3	4	SS10 ☐ 1 Brother ☐ 2 Sister ☐ 3 Both
	Children C10	1	2	3	4	CC10 ☐ 1 Son ☐ 2 Daughter ☐ 3 Both

RESPONDENT I.D. # _____

In this section, I will ask you about your physical characteristics.

8. PHYSICAL CHARACTERISTICS

8.1* Current measured height . . . . . ECURHTF10 _____ feet ECURHTI10 _____ inches - OR - ECURHTC10 _____ cm
UNMEAS10 ☐ Unable to measure

82* Current measured weight . . . . . ECURWTP10 _____ lbs - OR - ECURWTK10 _____ kg ☐ UNWEIGH10 Unable to weigh

8.3 **SINCE YOUR LAST INTERVIEW**
have you lost any height? . . . . . LOSTHGT10 ☐ 1 Yes ☐ 2 No ☐ 3 Don't know

8.4 **SINCE YOUR LAST INTERVIEW**, EHIWP10 EHIWK10
what has been your **GREATEST** weight? . . . . . _____ lbs - OR - _____ kg ☐ Don't know

8.5 **SINCE YOUR LAST INTERVIEW**, ELOWP10 ELOWK10
what has been your **LOWEST** weight? . . . . . _____ lbs - OR - _____ kg ☐ Don't know

8.6* **SINCE YOUR LAST INTERVIEW**, have you lost more than 10 pounds (*4.5 kg*)?
(Other than after childbirth, re: one year post-partum)

EEVRTEN10 ☐ 1 Yes ☐ 2 No

Did you regain the lost weight?
EREGAIN10 ☐ 1 Yes ☐ 2 No

ETTLOSP10 ETTLOSK10
How much did you lose ? _____ lbs -OR- _____ kg

How many times have you lost
and regained 10 pounds (*4.5 kg*) or more? E10MLGN10

8.7 **SINCE YOUR LAST INTERVIEW**,
did you lose more than 10 pounds (4.5 *kg*) ELSTINT10
intentionally by changing your diet and or your exercise? . . . . . ☐ 1 Yes ☐ 2 No

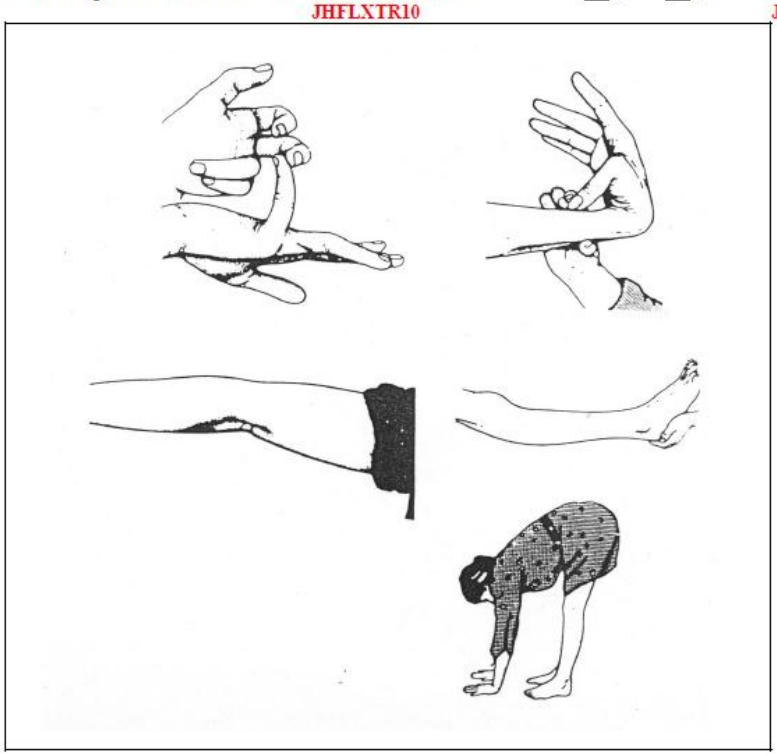
RESPONDENT I.D. # _____

NOTE: Ask question 8.8 to participants who were ≤ 40 years of age at study entry.
For all other participants : Go to section 9 - Tobacco

8.8* Joint hypermobility: Ask respondent to try to perform on his own, each of the following.
(Check the appropriate box for the right and left side)

	Right		Left	
	Able	Unable	Able	Unabl
➤ Passive dorsiflexion of the little finger beyond 90° JHFNGRT10 JHFNGLT10	☐1	☐2	☐1	☐2
➤ Passive apposition of the thumbs to the flexor aspects of the forearm JHTHMRT10 JHTHMLT10	☐1	☐2	☐1	☐2
➤ Hyperextension of the elbow beyond 10° JHELBRT10 JHELBLT10	☐1	☐2	☐1	☐2
➤ Hyperextension of the knee beyond 10° JHKNERT10 JHKNELT10	☐1	☐2	☐1	☐2
➤ Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor JHFLXTR10	☐1	☐2		

JHSCORE10



RESPONDENT I.D. # _____

CAMOS3BD10

Now the questions I will ask will relate to the use of tobacco

9. TOBACCO

9.1 **SINCE YOUR LAST INTERVIEW**, have you smoked cigarettes **DAILY** for at least 6 months? . . . . . **FCIG10** ☐ 1 Yes ☐ 2 No

9.2* **SINCE YOUR LAST INTERVIEW**, did you start smoking for the first time? . . . . . **FCIGFRS10** ☐ 1 Yes ☐ 2 No

At what age did you begin to smoke cigarettes daily ? *(for at least 6 months)* **FCIGSTR10** ____ years

9.3 Are you currently smoking? . . . . . **FCIGNOW10** ☐ 1 Yes ☐ 2 No

At what age did you stop? **FCIGSTP10** ____ years

9.4 Approximately how many cigarettes do/did you smoke every day? **FCIGAMT10**

9.5* **SINCE YOUR LAST INTERVIEW**, have you temporarily stopped smoking cigarettes and started again ? . . . . . **FCIGTSP10** ☐ 1 Yes ☐ 2 No

If you total up the periods, **SINCE YOUR LAST INTERVIEW**, for how many months have you stopped . . . . . **FCIGTMP10** ____ months

9.6 On average, **OVER THE LAST MONTH**, have you been exposed to the tobacco smoke of others? **FETSMON10**
(i.e. environmental tobacco smoke (ETS)

☐ 1 Not at all
☐ 2 < 3 hours/day
☐ 3 3-8 hours/day
☐ 4 9 or more hours/day

9.7 **SINCE YOUR LAST INTERVIEW**, have you been exposed to ETS for more than 6 months? . . . . . **FETSINT10** ☐ 1 Yes ☐ 2 No

FETSYES10 → ☐ 1 < 3 hours/day ☐ 2 3-8 hours/day ☐ 3 9 or more hours/day

→ Number of months of exposure **SINCE YOUR LAST INTERVIEW**? **FETSYMN10**

 * See notes in manual

RESPONDENT I.D. # _____

CAMOS4D10

Now I will ask you in detail about the foods you eat

10 FOOD INTAKE

10.1* How often *(on the average)* have you eaten the following items **DURING THE PAST 12 MONTHS?**

Food		Never	Servings per month	Servings per week	Servings per day	Serving size
Milk to drink * *(incl. milk flavoured with powder)* * *(commercial choc. milk is not calcium fortified)*	Not fortified with calcium	FMDNFUN10 ☐1	(2).....	FMDNFQU10 (3).....	(4).....	FMDNFSZ10 ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup) ☐ 375 ml (1.5 cups)
	Fortified with calcium	FMDFCUN10 ☐1	(2).....	FMDFCQU10 (3).....	(4).....	FMDFCSZ10 ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup) ☐ 375 ml (1.5 cups)
Soy beverage	Not fortified with calcium	FSYNFUN10 ☐1	(2).....	FSYNFQU10 (3).....	(4).....	FSYNFSZ10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
	Fortified with calcium	FSYFCUN10 ☐1	(2).....	FSYFCQU10 (3).....	(4).....	FSYFCSZ10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
Milk in cereal	Not fortified with calcium	FMCNFUN10 ☐1	(2).....	FMCNFQU10 (3).....	(4).....	FMCNFSZ10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
	Fortified with calcium	FMCFCUN10 ☐1	(2).....	FMCFCQU10 (3).....	(4).....	FMCFCSZ10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
Soy beverage in cereal	Not fortified with calcium	FSCNFUN10 ☐1	(2).....	FSCNFQU10 (3).....	(4).....	FSCNFSZ10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
	Fortified with calcium	FSCFCUN10 ☐1	(2).....	FSCFCQU10 (3).....	(4).....	FSCFCSZ10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
Milk desserts * *(tapioca, rice pudding)* * *(fortified only applies for homemade desserts)*	Not fortified with calcium	FMENFUN10 ☐1	(2).....	FMENFQU10 (3).....	(4).....	FMENFSZ10 ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
	Fortified with calcium	FMEFCUN10 ☐1	(2).....	FMEFCQU10 (3).....	(4).....	FMEFCSZ10 ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
Cream soups made with milk		FSUNIT10 ☐1	(2).....	FSQU10 (3).....	(4).....	FSSIZE10 ☐ 125 ml (0.5 cup) ☐ 160 ml (2/3 cup) ☐ 250 ml (1 cup)
Milk /Cream in tea/coffee		FMTUNIT10 ☐1	(2).....	FMTQU10 (3).....	(4).....	FMTSIZE10 ☐ 15 ml (1 tbsp) ☐ 30 ml (2 tbsp) ☐ 60 ml (4 tbsp)

RESPONDENT I.D. # _____

Food	Never	Servings per month	Servings per week	Servings per day	Serving size
Ice cream, ice milk or frozen yogurt	FIUNIT10 ☐1 (2).....		FIQU10 (3).....	(4).....	FISIZE10 ☐ 125 ml (0.5 cup) ☐ 160 ml (2/3 cup) ☐ 250 ml (1 cup)
Yogurt – Not fortified with vitamin D	FYNFSSUN10 ☐1 (2)		FYNFSSQU10 (3)	(4)	Individual Serving
	FYNFUN10 ☐1 (2).....		FYNFQU10 (3).....	(4).....	FYNFSIZE10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 200 ml (0.75 cup) ☐ 250 ml (1 cup)
Yogurt – Fortified with vitamin D	FYFDSSUN10 ☐1 (2)		FYFDSSQU10 (3)	(4)	Individual Serving
	FYFDUN10 ☐1 (2).....		FYFDQU10 (3).....	(4).....	FYFDSIZE10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 200 ml (0.75 cup) ☐ 250 ml (1 cup)
Hard cheese *(in sandwich or mixed dish)*	FHCUNIT10 ☐1 (2).....		FHCQU10 (3).....	(4).....	FHCSIZE10 ☐ 15 g (0.5 oz) ☐ 30 g (1.0 oz) ☐ 60 g (2.0 oz)
Calcium fortified orange juice	FOJFCUN10 ☐1 (2).....		FOJFCQU10 (3).....	(4).....	FOJFCSZ10 ☐ 125 ml (0.5 cup) ☐ 160 ml (2/3 cup) ☐ 250 ml (1 cup)
Canned salmon or sardines with bones	FCSUNIT10 ☐1 (2).....		FCSQU10 (3).....	(4).....	FCSSIZE10 ☐ 30 g (1 oz) ☐ 60 g (2 oz) ☐ 90 g (3 oz)
Broccoli	FBRUNIT10 ☐1 (2).....		FBRQU10 (3).....	(4).....	FBRSIZE10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
Dark leafy greens *(bok choy, kale, gailan (chinese broccoli), collards, dandelion greens)*	FDLUNIT10 ☐1 (2).....		FDLQU10 (3).....	(4).....	FDLSIZE10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
Dried beans or peas *(navy, pinto, kidney)*	FPBUNIT10 ☐1 (2).....		FPBQU10 (3).....	(4).....	FPBSIZE10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)
White bread, buns, rolls, bagels, etc	FWBUNIT10 ☐1 (2).....		FWBQU10 (3).....	(4).....	1 serving = 1 slice ½ bagel ½ pita
Whole wheat bread, buns, rolls, bagels, etc	FWWUNIT10 ☐1 (2).....		FWWQU10 (3).....	(4).....	1 serving = 1 slice ½ bagel ½ pita
Tofu	FTFUNIT10 ☐1 (2).....		FTFQU10 (3).....	(4).....	FTFSIZE10 ☐ 60 ml (0.25 cup) ☐ 125 ml (0.5 cup) ☐ 250 ml (1 cup)

RESPONDENT I.D. # _____

Now some questions about the beverages you might choose to drink.

BEVERAGES

10.2* How many of the following drinks did you consume **IN THE PAST 12 MONTHS**?

In these questions, one serving of alcoholic beverage is:

- *1 bottle or can of beer or a glass of draft (12 oz)*
- *1 straight or mixed drink with (1-1½ oz) hard liquor*
- *1 glass of wine or a wine cooler (4-5 oz)*
- *the reference measure for 1 serving of tea or coffee is 6 oz (180 ml)*
- *the reference measure for 1 serving of cola is 12 oz - 1 can (355 ml)*

Beverages		Never	Servings per month	Servings per week	Servings per day
Coffee	caffeinated	FCF12UN10 ☐1	(2) FCF12QU10	(3)	(4) .....
	decaffeinated	FCF12UD10 ☐1	(2) FCF12QD10	(3)	(4) .....
Tea	caffeinated	FTE12UN10 ☐1	(2) FTE12QU10	(3)	(4) .....
	decaffeinated	FTE12UD10 ☐1	(2) FTE12QD10	(3)	(4) .....
Colas	caffeinated	FCL12UN10 ☐1	(2) FCL12QU10	(3)	(4) .....
	decaffeinated	FCL12UD10 ☐1	(2) FCL12QD10	(3)	(4) .....
Alcoholic beverages		FAL12UN10 ☐1	(2) FAL12QU10	(3)	(4) .....

RESPONDENT I.D. # _____

In this section I will ask you about your physical activities and exercise.

11. PHYSICAL ACTIVITY

11.1 During a typical week **IN THE PAST 6 MONTHS**, how much time did you usually spend walking?
(to work, school, while doing errands, for leisure)

GWALK10
- ☐ 1 None
- ☐ 2 Less than 1 hour
- ☐ 3 Between 1-5 hours
- ☐ 4 Between 6-10 hours
- ☐ 5 Between 11-20 hours
- ☐ 6 More than 20 hours

11.2 **SINCE YOUR LAST INTERVIEW**, which of the following describes the paid work you usually do or what you consider your job?

Or if retired *(since last interview)* or unemployed, which best describes your *(most recent)* job?

GPAIDW10
- ☐ 1 I am usually sitting during the day and do not walk around very much
- ☐ 2 I stand or walk quite a lot during the day but I do not have to lift or carry heavy things
- ☐ 3 I usually lift or carry light loads or I often have to climb stairs or hills
- ☐ 4 I do heavy work or have to carry loads
- ☐ 5 N/A ..... Subject retired before last interview

11.3* Do you **CURRENTLY** participate in any regular physical activity or programme *(either on your own or in a formal class)*? . . . . . GREGACT10 ☐ 1 Yes ☐ 2 No

→ How many times/week? GACTWK10

→ How long per session? GACTMIN10 minutes

11.4 **SINCE YOUR LAST INTERVIEW**, have you engaged in a physical activity/sport at a competitive level? . . . . . GPACMPL10 ☐ 1 Yes ☐ 2 No

Sport/Activity	Age started competing	Age stopped competing	Level of competition *(indicate all that apply)*				
			local	provincial	university	national	international
GSPAC1_10	GSAST1_10	GSASP1_10	GSLVC1110 ☐ 1	GSLVC1210 ☐ 2	GSLVC1310 ☐ 3	GSLVC1410 ☐ 4	GSLVC1510 ☐ 5
GSPAC2_10	GSAST2_10	GSASP2_10	GSLVC2110 ☐ 1	GSLVC2210 ☐ 2	GSLVC2310 ☐ 3	GSLVC2410 ☐ 4	GSLVC2510 ☐ 5
GSPAC3_10	GSAST3_10	GSASP3_10	GSLVC3110 ☐ 1	GSLVC3210 ☐ 2	GSLVC3310 ☐ 3	GSLVC3410 ☐ 4	GSLVC3510 ☐ 5

* See notes in manual

RESPONDENT I.D. # _____

11.5* On the average **DURING THE LAST YEAR**, how many hours **IN A WEEK** did you spend in the following activities?

	Never	½ - 1 hr	2 - 3 hrs	4 - 6 hrs	7 - 10 hrs	11 - 20 hrs	21 - 30 hrs	31 hrs & over
➤ Strenuous Sports . . . . . GSTREN10 *(such as jogging, bicycling on hills, tennis, racquetball, swimming laps, aerobics)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8
➤ Vigorous Work . . . . . GVIGOR10 *(such as moving heavy furniture, loading or unloading trucks, shovelling, weight lifting or equivalent manual labour)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8
➤ Moderate Activity . . . . . GMODACT10 *(such as housework, brisk walking, golfing, bowling, bicycling on level ground, gardening)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8

11.6* On the average **DURING THE LAST YEAR**, how many hours **IN A DAY** did you spend in the following sitting activities?

	Never	<than 1 hr	1 - 2 hrs	3 - 4 hrs	5 - 6 hrs	7 - 10 hrs	11 hrs & over	N/A
➤ Sitting in a car or bus GSITCAR10	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	
➤ Sitting at work / school GSITWRK10	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8
➤ Watching TV GSITTV10	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	
➤ Sitting at meals GSITEAT10	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	
➤ For leisure- sitting at computer GSITCOM10	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	
➤ Other sitting activities . . . . . GSITOTH10 *(such as reading, playing cards, sewing)*	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	

11.7 On the average, **DURING THE LAST YEAR**, how many hours **IN A DAY** *(over a 24 hr period)* did you sleep *(include naps)* ?

GAVSLP10

☐ 1 5 hours or less
☐ 2 6 hours
☐ 3 7 hours
☐ 4 8 hours
☐ 5 9 hours
☐ 6 10 hours or more

11.8 Rate your overall level of physical activity compared to your peers **DURING THE LAST YEAR**.

GPEERPY10

☐ 1 A lot less active
☐ 2 Somewhat less active
☐ 3 About the same
☐ 4 Somewhat more active
☐ 5 A lot more active

RESPONDENT I.D. # _____

Now I want to ask you a question about being in the sunlight

12. SUNLIGHT EXPOSURE

12.1* **IN THE PAST 12 MONTHS**, did you ever expose a considerable part of your body to direct sunlight? . . . . . GSUNPY10 ☐ 1 Never ☐ 2 Seldom ☐ 3 Regularly ☐ 4 Often

Considerable part of the body =	*part of the body exposed for 30 minutes or more in a socially acceptable swimsuit or equivalent*
Never	*did not expose considerable part of my body to direct sunlight for at least 30 minutes each day*
Seldom	*sometimes but less than 3 months of the year*
Regularly	*3 to 6 months of the year*
Often	*more than 6 months of the year*

12.2 **IN THE PAST 12 MONTHS**, have you used sunscreen or face cream with SPF to protect your skin against sunlight? . . . . GSUNSCR10 ☐ 1 Yes ☐ 2 No

GSCROFT10 ☐ 1 Sometimes ☐ 2 Usually ☐ 3 Always

12.3* **IN THE PAST 5 YEARS**, have you spent one month or more in a Southern location? *(Outside Canada)* . . . . . GSTHLOC10 ☐ 1 Yes ☐ 2 No

Some communities add fluoride to their drinking water. The following questions ask about how long you have lived in your current community in order to determine your most recent fluoride intake and your primary source of drinking water.

13. FLUORIDE

13.1* How long have you lived in the community you now live in? GCLIVYR10 years GCLIVMN10 months

13.2 What is your current primary source of drinking water? . . . . DRNKWTR10 ☐ 1 Municipal *(tap)* ☐ 2 Well ☐ 3 Bottled

 * See notes in manual

RESPONDENT I.D. # _____

Question 14.1 to 14.3 Ask these questions to participants who were 55 years of age and older at study entry

The next set of questions are concerned with any limitations you may have in routine activities as well as your day to day health. Not all the questions may apply to you but please be patient in responding.

14. DISABILITY AND HEALTH STATUS *

14.1 Do you need the help of another person with personal care such as eating, bathing, dressing or getting around inside the house because of any impairment or health problem? . . HLPPC10 ☐ 1 Yes ☐ 2 No

Who provides this help?

HLPPCWH10
- ☐ 1 A spouse/partner or relative living in your household
- ☐ 2 A spouse/partner or relative not living in your household
- ☐ 3 A non-relative, regardless of where he/she lives
- ☐ 4 A combination of the previous categories

14.2 Do you need the help of another person in looking after personal affairs, doing everyday household chores, going shopping or getting around outside the house, because of any impairment or health problem? . . . . . HLPPA10 ☐ 1 Yes ☐ 2 No

Who provides this help?

HLPPAWH10
- ☐ 1 A spouse/partner or relative living in your household
- ☐ 2 A spouse/partner or relative not living in your household
- ☐ 3 A non-relative, regardless of where he/she lives
- ☐ 4 A combination of the previous categories

14.3 Compared to other people of the same age in good health, are you limited in the kind or amount of activity you can do because of a long-term physical or mental condition or health problem? . . . CMPPEER10 ☐ 1 Yes ☐ 2 No

Please administer MMSE if respondent is **currently** 65 years of age and older

RESPONDENT I.D. # _____

CAMOS5D10

Now I would like to ask you how your health has been on the average, over the past week. I will ask you about different areas of general health. For some of the questions, I want you to tell me which statement most closely describes how you felt.

15. HEALTH STATUS QUESTIONNAIRE : * TORRANCE QUESTIONNAIRE

INTERVIEWER ADMINISTERED VERSION

Interviewer: For each question that lists a number of choices, circle the letter for the one choice that the respondent feels best describes the usual level of ability over the past week.

1.1 Are you able to see well enough without glasses or contact lenses to read ordinary newsprint?

HT1_10 ☐ Yes ⇢ Go to 2.1
☐ No

1.2 If not, which of the following describes your *usual* ability to see well enough to read ordinary newsprint? Are you:

HT2_10 a. Able to see well enough but with glasses or contact lenses.
b. Unable to see well enough even with glasses or contact lenses.
c. Unable to see at all.

