METHODOLOGICAL ISSUES FOR OSTEOPOROSIS

RB HOPKINS

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METHODOLOGICAL ISSUES IN THE STUDY OF OSTEOPOROSIS

By

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ABSTRACT

Background and Objectives: There are methodological challenges with research in osteoporosis. The first is to predict the lifetime risk of hip fracture incorporating trends in the rates of hip fracture and mortality. The second is to identify optimum pharmacotherapy to reduce fractures in the absence of active-comparator trials. A third is to isolate the costs for incident and prevalent fractures. The objective of this thesis is to investigate these issues and to provide recommendations for future research.

Methods:

Project 1: From national administrative data, we estimated the lifetime risk of hip fracture for age 50 years to end of life using life tables. We projected lifetime risk incorporating national trends in hip fracture and mortality from Poisson regressions.

Project 2: A literature review identified randomized placebo-controlled trials with nine drugs for post-menopausal women. Odds ratios for fractures were derived using Bayesian and classical approaches. The most efficacious drug had the highest posterior odds ratio or the highest effect size.

Project 3: From provincial administrative data from Manitoba, cases were selectively matched to non-fracture controls. Excess costs relative to controls were estimated assuming normality and in the absence of estimates of variance the mean was set equal to the standard deviation, and these assumptions were tested in sensitivity analyses.

Results and Conclusions:

Project 1: For women and men, the crude lifetime risks of hip fracture was 12.1% and 4.6% respectively, and lower after incorporating trends, 8.9% and 6.7%. The risk is expected to continue to fall for both women and men.

Project 2: Three drugs, zoledronic acid, teriparatide and denosumab, had the highest odds of reducing fractures and the largest effect sizes. Estimates were consistent between Bayesian and classical approaches.

Project 3: All incident fracture types and most prevalent fractures had significant excess costs, and the results were robust. Excluding prevalent fractures underestimates the cost of illness of fractures.

PREFACE

This thesis is a “sandwich thesis”, which combines three individual projects prepared for publication in peer-reviewed journals. The following are the contributions of R. Hopkins in all of the papers included in the dissertation: developing the research ideas and research questions; developing the analysis plans; conducting all statistical analysis; writing all of the manuscripts; submitting the manuscripts; and responding to reviewers’ comments. The work of this thesis was conducted between September 2008 and February 2012.

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List of Abbreviations

BMD	Bone Mineral Density
CADTH	Canadian Agency for Drugs and Technologies in Health
CCI	Canadian Classification of Health Interventions
CI	Confidence Interval
CIHI-DAD	Canadian Institute for Health Information –Discharge Abstract Database
Cr I	Credibility Interval
DTC	Direct Treatment Comparison
FRAX	Fracture Assessment Tool
ICD-CA	International Classification of Diseases- Canada
ITC	Indirect treatment comparison
NNT	Number Needed to Treat
NR	Not reported
OR	Odds ratio
RPCT	Randomized Placebo-Controlled Trials
SD	Standard Deviation
WinBUGS	Bayesian inference Using Gibbs Sampling for Windows

CHAPTER 1

Introduction of the thesis

Osteoporosis is defined as having a Bone Mineral Density (BMD) that is 2.5 standard deviations below peak bone mineral density [1]. Peak BMD occurs in early stages of young adulthood and often peaks about the age of 30 years for both men and women. Afterwards, both men and women experience a progressive loss of bone mass with age. For women there is a further acceleration of bone mass loss of 20 to 30% on average occurring 3 to 6 years after menopause.

Osteoporosis affects over 200 million people worldwide including 40% of women aged 80 years and over, and over 65% of women aged 90 years and over [2]. The current estimate of the prevalence is 26% for women and 7% for men age 50+ in Canada [3]. With increased longevity, the probability of developing osteoporosis over a lifetime has also increased. Specifically, the number of cases with osteoporosis will escalate rapidly as the Canadian population over age 50 years is estimated to increase by 6.2% per year until the year 2041 [4].

The major concern with low BMD is the high risk of fractures to vertebral and non-vertebral bones such as the hip or the wrist. Vertebral fractures are identified by clinical assessment through decreased patient height (i.e., stooped posture) or with

compressed spinal vertebra that can be radiologically assessed [5]. A hip fracture requires surgical repair and often requires extended hospital stay and rehabilitation therapy, and is associated with increased risk of death [6]. Hip fractures pose a serious morbidity and mortality burden on individuals and society. In the year 2000, there were over 9 million new fractures worldwide, of which 1.6 million were hip fractures [7]. There were over 28,000 hospitalizations for hip fractures in Canada in 2007 [8].

To address the risk of fractures due to osteoporosis, drugs have been introduced to reduce the rate of bone loss and to increase the strength of the bones. The first bisphosphonate available in Canada was etidronate in 1995 followed by alendronate in 1998. Current drugs include the bisphosphonates (alendronate, etidronate, risedronate or ibandronate), Selective Estrogen Receptor Modulators (raloxifene) and anabolic agents (teriparatide). All of these have shown to be effective in reducing the rate of fractures relative to placebo [9]. Recent additions to pharmacotherapy for osteoporosis include denosumab, strontium and zoledronic acid although the relative efficacy versus the previous five drugs is unknown.

To appreciate the importance of reducing the rate of fractures, a robust estimate of the direct health care costs of fractures is required. In Europe the direct cost of new fractures was €31.7 billion [10] while in United States the direct cost was 25 billion US $ [11]. In Canada in 2008, the acute care cost of incident fractures was 1.3 billion CAN$ [12]. The additional cost of long term care for patients with a history of fractures adds another 1.6 billion CAN$ [12]. However, there are costs other than long term care that

can be attributed to fractures and it would be important to isolate these costs for prevalent fractures.

Clinical and Methodological Issues for Osteoporosis

There are methodological challenges with research in osteoporosis. The first is to assess if there has been a change in the unadjusted lifetime risk of hip fractures. In addition, it would be important to predict the lifetime risk of hip fracture adjusting for trends in the rates of hip fracture and mortality. The second challenge is to identify optimum pharmacotherapy to reduce fractures in the absence of active-comparator trials. A third challenge is to isolate the costs for incident and prevalent fractures. The objective of this thesis is to investigate these issues and to provide recommendations for future research.

Issue 1: Estimating the lifetime risk of hip fracture

For public providers of health care, being aware of the health care burden and knowing the return on investment through adopting cost effective strategies that reduce hip fractures would be important. For this type of analysis, lifetime fracture estimates of risk are required to build an economic model for evaluating policy trade-offs [13]. One method to estimate the lifetime risk of fracture is to longitudinally track a cohort over their lifetimes and count the number of individuals with a hip fracture. However, this method would not represent the projected future risk of hip fracture, as rates of hip fracture and rates of mortality by age may have changed over the life of the cohort.

Alternatively, one could simulate a life profile using the prevalence-based life table method. This type of analysis has been conducted in 1989 for Canada which estimated the lifetime risk of hip fracture to 14.0% for women and 5.2% for men [14], but to our knowledge this estimate has not been updated.

The problem is that an unadjusted life table incorporates the rates of mortality and hip fracture at each age and sex assuming them to be constant. However, the age-sex rates of hip fractures in Canada have been changing over time [15], and have been declining at a faster rate in recent years. In addition, the rates of mortality and thus exposure to hip fractures have also been decreasing over time as life expectancy has been almost constantly increasing every year in this century. To provide an accurate prediction of the future risk profile for hip fracture, the trends in the rates of hip fracture and the trends in mortality should be incorporated.

Issue 2- Optimal Pharmacotherapy for reducing the risk of fractures

To reduce the risk of fractures due to osteoporosis, drugs have been introduced to reduce the rate of bone loss and to increase the strength of the bones. Accordingly, it would be clinically important to know an estimate of the relative treatment efficacy or ranking of the most efficacious drugs. A major gap in the evidence to identify the most efficacious drugs is the lack of randomized active-controlled trials, i.e., direct treatment comparison (DTC) evidence [9].

DTC evidence for osteoporosis is absent because such later stage III trials are more complex, expensive, and require larger sample sizes than earlier phase II randomized placebo-controlled trials (RPCT) [16]. Meanwhile, osteoporosis drugs have been approved for use or listed under reimbursement formularies based on RPCT evidence. Indirect treatment comparisons (ITC) might be a promising technique that allows the synthesis of available RPCT evidence to make a suggestion on the effect of DTC [17]. Nine drugs are currently available in Canada, European or the United States for use with osteoporosis. The nine drugs include five drugs (zoledronic acid, alendronate, ibandronate, and risedronate) in the recent ITC analysis plus four more drugs that were not previously included (denosumab, raloxifene, strontium, and teriparatide).

Issue 3 – Cost of Incident and Prevalent Fractures

Estimating the cost of illness is not straightforward and there are various costing and methodological assumptions that produce different results. For example, the extent of attribution of a fracture to health care costs is uncertain. While the acute care admission for a fracture is logically attributable to the fracture, the attribution of post-fracture care is not as straightforward [18]. One possibility is to use adjudication to identify the attribution of costs [19]. However, without the certainty of attribution to one disease, cost of illness studies may be biased [20].

To reduce the possible bias due to inexact attribution of resource utilization and costs for osteoporosis and fractures, matching methods have been used. One type of

matching method is pre-post designs where the patient serves as their own control. A limitation with using pre-post incremental costs is that the pre and post period for costing must be specified, such as one year. The long-term costs of fractures such as the need for permanent assistance in daily living is not captured [12]. A different matching method is to estimate the excess cost of a patient with a fracture versus a patient without a fracture [21]. However, this method also limits the estimates of cost to a defined period such as the first year following a fracture.

An important gap in the estimation of the cost of fractures and osteoporosis with matching methods is the exclusion of multi-year costs after a fracture. Studies that look only at the first year after an incident fracture exclude the possibility of costs for prolonged care which may be fracture related. In addition, cost of illness studies of osteoporosis may also exclude the costs of preventive therapy in patients who have not incurred a fracture.

Outline of the Thesis

This thesis is a sandwich thesis of three papers mapped to each of the Issues (1-3) described above. The three papers are separated into different chapters beginning with Chapter 2.

In Chapter 2, we address the question ‘what is the current expected lifetime risk of hip fracture for men and women in Canada?’. We first provided an estimate of lifetime risk

of hip fracture with a life table to compare to the earlier value. Next, we estimated the expected future experience for a 50 year old today incorporating predicted trends in the rates of hip fracture and mortality into the life table estimates. We estimated the life table risk by incorporating trends that have occurred over a longer period, and then we re-estimated the lifetime risk using more recent trends. In addition, we estimated the lifetime risk of first hip fracture by incorporating from the literature the percentage of hip fractures that are second hip fracture.

In Chapter 3, we build on the previous estimation of relative efficacy between osteoporosis drugs for the prevention of fractures. First, we update the literature on osteoporosis drugs to include recent additions in pharmacotherapy and recent RPCTs by conducting a multiple database systematic literature review. Second, we estimate the relative efficacy of reducing fractures of each drug versus placebo and between the drugs with Bayesian ITC analysis. Third, we conduct the ITC analysis using Bucher's method, a classical analysis approach. Finally, we tested if baseline differences in the studies contributed to the estimate of relative efficacy.

In Chapter 4, we estimated with matching methods the excess cost of illness of osteoporosis and fractures that included prolonged care and non-fracture care. First, we estimated the average resource utilization and costs for each of three types of cases (incident fracture, prevalent fracture and non-fracture osteoporosis) versus matched controls. The analysis was conducted across subgroups divided by age, sex, and fracture type. The results of the subgroups were pooled to estimate the excess

resource utilization and excess costs of incident fractures, prevalent fractures and non-fracture osteoporosis compared with non-fracture non-osteoporosis controls. To test for significance, we made assumptions about the mean-standard deviation relationship and then assessed these assumptions in sensitivity analyses. In addition, we assessed the factors that were associated with higher excess costs with meta-regression techniques.

Lastly, in Chapter 5 we summarized the key findings, limitations and the implications of the thesis. First, we report that the lifetime risk of hip fracture has fallen from 1989 to 2008 for women and men. However, adjustments for trends in mortality and rates of hip fracture with removing second fractures produced non-significant differences in estimates. Second, of the 9 available osteoporosis drugs that are available, 3 drugs (teriparatide, zoledronic acid and denosumab) have higher efficacy than the other drugs for reducing the risk of non-vertebral and vertebral fractures. The estimates from indirect comparisons were robust to differences in methodology. Finally we note that there exists large and significant excess costs for patients with incident fractures and for prevalent hip, humerus, multiple and traumatic fractures and our assumptions were consistent with other studies. We suggest that cost of illness estimates for osteoporosis that include only incident fractures underestimate the overall cost of osteoporosis and fractures.

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CHAPTER 2

Estimation of the lifetime risk of hip fracture for women and men in Canada

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Abstract

Summary: In Canada in 2008, based on current rates of fracture and mortality, a woman or man at age 50 will have a projected lifetime risk of fracture of 12.1% and 4.6%, respectively, and 8.9% and 6.7% after incorporating declining rates of hip fracture and increases in longevity.

Introduction: In 1989, the lifetime risk of hip fractures in Canada was 14.0% (women) and 5.2% (men). Since then, there have been changes in rates of hip fracture and increased longevity. We update these estimates for 2008 adjusted for these trends, and in addition, we estimated the lifetime risk of first hip fracture.

Methods We used national administrative data from fiscal year April 1, 2007 to March 31, 2008 to identify all hip fractures in Canada. We estimated the crude lifetime rates of hip fracture for age 50 years to end of life using life tables. We projected lifetime risk incorporating national trends from Poisson regressions. Finally, we removed the estimated percentage of second hip fractures to estimate the lifetime risk of first hip fracture.

Results: From April 1, 2007 to March 31, 2008, there were 21,687 hip fractures: 15,742 (72.6%) for women and 5,945 (27.4%) for men. For women and men, the crude lifetime risk was 12.1% (95% CI: 12.1, 12.2%) and 4.6% (95% CI: 4.5, 4.7%), respectively. When trends in mortality and hip fractures were both incorporated, the lifetime risks of hip fracture were 8.9% (95% CI: 2.3, 15.4%) and 6.7% (95% CI: 1.2, 12.2%). The corresponding lifetime risks for first hip fracture were 7.3% (95% CI: 0.8, 13.9%) and 6.2% (95% CI: 0.7, 11.7%).

Conclusions: The lifetime risk of hip fracture has fallen from 1989 to 2008 for women and men. Adjustments for trends in mortality and rates of hip fracture with removing second fractures produced non-significant differences in estimates.

Introduction

Hip fractures pose a serious morbidity and mortality burden on individuals and society. There were over 28,000 hospitalizations for hip fractures in Canada in 2007 [1]. Each hip fracture typically results in a hospitalization that lasts more than 10 days [2] and is often followed by prolonged rehabilitation, with less than half of patients with hip fracture regaining their ability to perform activities of daily living [2]. In addition, the absolute rate of mortality in Canada for hip fractures was 23.5% at 5 years [3], and if a second hip fracture occurs, the mortality rate can be 66.5% at 5 years [4]. Hip fractures can also have a substantial financial toll. The average cost of care following a hip fracture can be over $44,000 [2]. In 2008, the acute care costs of hip fracture in Canada was 650 million CAN $ [5].

For public providers of health care, being aware of the health care burden and knowing the return on investment through adopting cost effective strategies that reduce hip fractures would be important. For example, vitamin D and bisphosphonates have been shown to reduce fractures and falls [6,7,8], and funding drugs to seniors may be more cost-effective than spending future health care dollars on fracture care and institutionalization [9]. Similarly, screening programs that seek to prevent first or second hip fractures can be cost effective [10]. For this type of analysis, lifetime fracture estimates of risk are required to build an economic model for evaluating policy trade-offs [11].

One method to estimate the lifetime risk of fracture is to longitudinally track a cohort over their lifetimes and count the number of individuals with a hip fracture. However, this method would not represent the projected future risk of hip fracture, as rates of hip fracture and rates of mortality by age may have change over time. Alternatively, one could simulate a life profile using the prevalence-based life table method. The life table is constructed with a hypothetical cohort who, for example, is 50 years old today and their risk of hip fracture for the remaining years of their life is subject to the age-sex-specific rates of hip fractures experienced by an actual population during the past year. The lifetime risk of hip fracture is then estimated by combining the probabilities of surviving into the next years for each age with the probabilities of having had a hip fracture for each age. This type of analysis has been conducted in 1989 for Canada which estimated the lifetime risk of hip fracture to be 14.0% for women and 5.2% for men [12-14], but to our knowledge this estimate has not been updated.

Since 1989 there have been changes in the levels of risk factors such as use of tobacco, alcohol, and rate of obesity which is a protective factor [15,16]. Providing a current life table estimate would be important to provide a comparison to the earlier value for Canada, but a life table method using the same method may not truly reflect a person's expected future risk. The problem is that a life table incorporates the rates of mortality and hip fracture at each age and sex assuming them to be constant. For example, the expected rate of hip fracture for a 50 year old in 10 years at age 60 years is assumed to be the same rate as a 60 year old today. However, the age-sex rates of hip fractures in Canada have been changing over time [17], and have been declining at

a faster rate in recent years. In addition, the rates of mortality and thus exposure to hip fractures have also been decreasing over time as life expectancy has been almost constantly increasing every year in this century. To provide an accurate prediction of the future risk profile for hip fracture, the trends in the rates of hip fracture and the trends in mortality should be incorporated.

A further problem with the life table method is the possibility of a person having a repeated event. The life table method assumes the risk estimated by age-sex are for unique individuals, yet we know that there exists a probability of second hip fracture. The rate of second hip fracture within 10 years after the first fracture has been estimated to be about 10% [18]. To estimate the lifetime risk of having a first hip fracture, the lifetime risk estimate needs to remove the percentage of hip fractures that are second hip fractures.

This paper addresses the question ‘what is the current expected lifetime risk of hip fracture for men and women in Canada?’ We first provided an estimate of lifetime risk of hip fracture with a life table to compare to the earlier value. Next, we estimated the expected future experience for a 50 year old today incorporating predicted trends in the rates of hip fracture and mortality into the life table estimates. We estimated the life table risk by incorporating trends that have occurred over a longer period, and then we re-estimated the lifetime risk using more recent trends. In addition, we estimated the lifetime risk of first hip fracture by incorporating from the literature the percentage of hip fractures that are second hip fracture.

Methods

Primary Data Source

We used national administrative healthcare data from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) which provides data on all acute care hospitalizations that occur in Canada except for the province of Quebec (23% of the Canadian population) [19]. These data have been validated and show high sensitivity and specificity for hip fracture diagnoses and fracture interventions [20]. National numbers of hip fractures for each year of age and gender were extrapolated from the CIHI-DAD database after adjusting for the missing Quebec data using the gender and age population structure of Quebec relative to the rest of the country.

Identification of fractures

We identified hip fractures between April 1 2007 to March 31, 2008 based on International Classification of Diseases (ICD) version 10 (ICD-10 CA) diagnosis codes [21]. Specific anatomical sites of interest based on ICD-10 CA codes were S72.0 (fracture of the neck of the femur), S72.1 (pertrochanteric fracture which includes intertrochanteric fracture and trochanteric fractures) and S72.2 (subtrochanteric fracture). A Canadian Classification of Health Interventions (CCI) interventional code for fixation, implantation of an interval device, open or closed reduction, immobilization

or partial excision at hip fractures sites was also required. We excluded hospitalizations that did not have an intervention (these may indicate initial admission to a centre without surgical facilities with subsequent transfer to a surgical centre, or re-admission following an intervention for rehabilitation or complications).

Estimating fracture risk

The primary outcome was the life table estimate of risk of hip fracture for men and women beginning at age 50 until the end of life. In Canada the life expectancy is approximately 83 years for women and 78 years for men, and life expectancy after reaching age 65 is another 21.3 years in women, and 18.1 years in men [22]. The life table estimate [23] provides an estimate at age 50 in the year 2008 for the general population of the expected lifetime risk of hip fracture where death is a competing risk [23]. To estimate these risks, we generated the age and gender specific rate of having a hip fracture as number of fractures per population at risk from national census data [24]. Next, using the life table method we summed the probability of survival at age multiplied by the probability of a hip fracture.

Statistical Analysis

The lifetime risk of hip fracture was estimated without and then with adjustments for trends in mortality, for trends in rates of hip fracture, and for recurrent hip fractures. To predict the future trends in age-gender specific mortality, two time periods were

evaluated. The first period included the longer term trends in mortality for available years 1991 to 2008 for the national population using census data [22], and the national trends in the rates of hip fracture was provided for years 1985 to 2006 [17]. The second period included recent trends that occurred in the period 2001 to 2007 only since the trend in rates of hip fractures has changed since 2001. Both trends in mortality and hip fracture were derived with Poisson regression, as described in the technical appendix of earlier work [25]. Linear trends were also investigated and based on regression diagnostics the linear regression predictions fit the data as well as Poisson regression trends, but the predictions were not sensible and the results are not presented.

Finally, to account for the chance that a person may experience two hip fractures during their lifetime, we estimated the lifetime risk of a first hip fracture. National data on the rate of second hip fractures is not available. To account for second hip fractures, we applied the literature values from one study from Denmark that provided rates of second hip fracture by age and gender [26]. The percentage of hip fractures that are first fracture was 80.6% for women age 50 years declining to 77.2% for ages 90 years and over, and 85.7% for men age 50 years declining to 79.6 for ages 90 years and over These rates were used to reduce the rates of hip fractures to estimate the life time risk of first hip fractures.

Uncertainty

Uncertainty existed for rates of hip fractures, mortality, and second hip fracture, regression prediction errors, and life table summation errors. For rates of hip fractures, mortality, and second hip fracture, a binomial approximation was made for the estimated variance. From the regression prediction for future rates of hip fracture and mortality, the standard error of the prediction was derived. When constructing the life table, the uncertainty of rates of hip fractures and mortality were combined under the assumption of independence as random variables. Means and standard errors are reported for prediction trends, and means and 95% confidence intervals (95% CI) are reported for final estimates. We conducted the analysis in Microsoft Excel 2010 and STATA 11.0 SE [27].

Results

Between April 1 2007 and March 31, 2008, there were 21,687 hip fractures in Canada for age 50 years and over that required hospitalization and a surgical procedure, of which 15,742 (72.6%) were in women and 5,945 (27.4%) were in men. For the hip fractures, the most common procedures were fixation (60.4%), and implant internal device (38.0%); immobilization, reduction and partial excision each contributed less than 1%. There were 1,283 unique admissions (5.6% of all admissions) that did not require surgery and were excluded.

Descriptive statistics of rates of hip fracture by age and gender

Table 1 lists the numbers and rates of hip fracture by gender and age groups. The rate of hip fracture increased from age 50 years for both men and women, and this was particularly striking after age 70 years. Most hip fractures occurred between the ages 80 to 90 for both women and men, though the rate of fracture per population was highest after age 90 years. In women, 66% of hip fractures occurred after the age of 80 and 17% occur after the age of 90 (48% and 10% for men respectively). The simple sum of the age-specific rates of hip fracture for women was 18.4% at age 90 (2.9% for all ages including age 100+), and for men 10.4% at age 90 (27.9% for 100+). The cumulative risk translated into approximately 1 in 5 women and 1 in 10 men. The lifetime fracture risk for women assuming reaching age 90 were 12.0% for the neck of the femur, 9.8% for pertrochanteric, and 1.3% for subtrochanteric (7.2%, 5.7% and 1.0% for men).

Trends in the rate of mortality and hip fracture

To account for trends in the rate of mortality, the exponential trend in age-gender specific mortality was estimated for the years 1991 to 2007 as between 1% and 3% depending on the age group (see Table 2). For women, the rate of decline of hip fracture was higher than the decline in rate of mortality at all ages. For men, the opposite was true with the decline in the rate of hip fracture being lower than the rate

decline in the rate of mortality at all ages. Figure 1 shows the actual and projected rates of mortality and hip fracture for ages 85 years and over until the year 2020. The rates of decrease in mortality are similar, while the rate of hip fracture for women is falling faster than the decline in the rate of mortality.

When we included only recent trends in the trends in hip fracture and mortality, there was a smaller difference in the rate of hip fracture relative to mortality for women for most of the age groups. For men, the trends were similar to the long term trends, except for age 85 and over where in the recent period, the decline in the rate of hip fracture is higher than the decline in the rate of mortality.

Lifetime risk of hip fracture

The life table estimate for the risk of hip fracture for women was 12.1% (95% CI: 12.1% to 12.2%) and for men 4.6% (95% CI: 4.5% to 4.7%) (Table 3). Applying the declining trend for hip fracture alone decreased the estimated life time risk of hip fracture to 5.6 % (95% CI: 0.7% to 10.5%) for women and 1.7% (95% CI: 0.0% to 7.0%) for men. Applying the declining trend for mortality alone increased the estimated life time risk of hip fracture to 18.8% (95%CI: 14.5% to 23.3%) for women and 10.9% (7.2% to 14.0%) for men. When declining rates of hip fracture and mortality were both applied, the lifetime risk of hip fracture was 8.9% (95% CI: 2.3% to 15.4%) for women and 6.7% (95% CI: 1.2% to 12.2%) for men. Finally, when the number of fractures was adjusted downward by the proportion of fractures by age and gender that are only first fractures,

the lifetime risk of first hip fracture was 6.8% (95% CI: 0.3% to 13.4%) for women and 6.2 % (95% CI: 0.7% to 11.7%) for men.

Similarly, the estimate for the lifetime risk of hip fracture using the most recent trends was estimated with adjustment for trends in mortality, rates of hip fracture and second fractures. For women, the risk is lower, while for men the risk of lifetime hip fracture is unchanged However, the confidence intervals for the predications using the most recent data are wider than the confidence intervals for prediction over the longer trend and these differences are not significant

Discussion

In 1993, Melton provided an estimate of the lifetime risk of hip fracture if a person lived to reach age 90 as 1 in 3 women and 1 in 9 men for United States [28], while we estimate 1 in 5 for women and 1 in 10 for men. The United States estimate was derived from the simple cumulative sum of the risk of fracture at each age. In Canada, the lifetime risk based on life table methods during similar years was 14.0% for women and 5.2% for men [12 -14]. In 2008, we estimated the unadjusted life table lifetime risk of hip fracture was lower at 12.1% for Canadian women and 4.6% for Canadian men. When projected rates of mortality and hip fracture were both included in the estimation, the lifetime risk of hip fracture was not significantly different for women or men.

The declining risk of hip fracture has also been reported in United States [29] and follows a similar pattern to Canada. In addition, during the period 1986 to 2005 there was a break in the association of hip fracture and mortality. Before 1995 both the rates of hip fracture and mortality after hip fracture were decreasing. Since 1996, the rate of hip fracture continued to fall but the rate of mortality after a hip fracture has remained constant while overall mortality rates continued to decline. In France, overall mortality is falling faster than fracture-related mortality [30] and the risk of mortality following a hip fracture is still a great concern. Moreover, declining risk in hip fracture has not been achieved in other countries [29].

Factors that may have contributed to decreased population risk of hip fracture in Canada and the United States include the increased use of calcium and vitamin D supplements and recent introduction and uptake of bisphosphonates among other osteoporosis medications [31]. The first bisphosphonate introduced in Canada was etidronate in 1995 followed by alendronate in 1998. In 2005, alendronate became generic, which introduced a large increase in the uptake of these drugs. Lifestyle changes have also occurred such as a decrease in smoking in Canada from 35% in 1993 to 21% in 2009, while the percent of the population that would be classified as obese by body mass index has increased [16]. However, analysis that included the above factors has not been able to account for all of the changes in the risk hip fractures elsewhere [7].

One negative consequence of reduced fracture rates and increased longevity is that hip fractures may occur at a later age. This is concerning because with longevity there is an increased risk of developing comorbidities such as dementia, diabetes, peripheral neuropathy which are known predictors of falls and fractures [8]. In addition, the rate of mortality and costs of hip fractures increases with the number of comorbidities and age. In addition, the rate of morbidity, mortality and costs following an intertrochanteric fracture, which has an increased proportion of total hip fractures with age for both women and men, is higher than other hip fractures sites [8].

Despite these qualifications, the overall pattern of declining risk of hip fracture and mortality is hopeful for society. However, for the individual patient the immediate period of 10 years is more urgent and now the target of new fracture prediction by the World Health Organization's fracture assessment tool (FRAX) [32]. Still, for society the estimate of lifetime risk of hip fracture is more relevant for public health policy and making projections.

The strengths of this analysis are that we relied on national data for hip fractures and mortality over a common period, and we identified fractures from mandatory reporting in our public health care system. There are also limitations. One limitation was that we used the rates of second hip fracture from a different country and time period, although similar estimates of the rate of second hip fractures are found elsewhere [18,33]. Future research on whether the percent of fractures that are first or second by age is changing over time would be helpful. Another limitation was in the projection of the

rates of hip fractures and mortality into the future, which is admittedly uncertain and could continue, stabilize or even reverse.

Statistics Canada predicts that the population over age 80 years will increase by an average rate of 6.4 % per year until the year 2041 [22]. While the rate of hip fractures have been declining for women and less so for men, there will be a rise the absolute numbers of hip fractures. If the risk of hip fracture can continue to decline or further accelerate, some mitigation of the burden due to the increased numbers of hip fracture arising from an ageing population may occur.

Conflict of Interest: None

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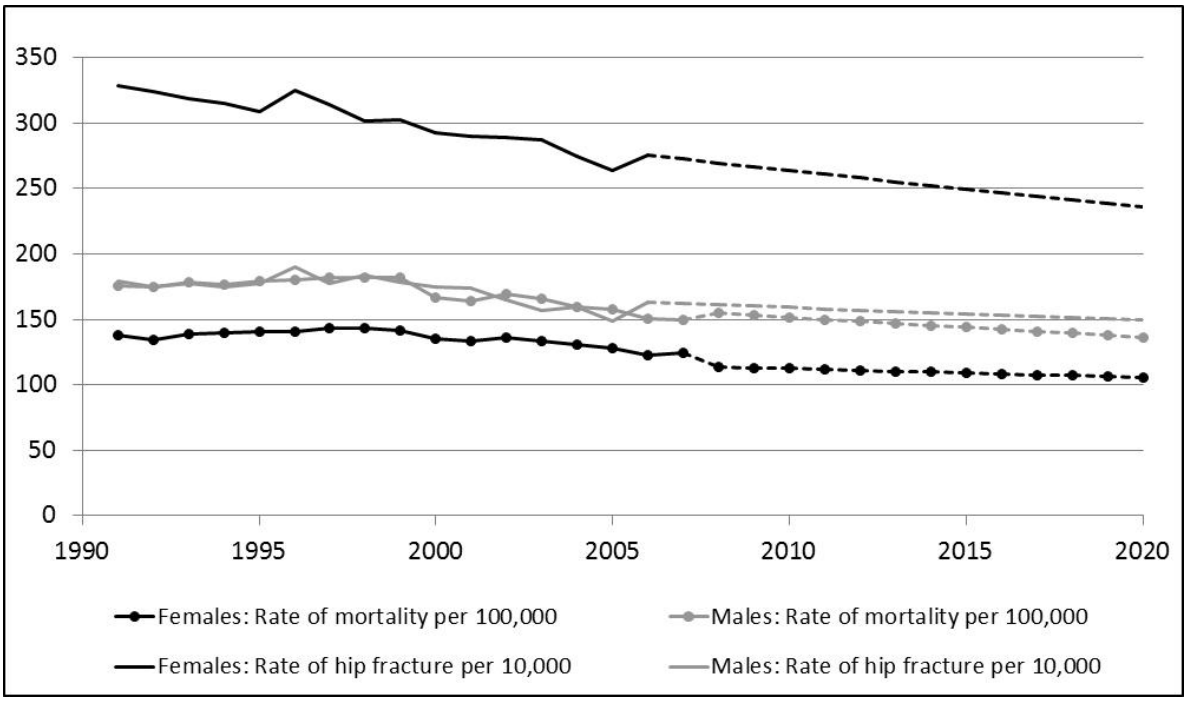
Figure 1: Trend in Rates of Mortality and Hip Fracture, predicted to year 2020, for ages 85+ years



For women, the rate of decline for hip fractures is higher than the rate of decline for mortality, while for men the rate of decline for hip fractures is less than the rate of decline for mortality.