2.1 Are you able to see well enough without glasses or contact lenses to recognize a friend on the other side of street?

HT3_10 ☐ Yes ⇢ Go to 3.1
☐ No

2.2 If not, which one of the following best describes your *usual* ability to see well enough to recognize a friend on the other side of the street? Are you:

HT4_10 a. Able to see well enough but with glasses or contact lenses.
b. Unable to see well enough even with glasses or contact lenses.
c. Unable to see at all.

3.1 Are you able to hear what is said in a group conversation with at least three other people *without* a hearing aid?

HT5_10 ☐ Yes ⇢ Go to 4.1
☐ No

* GW Torrance and DH Feeny, McMaster University
Questionnaire development supported through research grants funded by the
Ontario Ministry of Health and US Agency for Health Care Policy and Research

RESPONDENT I.D. # _____

3.2 If not, which statement describes your *usual* ability to hear in a group conversation with at least three other people? Are you:

HT6_10
a. Able to hear what is said with a hearing aid.
b. Unable to hear what is said even with a hearing aid.
c. Unable to hear what is said, but don't wear a hearing aid.
d. Unable to hear.

4.1 Are you able to hear what is said in a conversation with one other person in a quiet room without a hearing aid?

HT7_10 ☐ Yes ⋯➤ Go to 5.1
☐ No

4.2 If not, which one of the following best describes your *usual* ability to hear what is said in a conversation with one other person in a quiet room? Are you:

HT8_10
a. Able to hear what is said with a hearing aid.
b. Unable to hear what is said even with a hearing aid.
c. Unable to hear what is said, but don't wear a hearing aid.
d. Unable to hear.

5.1 Are you able to be understood when speaking the same language with strangers?

HT9_10 ☐ Yes ⋯➤ Go to 6.1
☐ No

5.2 If not, which of the following best describes your *usual* ability to be understood when speaking the same language with strangers? Are you:

HT10_10
a. Able to be understood partially.
b. Unable to be understood.
c. Unable to speak at all.

6.1 Are you able to be understood when speaking the same language with people who know you well?

HT11_10 ☐ Yes ⋯➤ Go to 7.1
☐ No

6.2 If not, which of the following best describes your *usual* ability to be understood when speaking the same language with people who know you well? Are you:

HT12_10
a. Able to be understood partially.
b. Unable to be understood.
c. Unable to speak at all.

RESPONDENT I.D. # _____

7.1 Which one of the following best describes how you usually feel? Are you:

HT13_10
a. Happy and interested in life.
b. Somewhat happy.
c. Somewhat unhappy.
d. Very unhappy.
e. So unhappy that life is not worthwhile.

8.1 Are you free of pain and discomfort?

HT14_10 ☐ Yes ⋯➤ Go to 9.1
☐ No

8.2 If not, which one of the following best describes your level of pain? Do you have:

HT15_10
a. Mild to moderate pain that prevents no activities.
b. Moderate pain that prevents a few activities.
c. Moderate to severe pain that prevents some activities.
d. Severe pain that prevents most activities.

9.1 Are you able to walk around the neighbourhood **without** difficulty and **without** walking equipment, and have no health limitation in vigourous activities such as running and strenuous sports?

NOTE: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

HT16_10 ☐ Yes ⋯➤ Go to 10.1
☐ No

9.2 If not, which one of the following best describes your *usual* ability to walk? Are you:

HT17_10
a. Able to walk around the neighbourhood without difficulty and without walking equipment, and have some health limitation in vigourous activities such as running and strenuous sports
b. Able to walk around the neighbourhood with difficulty, but without walking equipment or a helper.
c. Able to walk around the neighbourhood with walking equipment, but without a helper.
d. Able to walk only short distances with walking equipment. Able to walk short distances with a helper, and require a wheelchair to get around the neighbourhood.
e. Unable to walk alone, even with walking equipment. Able to walk short distances with a helper, and require a wheelchair to get around the neighbourhood.
f. Cannot walk at all

RESPONDENT I.D. # _____

10.1 Do you have full use of two hands and ten fingers?

HT18_10 ☐ Yes ⋯➤ Go to 11.1
☐ No

10.2 If not, which one of the following best describes *usual* ability to use your hands and fingers? Do you have:

HT19_10
a. Limited use of hands or fingers, but do not require special tools or help from others.
b. Limited use of hands or fingers, require special tools but do not require help from others.
c. Limited use of hands or fingers, require the help of another person for some tasks.
d. Limited use of hands or fingers, require the help of another person for most tasks.
e. Limited use of hands or fingers, require the help of another person for all tasks.

11.1 Are you able to remember most things?

HT20_10 ☐ Yes ⋯➤ Go to 12.1
☐ No

11.2 If not, which one of the following best describes *usual* ability to remember things?

HT21_10
a. Somewhat forgetful.
b. Very forgetful.
c. Unable to remember anything at all.

12.1 Are you able to think clearly and solve day to day problems?

HT22_10 ☐ Yes ⋯➤ Go to 13.1
☐ No

12.2 If not, which one of the following best describes *usual* ability to think and solve day to day problems? Do you:

HT23_10
a. Have a little difficulty when trying to think and solve day to day problems
b. Have some difficulty when trying to think and solve day to day problems
c. Have great difficulty when trying to think and solve day to day problems

or are you:

d. Unable to think or solve day to day problems

RESPONDENT I.D. # _____

JUST A FEW MORE QUESTIONS IN THIS SECTION

13.1 Do you eat, bathe, dress and use the toilet normally?

HT24_10 ☐ Yes ⇢ Go to 14.1
☐ No

13.2 If not, which one of the following best describes *usual* ability to perform these basic activities?

HT25_10 a. Eat, bathe, dress and use the toilet **independently, with difficulty.**
b. Requires mechanical equipment to eat, bathe, dress or use the toilet independently.
c. Requires the help of another person to eat, bathe, dress or use the toilet.

14.1 Are you generally happy and free from worry?

HT26_10 ☐ Yes ⇢ Go to 15.1
☐ No

14.2 If not, which one of the following best describes how you usually feel?

HT27_10 a. Occasionally fretful, angry, irritable, anxious or depressed.
b. Often fretful, angry, irritable, anxious or depressed.
c. Almost always fretful, angry, irritable, anxious or depressed.
d. Extremely fretful, angry, irritable, anxious or depressed, usually requiring hospitalization or psychiatric institutional care.

THIS IS THE LAST QUESTION IN THIS SECTION. IT IS A DIFFERENT QUESTION ABOUT PAIN. JUST TO REMIND ME:

15.1 Are you free of pain and discomfort?

HT28_10 ☐ Yes ⇢ Go to next page - *Socio-Demographic Information*
☐ No

15.2 If not, which one of the following best describes your *usual* level of pain?

HT29_10 a. Occasional pain. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.
b. Frequent pain. Discomfort relieved by oral medicines with occasional disruption of normal activities.
c. Frequent pain. Frequent disruption of normal activities. Discomfort requires prescription narcotics for relief.
d. Severe pain. Pain not relieved by drugs and constantly disrupts normal activities.

RESPONDENT I.D. # _____

There are a few more question for you to answer before completing a questionnaire by yourself.

16. ADDITIONAL INFORMATIONS

16.1 For statistical purposes only, we need to know the range of your total, gross household income last year. Now, could you please indicate from the following list, in what range your household income falls?
(If there is hesitation, tell them they may choose not to respond)
HSHLINC10

- ☐ 1 Under $20,000
- ☐ 2 $20,000 to $40,000
- ☐ 3 $41,000 to $60,000
- ☐ 4 $61,000 to $80,000
- ☐ 5 Over $80,000
- ☐ 6 Refuses to answer

RESPONDENT I.D. # _____

In this section, I will give you a small questionnaire for you to complete by yourself. For each question, you are asked to read the question, and then circle the number you choose as closest to your experience.

17. RAND HEALTH SCIENCE PROGRAM (SF-36)

1. In general, would you say your health is:

(Circle One Number)

HHS1_10

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, how would you rate your health in general now?

(Circle One Number)

HHS2_10

Much better than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse than one year ago	4
Much worse now than one year ago	5

RESPONDENT I.D. # _____

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(*Circle One Number on Each Line*)

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a.	Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports HHS3_10	1	2	3
b.	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf HHS4_10	1	2	3
c.	Lifting or carrying groceries HHS5_10	1	2	3
d.	Climbing several flights of stairs HHS6_10	1	2	3
e.	Climbing one flight of stairs HHS7_10	1	2	3
f.	Bending, kneeling or stooping HHS8_10	1	2	3
g.	Walking more than one mile HHS9_10	1	2	3
h.	Walking several blocks HHS10_10	1	2	3
I.	Walking one block HHS11_10	1	2	3
j.	Bathing or dressing yourself HHS12_10	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or regular daily activities as a result of your physical health?

(*Circle One Number on Each Line*)

		Yes	No
a.	Cut down the amount of time you spent on work or other activities HHS13_10	1	2
b.	Accomplished less than you would like HHS14_10	1	2
c.	Were limited in the kind of work or other activities HHS15_10	1	2
d.	Had difficulty performing the work or other activities (for example, it took extra effort) HHS16_10	1	2

RESPONDENT I.D. # _____

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(Circle one number on each line)

		Yes	No
a.	Cut down the amount of time you spent on work or other activities HHS17_10	1	2
b.	Accomplished less than you would like HHS18_10	1	2
c.	Didn't do work or other activities as carefully as usual HHS19_10	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(Circle one number)

HHS20_10

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

7. How much bodily pain have you had during the past 4 weeks?

(Circle one number)

HHS21_10

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

RESPONDENT I.D. # _____

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(Circle one number)

HHS22_10

Not a bit 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks.

(Circle one number on each

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of pep? HHS23_10	1	2	3	4	5	6
b. Have you been a very nervous person? HHS24_10	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up? HHS25_10	1	2	3	4	5	6
d. Have you felt calm and peaceful? HHS26_10	1	2	3	4	5	6
e. Do you have a lot of energy? HHS27_10	1	2	3	4	5	6
f. Have you felt downhearted and blue? HHS28_10	1	2	3	4	5	6
g. Did you feel worn out? HHS29_10	1	2	3	4	5	6
h. Have you been a happy person? HHS30_10	1	2	3	4	5	6
I. Did you feel tired? HHS31_10	1	2	3	4	5	6

RESPONDENT I.D. # _____

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(Circle one number)

HHS32_10

All of the time 1

Most of the time 2

Some of the time 3

A little of the time 4

None of the time 5

11. How TRUE or FALSE is each of the following statements for you?

(Circle one number on each line)

		Definitely True	Mostly True	Don't know	Mostly False	Definitely False
a.	I seem to get sick a little easier than other people HHS33_10	1	2	3	4	5
b.	I am as healthy as anybody I know HHS34_10	1	2	3	4	5
c.	I expect my health to get worse HHS35_10	1	2	3	4	5
d.	My health is excellent HHS36_10	1	2	3	4	5

THAT ENDS THE QUESTIONNAIRE.
THANK YOU VERY MUCH FOR YOUR HELP.

RESPONDENT I.D. # _____

INTERVIEWER'S ASSESSMENT

As an interviewer my assessment of the process and the respondent was:

(Circle one number on each line)

	Not at all	A little	Neutral	Somewhat	A great deal
a. The respondent appeared or seemed interested in the research HASS1_10	1	2	3	4	5
b. The respondent seemed to cooperate with me HASS2_10	1	2	3	4	5
c. I believe that the respondent understood the questions HASS3_10	1	2	3	4	5
d. I believe that the respondent listened well HASS4_10	1	2	3	4	5
e. I perceived that the respondent was restless or wanted to hurry the process HASS5_10	1	2	3	4	5
f. The respondent expressed feelings of tiredness during the interview HASS6_10	1	2	3	4	5

HASS7_10

The respondent required assistance with the Rand SF-36 ☐ Yes ☐ No

Comments :

_____

_____

_____

_____

_____

_____

_____

_____

Time finished _____ hrs _____min.

APPENDIX C: Chapter 3 Details

C.1 Detailed Methods

C.1.1 FRAX Development and Validation Cohorts

To develop the original FRAX model nine prospective population-based cohorts were used, including populations from around the world (1). Detailed information on the aforementioned studies has been previously described (2-12). In the validation cohort eleven independent cohorts were used, including populations from around the world (1). The validation cohort was comprised of randomized control trials, prospective and retrospective cohorts, and case-control studies (1). Detailed information on the aforementioned cohorts has been previously described (13-23). The major differences between the development and validation cohorts and the cohort used in chapter 3, include: the mean age of individuals is higher in chapter 3, the time frame is in a later calendar period, and the percentage of females is lower (compared to the validation cohort) (Table C.1).

Table C. 1. Comparison of the FRAX development cohort, internal validation cohort and the CaMos cohort

	Development Cohort (n=46,340)	**Internal Validation Cohort** (n=230,486)	**CaMos cohort (eGFR <60 mL/min/1.73 m^2)** (n=320)
Predictors			
Women	68%	100%	71%
Age (yr)	65	63	75
Body mass index kg/m^2	26.2	26.7	27.6%
Maternal history of fracture[†]	7%	12%	10.9%
Glucocorticoids	4%	2%	3.4%
Prior fracture	29%	16%	25.3%
Ever smoked	20%	27%	7.5%
High alcohol use	11%	21%	0
Rheumatoid arthritis	5%	3%	0.94%
Outcome	-Self-report and/or verified by hospital or databases -Locations: differed by cohort (two cohorts: hip, forearm, spine, humerus; one cohort: spine, pelvis,	-Self-report and/or verified by hospital, imaging databases, family physician -Locations: not specified	-Self-report and /or verified by hospital -Locations: hip, forearm, clinical spine, humerus

	ribs, distal forearm, forearm, and hip; other cohorts osteoporotic fracture sites)		
Cohort eligibility years	1980s-late 1990s[¥]	1970s-2000s[¥]	2006-2011

Abbreviation: eGFR, estimated glomerular filtration rate
[†]The CaMos cohort used in this study looked at parent fracture hip not just maternal.
[¥] Years were not clearly described
Source: Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. *Osteoporos Int* 2007;18:1033-1046.

To develop the FRAX prediction model Poisson regression was used and predictors were selected into the model using stepwise regression (1). Risk factors for fracture and interaction terms to potentially be included in the final predictive model were determined through meta-analyses (1). To evaluate the performance of the model gradients of risk (risk ratios) per standard deviation increase in FRAX score were used (1).

C.1.2 Data Source Details

To determine the prognostic value of the Fracture Risk Assessment tool (FRAX) in individuals with reduced kidney function data from the Canadian Multicentre Osteoporosis Study (CaMos) was utilized. CaMos is an ongoing prospective cohort study which includes non-institutionalized adults aged ≥ 25 years and began in 1996 (2). The original objective of CaMos was to determine the incidence of fracture and the impact that osteoporosis has on adults across Canada to aid in the development of fracture and osteoporosis prevention programs (2). Adult Canadians were selected to participate in CaMos through identifying a region-,sex-, and age- stratified random sample of individuals who lived within 50 kilometers of the following Canadian cities: St.John's, Halifax, Quebec City, Toronto, Hamilton, Kingston, Saskatoon, and Calgary (2). This criteria covered approximately 40% of Canadians (2). The only major group that was excluded were individuals living in northern Canada (2). Based on postal codes from the pre-specified geographic regions a random sample of telephone numbers was generated (2). At baseline approximately 72% (n=9423) of contacted individuals participated (fully 42%; partially 30%) (24). Partial participation was defined as individuals who refused to participate in the study but agreed to complete a refusal questionnaire; the refusal

questionnaire obtained information on key risk factors for osteoporosis (e.g. sex, previous fracture) (24). Starting at baseline, standardized interviewer-administered questionnaires were given every 5 years (2). For this chapter data was utilized from years 10-15 of the CaMos study; however, baseline information, such as sex, that was collected at year 1 was also utilized. At year 1 of CaMos an in-person interviewer-administered questionnaire (Appendix B), two questionnaires that focused on health status (SF-36 (25) and McMaster University's health status assessment [Health Utilities Index Mark 2 and 3] (26, 27)), Mini-Mental State exam (28), and a variety of physical measurements (height, weight, dual energy x-ray absorptiometry, ultrasound assessment of the calcaneus, and x-ray of lateral thoracic and lumbar spine for individuals aged ≥ 50 years) were given (2). Follow-up was maintained through the following mechanisms: greeting cards, birthday cards, and a yearly questionnaire was mailed to obtain information on fractures and other new diagnoses that may have occurred within the last year (2). Moreover, contact information for next of kin was obtained to help contact individuals who may have moved (24).

The questionnaire used in the study was developed specifically for CaMos. No previously validated questionnaires covered the scope of information that the CaMos questionnaire wanted to capture and therefore a new questionnaire was developed. Nadalin *et al.* assessed the test-retest reliability of a section of the CaMos questionnaire through first collecting information by personal interview then three to five months later the participants were administered the same questions by telephone interview (29). Employment status, height, weight, and female reproductive history had a high reliability (kappa >0.80 or intra-class correlation coefficient >0.80) (29). However, physical activity, sun exposure, and previous weight loss demonstrated lower reliability (kappa ranged from 0.30 to 0.58). Kmetic *et al.* evaluated nonresponse bias for the CaMos questionnaire through using multiple imputation to adjust for nonresponse bias (30). Individuals who did not agree to participate in the study were asked to complete a brief questionnaire which assessed major risk factors for osteoporosis (30). Multiple imputation then used osteoporotic risk factors to estimate the osteoporosis status for individuals who did not agree to participate (30). The results found that selection bias is of most concern in elderly individuals (>80 years) (30).

C.1.3 Data Cleaning

Data cleaning and data checking for the CaMos data was performed at McGill University (CaMos coordinating centre) by a biostatistician. Kyla Naylor performed additional data checking through the use of histograms and minimum and maximum values for categorical variables. Means (standard deviations), medians (interquartile range), and minimum and maximum values were assessed for continuous variables. All fracture dates were also checked by Kyla Naylor. Any concerns about potentially implausible values were brought to the coordinating centre's attention. For example, several fracture dates were brought to the coordinating centre's attention and were checked by contacting the hospital in which the fracture occurred to confirm the date of the fracture; if there were any discrepancies the date was then corrected using the date recorded at the hospital as the gold-standard.

C.1.4 Sample Size Calculations

Based on data from a Jamal *et al*. study which used CaMos data to examine fracture risk in individuals with reduced kidney function it was estimated that 7% of individuals with reduced kidney function would fracture over 5-years of follow-up (31). Sample size was calculated using the area under the receiver operating characteristic curve sample size method proposed by Hanley *et al.* (32). An alpha of 0.05, 80% power, and a null area under the curve (AUC) value of 0.5 were used (Table C.2). Based on 2251 individuals with a serum creatinine measurement at year 10 of CaMos it was expected that 20% of individuals would have CKD (n=450) (based on results from the Jamal *et al.* study using CaMos data) (31). Therefore, based on our sample size estimates it was expected that we would have 80% power to detect an AUC of 0.65 (Table C.2). Based on a study conducted by Jamal *et al.* assessing the predictive ability of FRAX in patients with CKD it was hypothesized that an AUC of approximately 0.7 would be found (33). In chapter 3 there were only 16 major osteoporotic fracture events in individuals with CKD; as a result of the low number of fracture events and corresponding wide 95% confidence intervals, conclusions from chapter 3 were very cautious. Specifically, it was emphasized in the conclusion of chapter 3 and the overall discussion section in chapter 7 of this thesis that further study is needed with larger samples before FRAX should be routinely used in clinical practice.

Table C. 2. Estimated sample size requirements for individuals with CKD

Number of Individuals with a Fracture	Number of Individuals without a Fracture	Area Under the Curve Value
286	3718	0.55
32	416	0.65
18	234	0.7
12	156	0.75

Sources: Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; 143: 29-36. Obuchowski NA. Sample size calculations in studies of test accuracy. *Statistical Methods in Medical Research* 1998; 7: 371-392.

C.2 Additional Analyses

C.2.1 Missing Data

For this chapter the main analyses were all done with a complete case analysis. A large number of individuals were excluded (n=2520) due to missing an estimated glomerular filtration rate (eGFR). The reason for missing data was the refusal to participate in blood collection. Those who did not participate may be systematically different than those who consented and exclusion of these people could bias estimates. Therefore, in a secondary analysis multiple imputation was performed to impute missing eGFR values for individuals who refused to participate to determine the robustness of the results on the basis of all available data. Multiple imputation was not performed in the primary analysis as previous research has suggested that caution should be exercised when imputing exposures (eGFR), particularly when the missingness is high (excluded n=2520, 45.3% of individuals due to missing eGFR) (34, 35); additionally the benefits of imputing the exposure have been found to be low (35). Individuals who did not have a BMD measurement at year 10 were also excluded from the study (n=52, 0.9%); previous research has found that when the missingness is <10% minimal differences exist between complete case analysis and multiple imputation (36). Individuals were missing a BMD measurement if they did not consent to getting the test done.

Multiple imputation deals with missing data through imputing each missing value multiple times while accounting for the uncertainty of the data through creating numerous imputed data sets (37); the results of the imputed data sets are then combined to provide a single estimate (37). Multiple imputation was also used to handle missing FRAX with BMD (approximately 19% of individuals with a missing eGFR were missing FRAX with

BMD) in addition to missing eGFR. Given that only approximately 10% (n=269) of individuals with a missing eGFR were missing a body mass index (BMI) measurement, single mean imputation was used to impute the missing BMI value for these individuals. Previous research has found that when approximately 10% of the data is missing single mean imputation produces similar results to multiple imputation (38, 39).

Missing data can be described as missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). MCAR is often considered an unrealistic assumption and only occurs when the pattern of missingness is not related to any of the variables under study (40). MAR is more realistic, although you are not able to test for this assumption; it assumes that missingness does not depend on unobserved values but rather on observed values (40). NMAR assumes that observed and unobserved values determine missingness. In this analysis it was assumed the data was MAR as previous literature has stated it is reasonable to assume this pattern of missingness unless previous knowledge about the data indicates missing values are dependent on unobserved values (40).