Table 1 Number and Rates of Hip Fractures for Age Group and Gender

	Women		Men	
Age Group, years	Population	Hip fractures n (annual rate %)	Population	Hip fractures n (annual rate %)
51 to 60	2,302,817	556 (0.0 %)	2,254,334	521 (0.0 %)
61 to 70	1,526,056	1,281 (0.1 %)	1,445,481	835 (0.1 %)
71 to 80	1,028,925	3,829 (0.4 %)	857,457	1,742 (0.2 %)
81 to 90	596,906	7,424 (1.2 %)	350,175	2,223 (0.6 %)
91 +	112,863	2,652 (2.3 %)	38,977	624 (1.6 %)
Cumulative 80 years	4,857,798	5,666 (4.3 %)	4,557,272	3,098 (3.0 %)
Cumulative 90 years	5,454,704	13,090 (15.6 %)	4,907,447	5,321 (9.8 %)
Cumulative – all years	5,567,567	15,742 (42.9 %)	4,946,424	5,945 (25.8 %)

Annual rate percent: indicates average annual rate of fracture
Cumulative indicates from 50 to 80 years, 50 to 90 years, etc.

Table 1 Annual trends in the changes in rate of mortality, hip fracture and difference between mortality and hip fracture age groups and gender for Canada

	Women			Men		
	Mortality (M)	Fractures (F)	Difference (F- M)	Mortality (M)	Fractures (F)	Difference (F- M)
Long term trends derived from the years 1985 to 2007						
<55	-1.41 (2.32) %	-1.71 (5.15) %	-0.30 (5.65) %	-1.80 (2.94) %	-0.93 (3.77) %	0.86 (4.78) %
55 to 64	-1.75 (1,62) %	-3.62 (1.35) %	-1.87 (2.11) %	-2.53 (2.11) %	-1.89 (1.57) %	0.64 (2.63) %
65 to 74	-1.52 (1.00) %	-2.32 (0.69) %	-0.79 (1.21) %	-2.66 (1.32) %	-1.39 (0.92) %	1.27 (1.60) %
75 to 84	-1.44 (0.62) %	-1.54 (0.34) %	-0.10 (0.70) %	-2.16 (0.78) %	-1.16 (0.49) %	1.00 (0.92) %
85+	-0.65 (0.38) %	-1.09 (0.20) %	-0.44 (0.43) %	-1.04 (0.43) %	-0.62 (0.27) %	0.42 (0.51) %
Recent trends derived from the years 1997 to 2007						
<55	-1.07 (5.89) %	0.50(20.89) %	1.58 (21.70)%	-1.03(4.66)%	0.04(14.63)%	1.07(15.35)%
55 to 64	-1.78 (4.21) %	-2.02(5.56) %	-0.25(6.97)%	-2.35(3.27)%	-0.55(6.12)%	1.80(6.94)%
65 to 74	-1.87 (2.61) %	-2.41(2.67) %	-0.55(3.73)%	-3.19(2.00)%	-2.50(3.48)%	0.69(4.01)%
75 to 84	-1.97 (1.55) %	-2.29(1.29) %	-0.32(2.02)%	-2.98(1.23)%	-1.74(1.84)%	1.25(2.21)%
85+	-1.53 (0.83) %	-1.81(0.76)%	-0.29(1.13)%	-2.01(0.74)%	-2.38(1.00)%	-0.37(1.24)%

Means (standard errors) from standard errors of prediction from Poisson regressions.

Example: For age 85+ for women during the years 1985 to 2007, the rate of mortality have been declining by -0.65 % per year, the rate of hip fractures has been declining -1.09 % per year, and rate of hip fracture is falling faster than the rate of mortality by -0.44% per year.

Table 3 Estimated lifetime risks of hip fracture using prevalence-based life tables under different assumptions

Life table estimate of lifetime hip fracture	Women	Men
Based on trends from the years 1985 to 2007		
- unadjusted	12.14% (12.07% to 12.21%)	4.58% (4.51% to 4.66%)
- adjusted for longevity	18.79% (14.45% to 23.13%)	10.68% (7.15% to 14.22%)
- adjusted for fracture trends	5.64% (0.74% to 10.53%)	2.76% (0% to 6.97%)
- adjusted for longevity and fracture trends	8.85% (2.31% to 15.39%)	6.70% (1.21 to 12.20%)
- adjusted for second fracture	9.40% (9.07% to 9.73%)	3.75% (3.30% to 4.21%)
- adjusted for second fracture, longevity and fracture trends	6.83% (0.28% to 13.38%)	6.18% (0.67% to 11.69%)
Based on trends from the years 1997 to 2007		
- unadjusted	12.14% (12.07% to 12.21%)	4.58% (4.51% to 4.66%)
- adjusted for longevity	21.14% (12.46% to 29.82%)	12.10% (4.98% to 19.21%)
- adjusted for fracture trends	5.19% (0% to 26.09%)	2.11% (0% to 18.42%)
- adjusted for longevity and fracture trends	8.68% (0% to 31.31%)	4.49% (0% to 22.28%)
- adjusted for second fracture	9.40% (9.076% to 9.73%)	3.75% (3.30% to 4.21%)
- adjusted for second fracture, longevity and fracture trends	6.71% (0% to 29.34%)	3.65% (0% to 21.45%)

Risks (95% confidence intervals).

CHAPTER 3

The relative efficacy of nine osteoporosis medications for reducing the rate of fractures in post-menopausal women.

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Special Note: article is listed as **Highly Accessed**.

Abstract

Purpose: In the absence of head-to-head trials, indirect comparisons of randomized placebo-controlled trials may provide a viable option to assess relative efficacy. The purpose was to estimate the relative efficacy of reduction of fractures in post-menopausal women, and to assess robustness of the results.

Methods: A systematic literature review of multiple databases identified randomized placebo-controlled trials with nine drugs for post-menopausal women. Odds ratio and 95% credibility intervals for the rates of hip, non-vertebral, vertebral, and wrist fractures for each drug and between drugs were derived using a Bayesian approach. A drug was ranked as the most efficacious if it had the highest posterior odds ratio, or had the highest effect size.

Results: 30 studies including 59,209 patients reported fracture rates for nine drugs: alendronate (6 studies), denosumab (1 study), etidronate (8 studies), ibandronate (4 studies), raloxifene (1 study), risedronate (7 studies), strontium (2 studies), teriparatide (1 study), and zoledronic acid (1 study). The drugs with the highest probability of reducing non-vertebral fractures was etidronate and teriparatide while the drugs with the highest probability of reducing vertebral, hip or wrist fractures were teriparatide, zoledronic acid and denosumab. The drugs with the largest effect size for vertebral fractures were zoledronic acid, teriparatide and denosumab, while the drugs with the highest effect size for non-vertebral, hip or wrist fractures were alendronate or risedronate. Estimates were consistent between Bayesian and classical approaches.

Conclusion: Teriparatide, zoledronic acid and denosumab have the highest probabilities of being most efficacious for non-vertebral and vertebral fractures, and having the greatest effect sizes. The estimates from indirect comparisons were robust to differences in methodology.

Introduction

Osteoporosis defined by low Bone Mineral Density (BMD) (i.e., 2.5 standard deviations below peak gender specific BMD), is a progressive disease with high prevalence affecting 1 in 3 women and 1 in 8 men by the time they reach 90 years of age [1]. The major concern with low BMD is the high risk of fractures to non-vertebral bones such as the wrist or to the hip. A hip fracture may require extended hospital stay, surgical repair and rehabilitation therapy, and is associated with increased risk of death [2]. In addition, osteoporosis can lead to vertebral fractures which are identified by clinical assessment through decreased patient height (i.e., stooped posture) or with compressed spinal vertebra that can be radiologically assessed [3].

To reduce the risk of fractures due to osteoporosis, drugs have been introduced to reduce the rate of bone loss and to increase the strength of the bones. The first bisphosphonate available in Canada was etidronate in 1995 followed by alendronate in 1998. In 2005, alendronate became generic, which introduced a large increase in the uptake of these drugs. In Canada in 2010 about 9% of the population age 50 years and over were receiving an osteoporosis drug. These drugs include the bisphosphonates (alendronate, etidronate, risedronate or ibandronate), Selective Estrogen Receptor Modulators (raloxifene) and anabolic agents (teriparatide). All of these have shown to be effective in reducing the rate of fractures relative to placebo [4]. Recent additions to pharmacotherapy for osteoporosis include denosumab, strontium and zoledronic acid. Accordingly, it would be clinically important to know an estimate of the relative treatment

efficacy or ranking of the most efficacious drugs. A major gap in the evidence to identify the most efficacious drugs is the lack of randomized active-controlled trials, i.e., direct treatment comparison (DTC) evidence [4].

DTC evidence for osteoporosis is absent because such later phase III trials are more complex, expensive, and require larger sample sizes than earlier phase II randomized placebo-controlled trials (RPCT) [5]. Meanwhile, osteoporosis drugs have been approved for use or listed under reimbursement formularies based on RPCT evidence, even though there are skeptics on the benefits of RPCTs for estimating relative efficacy compared to currently available drugs and that RPCTs are unethical.

In a recent New England Journal of Medicine debate, Stein [6] argued that RPCTs are unethical because of the withholding of proven therapies in the placebo allocation, while Rosen [7] argued that the therapies are only proven in high risk patients (prior fracture, BMD < -3, or higher fracture risk assessment) and the inclusion criteria that possess true equipoise should only include individuals who are at low risk or are non-responsive to mild therapies. However in Canada the Tri-Council Policy Statement on the Ethical Conduct for Research Involving Humans suggest that RPCTs are acceptable to establish existence of effect and adverse events of drugs with new pharmacological mechanisms [8]. In the absence of DTC evidence, indirect treatment comparisons (ITC) might be a promising technique that allows the synthesis of available RPCT evidence to make a suggestion on the effect of DTC [9].

The theoretical foundations of the ITC method were provided in 1997 by Bucher [10] for the pair wise division of odds ratios to produce a common odds ratio thereafter referred to as the Bucher Method (i.e., for 2 drugs A and C and placebo B, the odds ratio of A/B divided by odds ratio C/B produces an odds ratio of A/C). While DTC is the highest level of clinical evidence, there exists the rationale to use ITC analysis where DTC is absent and not likely to be forthcoming [10]. Even if DTC evidence was available, ITC evidence based on other trials may be useful because of differences in patient characteristics and study characteristics such as length of follow-up [11].

In the absence of DTC evidence for osteoporosis drugs, two ITC analyses have been conducted to assess the relative efficacy at reducing the rates of fractures in post-menopausal women [12,13]. The first using a Bayesian analysis that looked at seven studies including four drugs zoledronic acid (1 study), alendronate (3 studies), ibandronate (1 study) and risedronate (2 studies). This indicated that zoledronic acid had the highest efficacy in preventing vertebral fractures [12]. The second and more comprehensive analysis included eight RPCTs which was an update involving the above four medications adding etidronate (1 study). Of the five medications analyzed zoledronic acid had the highest efficacy in preventing vertebral and hip fractures while risedronate had the highest efficacy in reducing non-vertebral non-hip fractures [13].

We believe we can build on this pioneering work. First, nine drugs are currently available in Canada, European or the United States for use with osteoporosis. The nine drugs include the above five (zoledronic acid, alendronate, ibandronate, and

risedronate) in the recent ITC analysis plus four more drugs that were not previously included (denosumab, raloxifene, strontium, and teriparatide). In addition, there are key differences in patient characteristics across the studies such as age, BMD, and fracture history. Further adjustment for these factors might affect estimates of the relative efficacy between treatments.

The purpose of this paper is to build on the previous estimation of relative efficacy between osteoporosis drugs for the prevention of fractures. First, we update the literature on osteoporosis drugs to include recent additions in pharmacotherapy and recent RPCTs by conducting a multiple database systematic literature review. Second, we estimate the relative efficacy of reducing fractures of each drug versus placebo and between the drugs with Bayesian ITC analysis. Third, we conduct the ITC analysis using Bucher's method, a classical analysis approach. Finally we estimated the relative efficacy after adjustment for baseline patient characteristics.

Methods

Literature Search

An electronic search of the following databases restricted to English was conducted from January 1990 to October 2009, and the search was continually updated by alerts until September 2010: EMBASE, Medline, Medline in Process, and Cochrane Database for Systematic Reviews, Evidence Based Reviews – American College of Physicians

Journal, National Health Service (NHS) Database of Assessment of Reviews and Effectiveness (DARE), CINAHL. Specific searches were developed for each database with the aid of professional librarian and were based on MeSH headings and keywords: osteoporosis, fractures, and bones. Methodological filters for randomization were applied to Medline and EMBASE (see appendix 1 for the search strategy). We also conducted a bibliographic search on each article that was identified. Following the literature searches, all citations were incorporated into Reference Manager citation database software [14] and duplicates were identified and removed.

The inclusion criteria was that each article must have; 1) one of the nine osteoporosis drugs: alendronate, denosumab, etidronate, ibandronate, raloxifene, risedronate, strontium, teriparatide, or zoledronic acid, 2) have a RPCT design, 3) have only post-menopausal women as an inclusion criterion, and 4) report the rate of fractures as a primary or secondary outcome. Studies were excluded if they were studies that combined different trials, were subgroup analysis, or the outcomes were not fractures such as BMD.

Selection of trials for inclusion and data abstraction

At the first level of screening of the publications, the titles and abstracts of the citations that were obtained from the search strategy were reviewed for relevance and inclusion for full-text review. Of these articles passing to level two, the articles were reviewed as full text for relevance. After inclusion, data was abstracted to pre-specified abstraction

forms and then entered into Microsoft Excel and the Bayesian meta-analysis software WinBUGS (**B**ayesian inference **U**sing **G**ibbs **S**ampling for Windows) [15]. For the literature retrieved based on the targeted review for systematic reviews and meta-analysis, the same 4 inclusion criteria applied. Literature screening was conducted by two independent reviewers, with consensus reached on all discrepancies.

Outcomes

The main outcomes were the rates of vertebral, non-vertebral, hip and wrist fractures. In addition, study characteristics (country, numbers of study centres, and patient follow up in years) and baseline patient characteristics (age in years, years since menopause, BMD of the hip reported as g/cm^2, and history of fractures) were abstracted. Data abstraction was verified by a second independent reviewer. For each outcome, the unadjusted odds ratio is derived from combining the odds ratio of each comparator versus a common group (i.e., Odds ratio of A/B = odds ratio (A/B) divided by odds ratio of C/B) and 95% credibility intervals (CrI) for fracture versus placebo were estimated. In addition, the odds ratio between each drug comparator was estimated along with its 95% CrI.

Primary Statistical Analysis: Bayesian ITC estimate of relative efficacy versus placebo and other drugs

ITC was conducted for the unadjusted analysis using Bayesian methods in WinBUGS software version 1.4.3 1 [15], which performs Bayesian analysis using Markov Chain Monte Carlo methods. We reported the analysis according to the Reporting Of Bayes used in clinical STudies (ROBUST) criteria [16]. The outcome estimated was the mean and the 95% credibility interval of the posterior distribution of the odds ratio of the rate of fracture versus placebo and other drugs, for each fracture.

For the Bayesian analysis, priors were predefined for the mean log odds ratio as a normal distribution with mean zero, and precision 0.001 representing weak prior information. Weak priors were chosen so that the final estimates for odds ratios are driven by the data, and not by any assumption made. For each outcome, we performed 100,000 simulations discarding the first 50,000 simulations to allow burn-in; two chains were run simultaneously. Convergence was assessed using all of the Geweke, Raftery-Lewis, Gelman-Rubin and Heidelberger-Welch tests. To make a comparison of all drugs to each in order to determine the most effect efficacious drug, the proportion of Markov chain iterations in which a drug had the highest odds ratio represented the probability of that drug being ranked the most efficacious. In addition, the effect size was estimated for each drug versus placebo, where effect size was defined as the ratio of the odds ratio for fracture of placebo versus drug divided by the standard error of the estimate of the odds ratio. A higher effect size indicates the drug has lower odds for

fractures than placebo and/or that the standard error is small. Software code for WinBUGS is provided in appendix 2.

Assessing robustness: homogeneity and consistency of evidence

A number of steps were taken to assess the integrity of the ITC analysis [10,17-20]. The assessments included; 1) assessing homogeneity in meta-analysis of each comparator and across comparators, and 2) checking the consistency of the ITC analysis between Bayesian and classical software, and 3) checking the consistency of the ITC analysis to DTC if available. If there is homogeneity within drugs and across drugs, and the ITC evidence is consistent across methodologies or with DTC evidence, then the ITC evidence in considered strong and free of bias [19].

Homogeneity with each drug and across all drugs was assessed with Review Manager 5 software [21]. Heterogeneity was assessed with I^2 with greater than 50% being moderate heterogeneity and greater than 70% being considerable heterogeneity as suggested by the Cochrane Handbook of Systematic Reviews [22]. Consistency of evidence was assessed by comparing the results of the Bayesian analysis to free software specifically created for ITC analysis [23]. This software package for ITC was released by the Canadian Agency for Drugs and Technologies in Health (CADTH) [24], a national agency in Canada that provides evidence based decisions and associated services for the national and provincial level governments. Checking consistency of ITC

evidence versus DTC evidence was conducted by a search for meta-analysis of DTC evidence.

Adjustment for difference in baseline characteristics

Lastly, we checked whether differences in patient characteristics across drugs contributed to the relative efficacy estimates in the ITC analysis. We estimated the odds ratios for fracture reduction with classical meta-analysis with meta-regression with the log of the odds ratio as the dependent variable, and dummy variables were added for each of the drugs. Following the unadjusted results, we adjusted the ITC estimates with meta-regression to include the age in years, BMD in g\cm^2, percent of subjects with history of a vertebral fracture. Meta-regression was conducted with STATA version 11.0 using the command *metareg*.

Results

Based on the literature review, 30 RPCTs that investigated the effect of drugs on the rate of fractures were identified. The results of the screening process are provided in the PRISMA diagram [25] in Figure 1 and the descriptions of the included studies are presented in Table 1. For the 9 drugs, 6 studies were for alendronate [26-31], 1 study for denosumab [32], 8 studies for etidronate [33-40], 4 studies for ibandronate [41-44], 1 study for raloxifene [45], 6 studies for risedronate [46-51], 2 studies for strontium [52,53], 1 for teriparatide [54], and 1 for zoledronic acid [55]. The participants in the

studies included 59,209 patients. The participants had a mean age ranging in studies between 52 and 72 years of age, years since menopause ranged from 2.7 to 31.9 years, and the study durations were from 1 to 4 years. Baseline BMD in the hip ranged from 0.28 to 1.08 and the percentage of participants that had previous vertebral fractures were from 0% to 100%.

Bayesian ITC estimate of relative efficacy versus placebo and other drugs

The estimates of relative efficacy of each drug versus placebo in the Bayesian meta-analysis is reported in Table 2. For non-vertebral fractures, only alendronate OR=0.81 (95% CrI: 0.66, 0.96) and risedronate OR=0.77 (95% CrI: 0.60, 0.91) had significant reduction. Etidronate had the highest probability of being most efficacious (0.41) along with teriparatide (0.41). All other drugs had less than 0.10 probability of being most efficacious. However, the drugs with the highest effect size were risedronate (16.4) and alendronate (16.1), but these effect size were smaller than the effect sizes for vertebral fractures. Based on the probabilities of being most efficacious, etidronate and zoledronic acid are the most efficacious drugs. However since etidronate does not have significant effect versus placebo, teriparatide is the most efficacious drug. In the ITC head-to-head analysis (Table 3) there is not enough evidence to detect differences in efficacy between any of the drugs for non-vertebral fractures, although teriparatide, zoledronic acid and denosumab have the lowest numbers need to treat to prevent a non-vertebral fracture versus the other drugs.

For vertebral fractures, all drugs except etidronate had significant reductions in the odds of a fracture. The drugs with the highest probability of being most efficacious are teriparatide (0.30), zoledronic acid (0.40) and denosumab (0.20). However, the drugs with the highest effect size were also teriparatide (29.8), zoledronic acid (66.2) and denosumab (53.6) Based on probabilities and effect size these three drugs are most efficacious. In addition, these three drugs also had the lowest number needed to treat versus the other drugs (Table 3). In the ITC head-to-head analysis, teriparatide had significant reduction in vertebral fracture versus ibandronate and raloxifene, while denosumab had significant reductions versus alendronate, raloxifene, and risedronate. Zoledronic acid had significant reductions versus alendronate, raloxifene, and risedronate (Table 3).

For hip fractures, only alendronate has a significant reduction in relative rate of fractures, OR= 0.59 (95%CrI: 0.29 to 0.99). The drugs that had the highest probability of being most efficacious were teriparatide (0.44) and etidronate (0.19). The drugs with the highest effect size were alendronate (9.49) and risedronate (5.71). Based on probabilities and effect size it is unclear which drug might be ranked most efficacious out of the choices of teriparatide or alendronate. In the ITC head-to-head analysis, the relative efficacy of teriparatide versus alendronate was OR=1.35 (95% CrI: 0.07, 5.71) which is a non-significant finding. There were no drugs that had a significant benefit for hip fractures versus the other drugs (Table 3).

For wrist fractures, there were no drugs that a significant protective effect versus placebo, although no wrist fracture data was available for denosumab, ibandronate or zoledronic acid. The drugs that had the highest probability of most efficacious were teriparatide (0.41) and risedronate (0.22). The drugs with the highest effect size were alendronate (1.80) and risedronate (1.37), although the magnitude of the effect size was considerably lower than for other fractures. Based on probabilities and effect size it is unclear which drug might be ranked most efficacious out of the choices of teriparatide or alendronate. In the ITC head-to-head analysis, the relative efficacy of teriparatide versus alendronate was OR=1.69 (95% CrI: 0.04, 8.09) which is a non-significant finding. There were no drugs that had a significant benefit for wrist fractures versus the other drugs (Table 3).

Assessing robustness: homogeneity and consistency of evidence

There was no difference between the estimates of the odds ratio and confidence or credibility intervals between the classical ITC software and the Bayesian WinBUGS ITC analysis.

For non-vertebral fractures, the evidence was considered to be strong and free of bias as a result of low heterogeneity, and similarity of classical results to the Bayesian analysis. For non-vertebral fractures, the overall odds ratio across all drugs was OR = 0.81 (95% CI: 0.77, 0.86), (P<0.01) indicating a protective effect of pharmacotherapy (Figure 2). There was no heterogeneity between types of drugs (I^2 = 0), although low heterogeneity (I^2=16%) existed for alendronate.

For vertebral fractures, the evidence is considered less strong than the evidence from non-vertebral fractures as a result of increasing heterogeneity (Figure 3), and the classical analysis having smaller confidence intervals than the Bayesian analysis. In the classical meta-analysis, the overall effect across all drugs was a protective effect in preventing vertebral fractures, OR = 0.49 (95% CI: 0.41, 0.58), and there was considerable heterogeneity across all drugs (I^2=84%), while there was no heterogeneity within drugs. All drugs except one provided significant predictive effects with the exception being etidronate which produced a p-value of 0.10. Conversely, in the Bayesian analysis only risedronate and alendronate had significant odds ratios relative to placebo.

For hip fractures, the evidence is considered less strong than the evidence from non-vertebral fractures as a result of decreased confidence intervals in the classical analysis (Figure 4). For hip fractures, there was an overall protective effect against hip fracture for all drugs, OR=0.73 (95% CI: 0.63, 0.84), and absence of heterogeneity (I^2 = 0%). Three drugs reported an independent statistical reduction in the rate of hip fracture, alendronate, OR=0.62 (95% CI: 0.40, 0.96), denosumab OR=0.60 (95% CI: 0.37, 0.98), and risedronate OR=0.74 (95% CI: 0.58, 0.94). This is in contrast to the Bayesian analysis where only alendronate reported a significant reduction in the odds ratios for hip fracture.

For wrist fractures, the evidence is considered weak as a result of increasing heterogeneity and differences in the classical versus Bayesian analysis when drugs were compared to placebo (Figure 5). For wrist fracture, there was not an overall protective effect OR = 0.88 (95% CI: 0.77, 1.01), and the heterogeneity was substantial (I^2 = 64%). The only drug that had a significant protective effect alone was risedronate OR=0.71 (95% CI: 0.56, 0.89). The analysis of alendronate alone had considerable heterogeneity (I^2 = 79%). Removing Cummings and Greenspan to produce comparable ITC evidence reduced the heterogeneity to 0% and the odds ratio to OR=0.44 (95% CI: 0.30 to 0.67) for alendronate versus placebo. Removing Cummings and Greenspan produced an overall odds ratio for all drugs OR=0.82 (95% CI: 0.71, 0.94: I^2=59%).

Adjustment for difference in baseline characteristics

The estimates of the relative efficacy with meta-regression for each drug versus placebo for each type of fracture were similar to the estimates of Bayesian analysis for odds ratios. Unfortunately, when baseline characteristics were added to the regression equation, there were not enough studies for the analysis and no estimate could be provided. This lack of result was created by the addition of the baseline characteristics age, BMD and rate of prior vertebral fractures which created multi-collinearity which was detected by exploded confidence intervals for each drug effect. When we ran the regression with only the top two drugs for each fracture along with adding in any of age, BMD or rates of prior vertebral fractures, the latter effects were significant while the drug effects was not significant. This suggests that the differences across studies in baseline

characteristics contribute more to variation in odds ratio of fractures across studies than changes in the drugs.

Discussion

The objective was to update the literature on the relative efficacy of different osteoporosis medications to prevent four types of osteoporosis-related fractures. Based on the combination of effect size and probability of being most efficacious, teriparatide zoledronic acid and denosumab are consistently ranked highest for reducing non-vertebral and vertebral fractures, the two most common types of fractures.

Etidronate is also ranked high on probability of being most efficacious but there are reservations with this result. First, etidronate does not have a statistically significant odds ratio versus placebo for non-vertebral fracture, but was ranked highest for being efficacious. The higher ranking may be due to a wide confidence interval that covers a lower region of odds ratio creating a favourable relative result over that region of low odds ratio. This suggests a limitation with this analysis where a requirement may be that the odds ratio for different drugs should have similar widths. A second caution with the results for etidronate is that the trials were small resulting in small effect sizes and the trials were conducted prior to the year 2000. This suggests that there is a lack of current strong evidence for the efficacy of etidronate versus placebo. As a result of these two limitations, this analysis suggests that etidronate should not be considered among the most efficacious drugs based on current evidence.

In addition, the number needed to treat analysis that treating as few as 10 patients with teriparatide, zoledronic acid or denosumab will produce 1 less fracture than if the patients were on other drugs.

This work updates the most recent study for ITC analysis in osteoporosis medications which looked at vertebral, hip and nonvertebral nonhip fractures [13] for five drugs, zoledronic acid, alendronate, ibandronate, risedronate and etidronate. Based on that analysis zoledronic acid had a 0.79 probability of being the most efficacious for vertebral fractures. In our analysis, teriparatide (0.40) and etidronate (0.40) had the highest probability of being the most efficacious. In our analysis, we included more studies for etidronate, alendronate, and risedronate in addition to adding denosumab, raloxifene, strontium and teriparatide. Similarly, the earlier work reported that zoledronic acid had the highest probability of preventing hip fractures, while our analysis indicates the most efficacious drugs are teriparatide (0.44), and that zoledronic acid (0.11), etidronate (0.19), denosumab (0.12) and alendronate (0.10) could be the most efficacious treatment. One key difference between inclusions of different studies was that we analyzed wrist fractures specifically while the earlier work reported on nonvertebral nonhip fractures [13]. We report that risedronate does have a high probability of being most efficacious similar to earlier work but we estimated that teriparatide has the highest probability of preventing wrist fractures (0.44).

The other objective of this analysis was to compare the results across two statistical methods. The first method was based on Bayesian ITC analysis in WinBUGS, and the

second method was the results from classical Bucher analysis with ITC specific software. The estimates differed only by the second decimal place when the results were statistically significant. However, there are key differences in the interpretation of the results. Based on the classical analysis we generated confidence intervals around the odds ratio and provided a test of association. In the Bayesian analysis, we generated a posterior distribution of the credible intervals for the true values of the odds ratio. In this analysis these values are similar, indicating that the priors used in the analysis were uninformative.

The analysis is limited in that the results are based on ITC comparisons. However, a recent review of the results of DTC and ITC analysis, described that out of 44 meta-analysis that were available with studies for meta-analysis by ITC and studies for meta-analysis by DTC, the DTC was similar in all but 3 cases to the ITC estimates for the same drugs and outcomes [8]. Of the 3 cases where the results were statistically different, 2 cases had the relative clinical benefit in the same direction while the third had differences in dosage regime in the studies. This result was also reported by Bucher in 1997 [10] where the ITC results were similar in direction as the DTC estimates. In addition, Bucher and Song both reported that the magnitude of the ITC results was larger between comparators than DTC comparisons, and the level of significance between comparators was less in ITC than DTC. In our ITC analysis, non-significant differences were estimated between drugs but the true effect between drugs may be even smaller.

The other assessment of strength of evidence in the indirect comparisons beyond looking at different classical versus Bayesian analysis was to look at heterogeneity within drugs and across drugs. The heterogeneity between comparators and heterogeneity within one comparator was small, with the exception of alendronate for wrist fractures. This heterogeneity was explained by two studies [28,29] for wrist fractures. These studies did not contribute to heterogeneity in the meta-analysis of vertebral fractures and non-vertebral fractures. However, these two studies included the one study [28] that was the longest study with duration of 4 years with a low risk patients and the largest study for alendronate, while the other study [29] was a small single centre study.

The interpretation of the heterogeneity, although not a major feature in this analysis, is an important factor for ITC analysis. Increased heterogeneity can be caused by differences in inclusion criteria or study design such as length of follow-up. These are also important factors for consideration for analysis of DTC studies [20]. Three studies that assessed the effect of patient characteristics to explain the level of heterogeneity in ITC analysis. In 2 studies [56,57] no baseline variables were significant while in the other study [58] the year of the study and baseline risk affected heterogeneity. Both of these factors may have also affected heterogeneity if the studies were randomized with an active comparator. In our analysis, we may not have enough power to detect the impact of baseline characteristics because of a low number of studies for each drug [21] . In addition, because of the high heterogeneity in the estimates of odds ratios for wrist fractures, the evidence for wrist fractures should be considered weak.

ITC is becoming a useful tool in the absence of DTC comparisons and increasing transparency of ITC analysis builds confidence for the evidence. In a review of 88 ITC analyses, many of the studies could have increased the believability of their results [9] but the missed elements would also concern DTC analysis. These include: incomplete searches or not assessing heterogeneity within a comparator. In 40/88 analysis there was no specific searches for active comparison studies to allow the comparison to the ITC evidence. For osteoporosis, this search was conducted and we found no published meta-analysis of DTC evidence.

In the future stronger evidence may come from head-to-head studies but this is unlikely, because based on this analysis differences between comparators are not significant and studies would require very large sample sizes. Alternatively the treatment analysis could come for pooling patient level data to compare the effects directly but this is unlikely due to propriety, and this analysis would diminish the benefits of randomization.

Conclusion

In light of the lack of DTC evidence, the ITC analysis of RPCTs may be the strongest evidence that will be available that answers the important clinical question of determining the most efficacious treatment for preventing fractures. In this analysis, teriparatide, zoledronic acid and denosumab have the highest probabilities of being most efficacious for non-vertebral and vertebral fractures, and having the greatest effect

sizes. The estimates from indirect comparisons were robust to differences in methodology.