Multiple imputation requires several steps. To determine which covariates to include in the imputation model an extensive literature search was performed to determine which variables were associated with the imputed variables (FRAX with BMD and eGFR). Associations between eGFR and the other variables were assessed using Pearson correlation for two continuous variables or the two-sample t-test for a continuous and binary variable. Variables were also included in the imputation model that were possibly related to the missingness of the variable based on comparing baseline characteristics between individuals with an eGFR (or FRAX with BMD) and individuals who were missing an eGFR (Tables C.3 and C.4). The dependent variable of interest was also included in the model (major osteoporotic fracture). The literature suggests that the imputation model should include the following variables: all variables included in the complete case analysis model (including the dependent variable), variables related to the missingness of the imputed variable, and variables associated with the imputed variable (41). The pattern of missingness was explored using PROC MI in SAS. The data did not demonstrate a monotone pattern of missingness; therefore, the fully conditional specification method was used to handle the arbitrary pattern of the data (42). The models

were then created and imputation was applied. FRAX with BMD was imputed first (variable with the least missingness is imputed first). The variables that were included in the model to predict FRAX with BMD were: major osteoporotic fracture, FRAX without BMD, age, sex, BMI, previous fracture, high alcohol use, corticosteroid use, rheumatoid arthritis, secondary osteoporosis, smoking, femoral neck BMD, and parental hip fracture. The variables that were included in the model to predict eGFR were: major osteoporotic fracture, FRAX without BMD, FRAX with BMD, diabetes, hypertension, health, age, sex, prior fracture, smoking and femoral neck BMD. Ten imputations were performed to ensure the efficiency of the model was ≥ 95% (36). SAS PROC LOGISTIC was used to analyze each imputed dataset. Finally, the average AUC values were calculated after imputing the missing eGFR and FRAX with BMD values. To calculate the Kaplan-Meier estimates 12 imputations were performed to ensure the efficiency was ≥ 95% for all imputed variables. To ensure all terms that were in the survival model were included in the imputation model total follow-up was included in addition to the variables described above. All imputation was performed using Statistical Analysis System (SAS version 9.3, SAS Institute, Cary, NC, USA).

Table C. 3. Comparison of characteristics in individuals with and without a missing estimated glomerular filtration rate measurement

Characteristic	**Missing eGFR** (n=2520)	**No Missing eGFR** (n=2107)	**p-value**
Age	70.6 ± 11.8	67 ± 10	<0.0001
Women	1857 (73.7%)	1485 (70.5%)	0.02
Kidney Disease	44 (1.7%)	30 (1.4%)	0.38
Body Mass Index (kg/m^2)	27.3 ± 4.9	27.2 ± 4.7	0.53
Previous fracture	537 (21.3%)	387 (18.4%)	0.013
Parent fractured hip	296 (11.8%)	267 (12.7%)	0.34
Current smoking	279 (11.1%)	180 (8.5%)	0.004
Corticosteroid use for >3 months	59 (2.3%)	33 (1.6%)	0.06
Rheumatoid arthritis	27 (1.1%)	16 (0.8%)	0.27
Secondary osteoporosis	105 (4.2%)	88 (4.2%)	0.99
≥ 3 alcoholic beverages per day	28 (1.1%)	21(1.0%)	0.70

Femoral neck BMD	0.71± 0.12	0.73 ± 0.12	<0.0001
Missing	477 (18.9%)		
FRAX without BMD	7.2 (95% CI 7.0-7.4)	5.7 (95% CI 5.5-5.9)	<0.0001
FRAX with BMD	5.9 (95% CI 5.7-6.1)	4.9 (95% CI 4.8-5.1)	<0.0001
Missing	477 (18.9%)		
Fall in the past 12 months	670 (26.6%)	542 (25.7%)	0.51
Bisphosphonate use[€]	667 (26.5%)	506 (24.0%)	0.06
Type 2 Diabetes	262 (10.4%)	159 (7.5%)	0.0008
Excellent, very good or good self-reported current health	2250 (89.3%)	1953 (92.7%)	<0.0001
Outcome Variable			
Major osteoporotic fracture[¶]	121 (4.8%)	64 (3.0%)	0.0023

Data are Mean ± SD, mean (95% CI), or n (%)
Abbreviations: BMD, bone mineral density; FRAX, Fracture Risk Assessment tool
[¶] Major osteoporotic fracture events occurred between years 11-15 of the study

Table C. 4. Comparison of characteristics in individuals with and without a missing FRAX with BMD

Characteristic	**Missing FRAX with BMD** (n=477)	**No Missing FRAX with BMD** (n=4150)	**p-value**
Age	74.9 ± 11.8	68.4 ± 11.0	<0.0001
Women	370 (77.6%)	2972 (71.6%)	0.006
Kidney Disease	10 (2.1%)	64 (1.5%)	0.36
Body Mass Index (kg/m^2)	27.2 ± 4.8	27.2 ± 4.8	0.9
Previous fracture	113 (23.7%)	811 (19.5%)	**0.03**
Parent fractured hip	61 (12.8%)	502 (12.1%)	0.66
Current smoking	50 (10.5%)	409 (9.9%)	0.66
Corticosteroid use for >3 months	12 (2.5%)	80 (1.9%)	0.38
Rheumatoid arthritis	4 (0.84%)	39 (0.94%)	1.00
Secondary osteoporosis	25 (5.2%)	168 (4.1%)	0.22
≥ 3 alcoholic beverages per day	0 (0%)	49 (1.2%)	0.008
FRAX without BMD	9.1 (8.6-9.7)	6.2 (6.0-6.3)	<0.0001
Fall in the past 12 months	138 (28.9%)	1074 (25.9%)	0.15
Bisphosphonate use[€]	124 (26.0%)	1049 (25.3%)	0.73
Type 2 Diabetes	56 (11.7%)	365 (8.8%)	0.03

Excellent, very good or good self-reported current health	406 (85.1%)	3797 (91.5%)	<0.0001
Outcome Variable			
Major osteoporotic fracture[¶]	34 (7.1%)	151 (3.6%)	0.0002

Data are Mean ± SD, mean (95% CI), or n (%)
Abbreviations: BMD, bone mineral density; FRAX, Fracture Risk Assessment tool
[¶] Major osteoporotic fracture events occurred between years 11-15 of the study

To determine if the results from multiple imputation were different from when complete case analysis was used, AUC values from the complete case analysis were compared to values obtained from multiple imputation (AUC values for FRAX and FRAX without BMD) (Table C.5). The results were similar to the complete case analysis with all AUC values still reaching statistical significance for individuals with reduced kidney function (eGFR <60 mL/min/1.73 m^2); however, the AUC confidence intervals were narrower reflecting increased precision. Similar to what was found in the complete case analysis, the 5-year observed major osteoporotic fracture risk (7.4%, 95% confidence interval [CI] 5.7 to 9.4%) was comparable to the FRAX predicted fracture risk (7.4%, 95% CI 7.1-7.7% with BMD; 9.4%, 95% CI 9.0%-9.7% without BMD) in individuals with an eGFR <60 mL/min/1.73 m^2; the fracture risk predicted by FRAX was within the observed fracture risks 95% CI. The observed fracture risk was higher than what was observed in the complete case analysis; however, this would be expected as individuals with a missing eGFR had more comorbidities.

Table C. 5. Comparison of area under the curve values for incident major osteoporotic fracture prediction according to complete case analysis versus multiple imputation

Complete Case Analysis				
	<60 mL/min/1.73 m^2		**≥60 mL/min/1.73 m^2**	
Risk Factor	**AUC**	**95% CI**	**AUC**	**95% CI**
FRAX with BMD	0.69	0.54- 0.83	0.76	0.70- 0.82
FRAX without BMD	0.65	0.52 - 0.79	0.74	0.67- 0.81
Multiple Imputation				
	<60 mL/min/1.73 m^2		**≥60 mL/min/1.73 m^2**	
Risk Factor	**AUC**	**95% CI**	**AUC**	**95% CI**

FRAX with BMD	0.70	0.62-0.77	0.76	0.72-0.80
FRAX without BMD	0.67	0.60-0.74	0.74	0.70-0.78

Abbreviations: AUC, area under the curve; BMD, bone mineral density; CI, confidence interval; FRAX, Fracture Risk Assessment tool

C.2.2 Loss to follow-up

Loss to follow-up is a concern as losses can bias results, decrease statistical power, and decrease generalizability (43, 44). Specifically, loss to follow-up can result in attrition bias (defined as systematic differences in the characteristics of individuals who are lost to follow-up resulting in selection bias) (45). The external and internal validity of results can be affected by attrition bias (46). In the literature there is a lack of consensus on acceptable levels of loss to follow-up, however, some journals require that a minimum of 80% follow-up is achieved (47). In this study there were a total of 81 (3.8%) individuals lost to follow-up (8.4% [n=27] with an eGFR <60 and 3.0% [n=54] with an eGFR ≥60 mL/min/ 1.73 m^2). Table C.6 (eGFR <60 mL/min/1.73 m^2) and Table C.7 (eGFR ≥60 mL/min/1.73 m^2) demonstrate differences in baseline characteristics between individuals with complete follow-up and individuals who were lost to follow-up.

Table C. 6. Comparison of baseline characteristics for individuals with complete follow-up versus lost to follow-up (eGFR <60 mL/min/1.73 m^2)

Characteristic	**Complete follow-up** (n=293)	**Loss to follow-up** (n=27)	**p-value**
FRAX Variables			
Age	75.4 ± 7.1	81.6 ± 4.8	**<0.0001**
Women	205 (70.0%)	22 (81.5%)	0.21
Body Mass Index (kg/m^2)	27.5 ± 4.6	28.1 ± 4.3	0.53
Previous fracture	72 (24.6%)	9 (33.3%)	0.32
Parent fractured hip	34 (11.6%)	1 (3.7%)	0.33
Current smoking	21 (7.2%)	3 (11.1%)	0.44
Corticosteroid use for >3 months	10 (3.4%)	1 (3.7%)	1.00
Rheumatoid arthritis	2 (0.7%)	1 (3.7%)	0.23
Secondary osteoporosis¶	22 (7.5%)	0	0.24
≥ 3 alcoholic beverages per day	0	0	_____

Femoral neck T-score	-1.2 ± 0.96	-1.6 ± 0.95	0.05
FRAX Score			
FRAX without BMD	8.0 (7.4-8.5)	10.6 (8.7-12.5)	**0.01**
FRAX with BMD	6.2 (5.7-6.7)	8.6 (6.9-10.3)	**0.01**
Comorbidities			
eGFR	49.6 ± 9.1	47.5 ± 8.3	0.23
Fall in the past 12 months	68 (23.2%)	9 (33.3%)	0.24
Bisphosphonate use[€]	75 (25.6%)	11 (40.7%)	0.09
Type 2 Diabetes	35 (12.0%)	7 (25.9%)	0.07
Excellent, very good or good self-reported current health	261 (89.1%)	19 (70.4%)	**0.01**

Note: Bolded p-values denote statistical significance

[¶]Defined as any of the following: chronic liver disease, type I diabetes, hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition/malabsorption and osteogenesis imperfecta. Source: *World Health Organization: FRAX World Health Organization Fracture Risk Assessment Tool, 2011. Available at: http://www.shef.ac.uk/FRAX/index.aspx. Accessed May 20, 2014.*

[€] Defined as a composite of alendronate, clodronate, etidronate, risedronate, ibandronate, pamidronate, zoledronate at cohort entry

Table C. 7. Comparison of baseline characteristics for individuals with complete follow-up versus lost to follow-up (eGFR ≥60 mL/min/1.73 m^2)

Characteristic	**Complete follow-up** (n=1733)	**Loss to follow-up** (n=54)	**p-value**
FRAX Variables			
Age	65.5 ± 9.9	70.8 ± 10.9	**0.0001**
Women	1218 (70.3%)	40 (74.1%)	0.55
Body Mass Index (kg/m^2)	27.1 ± 4.7	25.9 ± 4.5	0.06
Previous fracture	293 (16.9%)	13 (24.1%)	0.17
Parent fractured hip	223 (12.9%)	9 (16.7%)	0.41
Current smoking	153 (8.8%)	3 (5.6%)	0.62
Corticosteroid use for >3 months	22 (1.3%)	0	_____
Rheumatoid arthritis	13 (0.8%)	0	_____
Secondary osteoporosis[¶]	65 (3.8%)	1 (1.9%)	0.72
≥ 3 alcoholic beverages per day	21 (1.2%)	0	_____
Femoral neck T-score	-0.99 ± 1.0	-1.3 ± 0.9	**0.03**

FRAX Score			
FRAX without BMD	5.1 (4.9-5.3)	7.6 (6.1-9.1)	**<0.0001**
FRAX with BMD	4.6 (4.4-4.7)	6.0 (4.9-7.1)	**0.01**
Comorbidities			
eGFR	81.4 ± 11.4	77.9 ± 12.3	**0.03**
Fall in the past 12 months	451 (26.0%)	14 (25.9%)	0.99
Bisphosphonate use[€]	407 (23.5%)	13 (24.1%)	0.87
Type 2 Diabetes	112 (6.5%)	5 (9.3%)	0.40
Excellent, very good or good self-reported current health	1626 (93.8%)	47 (87.0%)	0.08

Note: Bolded p-values denote statistical significance
¶Defined as any of the following: chronic liver disease, type I diabetes, hyperthyroidism, hypogonadism, premature menopause (<45 years), chronic malnutrition/malabsorption and osteogenesis imperfecta. Source: *World Health Organization: FRAX World Health Organization Fracture Risk Assessment Tool, 2011. Available at: http://www.shef.ac.uk/FRAX/index.aspx. Accessed May 20, 2014.*
[€] Defined as a composite of alendronate, clodronate, etidronate, risedronate, ibandronate, pamidronate, zoledronate at cohort entry

For individuals with an eGFR <60 mL/min/1.73 m^2 individuals who were lost to follow-up were significantly older (81.6 versus 75.4 years; P<0.0001), significantly less likely to report excellent, very good or good health (87.0% versus 93.8%; P=0.001), and had a significantly higher FRAX with and without BMD score compared to individuals with complete follow-up. For individuals with an eGFR ≥ 60 mL/min/1.73 m^2 individuals who were lost to follow-up were significantly older (70.8 versus 65.5 years; P=0.0001), had a significantly lower mean eGFR (77.9 versus 81.4 mL/min/1.73 m^2; P=0.03), a significantly lower mean femoral neck T-score (-1.3 versus -0.99; P=0.03), and had a significantly higher FRAX with and without BMD score compared to individuals with complete follow-up. Bias due to loss to follow-up could potentially affect the external generalizability of the results; the results may not be generalizable to older and sicker individuals.

C.2.3 Competing Risk

A competing risk can be defined as an event (e.g. death) that eliminates an individual from being at risk for the event of interest (e.g. fracture) (45). If competing risks are not accounted for the outcome may be overestimated (44). In this study death was a potential competing risk with fracture. For example, if an individual dies before they fracture then death is considered a competing event. The traditional Kaplan-Meier

method would simply censor individuals at death; however, this is not the best method as after death a fracture can no longer occur (48). The competing risk of death is particularly important to consider when assessing fracture risk as many of the fracture risk factors (e.g. older age) are also risk factors for death (48). Therefore, the risk of fracture may be particularly overestimated in groups of individuals with higher mortality (e.g., older individuals) (48). FRAX already accounts for the competing risk of death when estimating the 10-year fracture probability (1). Therefore, when the observed probability of fracture is calculated the competing risk of death should also be taken into account particularly given the older mean age in this study (75.9 years in individuals with an eGFR <60 mL/min/1.73 m^2). To account for the competing risk of death a modified Kaplan-Meier method was used. Leslie *et al.* developed this modified Kaplan-Meier method and assessed it on a cohort of older men and women (aged ≥ 50 years) (48). They found that in subgroups that had a high risk of mortality (e.g. men) not accounting for the competing risk of death resulted in overestimating fracture risk using the traditional Kaplan-Meier method by 16-56% (48). This modified Kaplan-Meier method produced fracture estimates that were within 2% of the estimates produced by the cumulative incidence function (method that also takes into account competing risks) (48). The modified Kaplan-Meier method does not censor individuals when they die; individuals who die are instead followed until the end of follow-up and considered to remain fracture free (48); therefore, the only censoring event that was considered was loss to follow-up (48). In this chapter only 3.3% (n=69) died (5.9% [n=19] with an eGFR <60 and 2.8% [n=50] with an eGFR ≥60 mL/min/ 1.73 m^2), therefore, the competing risk of death was less of a concern. Table C.8 demonstrates that the traditional Kaplan-Meier method and the modified Kaplan-Meier method produced estimates that were similar.

Table C. 8. Kaplan-Meier estimates (traditional and modified) of fracture risk by estimated glomerular filtration rate

	<60 mL/min/1.73 m^2 (n=320)		**≥60 mL/min/1.73 m^2** (n=1787)	
	Traditional Kaplan-Meier, 95% CI	**Kaplan-Meier taking into account competing risk of death, 95% CI**	**Traditional Kaplan-Meier, 95% CI**	**Kaplan-Meier taking into account competing risk of death, 95% CI**
Major osteoporotic fracture	5.6 (3.4-9.0)	5.3 (3.3-8.6)	2.7 (2.0-3.6)	2.7 (2.1-3.6)

C.2.4 Observed and FRAX Predicted Fracture Estimates

In this chapter only information on years 10-15 of the CaMos data was able to be utilized; therefore, the 10-year FRAX predicted fracture risk was divided by two to get the 5-year FRAX predicted fracture risk. To ensure that this method was accurate the observed 5- and 10-year fracture risks of the entire CaMos cohort was analysed by sex and age group (Table C.9). It was found that the relationship between the 5-year and 10-year estimates was consistent. Specifically, the 5-year risk was close to half the 10-year risk even in older age groups.

Table C. 9. 5- and 10-year observed fracture risks in the entire CaMos cohort

10-year risks					
Men			**Women**		
	Fracture	**95% CI**		**Fracture**	**95% CI**
Age			**Age**		
45-54	8.0%	(5.9%-10.6%)	45-54	8.2%	(6.6%-10.0%)
55-64	7.6%	(5.6%-9.9%)	55-64	13.5%	(11.8%-15.3%)
65-74	11.1%	(9.0%-13.6%)	65-74	19.9%	(18.1%-21.7%)
75-84	16.7%	(12.8%-21.1%)	75-84	27.2%	(24.2%-30.3%)
5-year risks					
Men			**Women**		
	Fracture	**95% CI**		**Fracture**	**95% CI**
Age			**Age**		
45-54	4.5%	(3.0%-6.5%)	45-54	3.5%	(2.5%-4.7%)
55-64	4.7%	(3.2%-6.6%)	55-64	6.9%	(5.8%-8.3%)
65-74	6.3%	(4.8%-8.2%)	65-74	10.1%	(8.8%-11.4%)

75-84	8.3%	(5.8%-11.5%)	75-84	16.1%	(13.8%-18.5%)

Ratios comparing the 5- and 10-year risks of fracture			
Men		**Women**	
Age	**Ratio**	**Age**	**Ratio**
45-54	0.56	45-54	0.43
55-64	0.62	55-64	0.51
65-74	0.57	65-74	0.51
75-84	0.50	75-84	0.59

*Unreliable estimates for age <45 because of the low number of fracture events.

C.2.5 Hazard Ratio per Standard Deviation for Incident Fracture Prediction

To further examine the discriminative ability of FRAX hazard ratios per standard deviation were also assessed to provide information on the gradient of risk for fracture prediction. Cox proportional hazard regression was used to model time to first major osteoporotic fracture event. The proportional hazard assumption was assessed using the time-dependent covariate approach (e.g. FRAX*log(time)) and the ASSESS option in the SAS PROC PHREG command which plots the follow-up time against the observed score process (49). A p-value <0.05 was assumed to have violated the proportional hazard assumption. To ensure there were no departures from linearity martingale residuals were assessed for each continuous variable using SAS's PROC PHREG ASSESS statement which plots the cumulative martingale residuals against the continuous covariate; a p-value <0.05 was considered a violation of linearity (50). The proportional hazard assumption was met and there were no departures from linearity for all variables. Similar results to the area under the receiver operating characteristic curve analysis were found with all hazard ratios for incident major osteoporotic fracture prediction reaching statistical significance. These results (hazard ratio [HR] per standard deviation increase in FRAX with BMD 1.6, 95% CI 1.2-2.3; without BMD 1.5, 95% CI 1.02-2.2) were also comparable to the average hazard ratios found in the original FRAX validation study that included 11 international cohorts (HR FRAX with BMD 1.6; without BMD 1.5) (Table C.10) (1).

Table C. 10. Hazard ratio (HR) for incident major osteoporotic fracture prediction*

	<60 mL/min/1.73 m^2		≥60 mL/min/1.73 m^2	
Risk Factor	**HR**	**95% CI**	**HR**	**95% CI**
FRAX with BMD	1.6	1.2-2.3	1.6	1.4-1.8
FRAX without BMD	1.5	1.02-2.2	1.65	1.4-1.9
FRAX without BMD and with secondary osteoporosis	1.6	1.05-2.3		
Femoral neck T-score	2.1	1.2-3.7	2.4	1.7-3.3
Femoral neck T-score and prior history of fall	2.0	1.1-3.6	2.5	1.8-3.5
Age	2.5	1.4-4.6	2.0	1.5-2.8

* All hazard ratios are presented by standard deviation increase except for femoral neck T-score which is presented by standard deviation decrease.

C.2.6 Fracture Discrimination for All Fractures

A separate analysis was performed to assess the discrimination of FRAX including all fracture sites (excluding fingers, toes, and skull) resulting from low or high trauma (Table C.11). The rationale for assessing all fracture sites is that in contrast to the general population where major osteoporotic fractures are common fracture sites, individuals with reduced kidney function may have other fracture sites that are common (51). For example, in kidney transplant recipients, who have similar changes in bone mineral metabolism as chronic kidney disease patients, ankle fractures have been found to be common (52-54). Therefore, it would be useful to know if FRAX could also be used to accurately predict all fracture locations. There were a total of 202 (9.6%) all fracture events (46 [14.4%] with an eGFR <60 mL/min/1.73 m^2 and 156 [8.7%] with an eGFR ≥60 mL/min/1.73 m^2). There were no statistically significant differences in the predictive discrimination of T-scores alone, age alone, and T-scores with previous falls between individuals with an eGFR <60 versus ≥60 mL/min/1.73 m^2 for any fracture similar to when major osteoporotic fractures was assessed (P>0.05). Moreover, all AUC values were statistically significant (Table C.12)

Table C. 11. Fracture locations included for all fracture locations

Locations
Back
Hip

Ribs
Forearm/wrist
Pelvis
Arm/shoulder
Elbow
Hands
Knee
Ankle
Foot
Leg
Shoulder
Clavicle
Scapula
Neck
Sacrum
Coccyx

Table C. 12. Area under the curve for incident fracture prediction according to estimated glomerular filtration rate for any fracture

	<60 mL/min/1.73 m^2		**≥60 mL/min/1.73 m^2**			
Risk Factor	**AUC**	**95% CI**	**AUC**	**95% CI**	**AUC Difference, 95% CI**	**p-Value**
FRAX with BMD	0.71	0.62 to 0.80	0.64	0.59 to 0.68	0.07 (-0.03 to 0.17)	0.16
FRAX without BMD	0.67	0.59 to 0.76	0.63	0.58 to 0.67	0.04 (-0.06 to 0.14)	0.42
FRAX without BMD and with secondary osteoporosis	0.68	0.59 to 0.76				
Femoral neck T-score	0.66	0.57 to 0.74	0.61	0.56 to 0.66	0.05 (-0.05 to 0.15)	0.31
Femoral neck T-score and prior history of fall	0.67	0.59 to 0.76	0.61	0.56 to 0.66	0.06 (-0.04 to 0.16)	0.23
Age	0.60	0.51 to 0.69	0.57	0.53 to 0.62	0.03 (-0.07 to 0.13)	0.56

Abbreviations: AUC, area under the curve; BMD, bone mineral density; FRAX, Fracture Risk Assessment tool

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APPENDIX D: Chapter 4 Details

[a]A version of this appendix, in particular Figure D.2 and Tables D.2 and Table D.3, was published as, Naylor KL, Jamal SA, Zou G, McArthur E, Lam NN, Leslie WD, Hodsman AB, Kim SJ, Knoll GA, Fraser LA, Adachi JD, Garg AX. Fracture risk in adult kidney transplant recipients. *Transplantation* 2015.