Competing interests

Alexandra Papaioannou is or has been a consultant or on a speaker's bureau for Amgen, Aventis Pharma, Eli Lilly, Merck Frosst Canada, Novartis, Procter & Gamble Pharmaceuticals, Servier and Wyeth-Ayerst; she has conducted clinical trials for Eli Lilly, Merck Frosst Canada, Novartis, Procter & Gamble Pharmaceuticals and Sanofi-Aventis; and she has received unrestricted grants from Amgen, Eli Lilly, Merck Frosst Canada, Procter & Gamble Pharmaceuticals and Sanofi-Aventis. Jonathan Adachi has been a consultant or on a speaker's bureau for Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Merck Frosst Canada, Novartis, Nycomed, Pfizer, Procter & Gamble Pharmaceuticals, Roche, Sanofi-Aventis, Servier, Wyeth-Ayerst and Bristol-Myers Squibb; he has conducted clinical trials for Amgen, Eli Lilly, GlaxoSmithKline, Merck Frosst Canada, Novartis, Pfizer, Procter & Gamble Pharmaceuticals, Sanofi-Aventis, Roche, Wyeth and Bristol-Myers Squibb. Lehana Thabane provides biostatistics consultation to GlaxoSmithKline for design and methodological issues. Eleanor Pullenayegum, Ron Goeree, Feng Xie and Robert Hopkins have no competing interests.

Authors' contributions. RH carried out the literature review, data abstraction, statistical analysis and drafting of the manuscript. FX, EP, and LT provided guidance on the statistical analysis methodology. JD and AP provided guidance for the clinical

interpretation of manuscript. All authors read, provided comments and approved the final manuscript.

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Figure 1: PRISMA Flow Diagram describing selection process for included studies

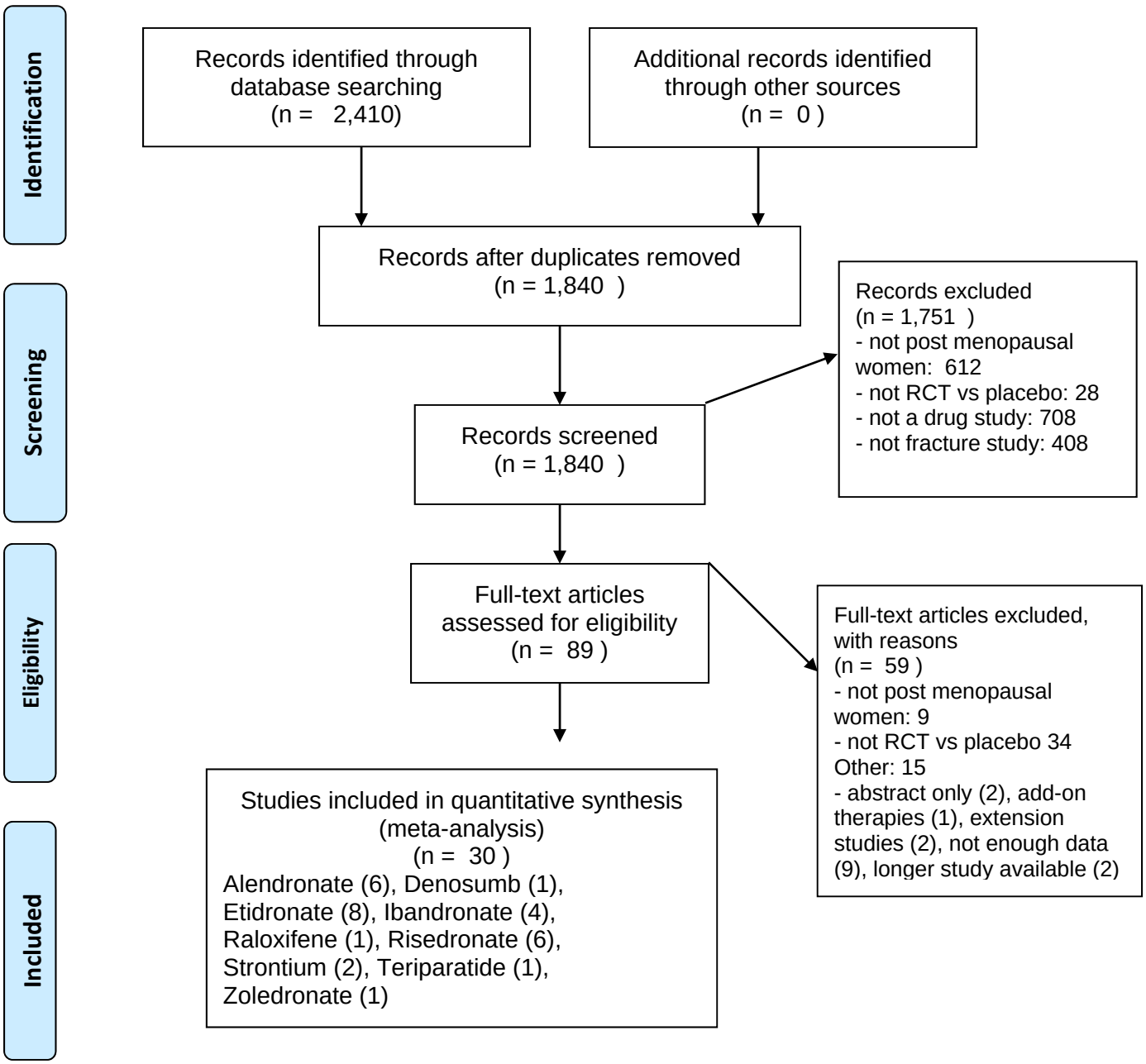

Figure 2. Forest plot non vertebral fractures. Odds ratio of non vertebral fractures for drugs versus placebo using Classical meta-analysis approach.

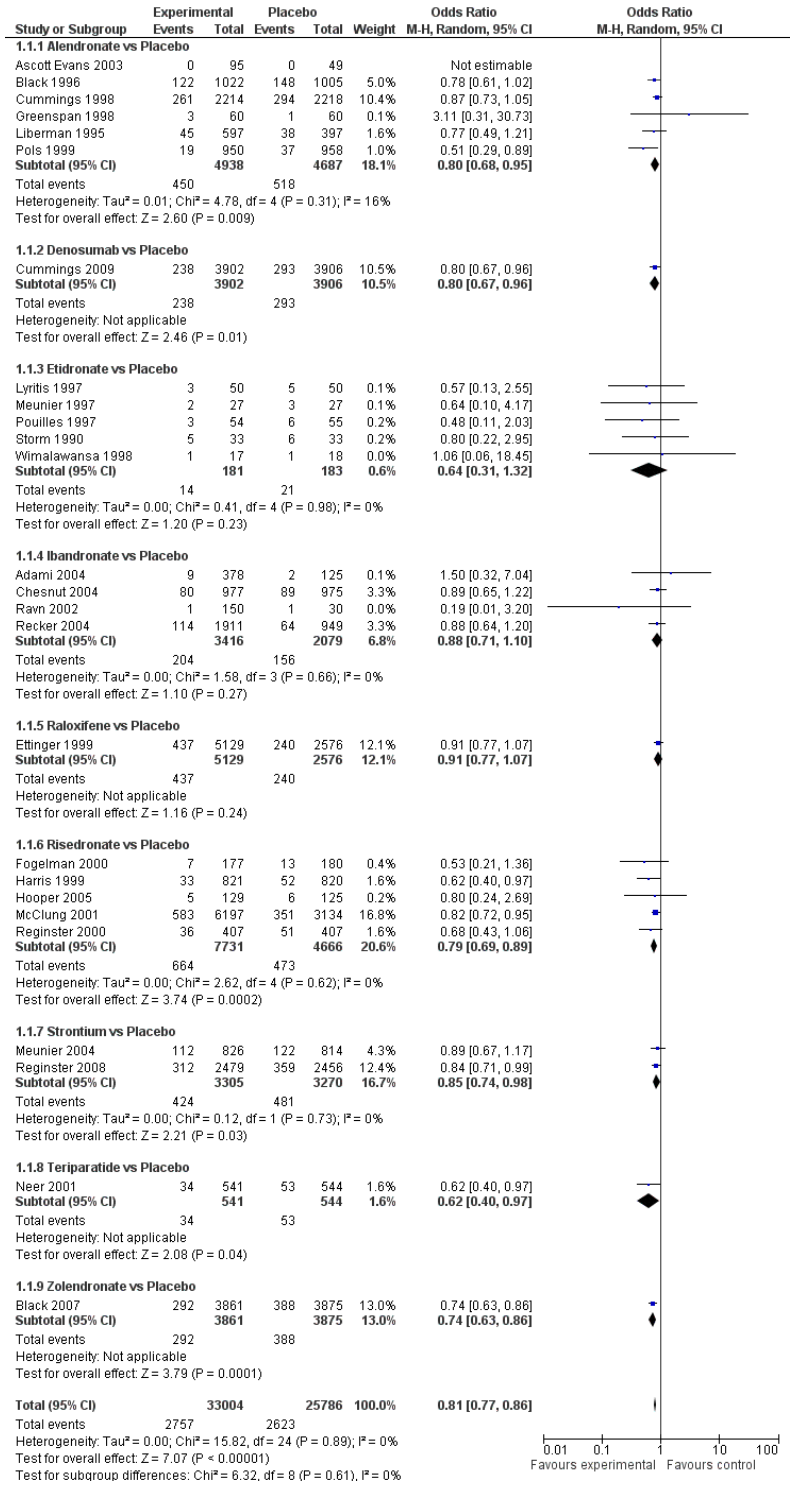

Figure 3. Forest plot vertebral fractures. Odds ratio of vertebral fractures for drugs versus placebo using Classical meta-analysis approach.

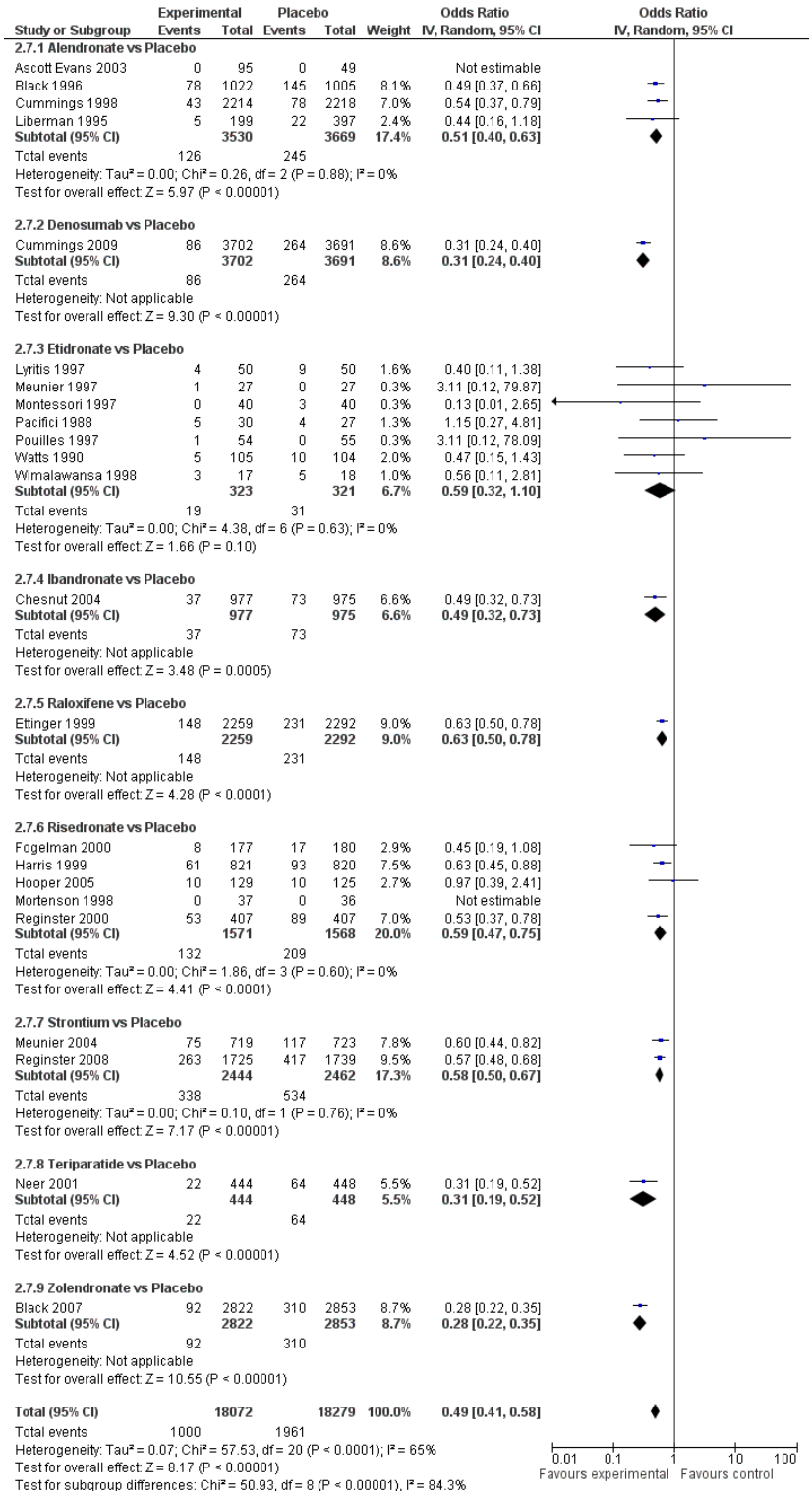

Figure 4. Forest plot hip fractures. Odds ratio of hip fractures for drugs versus placebo using Classical meta-analysis approach.

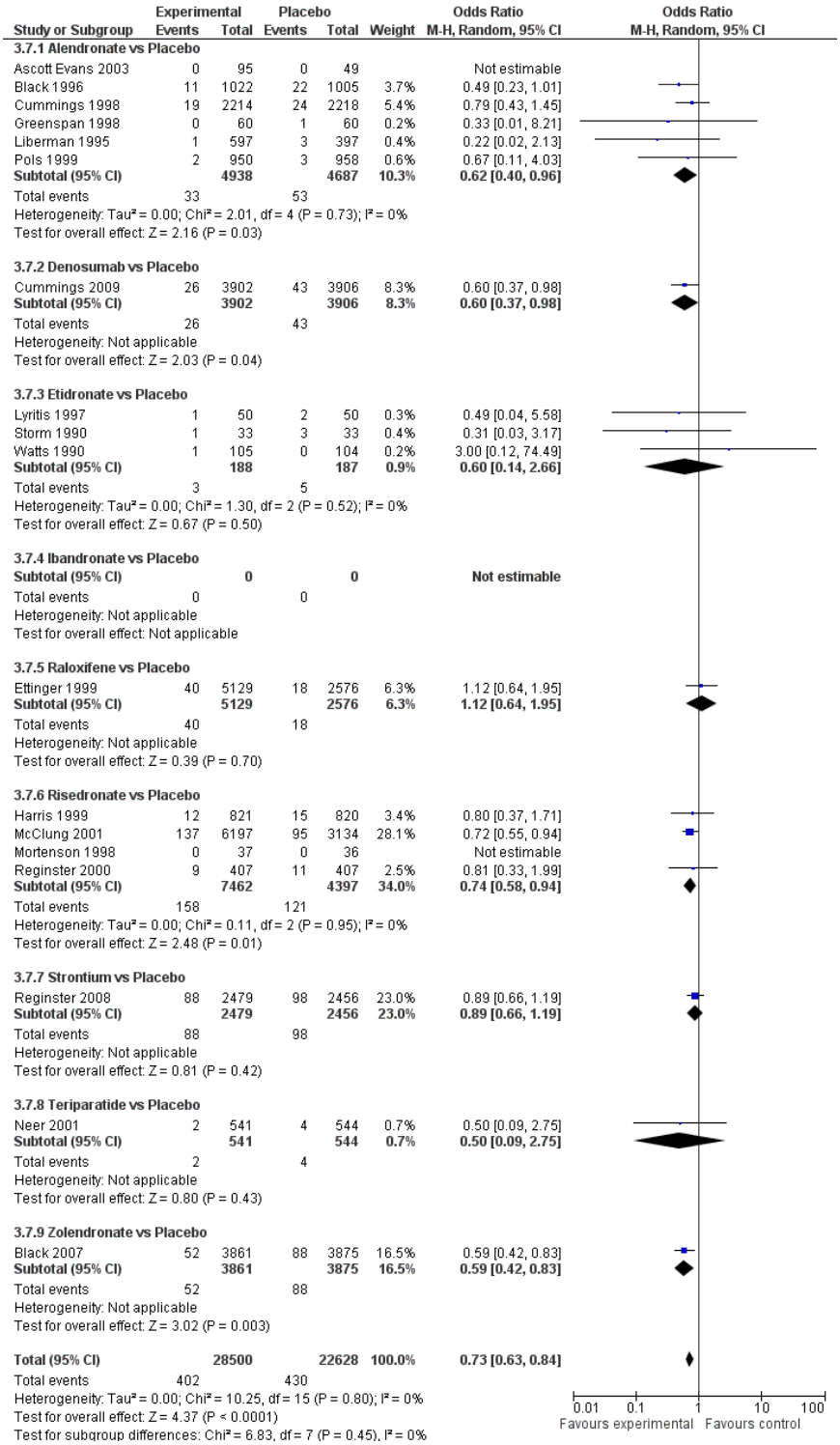

Figure 5. Forest plot wrist fractures. Odds ratio of wrist fractures for drugs versus placebo using Classical meta-analysis approach.