D.1 Detailed Methods

D.1.1 Database Codes and Data Sources

Database codes used for cohort creation, baseline characteristics, and censoring events are detailed in Table D.1. Databases codes used to identify fracture and fall events are detailed in Tables D.2 and D.3. A detailed summary of validation studies and the accuracy of database codes used to define fracture events are described in Tables D.4 and D.5 (1-8). A detailed description of Ontario's large healthcare databases used to investigate fracture in kidney transplant recipients (Chapters 4, 5, and 6) is provided below.

i) *Canadian Organ Replacement Register (CORR):* CORR is an information system that provides data on transplant recipients. CORR has excellent coverage with 98.5% of transplants recorded in CORR also being recorded in the Canadian Institutes for Health Information Discharge Abstract Database (9). A previous study assessing the validity of the CORR database found that there was >95% agreement for sex, date of birth, and health card number between CORR and the medical chart (10).

ii) *The Canadian Institute for Health Information Discharge Abstract Database, Same Day Surgery, and National Ambulatory Care Reporting System (CIHI-DAD, SDS, NACRS):* NACRS provides information on outpatient hospital visits, emergency department visits, and dialysis clinic visits (11). CIHI-DAD and SDS provide information on Ontario's acute, rehab, chronic, and day surgery institutions (11). Diagnostics are provided using the International Classification of Disease codes (ICD). These codes were used to identify fracture events, morbidities, and exclusion criteria. In a study determining the agreement between the CIHI databases and data collected from abstractors both the femoral fracture and ankle fracture code had a high (≥ 95) kappa, sensitivity, and positive predictive value (5).

iii) *The Ontario Health Insurance Plan (OHIP):* OHIP provides information on billing claims from Ontario physicians and laboratories. OHIP has good population coverage with approximately 94% of physician services billed through OHIP (12). Chart abstraction studies have found that agreement between abstracted fee codes and physician recorded codes on the chart was high; agreement for the most responsible diagnosis was over 90% and over 88% for procedural codes (13).

iv)*The Registered Persons Database (RPDB):* The RPDB provides information on demographics such as sex, age, and vital status (14). Information in the RPBD corresponds with information on population characteristics held at Statistics Canada (15).
v) *The Ontario Drug Benefit Plan (ODB):* ODB is a universal drug plan for individuals aged ≥ 65 years, which includes a wide range of routine outpatient medication prescriptions. Since April 1997 information is provided for individuals < 65 years of age who are eligible for the Trillium Drug Program or the Special Drugs Program, individuals with social assistance or individuals residing in long-term care facilities. The error rate in this database is minimal (~0.7%, 95% CI: 0.5 to 0.9%) (16).
vi) Institute for Clinical Evaluative Sciences Physician Database (IPDB): This database contains information on all Ontario physicians, including information on physician speciality, physician demographics, and physician activity (i.e., workload) (17). This database was used to determine physician speciality.

Table D. 1. Database codes used to define cohorts, baseline characteristics, and censoring events for chapters 4, 5, and 6

Characteristic	Database	Database Codes
Inclusion criteria for kidney transplant recipients		
Kidney transplant recipients	CORR	**Treatment_code** 171, 181 **Transplanted_organ_type_code [1-3]** 10, 11, 12, 18, 19
Exclusion criteria for kidney transplant recipients		
Non-Ontario resident	RPDB	Prcddablk Not equal to province code 35
Previous transplant	CORR CIHI-DAD OHIP	**GRAFT_NUM** ≥2 **ICD-9** V420, 99681 **ICD-10** T861, N165, Z940 **CCP** 6743, 675 **CCI** 1PC85 **OHIP Feecode** E762, S435, E769, S434, E771, Z631, G347, G348, G412, G408, G409
Evidence of combination transplant (e.g. kidney pancreas)	CORR	**Transplanted_organ_type_code [1-3]**
Baseline characteristics		
Age	RPDB	
Sex	RPDB	
Year of Transplant	CORR	**Treatment_date**
Hypertension	CIHI-DAD OHIP	**ICD-9** 401, 402, 403, 404, 405 **ICD-10** I10, I11, I12, I13, I15 **OHIP DX** 401, 402, 403

Diabetes	CIHI-DAD OHIP	**ICD-9** 250 **ICD-10 Codes** E10, E11, E13, E14 **OHIP DX** 250 **OHIP Feecode** Q040, K029,K030
Peripheral Vascular Disease	CIHI-DAD OHIP	**ICD 9** 4402, 4403, 4408, 4409, 5571, 4439, 444 **ICD 10** I700, I702, I708, I709, I731, I738, I739, K551 **CCP** 5125, 5129, 5014, 5016, 5018, 5028, 5038 **CCI** 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87 **OHIP Feecode** R787, R780, R797, R804, R809, R875, R815, R936, R783, R784,R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, E672, R813, R867,E649
Congestive heart failure	CIHI-DAD OHIP	**ICD9** 425, 5184, 514, 428 **ICD10** I500, I501, I509, I255, J81 **CCP** 4961, 4962, 4963, 4964 **CCI** 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR **OHIP Feecode** R701, R702, Z429 **OHIP DX** 428
Coronary artery disease	CIHI-DAD OHIP	**ICD9** 412, 410, 413, 414, 4292, 4295, 4296, 4297 **ICD10** I20, I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822 **CCI** 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76 **CCP** 4801, 4802, "4803, 4804, 4805, 481, 482, 483

		OHIP Feecode R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 **OHIP DX** 410, 412, 413
Prior non-vertebral fracture	CIHI-DAD OHIP NACRS	*Please refer to Table D.2.*
Race	CORR	**Racial_Origin_Code** Caucasian: 01 Asian: 02 Black: 03 Unknown: 98 Other/Multiracial:11, 99, 10, 08, 05, 09
Cause of end-stage renal disease	CORR	**Primary_Diagnosis_Kidney** Glomerulonephritis: 05, 06, 07, 08, 09, 10, 12, 13, 14, 15, 16, 19, 73, 74, 84, 85, 86, 88 Cystic Kidney Disease: 40, 41, 42, 43, 49 Diabetes: 80, 81 Renal Vascular Disease: 70, 71, 72, 79 Other: 20, 21, 22, 23, 24, 25,29, 30, 31, 32, 33, 39, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 66, 78, 82, 83, 87, 89, 90, 91, 92, 93, 94, 95, 96, 97, 99
Donor type	CORR	**Donor_Type_Code** Living: 02, 03, 04, 05, 06, 07, 10, 12, 13, 14, 15 Deceased: 01 Unknown/Missing: 98
Dialysis Modality[‖]	CORR	**Treatment_Code** Hemodialysis: 060,111, 112, 113, 121, 122, 123, 131, 132, 133, 211, 221, 231, 311, 312,313,321, 322, 323, 331, 332, 333, 413,423, 433 Peritoneal: 141,151, 152, 241, 242, 251, 252, 443, 453
Dialysis[¶] (years prior to transplant)	CORR	**Dialysis: Treatment_Date & Treatment_Code:** 060, 111, 112, 113, 121, 122, 123, 131, 132, 133, 141, 151, 152, 211, 221, 231, 241, 242, 251, 252, 311,312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, 443, 453 **Transplant: Treatment_Date & Treatment_Code:** 171
Delayed graft function	CIHI-DAD OHIP	*At least one code for dialysis appearing in the first 7 days after the transplant date.* **CCP** 5195, 6698

		CCI 1PZ21 **OHIP Feecode** R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295
Primary non-function	CIHI-DAD OHIP	*At least three codes for dialysis on three different days with at least one code appearing in the first 7 days after the transplant date, in the 8- 30 days after the transplant date, and in the 31-60 days after the transplant date.* **CCP** 5195, 6698 **CCI** 1PZ21 **OHIP Feecode** R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295
Pretransplant parathyroidectomy	CIHI-DAD OHIP	**CCP** 1FV59HAX7, 1FV83NZ, 1FV83NZAG, 1FV83PZ, 1FV83PZAG, 1FV87NZ, 1FV87NZAG, 1FV87PZ, 1FV87PZAG, 1FV89NZ, 1FV89NZAG, 1FV89PZ, 1FV89PZAG **CCI** 197, 1971, 1972, 1996 **OHIP Feecodes** S795, S796, E880, E885 , S792, E882, E883, E884
Charles Comorbidity Index*	CIHI-DAD	**ICD-9** and **ICD-10 codes**
Glucocorticoids	ODB	Prednisone
Cyclosporine	ODB	Cyclosporine
Tacrolimus	ODB	Tacrolimus
Bisphosphonates	ODB	Etidronic acid disodium, Clodronic acid disodium, Pamidronic acid disodium, Etidronic acid disodium, Calcium carbonate & etidronic acid sodium, Alendronate sodium, Risedronate sodium, Zoledronic acid, Alendronate, Alendronate sodium & cholecalciferol, Pamidronate disodium
Reference Groups Inclusion and Exclusion criteria		
Osteoporosis	CIHI-DAD NACRS OHIP	**ICD-9 Codes** *Osteoporosis unspecified:* 733.00 *Senile osteoporosis:* 733.01 *Idiopathic osteoporosis*: 733.02 *Disuse osteoporosis:* 733.03

		Other osteoporosis :733.09 **ICD-10 Codes** *Osteoporosis with pathological fracture*:M80 *Osteoporosis without pathological fracture*: M81 *Osteoporosis in diseases classified elsewhere:* M82 **OHIP DX** *Osteoporosis:*733
Dual energy x-ray absorptiometry	OHIP	**OHIP Feecode** *Bone mineral density by single proton method:* J654 *Total boday calcium proton actiation*: J655 *Bone min. content dual-photon absorbtiomet. 2 or more sites*: J656 *Bone mineral content by dual photon single site:* J688 *Bone mineral density by single photon method:* J854 *Total body calcium - neutron activation:* J855 *Bone min. content dual-photon absorbtiomet. 2 or more sites*: J856 *Bone mineral content by dual photon absorb*: J888 *BMD - baseline test, one site*: X145 *BMD - baseline test, two or more sites*: X146 *Bone mineral density high risk 1 site*: X149 *Bone mineral density low risk 1 site*: X152 *Bone mineral density low risk 2+ sites*: X153 *Bone mineral density high risk 2+sites:* X155 *Diag. rad. bone density (mineral content) measurement:* X157
Chronic kidney disease	CIHI-DAD NACRS OHIP	**ICD-9 Codes** *Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage i through stage iv, or unspecified:* 403.00 *Hypertensive chronic kidney disease, malignant, with chronic kidney disease stage v or end stage renal disease*:403.01 *Hypertensive chronic kidney disease, benign, with chronic kidney disease stage i through stage iv, or unspecified*: 403.10 *Hypertensive chronic kidney disease, benign, with chronic kidney disease stage v or end stage renal disease*: 403.11 *Hypertensive chronic kidney disease, unspecified, with chronic kidney disease stage i through stage iv, or unspecified:* 403.9 *Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage i through stage iv, or unspecified* 404.00 *Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage i through stage iv, or unspecified:* 404.01

		Hypertensive heart and chronic kidney disease, malignant, without heart failure and with chronic kidney disease stage v or end stage renal disease: 404.02 *Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage v or end stage renal disease*: 404.03 *Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage i through stage iv, or unspecified:* 404.11 *Hypertensive heart and chronic kidney disease, benign, without heart failure and with chronic kidney disease stage v or end stage renal disease:* 404.12 *Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage v or end stage renal disease:* 404.13 *Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage i through stage iv, or unspecified:* 404.90 *Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage i through stage iv, or unspecified:* 404.91 *Hypertensive heart and chronic kidney disease, unspecified, without heart failure and with chronic kidney disease stage v or end stage renal disease:* 404.92 *Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage v or end stage renal disease:* 404.93 *Chronic kidney disease, stage i:* 585.1 *Chronic kidney disease, stage ii (mild):* 585.2 *Chronic kidney disease, stage iii (moderate):* 585.3 *Chronic kidney disease, stage iv (severe):* 585.4 *Chronic kidney disease, stage v:* 585.5 *End stage renal disease:* 585.6 *Chronic kidney disease, unspecified:* 585.9 *Renal failure unspecified:*586 *Secondary hyperparathyroidism (of renal origin*):588.81 *Other specified disorders resulting from impaired renal function :* 588.9 *Diabetes with renal manifestations, type ii or unspecified type, not stated as uncontrolled:* 250.40 *Diabetes with renal manifestations, type i [juvenile type], not stated as uncontrolled:* 250.41 *Diabetes with renal manifestations, type ii or unspecified type, uncontrolled:* 250.42

		Diabetes with renal manifestations, type i, uncontrolled: 250.43 **ICD-10 Codes** *Type 1 diabetes mellitus with incipient diabetic nephropathy adequately or inadequately controlled with insulin, diet, oral agents:* E10.2 *Type 2 diabetes mellitus with incipient diabetic nephropathy adequately or inadequately controlled with insulin, diet, oral agents:* E11.2 *Other specified diabetes mellitus with incipient diabetic nephropathy adequately or inadequately controlled with insulin, diet, oral agents:* E13.2 *Unspecified diabetes mellitus with incipient diabetic nephropathy adequately or inadequately controlled with insulin, diet, oral agents:* E14.2 *Hypertensive renal disease:* I12 *Hypertensive renal and heart disease:* I13 *Glomerular disorders in diseases classified elsewhere:* N08 *Chronic renal failure:* N18 *Unspecified renal failure*: N19 **OHIP DX** *Hypertensive renal disease*: 403 *Chronic renal failure, uremia*: 585
Dialysis *(exclusion criteria)*	CORR	*Please refer to CORR codes for dialysis above*.
Dialysis *(reference group)*	CORR	*Please refer to CORR codes for dialysis above*.
Censoring events		
Non-vertebral fracture		*Please refer to Table D.2.*
Death	RPDB	
Additional censoring events		
Receipt of another kidney transplant‡	CORR	*Please refer to codes previously defined above.*
Dialysis¥	CORR	

Abbreviations: CCI=Canadian Classification of Health Interventions; CCP=Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI-DAD=Canadian Institutes for Health Information-Discharge Abstract Database; CORR= Canadian Organ Replacement Registry; DXA= dual-energy x-ray absorptiometry; DX, diagnostic code; ICD=International Classification of Diseases; OHIP=Ontario Health Insurance Plan; RPDB=Registered Persons Database.

‖We defined hemodialysis and peritoneal dialysis based on the modality they first received. We defined pre-emptive transplant as no evidence of hemodialysis or peritoneal dialysis prior to transplant.

¶Years on dialysis prior to transplant was calculated by (transplant date-dialysis start date)/365.25. Individuals who received a pre-emptive transplant were given 0 years as the time spent on dialysis.

* All recipients with a Charlson Comorbidity Index of 0 were given a score of 2 and recipients with a score of 1 were given a score of 3; one of the variables in the CCI is presence of end-stage renal disease which automatically gives individuals a score of 2. The Charlson comorbidity index includes the following variables: acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, rehuamtic-like diseases, digestive system ulcers, mild liver disease, diabetes (with and without complications), hemiplegia or paraplegia, renal disease, cancer (with and without secondary), liver disease (moderate/severe), and HIV/AIDS. Source: *Quan, H., V. Sundararajan, et al.. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005; **43**: 1130-1139*

‡ Defined as receipt of another transplant day 1 to 3 years after the initial transplant.

¥ Defined as chronic dialysis in the 31 days to 3 years after the initial transplant.

Table D. 2. Database codes used to identify non-vertebral fracture events

	Diagnostic codes		
Fracture Location[‡]	**ICD-9 Codes**	**ICD-10 Codes**	
Hip	*Neck of femur:* 8200, 8201, 8208, 8209 *Trochanteric/subtrochanteric:* 8202, 8203	*Neck of femur:* S720 *Trochanteric:* S721 *Subtrochanteric: S722*	
Forearm	813	S52	
Proximal Humerus	812	S422	
	Procedural codes[†]		
Fracture Location	**CCP Codes**	**CCI Codes**	**OHIP Fee Codes**
Hip	*Reduction:* 9104, 9124 *Reduction with fixation:* 9054, 9114, 9134 *Arthroplasty:* 935x, 936x	*Reduction:* 1VA73, 1VC73 *Fixation:* 1VA74, 1VA53, 1VC74 *Arthroplasty:* 1VA80	Not applicable
Forearm	*Reduction:* 9101, 9121, 9141 *Reduction with fixation:* 9111, 9131, 9052	*Reduction:* 1TV73 *Fixation:* 1TV74 *Immobilization:* 1TV03	*Reduction:* F014, F022, F023, F025, F026, F028, F030, F032, F033, F046 *Immobilization:* F024, F027, F031, Z203

Abbreviations: CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; ICD-9 CA, International Classification of Disease, Ninth Revision; ICD-10-CA, International Classification of Disease, Tenth Revision; OHIP, Ontario Health Insurance Plan

[‡]Fracture diagnoses accompanied by trauma codes were included.

[†]Procedural codes were required to accompany hip and forearm fractures for the diagnosis to be included as a fracture event. These procedural codes appeared within +/- 30 days of fracture diagnosis, using the respective hospital admission dates. We found that the proportion of diagnosis and procedural codes that had identical admission dates was very high (Hip, Canadian Institute of Health Research (CIHI) database, 99.4%; Forearm, CIHI, 98%; Forearm, OHIP, 83%).

Table D. 3. Database codes used to identify additional fracture events and fall events

	Diagnostic codes	
Fracture Location[‡]	**ICD-9 Codes**	**ICD-10 Codes**
Pelvis	*Sacrum/coccyx:* 8056, 8057 *Acetabulum/pubis/ilium/ischium /unspecified:* 808x	*Sacrum/coccyx:* S321, S322 *Acetabulum:* S324 *Pubis/ilium/ischium:* S323, S325 *Unspecified:* S327, S328
Vertebral	*Thoracic:* 8052, 8053 *Lumbar:* 8054, 8055	*Thoracic:* S220, S221 *Lumbar:* S320x
Femoral Shaft	*Shaft or unspecified part, closed:* 8210 *Shaft or unspecified part, open:* 8211	*Shaft of femur*: S723
Lower leg	*Fracture of ankle:* 824 *Fracture of tibia and fibula:* 823 *Fracture of patella:* 822	*Fracture of lower leg, including ankle:* S82
Rib/sternum/trunk	*Fracture of rib(s), sternum, larynx, and trachea:*807 *Fractures of bones of trunk:*809	*Fracture of rib(s), sternum and thoracic spine:* S22
Other	*Fracture of clavicle*: 810 S820 *Fracture of scapula*: 811	*Fracture of clavicle*: S420 S820 *Fracture of scapula*: S421
Falls with Hospital Presentation	*Accidental fall on or from escalator:*E880.0 *Accidental fall on or from sidewalk curb:* E880.1 *Accidental fall on or from other stairs or steps:* E880.9 *Accidental fall from ladder:* E881.0 *Accidental fall from scaffolding:* E881.1 *Accidental fall from or out of building or other structure:* E882 *Accident from diving or jumping into water (swimming pool):* E883.0 *Accidental fall into well:* E883.1 *Accidental fall into storm drain:* E883.2 *Accidental fall into other hole or other opening*	*Fall on same level involving ice and snow*: W00 *Fall on same level from slipping, tripping and stumbling:* W01 W02 *Fall involving ice-skates, skis, roller-skates or skateboards:* W02 W03 *Other fall on same level due to collision with, or pushing by, another person:*W03 *Fall while being carried or supported by other persons*: W04 *Fall involving wheelchair:* W05 *Fall involving bed:* W06 *Fall involving chair:* W07 *Fall involving other furniture:* W08 *Fall involving playground equipment:* W09 *Fall on and from stairs and steps:* W10 *Fall on and from ladder:* W11 *Fall on and from scaffolding:* W12

	in surface: E883.9 *Accidental fall from playground*: E884.0 *Accidental fall from cliff:* E884.1 *Accidental fall from chair:* E884.2 *Accidental fall from wheelchair:* E884.3 *Accidental fall from bed:* E884.4 *Accidental fall from other furniture:* E884.5 *Accidental fall from commode:* E884.6 *Other accidental fall from one level:* E884.9 *Accidental fall from (nonmotorized) scooter:* E885.0 *Accidental fall from roller skates:* E885.1 *Accidental fall from skateboard*: E885.2 *Accidental fall from skis*: E885.3 *Accidental fall from snowboard:* E885.4 *Accidental fall from other slipping tripping or stumbling:* E885.9 *Accidental fall on same level from collision pushing or shoving by or with other person in sports:* E886.0 *Other and unspecified accidental falls on same level from collision pushing or shoving by or with other person*: E886.9 *Fracture cause unspecified:* E887 *Accidental fall resulting in striking against sharp object:* E888.0 *Accidental fall resulting in striking against other object::*E888.1 *Other accidental fall :*E888.8 *Unspecified accidental fall:* E888.9	*Fall from, out of or through building or structure:* W13 *Fall from tree:* W14 *Fall from cliff:* W15 *Diving or jumping into water causing injury other than drowning or submersion*: W16 *Other fall from one level to another:* W17 *Other fall on same level:* W18 *Unspecified fall:* W19	
	Procedural codes[†]		
Fracture Location	**CCP Codes**	**CCI Codes**	**OHIP Fee Codes**
Femoral Shaft Fracture	*Reduction:* 9104, 9124 *Reduction with fixation:* 9054, 9114, 9134	*Reduction:* 1VC73x *Fixation:* 1VC74x *Immobilization:* 1VC03x *Other repair:* 1VC80x	*Reduction:* F095, F096, F097 *Immobilization:* Z211

Abbreviations: CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; ICD-9, International Classification of Disease , Ninth Revision;ICD-10-CA, International Classification of Disease, Tenth Revision; OHIP, Ontario Health Insurance Plan

[‡]Fracture diagnoses accompanied by trauma codes were included.

[†]Procedural codes were required to accompany femoral shaft fractures for the diagnosis to be included as a fracture event.

Table D. 4. Summary of validation studies of fracture code algorithms (description of studies)

Study, Country, Year	Study Population	Database and source of data	Validation Years	Fracture Location	Validated codes	Possible Flags for Diagnostic Codes	Gold Standard
Hudson *et al.*, Multinational, (2013)	-Systematic review of validation studies	-In-/outpatient records and pharmacy data -Group Health Plan -Local database and national register	1987-2006	Hip	ICD-9 820-821	Any discharge diagnosis	-Bone mineral density -Chart review -Self report -Radiology and medical reports
Jean *et al.*, Canada, (2012)	-Women ≥50 years	-Quebec provincial database for medical service -Outpatient records	2003-2006	-Hip, femur -Forearm, wrist, elbow -Foot, ankle -Pelvis - Tibia, fibula -Vertebra, sacrum, coccyx -Shoulder, humerus *Fracture care method* -open reduction -closed reduction -immobilization	ICD-9 820-821 ICD-9 8130–8133 ICD-9 825 ICD-9 8080–8089 ICD-9 823 ICD-9 805–806 ICD-9 810, 811, 812	At least one fracture claim combined with a procedural code for fracture treatment OR Visit with an orthopedic surgeon	Chart review

Table D.4. (continued)

Study, Country, Year	Study Population	Database and source of data	Validation Years	Fracture Location	Validated codes	Possible Flags for Diagnostic Codes	Gold Standard
Curtis *et al.*, USA, (2009)	Gen. pop. ≥18	Insurance company (non-profit) administrative claims data	2003-2004	Spine	ICD 9-CM: 8052, 8054, 8058, 73313	Primary diagnosis	Two reviewers independently looked at medical records and radiology reports
Henderson *et al.*, Australia, (2006)	Sample of hospital admissions from Victoria, Australia	Hospital discharge data	2000-2001	Hip	ICD 10-AM: S720, S721	Discharge Diagnostic code	-Auditors with coding experience (majority had 10 or more years of experience)
Juurlink *et al.*, Canada, (2006)	18 Hospitals from Ontario	Hospital discharge data	2002-2004	Femur Lower leg including ankle	ICD 10-CA: S72 ICD 10-CA: S82	Most responsible Diagnostic Code	Reabstractors trained by CIHI
Joakimsen *et al.*, Norway, (2001)	-Tromso Norway residents -Male residents born between 1925-1959; female residents (1930-1959)	Self-report and computer linkage to radiographic archives from a University Hospital in Norway	1988-1995	Hip Forearm	ICD-9: 820 ICD-9:813	Discharge diagnostic code	Radiographs

Table D.4. (continued)

Study, Country, Year	Study Population	Database and source of data	Validation Years	Fracture Location	Validated codes	Possible Flags for Diagnostic Codes	Gold Standard
Tamblyn *et al.*, Canada, (2000)	General elderly population (≥65 years)	-Quebec outpatient physician Claims	1993-1994	Skull & face Thorax Pelvis Scapula/clavicle Humerus Radius/ulna Carpal/hand Femoral shaft Patella Tibia/fibula Ankle Foot Hip	ICD-9 800-804 ICD-9 807,809 ICD-9 8-8 ICD-9 810,811 ICD-9 812 ICD-9 813 ICD-9 814-817 ICD-9 821 ICD-9 822 ICD-9 823 ICD-9 824 ICD-9 825,826 ICD-9 820	Emergency department diagnostic code	Trained abstractor performed a chart review

Table D.4. (continued)

Study, Country, Year	Study Population	Database and source of data	Validation Years	Fracture Location	Validated codes	Possible Flags for Diagnostic Codes	Gold Standard
Ray *et al.*, USA, (1992)	Gen. pop. ≥65	In-/outpatient records	1987	Rib/sternum Pelvis/sacrum/coccyx Ankle Femoral Shaft Hand Tibia/Fibula Skull/face Foot Clavicle/Scapula Patella	ICD-9:8070-8074 ICD-9: 8056, 8057, 8066, 8067, 808 ICD-9: 824 ICD-9: 821 ICD-9: 814-817 ICD-9: 823 ICD-9: 800-804 ICD-9: 825, 826 ICD-9: 810,811 ICD-9: 822	Diagnostic codes unless the code meets the following exclusion criteria: - no corresponding procedural code for fracture in a clinic - absence of fracture discharge code after admission to hospital for a fracture - primary diagnosis of arthroplasty - follow-up treatment of an old fracture as identified through procedural codes	Medical chart review

Abbreviations: CIHI=Canadian Institute for Health Information; ICD-9= 9th version of the International Classification for Disease; ICD 9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; ICD 10-AM= Australian Modification of the International Classification of Diseases, 10th revision; ICD 10-CA= 10th version of the Canadian Modified International Classification of Disease system

Table D. 5 Accuracy of fracture database codes used in validation studies

Study, Country, Year	Database	Fracture event	Sample Size	Prevalence (%)	Sensitivity	Specificity	PPV	NPV	Kappa
Hudson *et al.*, Multinational, (2013)	Hospital discharge data	Hip	12 studies	n.r.	69-97% With the addition of procedural codes 83-97	n.r.	63-96% With the addition of procedural codes 86-98	n.r.	n.r.
Jean *et al.*, Canada, (2012)	Quebec provincial database for medical service	Hip, femur	41,288 *1506 for subsample*	368 (24.4)	99 (97-100)	n.r.	83 (79-87)	n.r.	n.r.
		Forearm, wrist, elbow		396 (26.3)	95 (94-97)		90 (87-93)		
		Foot, ankle		236 (15.7)	92 (89-95)		78 (72-83)		
		Pelvis		30 (2.0)	82 (66-98)		63 (46-81)		
		Tibia, fibula		83 (5.5)	91 (87-96)		75 (64-83)		
		Vertebra, sacrum, coccyx		25 (1.7)	50 (19-81)		76 (59-93)		
		Shoulder, humerus		238 (15.8)	93 (90- 96)		81 (76-86)		
		Fracture care method Open reduction		454 (30.1)			96 (94-97)		
		Closed reduction		214 (14.2)			98 (96-100)		
		Immobilization		191 (12.7)			84 (77-89)		

Table D.5. (continued)

Study, Country, Year	Database	Fracture event	Sample Size	Prevalence (%)	Sensitivity	Specificity	PPV	NPV	Kappa
Curtis *et al.*, USA, (2009)	Insurance company (non-profit) administrative claims data (USA)	Spine (vertebral compression fracture)	259	63 (24.3)	32 (22-44)	99 (96-100)	91 (72-97)	82 (77-86)	0.39 (0.27-0.51)
Henderson *et al.*, Australia, (2006)	A sample of Australian Hospital Discharge Data	Hip	7,631	4579 (0.60)	95 (94-96)	856 (85-87)	91 (90-92)	92 (91-93)	0.82 (0.80-0.84)
Juurlink *et al.*, Canada, (2006)	CIHI-DAD	Femur	13 803	356 (2.6)	95 (93 - 97)	n.r.	95 (92 -97)	n.r.	0.95 (0.94-0.97)
		Lower leg including ankle		68 (0.5)	99 (92 - 100)	n.r.	99 (92- 100)	n.r.	0.99 (0.96-1.00)
Joakimsen *et al.*, Norway, (2001)	Local Norwegian Hospital Discharge Abstract Database	Hip	21,441	54 (0.25)	87 (76-94)	100	90 (79-96)	100	0.89 (0.88-0.90)

Table D.5. (continued)

Study, Country, Year	Database	Fracture event	Sample Size	Prevalence (%)	Sensitivity	Specificity	PPV	NPV	Kappa
Tamblyn *et al.*, Canada, (2000)	Quebec outpatient physician Claims	Skull & face	915	15 (1.6)	0a; 27[b]; 27[c]	n.r.	n.r.	n.r.	n.r.
		Thorax		47 (5.1)	0[a]; 26[b]; 26[c]				
		Pelvis		26 (2.8)	15[a];54[b];62[c]				
		Scapula/clavicle		13 (1.4)	62[a]; 69[b]; 77[c]				
		Humerus		88 (9.6)	52[a]; 56[b]; 69[c]				
		Radius/ulna		110 (12.0)	64[a]; 41[b]; 66[c]				
		Carpal/hand		44 (4.8)	50[a]; 41[b]; 61[c]				
		Femoral shaft		15 (1.6)	93[a]; 60[b]; 93[c]				
		Patella		16 (1.7)	50[a]; 56[b]; 63[c]				
		Tibia/fibula		18 (2.0)	56[a]; 38[b]; 63[c]				
		Ankle		41 (4.5)	54[a]; 61[b]; 73[c]				
		Foot		31 (3.4)	61[a]; 42[b]; 68[c]				
		Hip		178 (19.5)	94[a]; 83[b]; 97[c]				

Table D.5. (continued)

Study, Country, Year	Database	Fracture Event	Sample Size	Prevalence (%)	Sensitivity	Specificity	PPV	NPV	Kappa
Ray *et al.*, USA, (1992)	Medicaid (Parts A and B)	Hip	1,311	538 (41.0)	97	n.r.	98	n.r.	n.r.
		Radius/ulna		162 (12.4)	93		96		
		Humerus		109 (8.3)	90		95		
		Ribs/sternum		107 (8.2)	82		84		
		Pelvis		67 (5.1)	89		93		
		Femoral shaft		53 (4.0)	75		87		
		Hand		43 (3.3)	87		86		
		Tibia/fibula		47 (3.6)	87		79		
		Foot		40 (3.1)	90		95		
		Clavicle/scapula		21 (1.6)	91		86		
		Patella		17 (1.3)	100		82		
		Ankle		69 (5.3)	78		96		
		All		1311 (100)	91		94		

Abbreviations: CIHI-DAD, Canadian Institute for Health Information-Discharge Abstract Database; ICD-9, international classification of diseases; NPV, negative predictive value; n.r.=not reported; PPV, positive predictive value; a-procedure code alone; b- diagnostic code alone; c- procedure or diagnostic code

D.1.2 Power

Based on a recently conducted study using the CORR dataset that applied similar inclusion/exclusion criteria to this chapter it was expected there would be over 5000 kidney transplant recipients eligible for inclusion. It was anticipated that there would be over 1,000,000 adults who would meet the eligibility criteria for individuals with no kidney disease and with no prior non-vertebral fracture (18). The two-sample independent chi-square test which allows for unequal group sizes (1:3) was used to calculate power (alpha 0.05) (19). Based on these calculations it was expected there would be >80% power. See Table D.6 for a sensitivity analysis of power calculations and Figure D.1 for the power formula used in the calculations. Given the large sample size statistical significance may not equate to clinical significance. For this reason a priori clinical significance was defined as a ≥ 50% relative increase in non-vertebral fracture in kidney transplant recipients compared to individuals with no kidney disease and no prior non-vertebral fracture; this was chosen in consultation with transplant nephrologists and was defined as the magnitude of effect needed to influence the clinical care of kidney transplant recipients.

$$\sqrt{N}\,|\pi_e - \pi_c| = Z_\alpha\sqrt{\bar{\pi}\,(1-\bar{\pi}\,)(Q_e^{-1} + Q_c^{-1})} + Z_\beta\sqrt{\pi_e(1-\pi_e\,)\,Q_e^{-1} + \pi_c(1-\pi_c)Q_c^{-1}}$$

N= sample size
π_e =proportion kidney transplant recipients who fractured
π_c = proportion of individuals who do not have kidney disease and have not sustained a prior non-vertebral fracture and do not have an osteoporosis diagnosis who fractured
Z_α = 0.05
$\bar{\pi} = Q_e\pi_e + Q_c\pi_c$
Q_e^{-1} =sample size for kidney transplant recipients
Q_c^{-1} = sample size for individuals who do not have kidney disease and have not sustained a prior non-vertebral fracture and do not have an osteoporosis diagnosis.
Z_β =power to detect a statistically significant difference (this formula was solved for Z_β)

Figure D.1. Formula for power calculation

Table D. 6. Sensitivity analysis for power calculations (Objective 3b)

Percentage of kidney transplant recipients with non-vertebral fracture	Percentage of individuals with no kidney disease and no prior non-vertebral fracture	Power achieved*
1%	0.6%	0.806
2%	0.6%	>.999
4%	0.6%	>.999
6%	0.6%	>.999
8%	0.6%	>.999
10%	0.6%	>.999
12%	0.6%	>.999

*Based on access to 5000 kidney transplant recipients and randomly selecting 15,000 individuals who do not have kidney disease and have not sustained a prior non-vertebral fracture and do not have an osteoporosis diagnosis.

D.1.3 Cohort Creation Additional Details: Kidney Transplant Recipients

Inclusion Criteria:

i. Evidence of receipt of a kidney transplant between July 1st, 1994 and December 31st, 2009. *Rationale:* The reason for having the accrual period end December 31st, 2009 was to ensure that the incidence rate was useful for sample size calculations in future clinical trials; therefore, ending the accrual on December 31st, 2009 allowed for the three-year incidence rate of fracture to be determined (last date of follow-up December 31st, 2012). The length of follow-up in previously conducted systematic reviews on clinical trials assessing the relationship between fracture and bisphosphonate use in the non-transplant population was between one and four years (20-22). Although the mean length of follow-up in trials assessing interventions to prevent bone disease in kidney transplant recipients was 15 months a meta-analysis recommended that the length of follow-up was underestimated resulting in inadequate power to determine the effects of fracture prevention treatment on fracture rates (23).

ii. An age of ≥ 18 years at the date of transplant. *Rationale:* Adult recipients were the sole focus of Chapters 4, 5, and 6 as mechanisms underlying fracture

risk in children with decreased kidney function are different and would be the subject of other studies (24).

Exclusion Criteria:

i. Individuals with an invalid Institute for Clinical Evaluative Sciences (ICES) key number (IKN) [each individual has a unique IKN that is used allowing for linkage with other databases], missing sex, missing date of birth, and date of death prior to index date (date of transplant). *Rationale:* These were data cleaning steps.

ii. Non-Ontario residents. *Rationale:* These individuals would be more likely to go back to their province of residence after receiving the transplant and therefore follow-up data (e.g. death) would not be available for these individuals using ICES data sources.

iii. Recipient of multiple organ transplants (including multiple kidney transplants) or combination transplants (e.g. kidney-pancreas) prior to receiving a kidney transplant. *Rationale:* Recipients of multiple/combination transplants may have different comorbidities (24, 25). The focus of chapters 4, 5, and 6 was on first time kidney-only transplant recipients.

Figure D.2 describes the cohort selection for kidney transplant recipients. Figures D.3, D.4, and D.5 describe the cohort selection for the reference groups including: healthy segment of the general population with no previous non-vertebral fracture, healthy segment of the general population with a previous non-vertebral fracture, and non-dialysis chronic kidney disease.

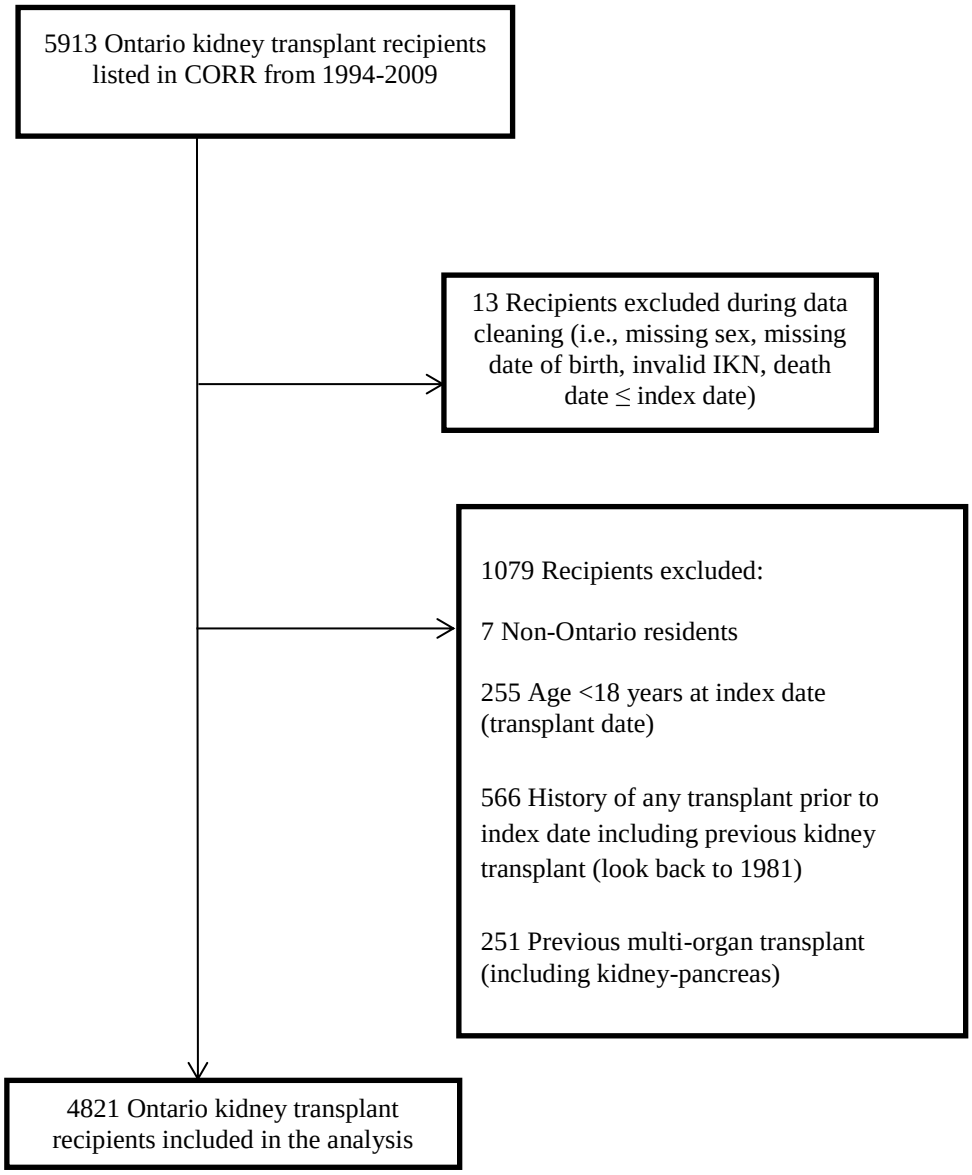


Figure D. 2. Cohort selection for kidney transplant recipients

Abbreviations: CORR, Canadian Organ Replacement Registry; IKN, Institute for Clinical Evaluative Sciences key number

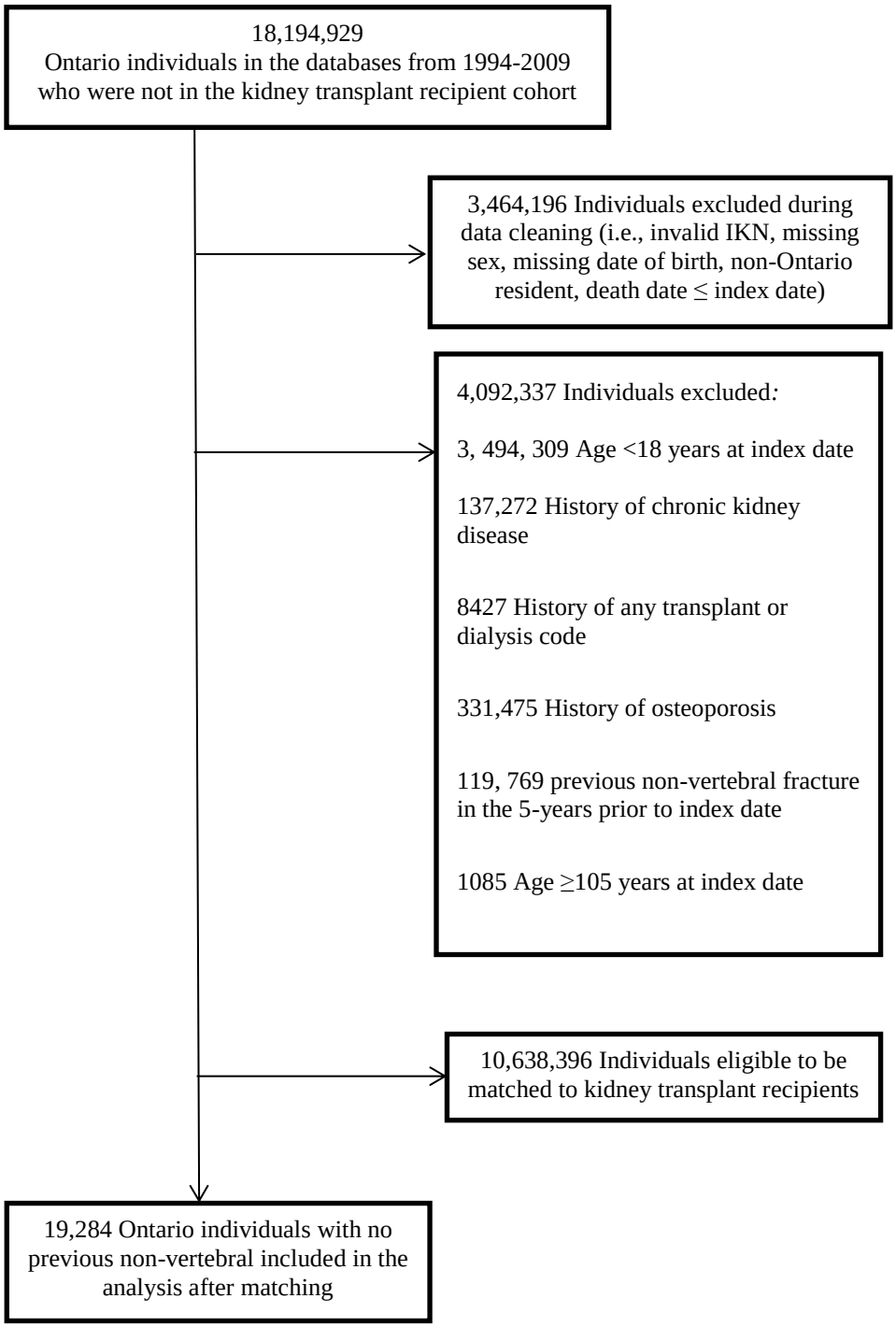


Figure D. 3. Cohort selection for the healthy segment of the general population with no previous non-vertebral fracture