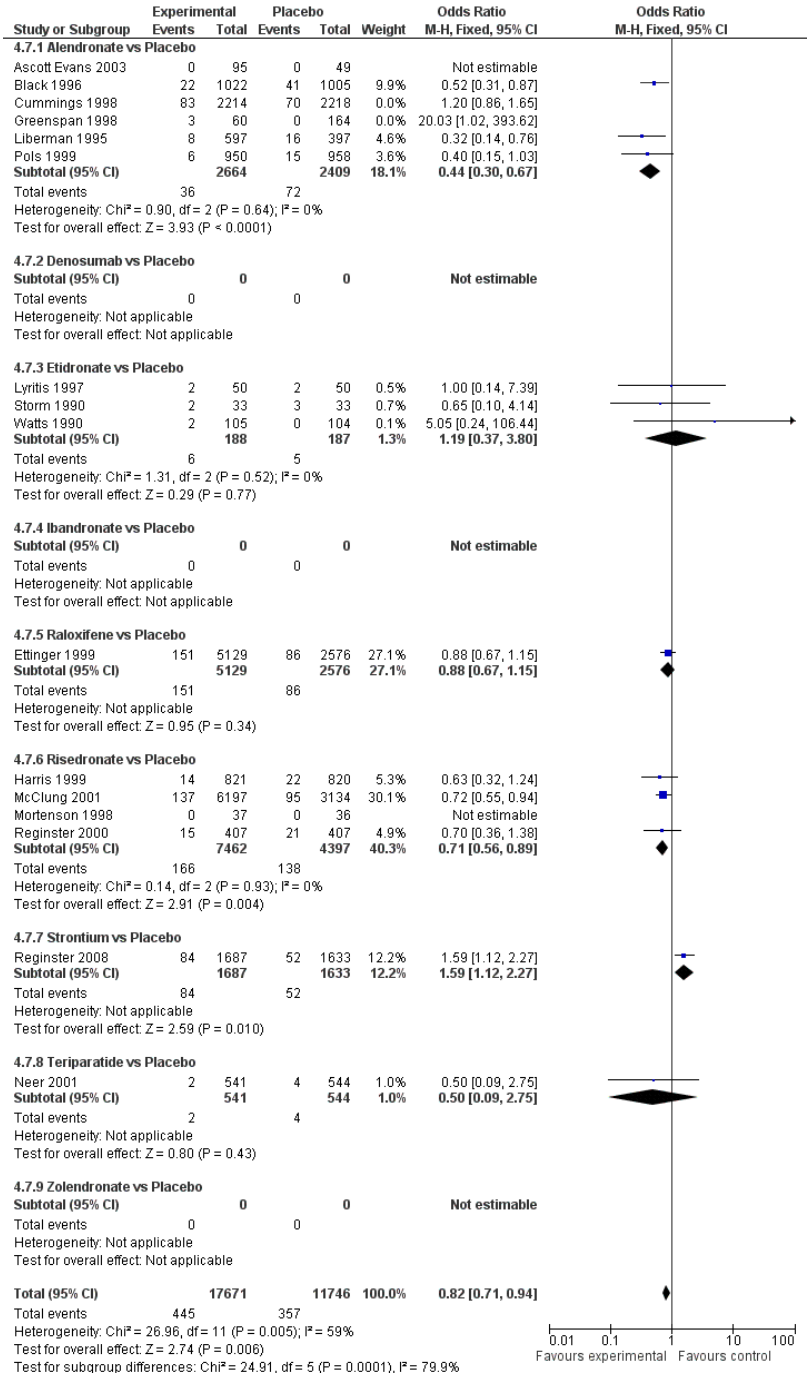

Table 1: Description of Study and Baseline Characteristics for Included Studies

Drug	Author Year	Study Duration (years)	Country/Region	Number of Centres	Age (yrs) Mean(SD)	Years Menopause Inclusion Criteria	Years Since Menopause Mean (SD)	BMD Hip g/cm^2 Mean (SD)	Prior Vertebral Fracture %
Alendronate	Ascott Evans 2003	1	International	18	57.3 (6.6)	3	11.5 (7.3)	nr	0
Alendronate	Black 1996	3	North America	11	71.0 (5.6)	2	NR (NR)	0.57 (0.07)	100
Alendronate	Cummings 1998	4	North America	11	67.6 (6.1)	2	NR (NR)	0.84 (0.13)	0
Alendronate	Greenspan 1998	2.5	North America	1	70.0 (4.6)	NR	NR (NR)	0.57 (0.11)	NR
Alendronate	Liberman 1995	3	International	NR	64.0 (7.0)	5	16.5 (NR)	0.71 (NR)	21
Alendronate	Pols 1999	1	International	153	62.8 (7.4)	3	15.9 (1.5)	0.72 (0.08)	NR
Denosumab	Cummings 2009	3	International	182	72.3 (5.2)	NR	NR (NR)	NR (NR)	23.6
Etidronate	Lyritis 1997	4	Europe	1	72.0 (0.4)	NR	25.8 (1.7)	0.57 (NR)	100
Etidronate	Meunier 1997	2	Europe	1	52.7 (4.0)	0.5	2.4 (1.8)	0.90 (NR)	NR
Etidronate	Montesorri 1997	3	Europe	2	62.5 (6.2)	1	14.9 (6.1)	0.67 (NR)	36
Etidronate	Pacifici 1988	2	U.S.A	1	61.0 (7.8)	NR	13.8 (9.5)	0.79 (0.26)	100
Etidronate	Pouilles 1997	2	Europe	7	53.8 (3.1)	0.5	2.6 (1.4)	0.96 (NR)	NR
Etidronate	Storm 1990	3	Europe	1	68.3 (7.3)	NR	21.6 (10.2)	NR (NR)	100
Etidronate	Watts 1990	2	U.S.A	7	65.1 (13.0)	1	17.9 (16.5)	0.86 (NR)	100
Etidronate	Wimalawansa 1998	4	NR	NR	64.9 (7.8)	NR	15.1 (6.8)	0.83 (NR)	100
Ibandronate	Chesnut 2004	3	Europe, U.S.A	73	69.0 (11.0)	5	21 (20.8)	0.78 (NR)	93
Ibandronate	Ravn 2002	1	Europe	1	64.5 (5.9)	10	NR (NR)	0.87 (0.13)	28
Ibandronate	Adami 2004	1	Europe	NR	65.9 (4.5)	5	17.9 (4.0)	0.77 (0.09)	45
Ibandronate	Recker 2004	3	Europe	NR	67.0 (5.1)	5	NR (NR)	0.80 (0.11)	54

Table 1 (*continued*)

Drug	Author Year	Study Duration (years)	Country/Region	Number of Centres	Age (yrs) Mean(SD)	Years Menopause Inclusion Criteria	Years Since Menopause Mean (SD)	BMD Hip g/cm2 Mean (SD)	Prior Vertebral Fracture %
Raloxifene	Ettinger 1999	3	International	180	66.1 (6.9)	2	18.6 (7.9)	0.58 (NR)	38
Risedronate	Fogelman 2000	2	Europe	13	64.7 (7.2)	1	17.7 (9.4)	0.74 (0.08)	30
Risedronate	Harris 1999	3	North America	110	69.0 (7.3)	5	24.0 (9.9)	0.83 (0.16)	81
Risedronate	Hooper 2005	2	Australia	11	52.6 (3.3)	0.5	3.9 (5.6)	1.08 (0.12)	18.3
Risedronate	McClung 2001	3	International	183	78.0 (9.7)	NR	31.8 (19.3)	NR (NR)	42
Risedronate	Mortenson 1998	2	International	2	51.2 (3.8)	0.5	2.7 (1.7)	0.94 (0.11)	NR
Risedronate	Reginster 2000	3	Europe, Australia	80	71.0 (7.0)	5	24.4 (8.5)	0.79 (0.15)	100
Strontium	Meunier 2004	3	Europe, International	72	69.3 (7.3)	5	23.9 (8.7)	0.68 (0.11)	100
Strontium	Reginster 2008	3.5	International	75	76.7 (5.0)	0	28.4 (7.4)	0.55 (NR)	33.5
Teriparatide	Neer 2001	2	International	99	69.0 (7.0)	5	21.0 (8.0)	0.82 (0.17)	100
Zoledronate	Black 2007	3	U.S.A, Europe	60	73 (5.4)	0	NR (NR)	0.65 (0.91)	63.3

NR: Not reported. BMD: Bone Mineral Density. SD: Standard deviation. U.S.A: United States of America

Table 2: Odds Ratio for Fracture, Indirect Treatment Comparison Results of Drug versus Placebo (Classical and Bayesian analysis)

Classical analysis

	Non-vertebral fracture		Vertebral fracture		Hip fracture		Wrist fracture	
Drug vs placebo	OR (95% Cr I)	Placebo rate	OR (95% Cr I)	Placebo rate	OR (95% Cr I)	Placebo rate	OR (95% Cr I)	Placebo rate
Alendronate	0.80 (0.68, 0.95)	11.1%	0.51 (0.40, 0.63)	6.7%	0.62 (0.40, 0.96)	1.1%	0.44 (0.30, 0.67)	3.0%
Denosumab	0.80 (0.67, 0.96)	7.5%	0.31 (0.24, 0.40)	7.2%	0.60 (0.37, 0.98)	1.1%	NR	NR
Etidronate	0.64 (0.31, 1.32)	11.5%	0.59 (0.32, 1.10)	9.7%	0.60 (0.14, 2.66)	2.1%	1.19 (0.37, 3.80)	2.2%
Ibandronate	0.88 (0.71, 1.10)	7.5%	0.49 (0.32, 0.73)	7.5%	NR	NR	NR	NR
Raloxifene	0.91 (0.77, 1.07)	9.3%	0.63 (0.50, 0.78)	10.1%	1.12 (0.64, 1.95)	0.7%	0.88 (0.67, 1.15)	3.3%
Risedronate	0.79 (0.69, 0.89)	10.1%	0.59 (0.47, 0.75)	13.3%	0.74 (0.58, 0.94)	2.8%	0.71 (0.56, 0.89)	3.4%
Strontium	0.85 (0.74 (0.98)	14.7%	0.58 (0.50, 0.67)	21.7%	0.66 (1.19)	4.0%	1.59 (1.12, 2.27)	3.2%
Teriparatide	0.62 (0.40, 0.97)	9.7%	0.31 (0.19, 0.52)	14.3%	0.50 (0.09, 2.75)	0.7%	0.50 (0.09, 2.75)	2.4%
Zoledronic Acid	0.74 (0.63, 0.86)	10.0%	0.28 (0.22, 0.35)	10.9%	0.59 (0.83)	2.3%	NR	NR
All drugs vs placebo	0.81 (0.77, 0.86)	10.5%	0.49 (0.41, 0.58)	11.0%	0.73 (0.63, 0.84)	1.9%	0.82 (0.71, 0.94)	3.1%

Table 2 (*continued*)

Bayesian analysis

	Non-vertebral fracture			Vertebral fracture			Hip fracture			Wrist fracture		
Drug vs placebo	OR (95% Cr I)	Prob	Effect size	OR (95% Cr I)	Prob	Effect size	OR (95% Cr I)	Prob	Effect size	OR (95% Cr I)	Prob	Effect size
Alendronate	0.81 (0.66, 0.96)	0.01	16.1	0.51 (0.37, 0.68)	<0.01	25.3	0.59 (0.29, 0.99)	0.10	9.49	0.93 (0.30, 2.64)	0.10	1.80
Denosumab	0.80 (0.60, 1.06)	0.03	10.7	0.31 (0.21, 0.44)	0.20	53.6	0.67 (0.24, 1.47)	0.12	4.76	NR	NR	NR
Etidronate	0.64 (0.31, 1.27)	0.42	6.4	0.61 (0.29, 1.08	0.01	8.3	1.02 (0.12, 3.91)	0.19	1.01	2.42 (0.25, 10.54)	0.06	0.16
Ibandronate	0.90 (0.69, 1.16)	<0.01	9.3	0.50 (0.29, 0.78)	0.01	16.1	NR	NR	NR	NR	NR	NR
Raloxifene	0.91 (0.69, 1.20)	<0.01	8.4	0.63 (0.43, 0.90)	0.00	13.4	1.29 (0.45, 2.88)	0.01	1.25	1.76 (0.09, 8.22)	0.15	0.27
Risedronate	0.77 (0.60, 0.91)	0.04	16.4	0.60 (0.45, 0.79)	0.00	19.3	0.78 (0.44, 1.32)	0.01	5.71	0.91 (0.13, 3.27)	0.22	1.37
Strontium	0.86 (0.69, 1.07)	<0.01	12.0	0.59 (0.45, 0.76)	<0.01	21.8	0.98 (0.39, 2.01)	0.01	2.47	3.25 (0.17, 14.89)	0.06	0.08
Teriparatide	0.62 (0.38, 1.02)	0.41	9.9	0.32 (0.17, 0.57)	0.30	29.8	0.71 (0.04, 2.90)	0.44	1.93	1.23 (0.05, 5.64)	0.41	0.57
Zoledronic Acid	0.74 (0.56, 0.97)	0.08	12.9	0.28 (0.19, 0.40)	0.40	66.2	0.65 (0.25, 1.34)	0.11	5.53	NR	NR	NR

OR (95% Cr I): Odds ratio (95% Credibility Interval). Prob: probability of that drug being most efficacious.
Effect size evaluated as Odds ratio divided by corresponding standard error. NR: Not reported.