Abbreviation: IKN, Institute for Clinical Evaluative Sciences key number

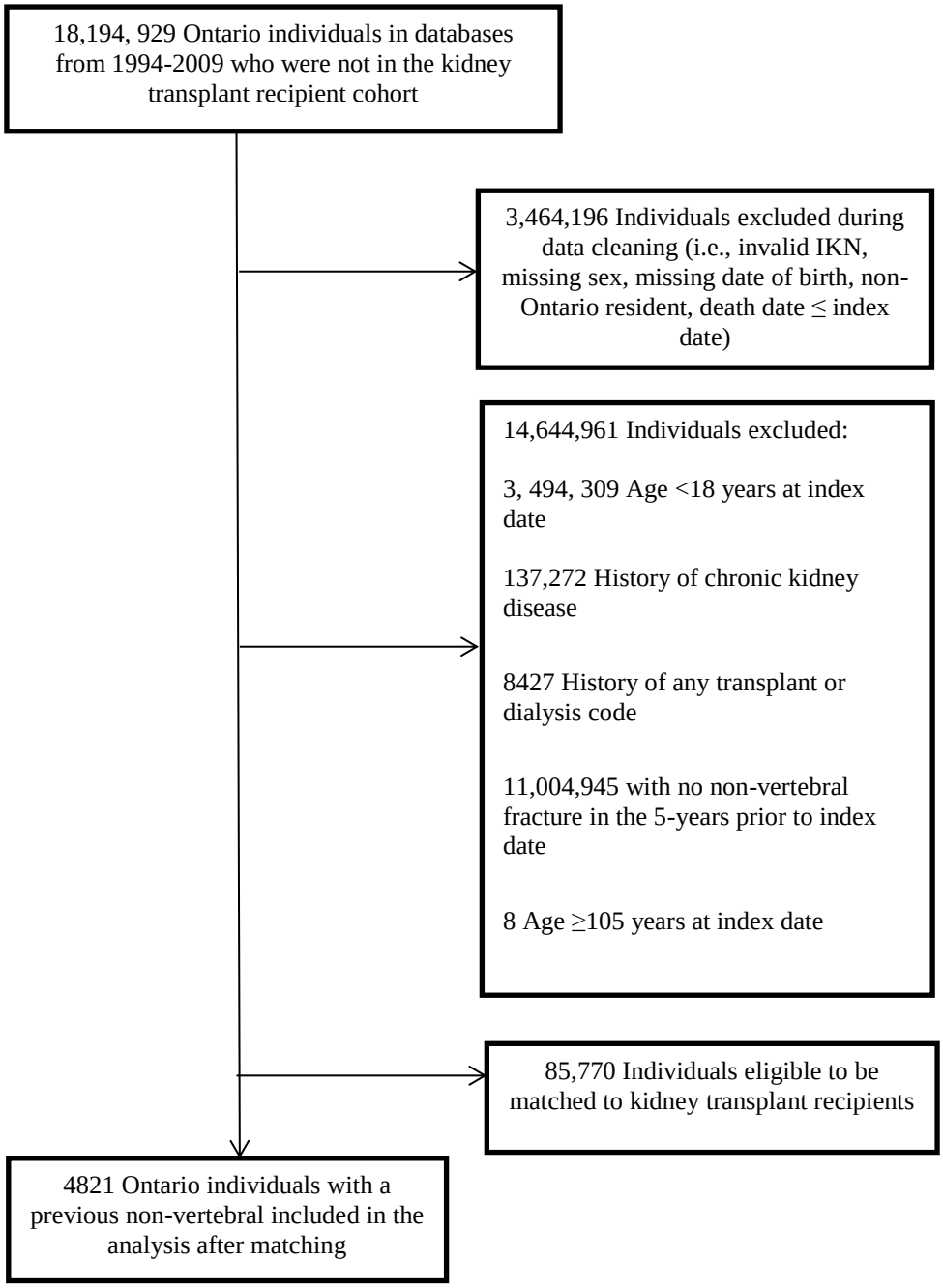


Figure D. 4. Cohort selection for the healthy segment of the general population with a previous non-vertebral fracture

Abbreviation: IKN, Institute for Clinical Evaluative Sciences key number

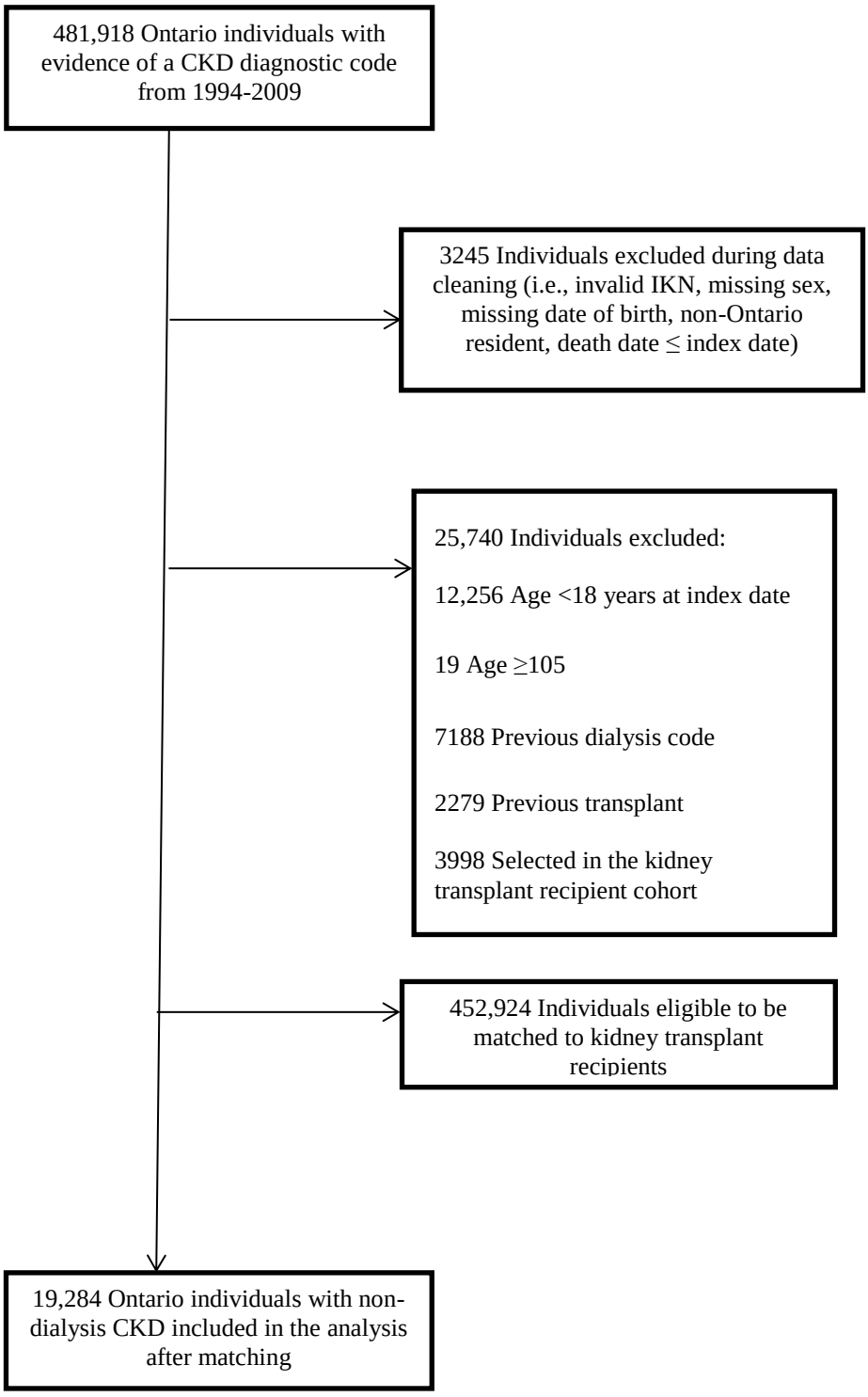


Figure D. 5. Cohort selection for non-dialysis chronic kidney disease (CKD)

Abbreviation: IKN, Institute for Clinical Evaluative Sciences key number

D.1.4 Confounders

Age (± one year), sex, and cohort entry date (index date) (± one year) were controlled through individual matching with the reference groups. Age and sex were both considered potential confounders as numerous studies in both the non-transplant and transplant population have found older age and female sex to be associated with an increased fracture risk (26-32). Index date was also controlled for as numerous changes in clinical practice (e.g. pharmacotherapy) and in the patient population (e.g. increase in obesity) have occurred from 1994-2009 (33-36). In an additional analysis diabetes was also adjusted for given that diabetes is an established risk factor for fracture (37). The reason other confounders were not controlled for was that the rationale for this study was to determine if kidney transplant recipients had a high risk of fracture; markers that are helpful to determine high risk individuals (e.g. kidney transplantation is a marker of an increased fracture risk) can be confounded (38). For example, even if recipients have a higher risk of fracture as a result of low activity levels (potential confounder) fractures are still more common in individuals with a kidney transplant and therefore potential preventative actions (e.g. bisphosphonates) should be considered. Therefore, a true statistical relationship even if it is confounded is helpful for public health as it identifies individuals who are at a high risk and therefore need to be screened (38).

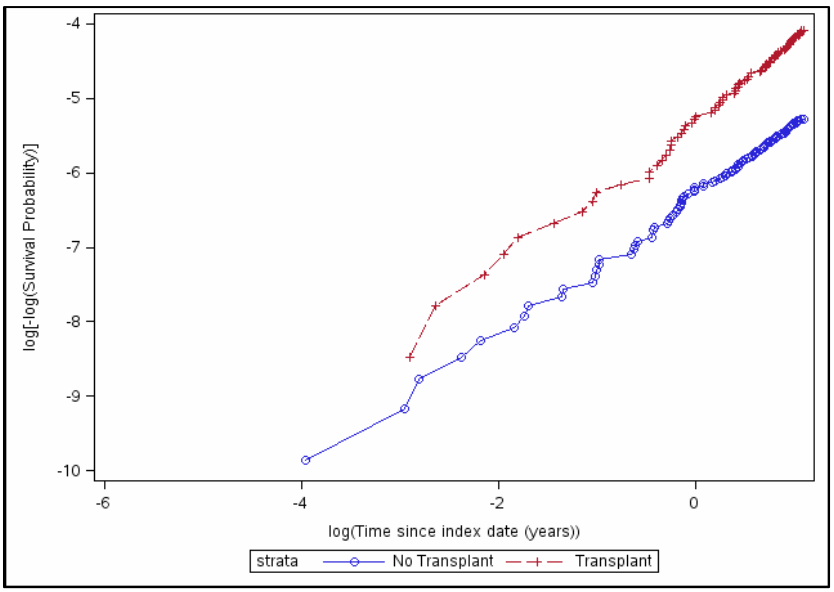
D.1.5 Cox Proportional Hazard Analysis

To ensure that the proportional hazard assumption was met it was assessed using two different methods. First, a graphical approach (log-log survival curves) was used to visually assess violations of the proportional hazard assumption (Figure D.6) (39). If the log-log survival curves did not appear parallel (e.g. lines cross-over, converged or diverged) then the Extend Cox model would be considered (39). Second, a statistical test was used to assess the proportional hazard assumption (40); if the p-value was <0.05 then the proportional hazard was considered violated. Specifically, the ASSESS option in PROC PHREG (SAS) was used which plots the follow-up time against the observed score process (41). The proportional hazards assumption was not violated in this chapter. However, it is important to note that when the log-log survival curve for CKD and transplantation was assessed the curves did cross-over; however, when assessing the proportional hazards assumption, using multiple methods, the p-values were all >0.05

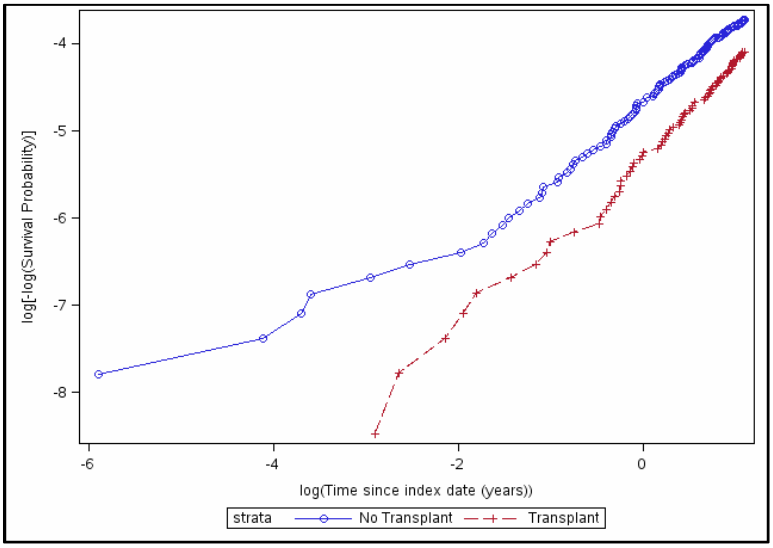
(Assess method in SAS, P=0.33; time-dependent method, P=0.23; Schoenfeld residuals, P=0.29). It is recommended that the extended Cox model should only be used if the evidence for non-parallelism is strong (39); therefore, the Cox proportional hazard model was used when comparing fractures in CKD and kidney transplant recipients.

Figure D. 6. Log-minus-log survival curves of the primary outcome (non-vertebral fracture) for each reference group

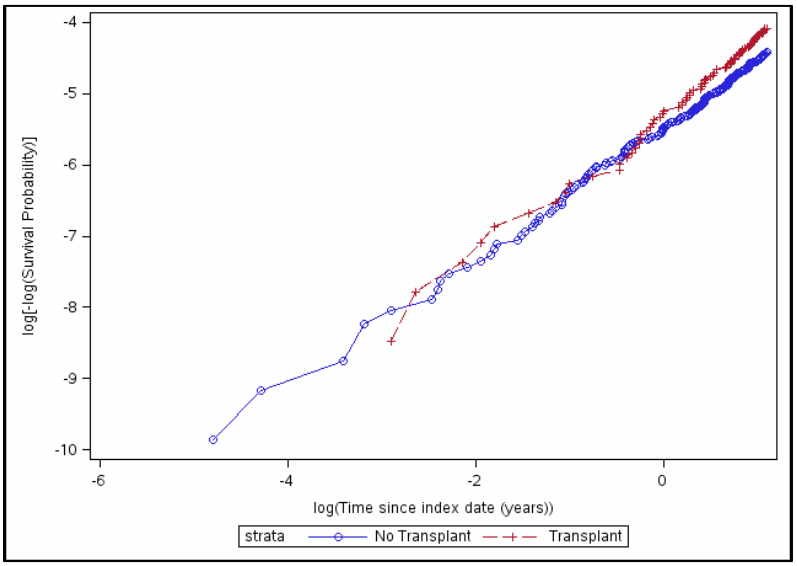
a) General population with no previous non-vertebral fracture



b) General population with a previous non-vertebral fracture

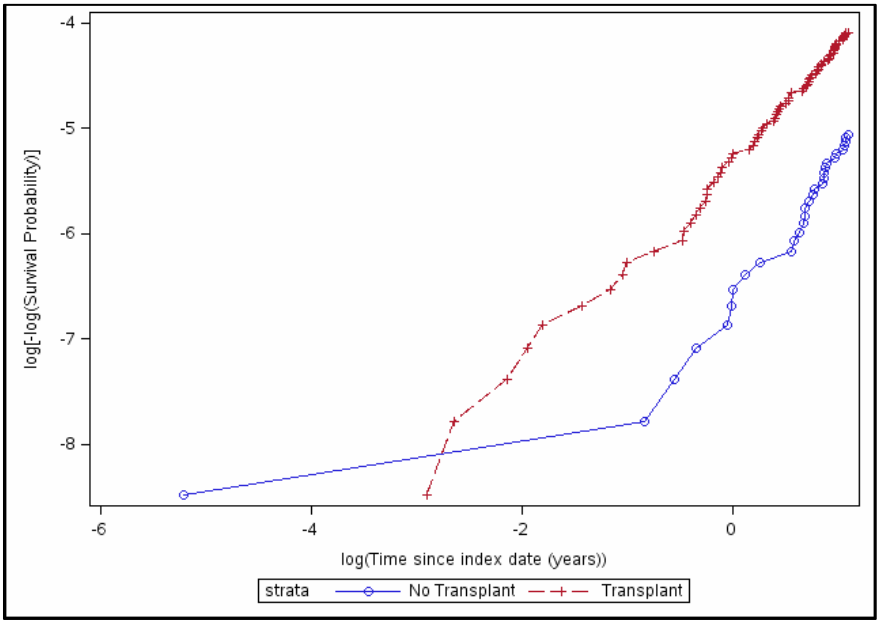


c) Non-dialysis chronic kidney disease (CKD)



Note: Although the two curves cross when assessing the proportional hazards assumption using multiple methods the p-values were all >0.05 (ASSESS method in SAS, P=0.33; time-dependent method, P=0.23; Schoenfeld residuals, P=0.29).

d) Rheumatoid arthritis



D.1.6 Competing Risk of Death

To take into account the potential competing risk of death the 3-year cumulative incidence of fracture was also calculated using the cumulative incidence function; this function estimates the cumulative probability of fracture while taking into account the competing risk of death (42, 43). Cumulative incidence estimates were nearly identical regardless of the method used. A modified version of the Cox proportional hazard analysis for cause-specific hazards proposed by Fine and Gray (1999) was used to assess competing risks (43); no substantial difference in hazard ratio estimates were found using the two methods; therefore, all results in chapter 4 were presented using standard Cox proportional hazard regression.

D.2 Additional Analyses and Results: *Rheumatoid Arthritis Reference Group*

Originally, it was proposed to include rheumatoid arthritis as a reference group to compare fracture rates with kidney transplant recipients allowing recipients to be compared to another group of individuals who are often prescribed steroids (a risk factor for fracture) (44). This reference group was not included in the main text of chapter 4. However, the methods and results of this analysis are presented below.

D.2.1 Rheumatoid Arthritis Cohort Selection

Databases were reviewed from July 1st, 1994-December 31st, 2009 for first evidence of one hospitalization for rheumatoid arthritis or three OHIP diagnostic codes for rheumatoid arthritis with at least one diagnostic code given by a rheumatologist, orthopedic surgeon, or general internist within a two year period (sensitivity 97%, 95% CI, 94-100%; specificity 85%, 95% CI 81-89%; positive predictive value 76%, 95% CI 70-82%; negative predictive value 98%, 95% CI 96-100%) (45). Individuals were excluded who met any of the following criteria: <18 years at index date, prior kidney disease, previous transplant, or selected for the kidney transplant recipient cohort. Figure D.7 describes the cohort selection for rheumatoid arthritis.

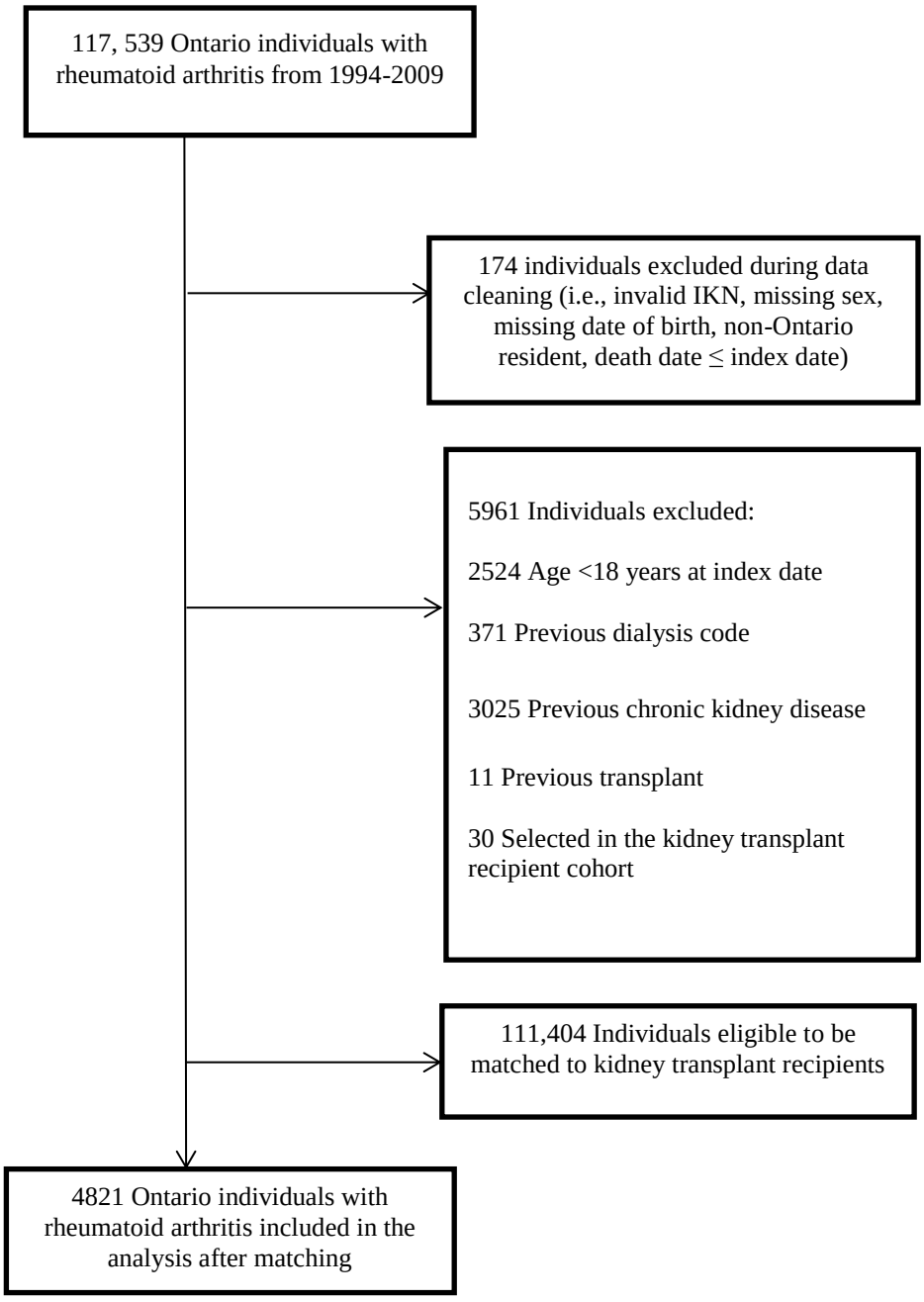


Figure D. 7. Cohort selection for rheumatoid arthritis

Abbreviation: IKN, Institute for Clinical Evaluative Sciences key number

D.2.2 Rheumatoid Arthritis Results

After matching (age [± 1 year], sex, and index date [± 1 year]) individuals with rheumatoid arthritis to recipients there were a total of 4821 individuals with rheumatoid arthritis (matched 1:1). Matching characteristics were similar between individuals with rheumatoid arthritis and kidney transplant recipients (Table D.7). Individuals with rheumatoid arthritis were followed for 14,200 person-years, 142 died (3.0%), and 30 (0.6%) sustained a non-vertebral fracture. The 3-year cumulative incidence of non-vertebral fracture was 0.6% (95% CI 0.4-0.9%) and was highest in women aged ≥ 50 years (1.6%, 95% CI 0.9-2.5%) (Table D.8). Recipients had a higher 3-year cumulative incidence of non-vertebral fracture (1.6%, 95% CI 1.3-2.0%) compared to individuals with rheumatoid arthritis (0.6, 95% CI 0.4-0.9%; P-value<0.001 by the log-rank test).