Table 3: Odds Ratio for Fracture , Indirect Treatment Comparison between drugs (Bayesian analysis)

	Non-vertebral fracture		**Vertebral fracture**		**Hip fracture**		**Wrist fracture**	
	OR (95% CrI)	NNT	OR (95% CrI)	NNT	OR (95% CrI)	NNT	OR (95% CrI)	NNT
Denosumab vs Alendronate	0.99 (0.72, 1.42)	1,063	0.63 (0.38, 0.97)	26	1.30 (0.38, 3.35)	-180	NR	NR
Denosumab vs Etidronate	1.26 (0.59, 2.69)	-42	0.58 (0.26, 1.15)	23	1.43 (0.13, 5.97)	-126	NR	NR
Denosumab vs Ibandronate	0.89 (0.61, 1.31)	96	0.67 (0.35, 1.19)	30	NR	NR	NR	NR
Denosumab vs Raloxifene	0.87 (0.59, 1.30)	81	0.51 (0.29, 0.83)	20	0.71 (0.14, 1.89)	184	NR	NR
Denosumab vs Risedronate	1.04 (0.76, 1.54)	-267	0.53 (0.32, 0.82)	21	0.94 (0.27, 2.24)	893	NR	NR
Denosumab vs Teriparatide	1.29 (0.73, 2.26)	-38	1.06 (0.50, 1.99)	-169	3.24 (0.17, 16.89)	-25	NR	NR
Denosumab vs Zoledronic Acid	1.08 (0.73, 1.62)	-134	1.16 (0.66, 1.88)	-65	1.36 (0.30, 3.48)	-150	NR	-14
Etidronate vs Alendronate	0.79 (0.38, 1.61)	50	1.22 (0.54, 2.28)	-48	1.91 (0.20, 7.43)	-60	3.48 (0.22, 16.27)	NR
Ibandronate vs Alendronate	1.13 (0.82, 1.60)	-83	1.00 (0.54, 1.69)	20,428	NR	NR	NR	NR
Ibandronate vs Etidronate	1.44 (0.68, 3.06)	-25	0.92 (0.37, 1.95)	121	NR	NR	NR	-22
Raloxifene vs Alendronate	1.12 (0.82, 1.55)	-90	1.28 (0.78, 1.98)	-38	2.47 (0.71, 6.55)	-38	2.60 (0.08, 11.84)	-39
Raloxifene vs Etidronate	1.41 (0.68, 2.96)	-27	1.17 (0.53, 2.29)	-62	2.76 (0.24, 11.66)	-32	1.87 (0.03, 9.82)	NR
Raloxifene vs Ibandronate	1.02 (0.70, 1.49)	-533	1.36 (0.71, 2.38)	-29	NR	NR	NR	-108
Risedronate vs Alendronate	0.95 (0.71, 1.23)	212	1.21 (0.79, 1.79)	-50	1.47 (0.62, 3.31)	-115	1.31 (0.10, 5.21)	3,328
Risedronate vs Etidronate	1.19 (0.57, 2.49)	-57	1.11 (0.52, 2.18)	-95	1.65 (0.18, 6.64)	-84	0.99 (0.03, 4.68)	NR
Risedronate vs Ibandronate	0.85 (0.60, 1.15)	70	1.29 (0.71, 2.19)	-36	NR	NR	NR	-25
Risedronate vs Raloxifene	0.84 (0.57, 1.15)	65	0.98 (0.61, 1.51)	622	0.79 (0.23, 1.96)	254	2.39 (0.05, 11.67)	-10
Strontium vs Alendronate	1.06 (0.81, 1.44)	-178	1.18 (0.78, 1.71)	-58	1.89 (0.61, 4.70)	-61	4.78 (0.14, 21.71)	NR
Strontium vs Denosumab	1.08 (0.75, 1.53)	-134	1.95 (1.20, 2.99)	-12	1.98 (0.44, 5.03)	-56	NR	-13
Strontium vs Etidronate	1.36 (0.65, 2.86)	-31	1.08 (0.51, 2.07)	-127	2.09 (0.20, 8.75)	-50	3.72 (0.05, 17.44)	NR
Strontium vs Ibandronate	0.95 (0.69, 1.34)	212	1.26 (0.70, 2.15)	-40	NR	NR	NR	-4

Table 3 (*continued*)

	OR (95% CrI)	NNT	OR (95% CrI)	NNT	OR (95% CrI)	NNT	OR (95% CrI)	NNT
Strontium vs Raloxifene	0.94 (0.66, 1.34)	176	0.96 (0.60, 1.46)	243	1.03 (0.23, 2.66)	-1,789	10.85 (0.08, 41.99)	-6
Strontium vs Risedronate	1.12 (0.86, 1.57)	-90	0.99 (0.67, 1.43)	1,890	1.37 (0.44, 3.10)	-146	8.00 (0.15, 38.56)	-3
Strontium vs Teriparatide	1.38 (0.80, 2.35)	-29	1.99 (0.95, 3.66)	-11	4.92 (0.26, 24.44)	-15	19.69 (0.12, 80.47)	NR
Strontium vs Zoledronic Acid	1.17 (0.83, 1.66)	-64	2.17 (1.34, 3.34)	-10	1.93 (0.47, 4.98)	-59	NR	-49
Teriparatide vs Alendronate	0.77 (0.46, 1.31)	45	0.65 (0.31, 1.26)	28	1.35 (0.07, 5.71)	-154	1.69 (0.04, 8.09)	-102
Teriparatide vs Etidronate	0.98 (0.40, 2.30)	531	0.70 (0.39, 1.45)	24	1.54 (0.03, 9.01)	-100	1.33 (0.02, 6.65)	NR
Teriparatide vs Ibandronate	0.69 (0.40, 1.22)	33	0.53 (0.25, 0.98)	32	NR	NR	NR	-13
Teriparatide vs Raloxifene	0.68 (0.39, 1.19)	32	0.55 (0.26, 0.98)	21	0.76 (0.03, 3.27)	223	3.68 (0.02, 15.16)	-16
Teriparatide vs Risedronate	0.81 (0.49, 1.41)	55	0.55 (0.34, 1.04)	22	1.00 (0.05, 4.18)	NR	3.20 (0.04, 14.42)	NR
Zoledronic Acid vs Alendronate	0.91 (0.66, 1.30)	117	0.56 (0.34, 0.88)	22	1.24 (0.39, 3.16)	-225	NR	NR
Zoledronic Acid vs Etidronate	1.16 (0.55, 2.45)	-68	0.52 (0.23, 1.04)	20	1.38 (0.12, 5.70)	-142	NR	NR
Zoledronic Acid vs Ibandronate	0.82 (0.56, 1.19)	58	0.60 (0.31, 1.06)	25	NR	NR	NR	NR
Zoledronic Acid vs Raloxifene	0.81 (0.54, 1.19)	55	0.46 (0.26, 0.74)	18	0.68 (0.15, 1.78)	167	NR	NR
Zoledronic Acid vs Risedronate	0.96 (0.71, 1.41)	265	0.48 (0.29, 0.74)	18	0.91 (0.28, 2.07)	595	NR	NR
Zoledronic Acid vs Teriparatide	1.19 (0.68, 2.08)	-57	0.95 (0.45, 1.83)	216	3.11 (0.17, 16.12)	-26	NR	NR

NR: Not reported. Results are reported as Odds ratio (95% Credibility Interval).

Appendix 1: Literature Search Strategy (Medline)

1. exp Osteoporosis, Postmenopausal/
2. exp Postmenopause Osteoporosis/
3. ((postmenopaus* or post-menopaus*) adj1 (osteoporo* or bone loss or bone reduction)).ti,ab.
4. Fractures, Bone/pc
5. or/1-4
6. (84449-90-1 or 66376-36-1 or 105462-24-6).rn.
7. (raloxifene or evista).ti,ab.
8. (alendronate or fosamax or fosavance).ti,ab.
9. (risendronate or risedronate or actonel).ti,ab.
10. exp Raloxifene/
11. exp Alendronic Acid/
12. exp Alendronate/
13. exp Risedronic Acid/
14. or/6-13
15. Meta-Analysis.pt.
16. Meta-Analysis.sh. or exp Technology Assessment, Biomedical/
17. ((systematic$ adj (literature review$ or review$ or overview$)) or (methodologic$ adj (literature review$ or review$ or overview$))).ti,ab.
18. ((quantitative adj (review$ or overview$ or synthes$)) or (research adj (integration$ or overview$))).ti,ab.
19. ((integrative adj2 (review$ or overview$)) or (collaborative adj (review$ or overview$)) or pool$ analy$).ti,ab.
20. (data synthes$ or data extraction$ or data abstraction$).ti,ab.
21. (handsearch$ or hand search$).ti,ab.
22. (meta analy$ or metaanaly$ or met analy$ or metanaly$ or health technology assessment$ or HTA or HTAs or biomedical technology assessment$ or bio-medical technology assessment$).ti,ab.
23. (meta regression$ or metaregression$ or mega regression$).ti,ab.
24. (Meta Analysis or Systematic Review or Biomedical Technology Assessment).sh.
25. or/15-24
26. 5 and 14 and 25

Appendix 2. WinBUGS code and data

```
#  vertebral fracture

model {
    for (i in 1:N) {logit(p[i])<-mu[s[i]]+delta[i] * (1-equals(t[i],b[i]))
                    r[i]~dbin(p[i],n[i])
            delta[i]~dnorm(md[i],tau)
            md[i]<-d[t[i]] - d[b[i]]  }

for (j in 1:NS) { mu[j]~dnorm(0, .001) }
d[1]<-0
for (k in 2:NT) { d[k] ~dnorm(0,.001) }
sd~dunif(0,2)
tau<- 1/pow(sd,2)

for (i in 1:N) {mu1[i]<-mu[s[i]]*equals(t[i],1) }
for (k in 1:NT) {logit(T[k]) <- sum(mu1[])/23+d[k] }


# ranking and probability { treatment is most effective}
for (k in 1:NT) {rk[k] <-rank(T[],k)
best[k]<-equals(rk[k],1)}

#all pairwise odds ratios
for (c in 1:(NT-1)) {for (k in (c+1):NT) {or[c,k] <- exp(d[k]-d[c])}}
}

#  s[] indicates study
#  t[] treatment
#  r[]numerator
#  n[]denominator
#  b[] comparator treatment for that trial , b[i]<=t[i]   ( =1 if all placebo based )


#  treatment
# 1 placebo
# 2 alendronate
# 3 etidronate
# 4 ibandronate
# 5 raloxifene
# 6 Risedronate
# 7 Teriparatide
# 8 ZA
# 9 Denosumab
# 10    Strontium
```

Data
list(N=46, NS=23, NT=10)

s[]	t[]	r[]	n[]	b[]
1	1	0	49	1
1	2	0	95	1
2	1	145	1005	1
2	2	78	1022	1
3	1	78	2218	1
3	2	43	2214	1
4	1	22	397	1
4	2	5	199	1
5	1	9	50	1
5	3	4	50	1
6	1	0	27	1
6	3	1	27	1
7	1	3	40	1
7	3	0	40	1
8	1	4	27	1
8	3	5	30	1
9	1	0	55	1
9	3	1	54	1
10	1	10	104	1
10	3	5	105	1
11	1	5	18	1
11	3	3	17	1
12	1	73	975	1
12	4	37	977	1
13	1	231	2292	1
13	5	148	2259	1
14	1	17	180	1
14	6	8	177	1
15	1	93	820	1
15	6	61	821	1
16	1	10	125	1
16	6	10	129	1
17	1	0	36	1
17	6	0	37	1
18	1	89	407	1
18	6	53	407	1
19	1	64	448	1
19	7	22	444	1
20	1	310	2853	1
20	8	92	2822	1

```
21 1   264    3691   1
21 9   86 3702   1
22 1   417    1739   1
22 10 263    1725   1
23 1   117    723    1
23 10 75 719    1
END
```

Addendum to Chapter 3

Most of the data used in Chapter 3 were obtained from published journal articles identified in the systematic review of the clinical literature databases. Secondary sources of data were used when data was not available. The secondary sources included data on the trial design that came from the clinical trial web site (http://clinicaltrials.gov). Incomplete data on the number and rates of non-vertebral, vertebral hip or wrist fractures for the drugs alendronate, etidronate, risedronate, raloxifene, teriparatide came from a government health technology assessment report [1]. Similar outcomes data on numbers and rate of fractures came from a pooled analysis of non-published data for ibandronate [2].

In addition, the analysis was conducted without the use of assessing the methodological quality of the randomized trials, such as with a 5 point Jadad scale assessing trials in terms of randomization, blinding, withdrawals, dropouts, and allocation concealment [3].

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CHAPTER 4

Estimating the excess costs for patients with incident fractures, prevalent fractures, and non-fracture osteoporosis.

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Summary. Based on a population age 50+, significant excess costs relative to matched controls exist for patients with incident fractures that are similar in relative magnitude to other chronic diseases such as stroke or heart disease. Prevalent fractures also have significant excess costs that are similar in relative magnitude to asthma/COPD.

Introduction. Cost of illness studies for osteoporosis that only include incident fractures may ignore the long-term cost of prevalent fractures and primary preventive care. We estimated the excess costs for patients with incident fractures, prevalent fractures and non-fracture osteoporosis relative to matched controls.

Methods. Men and women age 50+ were selected from administrative records in the province of Manitoba, Canada for the fiscal year 2007-2008. Three types of cases were identified: 1) patients with incident fractures in the current year (2007-2008), 2) patients with prevalent fractures in previous years (1995-2007), and 3) non-fracture osteoporosis patients identified by specific pharmacotherapy or low bone mineral density. Excess resource utilization and costs were estimated by subtracting control means from case means.

Results. 73% of provincial population age 50+, (52% of all men, and 91% of all women) were included; (121,937 cases, 162,171 controls). There were 3,776 cases with incident fracture (1,273 men, 2,503 women), 43,406 cases with prevalent fractures (15,784 men, 27,622 women) and 74,755 non-fracture osteoporosis cases (7,705 men, 67,050 women). All incident fractures had significant excess costs. Incident hip fractures had the highest excess cost: men $44,963 (95% CI: $38,498 to $51,428) and women $45,715 (95% CI: $36,998 to $54,433). Prevalent fractures (other than miscellaneous or wrist fractures) also had significant excess costs. No significant excess costs existed for non-fracture osteoporosis.

Discussion. Significant excess costs exist for patients with incident fractures and with prevalent hip, vertebral, humerus, multiple and traumatic fractures. Ignoring prevalent fractures underestimate the true cost of osteoporosis.

Introduction

An estimate of the cost of illness of osteoporosis and fractures is required to forecast the current and future health care burden for patients, payers and society. This is essential because of the high prevalence of osteoporosis and consequent fractures. The current estimate of osteoporosis prevalence in Canada is 26% of women and 7% of men age 50 years and older [1,1] Moreover, the number of cases with osteoporosis will escalate rapidly as the Canadian population over age 50 years is estimated to increase by 6.2% per year until the year 2041[2].

Estimating the cost of illness is not straightforward and there are various costing and methodological assumptions that can produce different results. For example, the extent of attribution to health care costs is uncertain. While the acute care admission for a fracture is logically attributable to the fracture, the attribution of post-fracture care is not as straightforward [3]. Specifically, for a patient who has dementia and suffers a fall resulting in a hip fracture, it may be inappropriate to attribute the cost of a subsequent transfer to a nursing home only to the fracture, thus disregarding dementia and other co-morbidities[4]. Similar arguments can be made for the attribution of other resource utilization such as physician visits and assisted daily living. One approach is to use adjudication to identify the attribution of costs [5]. However, without the certainty of attribution to one disease, cost of illness studies may be biased [4].

To reduce the possible bias due to inexact attribution of resource utilization and costs for osteoporosis and fractures, matching methods have been used. One type of matching method is pre-post designs where the patient serves as their own control. For example, the incremental costs (post minus pre) are attributed to the fracture, allowing for adjustment of factors such as total costs in prior year, number of comorbidities, or prior nursing home use[6]. A limitation with using pre-post incremental costs is that the pre and post period for costing must be specified, such as one year. The long-term costs of fractures, such as the need for permanent assistance in daily living, is not captured [7]. Similarly, including pre-fracture costs that are disease related, such as taking bisphosphonates to reduce the risk of fracture, would underestimate the incremental costs.

A different matching method is to estimate the excess cost of a patient with a fracture versus a patient without a fracture [8]. For example, some studies have estimated the excess cost of fractures in cases with fracture and osteoporosis to matched controls with osteoporosis without fracture [9-11]. A key difference in this method from a pre-post design is that the excess costs are focussed on the patient and not the clinical event which may reduce attribution bias[3,12]. However, this method also limits the estimates of cost to a defined period, such as the first year following a fracture.

An important gap in the estimation of the cost of fractures and osteoporosis with matching methods is the exclusion of multi-year costs after a fracture. Studies that look only at the first year after an incident fracture exclude the possibility of costs for

prolonged care which may be fracture related. In addition, cost of illness studies in osteoporosis may also exclude the costs of preventive therapy in patients who have not incurred a fracture.