Table D. 7. Baseline characteristics of kidney transplant recipients compared to rheumatoid arthritis

Characteristic	**Kidney transplant recipients** (n=4821)	**Rheumatoid Arthritis** (n=4,821)
Age, years	50 (38-59)	50 (38-59)
Women	1781 (36.9%)	1781 (36.9%)
Era		
1994-1997	914 (18.9%)	908 (18.8%)
1998-2001	1111 (23.1%)	1130 (23.4%)
2002-2005	1182 (24.5%)	1196 (24.8%)
2006-2009	1614 (33.5%)	1587 (32.9%)
Hypertension	3572 (74.1%)	1282 (26.6%)
Diabetes	1255 (26.0%)	533 (11.1%)
Cardiovascular disease[¶]	2068 (42.9%)	551 (11.4%)
Prior non-vertebral fracture[‡]	106 (2.2%)	55 (1.1%)

Data are medians (interquartile range) or n(%).

[¶]Cardiovascular disease was defined as the presence of peripheral vascular disease, congestive heart failure, or coronary artery disease.

[‡]Prior non-vertebral fracture defined as a composite of proximal humerus, forearm, hip fractures from 1991 to cohort entry. The median number of years (interquartile range) of baseline records prior to cohort entry is as follows: kidney transplant recipients, 11.9 years (7.5-15.6); rheumatoid arthritis 11.9 years (7.6-15.5).

Table D. 8. 3-year cumulative incidence, incidence rate, and hazard ratios of non-vertebral fracture (proximal humerus, forearm, or hip) in kidney transplant recipients compared to rheumatoid arthritis

Population	3-year cumulative incidence, % (95% CI)	Incidence rate per 1000 person years (95% CI)	Hazard Ratio‡ (95% CI)	Hazard Ratio* (95% CI)
Kidney transplant recipients (n=4821)	1.6 (1.3-2.0)	5.6 (4.4-6.9)	1.00 (reference)	1.00 (reference)
Rheumatoid arthritis (n=4821)	0.6 (0.4-0.9)	2.1 (1.4-3.0)	0.4 (0.3-0.6)	0.4 (0.3-0.7)

‡ Matched on age (±1 year), sex, and index date (±1 year)
*Matched on age (±1 year), sex, and index date (±1 year) and adjusting for diabetes.

D.3 Additional Analyses and Results: *Dialysis Reference Group*

It was proposed to compare fracture rates in kidney transplant recipients to dialysis patients on the kidney transplant waitlist. However, this reference group was not included in the main text of chapter 4 because kidney transplant waitlist data was not able to be accurately obtained from the ICES data holdings. Initially, kidney transplant waitlist data contained in the CORR database was to be used in this analysis; however, upon working with the data it was apparent the data was inaccurate with 99.9% of individuals on the kidney transplant waitlist receiving a transplant; this is inaccurate as in 2012 there were 115 individuals who withdrew from the waitlist and 34 individuals who died on the waitlist (46). Moreover, approximately 44% of individuals were missing information on whether they were active on the waitlist (eligible to receive a transplant when one becomes available) versus inactive (for short period of time medical reasons or other reasons prohibit an individual from receiving a transplant) (46). Only information on patients who were on dialysis, without indication of waitlist status, could be obtained. However, individuals on dialysis are not an adequate comparator group as many individuals are too sick to be on the waitlist and would never qualify for transplantation. Therefore, previous studies comparing outcomes in dialysis patients to transplant recipients have used waitlist data in an attempt to make the health status comparable between the two groups (47, 48). For this chapter multiple strategies were used in an attempt to create a "mock waitlist". For example, the Canadian Society of

Transplantation guidelines for transplant eligibility were used in an attempt to create a group of individuals who were likely on the waitlist based on eligibility (49). However, the guidelines state that transplants are contraindicated under the following conditions: active infections, non-adherence to medication, and substance abuse (49); it would be difficult to reliably obtain information on active infections and substance abuse from ICES databases. Moreover, there would be no way to determine medication adherence. Additionally, some of the guidelines depend on severity of disease and information on severity of disease is not available in ICES (49). After consultation with several transplant nephrologists across the province it was agreed that an accurate representation of individuals on the kidney transplant waitlist could not be reliably created. However, given it is still of interest to assess whether kidney transplant recipients have a higher fracture risk compared to dialysis patients this was conducted as an additional analysis and attempts were made to control for the differences in health status between the two groups.

D.3.1 Dialysis Cohort Selection

The CORR database was reviewed from July 1st, 1994- December 31st, 2009 for first evidence of chronic dialysis. Individuals were excluded under the following conditions: 1) <18 years of age at index date, 2) previous transplant, and 3) chronic dialysis prior to the index date (to ensure incident patients). The date of cohort entry (index date) was defined as the date of the first chronic dialysis code. In an attempt to include healthier dialysis patients, for individuals whose index date was within a hospital admission the index date became the date of hospital discharge and if the individual died during hospitalization they were excluded from the cohort. Moreover, if the discharge date was after the study accrual period (December 31, 2009) then these individuals were excluded. Figure D.8 describes the cohort selection for dialysis patients.

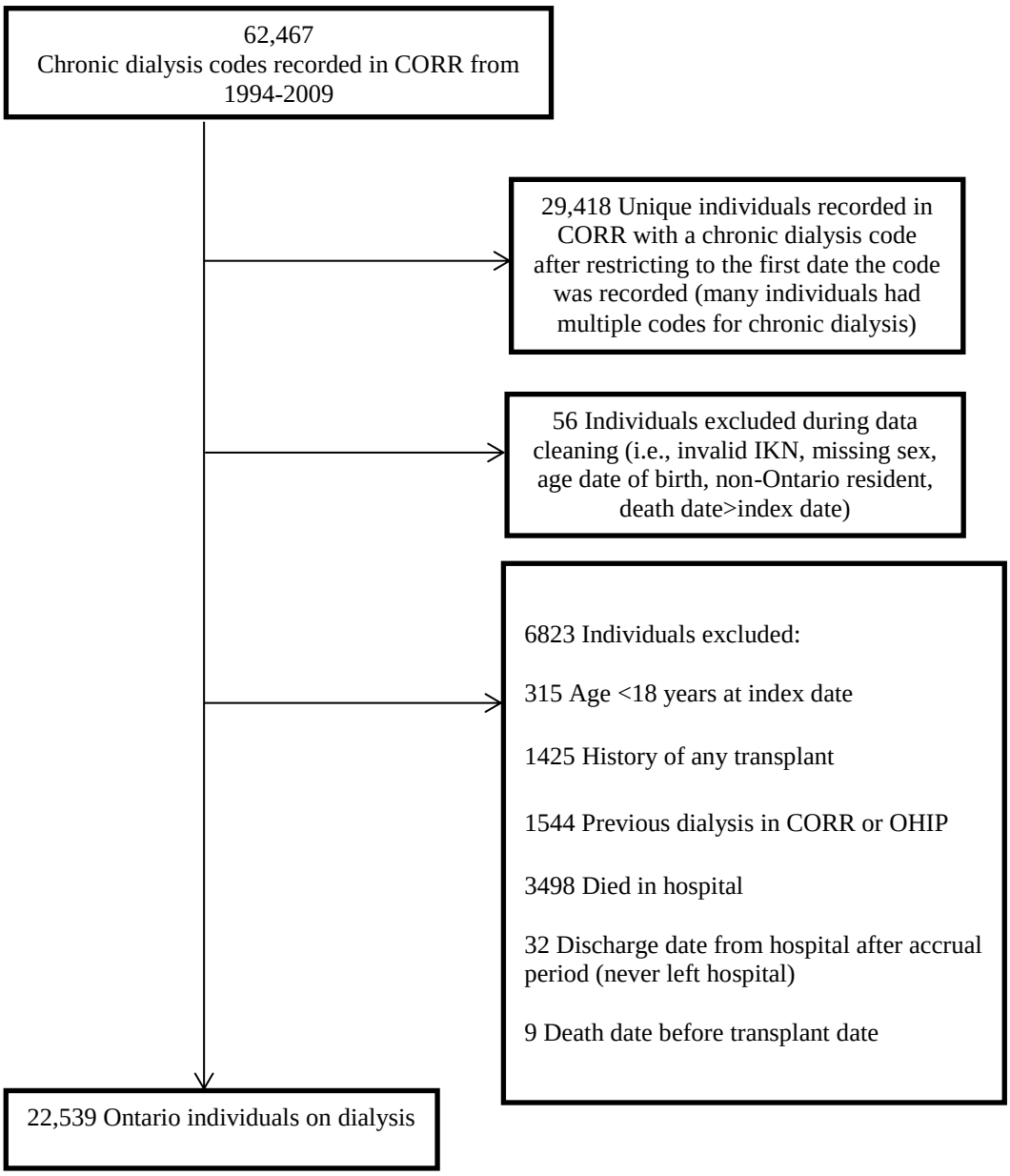


Figure D. 8. Cohort selection for dialysis population

Abbreviations: CORR, Canadian Organ Replacement Registry; IKN, Institute for Clinical Evaluative Sciences key number; OHIP, Ontario Health Insurance Plan

D.3.2 Dialysis Statistical Analysis

To assess whether kidney transplant recipients had a higher rate of non-vertebral fractures compared to dialysis patients a Cox model that allowed for time-dependent covariates, known as the Extended Cox model was used (39). This allowed for changes in treatment modality (dialysis patients receiving a transplant during follow-up) to be taken into account and modeled as a time-dependent covariate (39). Specifically, if an individual did not receive a transplant prior to being censored (censored at fracture, death, or end of follow-up [December 31, 2012]) they remained in the dialysis group; however, if an individual received a kidney transplant before being censored they were placed in the transplant group and followed forward in time for a fracture event. This method has been used in previous studies assessing changes in transplant status (50). Age at dialysis start date (continuous variable), sex, and index date (dialysis start date) were adjusted for in the Extended Cox model. In an additional analysis the Charlson comorbidity index (CCI) (continuous variable) was also adjusted for in an attempt to make the health status comparable between individuals who remained on dialysis and individuals who received a transplant. The CCI is a score that predicts 10-year mortality based on the presence of comorbid conditions (e.g. heart disease, dementia, liver disease, diabetes, tumor) (51) and has been found to be an accurate tool to assess comorbidities in kidney transplant recipients (52) and in dialysis patients (53). One of the comorbidities included in the CCI is presence of end-stage renal disease which is assigned 2 points; therefore, all individuals were given a minimum score of 2 (51); if individuals were found to have a score of 0 they were given a score of 2 and if they had a score of 1 they were given a score of 3. In an additional analysis a modified version of Cox hazard regression for cause-specific hazards proposed by Fine and Gray (1999) was used to account for the competing risk of death (43).

D.3.3 Dialysis Results

After the exclusion criteria was applied there were 22,539 adult Ontario individuals who were on dialysis with 19,075 individuals who remained on dialysis throughout the study period and 3464 individuals who received a transplant. When comparing individuals who remained on dialysis to individuals who received a transplant, individuals remaining on dialysis were older (median age 71 *vs* 48 years) and had more

comorbidities (diabetes 54.8% *vs* 33.7%; coronary artery disease 52.7% *vs* 23.3%; prior non-vertebral fracture 4.1% *vs* 1.0%) (Table D.9). Individuals on dialysis who never received a transplant were followed for 69,264 person-years (average 3.6 years), 14,640 died (76.7%), and 1645 (8.6%) sustained a non-vertebral fracture. Individuals on dialysis who eventually received a kidney transplant were followed for 33,606 person-years (average 9.7 years), 788 died (22.8%), and 150 (4.3%) sustained a non-vertebral fracture. The incidence rate of non-vertebral fracture in individuals who remained on dialysis was 23.8 fractures per 1000 person-years (95% CI % 22.6-24.9) (Table D.10). In individuals who received a transplant the incidence rate for non-vertebral fracture was 4.6 fractures per 1000 person-years (95% CI 3.8-5.2). Individuals who received a transplant during follow-up had a significantly lower fracture rate compared to individuals who remained on dialysis even after adjusting for comorbidities (HR 0.59, 95% CI 0.49-0.72) (Table D.10). Specifically, at any given time, the fracture hazard for an individual who has not received a transplant was approximately 1.7 times the hazard of fracture for an individual who already received a transplant at that time. However, it is important to remember that patients in the dialysis group could receive a transplant later on in follow up. When accounting for the competing risk of death the fracture rate was significantly higher in kidney transplant recipients compared to individuals who remained on dialysis after adjusting for relevant covariates (HR 1.61, 95% C I1.33-1.93) (Table D.10). A potential explanation for the change in direction of the hazard is that many dialysis patients died prior to being able to observe a fracture or receive a transplant. In the non-competing risk model, censoring for death leaves patients open to experiencing a fracture in follow up, suggesting that all we know is that the patient did not have a facture at the time of censoring (or death). In the Fine and Gray model, those patients who died are considered weighted so that they are not considered "censored" (43). Moreover, without accounting for the competing risk of death fracture risk was overestimated in dialysis patients. Clinically, it is plausible that kidney transplant recipients may have a higher fracture risk due to greater activity levels in recipients compared to dialysis patients (54-57). Ball *et al.* found similar results with kidney transplant recipients having a higher fracture risk in the first 630 days after transplant (adjusted relative risk 1.34, 95% CI 1.12-1.61) compared to dialysis patients who remained on the kidney transplant waitlist; after this

time period patients who continued with dialysis had a higher fracture risk (48). However, this study did not state whether they accounted for the potential competing risk of death.

Table D. 9. Baseline characteristics of dialysis patients and kidney transplant recipients[†]

	Dialysis with no transplant (n=19,075)	**Transplantation** (n=3,464)	**Total cohort** (n=22,539)
Age, years	71 (61-78)	48 (38-57)	68 (56-76)
Women	8035 (42.1%)	1232 (35.6%)	9267 (41.1%)
Era			
1994-1997	1764 (9.3%)	803 (23.2%)	2567 (11.4%)
1998-2001	5085 (26.7%)	981 (28.3%)	6066 (26.9%)
2002-2005	6084 (31.9%)	892 (25.8%)	6976 (31.0%)
2006-2009	6142 (32.2%)	788 (22.7%)	6930 (30.7%)
Diabetes	10,444 (54.8%)	1167 (33.7%)	11,615 (51.5%)
Hypertension	15,911 (83.4%)	2712 (78.3%)	18,623 (82.6%)
Peripheral vascular disease	1899 (10.0%)	146 (4.2%)	2045 (9.1%)
Congestive heart failure	8485 (44.5%)	350 (10.1%)	8835 (39.2%)
Coronary artery disease	10,057 (52.7%)	806 (23.3%)	10,863 (48.2%)
Fracture (hip, forearm, or proximal humerus) from 1991 to cohort entry[¥]	783 (4.1%)	36 (1.0%)	819 (3.6%)
Race			
Caucasian	13091 (72.9%)	2467 (71.2%)	16,373 (72.6%)
Black	777 (4.1%)	215 (6.2%)	994 (4.4%)
Asian	1097 (5.8%)	214 (6.2%)	1311 (5.8%)
Other[‡]	1818 (9.5%)	373 (10.8%)	2193 (9.7%)
Unknown	1482 (7.8%)	195 (5.6%)	1677 (7.4%)

Cause of end-stage renal disease			
Glomerulonephritis	1994 (10.5%)	1086 (31.4%)	3080 (13.7%)
Cystic kidney disease	554 (2.9%)	436 (2.6%)	990 (4.4%)
Diabetes	7347 (38.5%)	874 (25.2%)	8221(36.5%)
Renal vascular disease	4441 (23.3%)	322 (9.3%)	4763 (21.1%)
Other	2467 (12.9%)	429 (12.4%)	2896 (12.9%)
Unknown/missing	2272 (11.9%)	317 (9.2%)	2589 (11.5%)
Pre-transplant dialysis			
Hemodialysis	15,025 (78.8%)	2235 (64.5%)	17,260 (76.6%)
Peritoneal dialysis	4050 (21.2%)	1229 (35.5%)	5279 (23.4%)
Dialysis vintage		2.8 (1.4- 4.9)	
Charlson Comorbidity Index	3 (2-5)	2 (2-3)	3 (2-4)

Data are median (interquartile range) or n(%)
† Baseline characteristics were determined looking backwards in time from the dialysis start date. For example, age is shown as age placed on dialysis for both groups.
¥The median number of years (interquartile range) of baseline records prior to cohort entry (defined as date placed on dialysis) is as follows: dialysis patients with no transplant, 12.3 years (9.0-15.4); transplant, 10.2 years (6.8-14.2); total cohort, 12.0 years (8.6-15.2).
‡ Other was defined as a composite of Indian Sub-Continent, Pacific Islander, Aboriginal, Mid East/Arabian, Latin American, Other/Multiracial.

Table D. 10. 3-year cumulative incidence, incidence rate, and hazard ratio of non-vertebral fracture (hip, forearm, or proximal humerus) in kidney transplant recipients compared to dialysis patients

	Dialysis (n=19,075)	**Transplantation** (n=3464)
Cumulative incidence¥, % (95% CI)	11.1 (10.0-12.2)	7.3 (6.1-8.7)
Incidence rate per 1000 person years (95% CI)	23.6 (22.4-24.7)	4.6 (3.8-5.2)
Hazard ratios not accounting for the competing risk of death		
Hazard ratio (95% CI)*	1.00	0.29 (0.24-0.35)
Hazard ratio¶ (95% CI)	1.00	0.57 (0.47-0.69)
Hazard ratio‡ (95% CI)	1.00	0.59 (0.49-0.72)
Hazard ratios accounting for the competing risk of death		
Hazard ratio	1.00	1.00

(95% CI)*		(0.85-1.18)
Hazard ratio¶	1.00	1.61
(95% CI)		(1.33-1.93)
Hazard ratio‡	1.00	1.57
(95% CI)		(1.30-1.89)

¥Cumulative incidence was calculated using the cumulative incidence function was takes into account the competing risk of death.
*Hazard ratio was unadjusted.
¶Hazard ratio was adjusted for age placed on dialysis, sex, and date placed on dialysis.
‡ Hazard ratio was adjusted for age placed on dialysis, sex, date placed on dialysis, and Charlson comorbidity index at the date placed on dialysis.

It is important to note that these results should be interpreted with caution. As discussed in section D.3, information on dialysis patients who were on the kidney transplant waitlist was not able to be obtained; therefore, many individuals in the dialysis patient group who never transplanted may have been too sick to be eligible for a transplant, potentially impacting our findings. For example, Stehman-Breen *et al.,* found that dialysis patients had a higher fracture risk compared to kidney transplant recipients (58); however, the authors noted that fracture risk in recipients may have been underestimated as they included all dialysis patients, not just individuals on the waitlist; therefore dialysis patients would be less healthy compared to individuals on transplant waitlist (48).

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APPENDIX E: Chapter 5 Details

E.1 Detailed Methods

E.1.1 Data Sources

A description of the databases and codes used to determine risk factors for fracture are shown in Table E.1.

Table E. 1. Database codes used to determine risk factors for fracture

Variable	ICD -9	ICD-10	OHIP	Other
Age				RPDB
Sex				RPDB
Prior Major Fracture*	*Codes and validity of codes described in Appendix D*			
Prior Fall	*Codes described in Appendix D*			
Race£				CORR
Diabetes not as cause of ESRDβ	250	E10, E11,E13, E14	**DX:** 250 **Fee code:** K045, K046 ,K029, K030,Q040	
Donor Type				CORR
Dialysis Modality				CORR
End-stage Renal Disease Cause∞				CORR
Length of time on dialysis prior to transplant				CORR
Donor age/ donor sex				CORR

Abbreviations: CORR= Canadian Organ Replacement Registry; Dx, diagnostic code; ICD=International Classification of Diseases; OHIP=Ontario Health Insurance Plan; RPDB=Registered Persons Database

*Previous major fracture defined as a composite of proximal humerus, forearm, clinical vertebral, or hip fracture occurring from 1991 to cohort entry (date of transplant).

£ CORR validation study found agreement between CORR and the medical chart, assessed using the κ statistic, for race was 58%; many of the differences occurred when race was recorded in CORR but race was recorded as unknown in the medical chart. *Source: Moist LM, Richards HA, Miskulin D, Lok CE, Yeates K, Garg AX, et al. A validation study of the Canadian Organ Replacement Register. Clin J Am Soc Nephrol. 2011;6:813-818.*

β Defined diabetes as one hospital admission code for diabetes or one diagnosis code for OHIP or one OHIP fee code for diabetes in the 5 years prior to the transplant date.

∞ CORR validation study found that the agreement, assessed using the κ statistic, between CORR and medical chart review for the primary cause of ESRD was: glomerulonephritis (82.8, 95% CI 74.9-90.7); cystic kidney disease (89.1, 95% CI 77.0-100.0); hypertension/other vascular (66.7, 95% CI 56.5-77.0); diabetes (78.3, 95% CI 70.8-85.8); etiology uncertain or unknown (46.6, 95% CI 35.9-57.4); other (64.2, 95% CI 48.6-79.8). *Source: Moist LM, Richards HA, Miskulin D, Lok CE, Yeates K, Garg AX, et al. A validation study of the Canadian Organ Replacement Register. Clin J Am Soc Nephrol. 2011;6:813-818.*

E.1.2 Missing Data

Originally several additional risk factors that have been found to be associated with fractures in the non-transplant population were going to be assessed, including: body mass index (BMI), rheumatoid arthritis, smoking (chronic obstructive pulmonary disease used as a proxy), and high alcohol intake (alcoholism used as a proxy). However, there were several issues with including these variables. First, BMI had a considerable amount of missingness (76.2% missing for height and 80.9% missing for weight). Moreover, there were a large number of implausible values (e.g. BMI > 50 kg/m^2). Additionally, there was no date recorded for when the height and weight measurements occurred with many measurements occurring during dialysis. Therefore, the BMI could have changed considerably if the measurement was taken several years prior to transplant. Changes in BMI are common in ESRD patients due to changes in nutritional status and wasting (1). For example, one study found that approximately 16% of ESRD patients had a weight change ≥ 5% over a three month time frame (2). Regarding smoking, rheumatoid arthritis, and high alcohol intake there were too few individuals to assess with ≤ 5 individuals with these comorbidities experiencing a fracture event. Several transplant specific risk factors were also originally going to be assessed but were not due to the large amount of missingness, including: number of human leukocyte antigen mismatches (missing 41.8%) and cold ischemic time (missing 48.7%).

As described in chapter 5 missing data for categorical variables was handled by randomly assigning values based on the distribution of variables that were not missing (single imputation). For the cause of ESRD, prior to randomly assigning values, we looked for evidence of a diabetes diagnosis code or fee code in OHIP or a diagnosis code in CIHI in the five years prior to the transplant date; if there was evidence of diabetes the cause of ESRD was coded as diabetes. For donor age (continuous variable) the median age was used to supplement missing values. Table E.2 demonstrates the pattern of missingness before and after handling the missing values.

Table E. 2. Distribution of missing data before and after handling missing data

Variable	Before (n=2723)	After (n=2723)
Cause of end-stage renal disease		
Glomerulonephritis	891 (32.7%)	990 (36.4%)
Cystic	365 (13.4%)	416 (15.3%)
Diabetes*	525 (19.3%)	597 (21.9%)
Renal Vascular	269 (9.9%)	317 (11.6%)
Other	358 (13.2%)	403 (14.8%)
Missing/unknown	315 (11.6%)	0
Race		
Caucasian	1748 (64.2%)	1948 (71.5%)
Asian	184 (6.8%)	216 (7.9%)
Black	180 (6.6%)	205 (7.5%)
Other	320 (11.8%)	354 (13.0%)
Unknown	291 (10.7%)	0
Donor type		
Living	1133 (43.9%)	1195 (43.9%)
Deceased	1449 (56.1%)	1528 (56.1%)
Missing	21 (0.77%)	0
Donor age		
Median age	46 (36-54)	46 (36-54)
Missing	60 (2.2)	0
Donor Sex		
Female	1350 (49.6%)	1363 (50.1%)
Male	1349 (49.5%)	1360 (49.9%)
Missing	24 (0.88%)	0

Data are median (interquartile range) or n(%).

*Initially there were 501 recipients with diabetes as their primary cause of ESRD; however, after looking for previous evidence of diabetes there were 525 individuals with diabetes as their primary cause of ESRD. The primary cause of ESRD was then imputed based on the distribution of ESRD cause.

E.1.3 Proportional Hazards

To ensure that the proportional hazard assumption was met it was assessed using multiple methods. First, a statistical test was used to assess the proportional hazard assumption for both continuous and categorical variables; if the p-value was <0.05 then the proportional hazard was considered violated. Specifically, the ASSESS option in PROC PHREG (SAS) was used which plots the follow-up time against the observed

score process (3,4). Second, for categorical variables, a graphical approach (log-log survival curves) was also used to visually assess violations of the proportional hazard assumption (5). If the log-log survival curves did not appear parallel (e.g. lines cross-over, converged or diverged) then the Extend Cox model would be used (5). Third, for continuous variables (e.g. age) the proportional hazard assumption was assessed using the time-dependent variable approach which includes an interaction term comprised of the time-independent variable and time (e.g., age*log[time]); a p-value <0.05 was considered to violate the proportional hazard assumption (5). There were no violations of the proportional hazards assumption.

E.1.4 Departures from Linearity

To ensure there were no departures from linearity (e.g., threshold, quadratic) martingale residuals were assessed for each continuous risk factor (6), as implemented in the PROC PHREG ASSESS statement (SAS) which plots the cumulative martingale residuals against each continuous covariate; a p-value <0.05 was used as criteria for violation of linearity (6,7). To visually assess departures from linearity a martingale residual plot was created using the SAS command PROC PHREG which did not include the exposure variable for which the functional form was being assessed (8,9). A lowess line was then fit through the martingale residuals (8).

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APPENDIX F: ICES Privacy Impact Assessment Approval for Chapters 4, 5, and 6

INSTITUTE FOR CLINICAL EVALUATIVE SCIENCES
PROJECT-SPECIFIC PRIVACY IMPACT ASSESSMENT FORM
(FOR ALL ICES PROJECTS)

A. PROJECT TITLE
Fracture Risk in Adult Kidney Transplant Recipients

ICES Privacy Impact Assessment Form — Version 2.1 June 17, 2013

[redacted] — Signature of Investigator / Scientist — 03/09/13 — Date (dd/mm/yy)

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[redacted] — Signature of Site Director, if applicable — 03/09/13 — Date (dd/mm/yy)

[redacted] — CEO Approval — Sept 06, 2013 — Date (dd/mm/yy)

[redacted] — Privacy Office Approval — Aug 29, 2013 — Date (dd/mm/yy)

This section is for the use of Ontario Cancer Registry

Signature — Date (dd/mm/yy)

on behalf of
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☐ Cancer Research Program

***Reference:**

For more information, please refer to the *Personal Health Information Protection Act* (PHIPA) which is found at: http://www.e-laws.gov.on.ca/html/statutes/english/elaws_statutes_04p03_e.htm

The Regulation to the Act (Reg. 329/04) can be found at: http://www.e-laws.gov.on.ca/html/regs/english/elaws_regs_040329_e.htm

APPENDIX G: Copyright Releases

G.1 Copyright Information for Figure 2.2

Title:	The three-year incidence of fracture in chronic kidney disease
Author:	Kyla L Naylor, Eric McArthur, William D Leslie, Lisa-Ann Fraser, Sophie A Jamal et al.
Publication:	Kidney International
Publisher:	Nature Publishing Group
Date:	Jan 15, 2014

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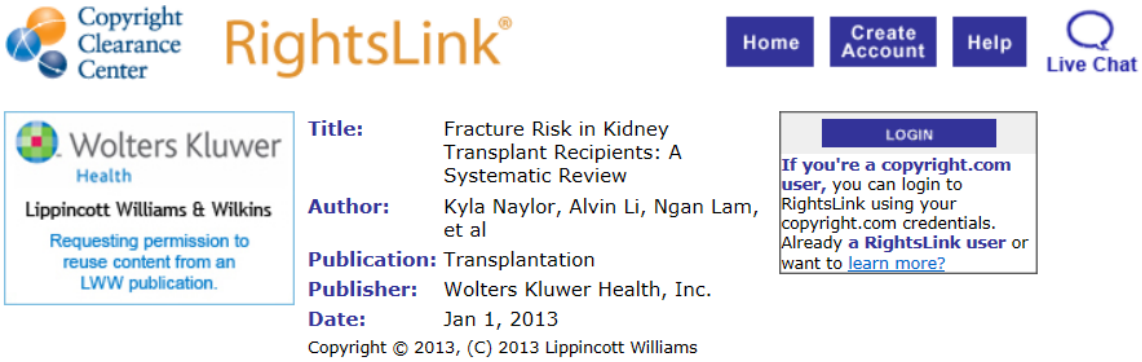
G.2 Copyright Information for Chapters 2 (sections 2.5 and 2.6), 4, and Appendix A



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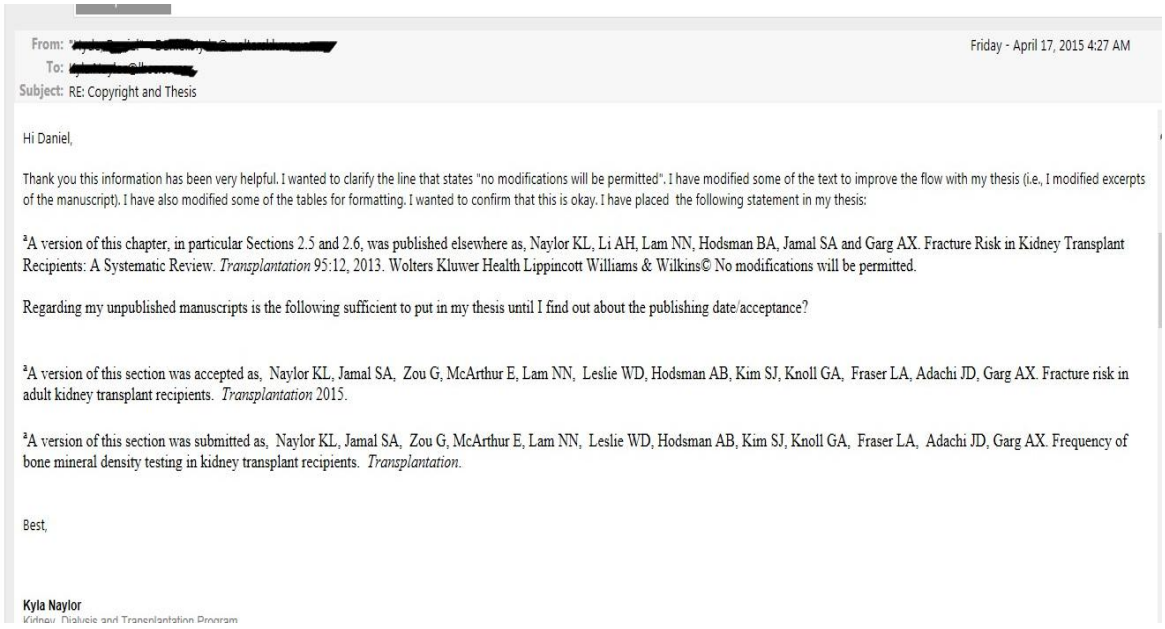

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Thank you this information has been very helpful. I wanted to clarify the line that states "no modifications will be permitted". I have modified some of the text to improve the flow with my thesis (i.e., I modified excerpts of the manuscript). I have also modified some of the tables for formatting. I wanted to confirm that this is okay. I have placed the following statement in my thesis:

[3]A version of this chapter, in particular Sections 2.5 and 2.6, was published elsewhere as, Naylor KL, Li AH, Lam NN, Hodsman BA, Jamal SA and Garg AX. Fracture Risk in Kidney Transplant Recipients: A Systematic Review. *Transplantation* 95:12, 2013. Wolters Kluwer Health Lippincott Williams & Wilkins© No modifications will be permitted.

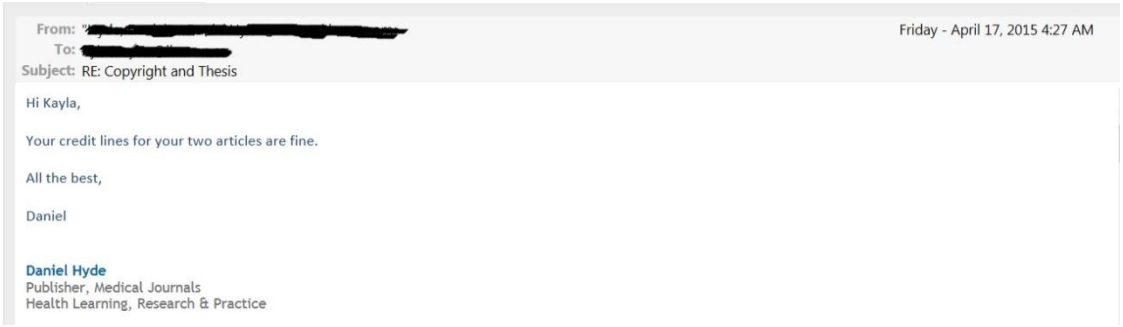
Regarding my unpublished manuscripts is the following sufficient to put in my thesis until I find out about the publishing date/acceptance?

[3]A version of this section was accepted as, Naylor KL, Jamal SA, Zou G, McArthur E, Lam NN, Leslie WD, Hodsman AB, Kim SJ, Knoll GA, Fraser LA, Adachi JD, Garg AX. Fracture risk in adult kidney transplant recipients. *Transplantation* 2015.

[3]A version of this section was submitted as, Naylor KL, Jamal SA, Zou G, McArthur E, Lam NN, Leslie WD, Hodsman AB, Kim SJ, Knoll GA, Fraser LA, Adachi JD, Garg AX. Frequency of bone mineral density testing in kidney transplant recipients. *Transplantation*.

Best,

Kyla Naylor
Kidney, Dialysis and Transplantation Program



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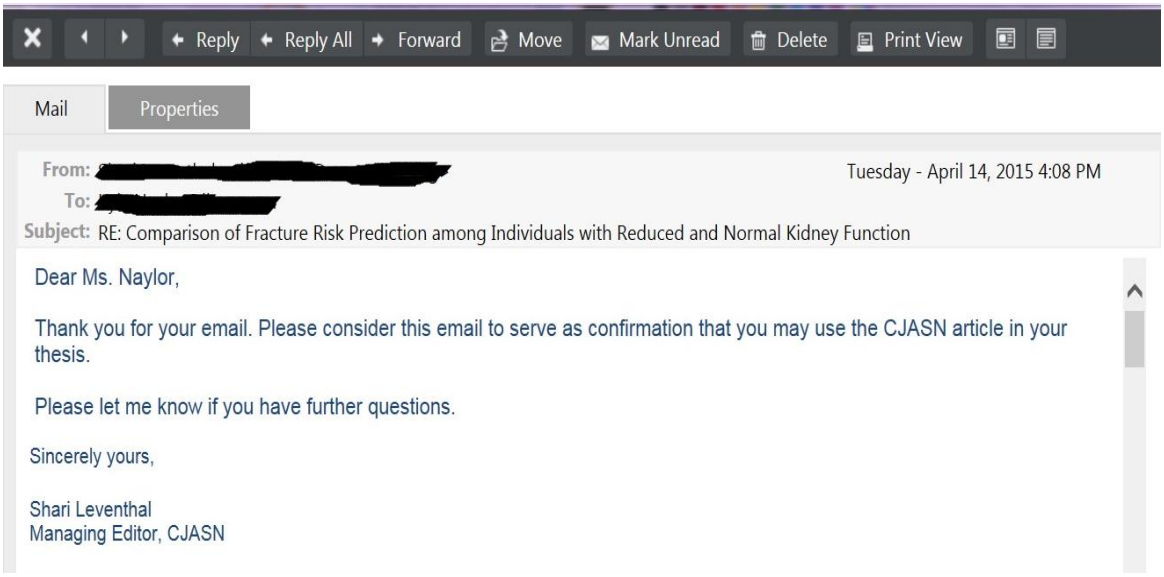
G.3 Copyright Information for Chapter 3



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From: [redacted] Tuesday - April 14, 2015 4:08 PM

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Subject: RE: Comparison of Fracture Risk Prediction among Individuals with Reduced and Normal Kidney Function

Dear Ms. Naylor,

Thank you for your email. Please consider this email to serve as confirmation that you may use the CJASN article in your thesis.

Please let me know if you have further questions.

Sincerely yours,

Shari Leventhal
Managing Editor, CJASN

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	Naylor KL, Jamal SA, Zou GY *et al.,*. Fracture risk in adult kidney transplant recipients. *Transplantation* 2015. *[Epub ahead of print]*. Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WD, Fraser LA, Adachi JD, Morin S, Goltzman D, Lentle B, Jackson SA, Josse RG, Jamal SA. Comparison of fracture risk prediction among individuals with reduced and normal kidney. *CJASN* 2015; 10: 646-653. Sood MM, Garg AX, Bota SE, Marisiddappa L, McArthur E, Naylor KL, Kapral MK, Kim J, Lam NN, Molnar AO, Harel Z, Perl J, Knoll GA. Risk of major hemorrhage after kidney transplantation. *American Journal of Nephrology* 2015*;*41:73-80. Fraser LA, Shariff SZ, McArthur E, Naylor KL, Garg AX. Calcium channel blocker-clarithromycin drug interaction did not increase the risk of non-vertebral fracture. A population-based study. *Annals of Pharmacotherapy* 2015; 49: 185-188. Fraser LA, Liu K, Naylor KL, Hwang YJ, Dixon SN, Shariff SZ, Garg AX. Falls and Fractures with Atypical Antipsychotic Medication Use in the Elderly: A Population-Based Cohort Study. *JAMA Internal Medicine* 2015; 175: 450-452. Li AH, Thomas SM, Farag A, Duffet M, Garg AX, Naylor KL. The Reporting Quality of Surveys: A Methodological Review of Nephrology Journals. *CJASN* 2014;9:2089-2094. Naylor KL, Garg AX. Bone Health in Living Kidney Donors. *Current Opinion in Urology* 2014; 24:624-628. Naylor KL, Garg AX, Hodsman AB, Rush D, Leslie WD. Long-term Changes in Bone Mineral Density in Kidney Transplant Recipients. *Transplantation* 2014; 86: 810-818. Naylor KL, Leslie WD, Hodsman AB, Rush D, Garg AX. FRAX Predicts Fracture Risk in Adult Kidney Transplant Recipients. *Transplantation* 2014; 97:940-945. Naylor KL, McArthur E, Leslie WD, Fraser LA, Jamal SA, Cadarette SM, Pouget JB, Lok CE, Hodsman AB, Adachi JD, Garg AX. 3-year Incidence of Non-vertebral Fracture in Chronic Kidney Disease. *Kidney International* 2014; 86:810-818.

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Abstracts and Presentations	Naylor K, Jamal S, Zou G, McArthur E, Lam N, Leslie W, Hodsman A, Kim J, Knoll G, Fraser L-A, Adachi J, Garg A. Fracture Incidence in Adult Kidney Transplant Recipients. *Am J Transplant* 2015; 15 (suppl 3). Naylor KL, Garg AX, Hodsman AB, Rush D, Leslie WD. Long-term Changes in Bone Mineral Density in Kidney Transplant Recipients. *J Bone Miner Res* 2014; 29 (Suppl 1). Naylor KL, Garg AX, Zou G, Langsetmo L, Leslie WD, Fraser LA, Adachi JD, Morin S, Goltzman D, Lentle B, Jackson SA, Josse RG, Jamal SA. The Effect of Kidney Function on the Performance of FRAX: A Population-based report from CaMos. *J Bone Miner Res* 2014; 29 (Suppl 1). Lam N, Naylor K, Shariff S, McArthur E, Knoll G, Kim S, Garg A. Secular Trends in Cardiovascular Disease Among Kidney Transplant Recipients. *American Journal of Transplantation* 2014;14:1-905. Naylor KL**,** McArthur E, Leslie WD, Fraser LA, Jamal SA, Cadarette SM, Pouget JB, Lok CE, Hodsman AB, Adachi JD, Garg AX. 3-year Incidence of Fragility Fracture in Chronic Kidney Disease. *J Am Soc Nephrol* 2013; 24: 147A. Naylor KL, Leslie WD, Hodsman AB, Rush D, Garg AX. FRAX Predicts Fracture Risk in Adult Kidney Transplant Recipients. *Journal of Bone and Mineral Research* 2013; (Sup 1). Naylor KL, L Li, AH, Lam NN, Hodsman BA, Jamal SA and Garg AX. Fracture Risk in Kidney Transplant Recipients: A Systematic Review. *American Journal of Transplantation* 2013; 13: 4-589.

	Garg AX, Pouget J, Young A, Huang A, Boudville N, Hodsman A, Adachi JD, Leslie WD, Cadarette SM, Lok CE, Monroy-Cuadros M, Prasad GVR, Thomas SM, Naylor K, Treleaven D Fracture risk in living kidney donors: A matched cohort study. *American Journal of Transplantation* 2012; 12: 27-542. Poster presentation, "Fracture incidence in adult kidney transplant recipients", American Transplant Congress, Philadelphia, Pennsylvania, 2015 Oral presentation, "Donation Transplant Research Interest Group", Institute for Clinical Evaluative Sciences Provincial Kidney, Dialysis and Transplantation Meeting, Toronto, Ontario, 2014 Oral presentation, "Fracture and dual energy x-ray absorptiometry in kidney transplant recipients", Research Partnerships for Better Transplantation, Toronto, Ontario, 2014 Oral presentation, "The Reporting Quality of Surveys: A Methodological Review of Nephrology Journals", London Health Sciences Centre Graduate, Fellows and Researcher Rounds, London, Ontario, 2014 Oral presentation, "Fracture Risk in Adult Kidney Transplant Recipients, Lawson Research Institute Talks on Fridays, London, Ontario, 2014 Oral presentation, "Fracture Risk in Adult Kidney Transplant Recipients", ICES Scientific Rounds, London, Ontario, 2014 Poster presentation, "Long-term Changes in Bone Mineral Density in Kidney Transplant Recipients", American Society of Bone Mineral Research Annual Meeting, Houston, Texas, 2014 Poster presentation, "The Effect of Kidney Function on Fracture Risk Prediction: A Population-based report from CaMos", American Society of Bone Mineral Research Annual Meeting, Houston, Texas, 2014 Oral presentation, "The Effect of Kidney Function on Fracture Risk Prediction: A Population-based report from CaMos", Renal Research Day, London, Ontario, 2014 Poster presentation, "3-year Incidence of Fragility Fracture in Chronic Kidney Disease", London Health Sciences Research

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Extracurricular	Reviewer: Osteoporosis International, European Journal of

Service	Internal Medicine, American Journal of Kidney Diseases, Transplantation. American Journal of Transplantation Reviewer, National University Scholarship Committee, 2013 Abstract Reviewer, Canadian Society for Epidemiology and Biostatistics Conference, 2013 Co-Chair, Retiring with Strong Minds, 2012-2014 Executive Member, Osteoporosis Canada's Executive Committee (London Chapter), 2012-2014