Our objective was to use matching methods to estimate the excess cost of illness of osteoporosis and fractures that included prolonged care and non-fracture care. First, we estimated the average resource utilization and costs for each of three types of cases (incident fracture, prevalent fracture and non-fracture osteoporosis) versus matched controls. The analysis was conducted across subgroups divided by age, sex, and fracture type. The results of the subgroups were pooled to estimate the excess resource utilization and excess costs of incident fractures, prevalent fractures and non-fracture osteoporosis compared with non-fracture non-osteoporosis controls. In addition, we assessed the factors that were associated with higher excess costs with meta-regression techniques.

Methods

The description of the methods and results follows the suggested reporting standard based on the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement for observational studies [13]. The analysis was conducted with residents in the province of Manitoba for men and women who were aged 50 years and over in fiscal year (FY) 2007/2008 (i.e., April 1, 2007 to March 31 2008.). This subset represents 389,440 potential cases and controls, which was 3.5% of Canadians age 50

and over (11.0 million in the year 2008) [2]. The sampling frame included all residents who had used the health care system in the province at any time during the FY2007/2008. For all patients, any record of hospital admission, physician billing, out-patient pharmacy drug dispensations, or results of BMD testing were linked by a unique anonymous patient identifier within the population-based Manitoba Centre for Health Policy Research Data Repository to identify cases and controls [14]. Residents in Manitoba without the use of health care with zero costs were not available in the database. The data were obtained in an aggregated format, i.e., without variance estimates, and a number of methods discussed later in this section were assessed to impute the variance estimates.

Cases and control definition

Cases and controls were identified from: a) bone mineral density's (BMDs) recorded in the provincial bone densitometry database, b) hospital admissions (International Classification of Diseases 10th revision, Canadian version ICD-10-CA coding) and physician billings (ICD-9th Revision Clinical Modification ICD-9-CM coding) 1995-2008, or c) retail pharmacy dispensations for osteoporosis pharmacotherapy in the previous 12 months. Low BMD levels were defined as a minimum T-score (lumbar spine or hip) of 2.5 or more standard deviation below white female peak BMD. For hospital an admission, a hospital abstract is completed when a patient is discharged from an acute care facility with diagnoses coded using the ICD-10-CA. The ICD-10CA code that corresponded to the greatest portion of the patient's length of stay or cost (the most

responsible diagnosis) was taken from the first diagnosis field. Similarly, physicians submit billing claims to the provincial Ministry of Health for almost all services, including office visits, outpatient and inpatient services; these claims contain a single three-digit ICD-9-CM diagnosis code and optional procedure codes.

Use of osteoporosis medications was obtained by linkage to the Manitoba Drug Programs Information Network (DPIN) database with drugs classified according to the Anatomical Therapeutic Chemical (ATC) system of the World Health Organization (WHO) [15]. A computerized record of all retail pharmacy dispensations is available since April 1st, 1995. The pharmacy database is accurate both for capture of drugs dispensed as well as most prescription details[16]. Each prescription record contains the date of dispensation and an exact identification of the dispensed drug, including substance, strength, route and dosage form. For purposes of the current analysis, osteoporosis pharmacotherapy was defined as any use of oral bisphosphonates, calcitonin, raloxifene, or teriparatide. This excluded secondary osteoporosis who received intravenous bisphosphonates administered in clinics.

Incident fracture cases included patients who had a fracture in FY2007/2008, regardless of previous fractures, osteoporosis medication use or BMD result. Fractures that were included were categorized by type: hip, humerus, vertebral, multiple, trauma and miscellaneous where miscellaneous included femur, lower leg, lower arm, ribs/sternum, shoulder, clavicle, pelvis, or patella.

Prevalent fracture cases included patients who had a previous fracture 1995-2007 without a fracture in the index FY2007/2008, regardless of medication use or BMD result. Non-fracture osteoporosis cases included patients with no history of fractures (incident or prevalent), but with use of pharmacotherapy for osteoporosis in the previous twelve months or low BMD result.

Non-disease controls included residents of Manitoba who did not have an incident fracture in FY2007/2008, a prevalent fracture in 1995-2007, low BMD or dispensation of an osteoporosis medication in the previous twelve months. Potential controls were also required to have at least one health care claim (drug dispensation, physician billing or hospital admission) identified in the healthcare administration records. This excludes residents without a health claim. For each case, up to three controls (if available) were matched based on age, sex and area of residence according to eleven health care regions referred to as Regional Health Authorities (RHAs).

Resource Utilization and Costs

Resource utilization that was captured for cases and controls included: the number of acute care, non-acute care or rehabilitation hospital admissions (and length of stay), number and types of physicians consulted (general practice, internal medicine, imaging specialists, and other specialists), retail pharmacy dispensations, rates of home care admission (and duration of care), and rate of admission to permanent resident nursing assisted Personal Care Homes (and length of stay). Unit costs specific to Manitoba

were applied to the resources identified to estimate costs that included costs for physician services and drugs[6]. In addition, unit costs specific to fracture care as part of home care service are available from Ontario at $24 per day[17] and Ontario had a fixed daily cost of $148 for long-term care [18]. These unit costs were multiplied by the number of days in home care and Personal care Homes, respectively, to estimate home care and Personal Care Home costs.

National average prices for hospital admission were applied based on resource intensity weights. The resource intensity weights for each hospital admission were estimated by the Canadian Institute for Health Information, where the value of the one unit represents the average resource intensity for all national hospital admissions. The value of the resource intensity weight is adjusted relative to the average value for: 1) the Case Mix Group, 2) five other factors that affect resource utilization and length of stay (age, comorbidity levels, flagged interventions, number of intervention events and out-of-hospital interventions), and 3) atypical length of stay or level of care. The national average cost per resource intensity weight ($5,399 per unit), was multiplied by the resource intensity weight to estimate the cost of each hospital admission [19].

Excess resource utilization and excess cost analysis

We estimated the average resource utilization and average costs stratified by 10-year age groups, sex, fracture history (prevalent or incident), and fracture type, which resulted in 150 possible subgroups. The number of possible subgroups were (sex (2) x

age (5) x fracture history (2) x fracture type (7) =140, plus non-fracture (1) times sex (2) x age (5) =10). Similarly, we estimated the average resource utilization and average costs for the matched controls. For each matched subgroup, we then estimated the excess by subtracting the mean resource utilization and mean costs of the controls from the cases. That is, for each of subgroup we generated excess costs for patients with incident fractures versus controls, excess costs for prevalent fractures versus controls, and excess costs for non-fracture osteoporosis versus controls. To provide an estimate of the average excess cost for patients with incident fractures, prevalent fractures or non-fracture osteoporosis regardless of age, we produced a weighted mean of the excess costs weighted by the frequency of the cases in each subgroup.

Uncertainty in evaluating magnitude and significance of excess costs

The data were obtained in aggregated form and no access to patient level data was available to determine the variances for the estimated means. The data for the present analysis were obtained under a previous project grant and it was not feasible to re-extract the data in order to obtain variance estimates. In the absence of variances for aggregated data, there are 25 different methods for handling missing variances[20]. Of these possible methods, four are possible in this analysis; 1) substitute the arithmetic mean for the standard deviation, 2) assume a value for the coefficient of variation (standard deviation/mean), 3) use external data sources that provide estimates of the standard deviation, and 4) acknowledge the missing data and provide a narrative review of the magnitude of the estimates of the excess costs.

Following all available methods, we generated 95% confidence intervals by assuming that the coefficient of variation was one (mean=standard deviation) which is a suggested solution to missing variance [21] and is consistent with similar work on the excess costs of diabetes [22].

Second, to assess the impact that the assumed standard deviation had on the significance of the estimates, we estimated the coefficient of variation for the cases and controls where the lower 95% confidence interval was zero. For example, if the mean cost for a subgroup was $10,000 and if coefficient of variation was six that set the 95% confidence interval to include zero, this implies that the standard deviation for the cases and the controls must be 6 times larger than the mean.

Third, we compared our derived coefficient of variation that created a significant excess cost to external data estimates. One estimate suggested that the coefficient of variation for cases of non-vertebral fractures for Medicare recipients was 1.15[10], while other estimates provided lower estimates of the coefficient of variation. We selected the higher value to be more conservative.

Finally, we simply looked at the magnitude of the estimates of excess costs and ignored whether the estimates may be significant. For this, we compared the magnitude of the excess costs to the excess costs of other diseases in the province of Manitoba[23]. This analysis was conducted with the same dataset using the same costing methodology for the years 2006-2007, but also included aged 19 and over” . The

excess costs for Arthritis, Asthma/Chronic Obstructive Pulmonary Disease (COPD), Diabetes, Coronary Heart Disease, and Stroke were available from the years 2006 and 2007. These excess costs were estimated using the general population as the control group and represented excess costs over a two-year period. To be included as a case, there must have been either two physician visits or one hospital admission where the reason for the visit or the admission was the disease. In addition to the narrative review of the cost ratios (cases/controls), we also estimated the total provincial excess costs for incident and prevalent fractures. Furthermore, we projected our provincial estimate to the national level and then compared our estimate with a national estimate of the cost of osteoporosis by Tarride et al. Tarride et al, using similar costing methods for the same year, estimated the cost of illness for Canada for incident fractures and included a sensitivity analysis from adding the cost of prevalent fractures that required long term care.

Assessment of predictors of excess cost

Methods for the analysis of predictors for aggregate cost data are not well established but random effects meta-regression has been suggested [24]. In the random effects model, the assumption is that the excess costs of different subgroups have a common random distribution component. To evaluate factors that predicted changes in the average excess costs, meta-regression was conducted with subgroup mean excess cost as the dependent variable. The independent variables included sex (women), fracture type (hip, humerus, multiple, miscellaneous, traumatic, vertebral and wrist)

separated by fracture history (incident fracture, prevalent fracture), and five age subgroups (from 50-59 to 90+ years), and the average cost of osteoporosis drugs for each subgroup. Data were available for 148 of 150 possible subgroups because 2 age categories of men did not have multiple fractures, and the base case for the regression was for non-fracture osteoporosis in men age 50-59 years. The meta-regression was conducted with STATA 11.0 SE using the command *metareg[25]*, with the assumption that the standard deviation of the excess costs was equal to the mean costs for each subgroup.

Assessing the effect of the assumption of normality

The assumption of normality was evaluated by performing a meta-regression with the natural log transform of costs and variance. Regression coefficients generated by the log-normal meta-regression were re-transformed to the original linear scale. Regression coefficients after transformation represent the geometric mean effect of the covariates, while the linear regression coefficients represent the arithmetic mean of effect of the covariates. The criterion for statistical significance was set at alpha = 0.05. All costs are reported in 2010 Canadian dollars.

Results

For FY2007/2008, we identified 284,108 individuals in Manitoba meeting the inclusion criteria (73% of the provincial population age 50 years and over, 52% of all men and

91% of all women 50 years and over). In total, 121,937 cases and 162,171 controls were selected, which averaged 1.33 controls for every case. There were 3,776 patients with incident fractures (66% women, 34% men), 43,406 patients with prevalent fractures (68% women, 32% men) and 74,755 non-fracture osteoporosis cases (90% women, 10% men) (see Table 1). For men, the median age occurred in the subgroup 60-69 years for incident, prevalent and non-fracture osteoporosis cases. For women, the median age occurred in the subgroup 70-79 years for incident and prevalent fractures and for the non-fracture osteoporosis cases in the subgroup 60-69 years. The ratio of controls to cases was lowest in elderly women, due to the majority of elderly women satisfying one of the case definitions (e.g., having incurred a fracture or taking osteoporosis medications).

For incident fractures, the most common type was miscellaneous with 37%, followed by wrist 20%, hip 20%, and humerus 11%; vertebral, multiple, and trauma each contributed less than 10%. For prevalent fractures, the most common type was miscellaneous with 40%, followed by wrist 27% and hip 10%; humerus, trauma, multiple and vertebral fractures each contributed less than 10%.

Resource utilization

The resource utilization associated with the controls increased with advancing age. For men in the control group, the annual number of physician visits rose from 7.4 per year for age 50-59 years to 15.3 per year at age 90 years and over. In addition, home care

use rose from 1.1% for men ages 50-59 years to 38.1% for age 90 years and over, and the use of Personal Care Homes rose from 0.2% for men ages 50-59 years to 38.1% for ages 90 years and over.

The excess resource utilization for incident hip fractures involved an extra 1.8 hospital admissions for men and 1.6 for women (Table 2) which includes the acute care admission, and transfers to non-acute beds or rehabilitation beds. There were also excess hospital admissions for incident humerus fractures (0.8 admissions for men and 0.6 admissions for women), but low excess hospital admissions for incident wrist fractures (0.2 for men and 0.3 for women). For all incident fracture sites combined there was excess mean length of stay, physician visits, home care and Personal Care Home use. Excess Personal Care Home use was greatest for incident hip fractures (30.3% excess use for men and 34.9% for women). For men, non-hip incident fractures had less than 10% excess use of Personal Care Homes while for women the excess Personal Care Home use was higher for multiple fractures (29.2%), traumatic fractures (34.7%), and vertebral fractures (10.9%). Incident wrist fractures for women and traumatic fractures for men both resulted in higher Personal Care Home use than for the controls.

For all fracture types, the excess resource utilization for prevalent fractures was smaller than for incident fractures. For prevalent fractures, there were still excess rates of hospital admissions, days in hospital, physician visits, drug use, home care and Personal Care Home use. The excess rates were higher in women than for men for

physician visits, drug use, home care and Personal Care Home use, while rates of hospital admission were similar between men and women.

For the non-fracture osteoporosis cases, there were still positive excess rates of health care utilization for men. However, for women the excess numbers of hospital admissions was 0.1 with zero excess length of stay, with slightly negative excess rates of admission to Personal Care Homes (i.e., use of Personal Care Homes was higher in the non-fracture non-osteoporosis controls than in the non-fracture osteoporosis cases).

Excess Costs

The average cost by sex and fracture type for the cases and the controls are provided in the Additional Files 1 and 2. The average total costs of the controls varied by the age composition of the matched cases, with values ranging from $4,730 to $13,146. The average costs of the cases were higher for incident fractures than prevalent fractures and non-fracture osteoporosis. The highest costs for women were incident traumatic fractures ($69,189) and for men was incident multiple fractures ($60,515),

There were excess costs associated with incident fractures, prevalent and non-fracture osteoporosis (Table 3). For men, the mean excess total cost ranged from $7,831 for an incident wrist fracture up to $44,963 for an incident hip fracture. Similarly, for women, the excess total cost ranged from $4,132 for an incident wrist fracture up to $45,715 for an incident hip fracture. Of the total excess costs, about 70% were associated with the costs of admissions to hospitals.

For prevalent fractures, the average excess total costs for men ranged from $2,767 for a wrist fracture up to $14,103 for a hip fracture. The excess costs for women were higher, ranging from $2,618 for a wrist fracture up to $16,894 for a hip fracture. For men, the excess cost of prevalent fracture largely came from hospital admissions (47%) followed by long-term care (38%), while for women the excess costs mostly came from long-term care (48%) followed by hospital admissions (34%).

For the non-fracture osteoporosis, there was an average excess total cost of $3,227 for men, which were made up of hospital admissions (48%), drugs (20%) and Personal Care Homes (17%). For women with non-fracture osteoporosis, the average excess cost was $689 of which drugs ($504) was the largest contributing factor.
The excess cost estimates were significantly greater than zero for all incident fracture sites, some prevalent fracture sites, but not for non-fracture osteoporosis (Table 4). Both men and women with prevalent fracture had significant excess costs for hip, humerus, multiple and traumatic fractures, but these were not significant for miscellaneous or wrist fractures.

Uncertainty in evaluating magnitude and significance of excess costs

Adjusting the coefficient of variation for the cases and controls until the 95% confidence interval included zero produced large values for incidence fractures ranging from a coefficient of variation of 2.1 for incident multiple fractures in women to 36.7 for multiple

fractures in men. For prevalent fractures, the coefficient of variation was above 1.15 for prevalent fractures except for miscellaneous and wrist fractures. The coefficient of variation for men with non-fracture osteoporosis was 0.5 and for women was 0.1, which indicated the unlikely occurrence that the standard deviation must be half the mean for men and one-tenth the value of the mean excess costs before the excess costs for non-fracture osteoporosis would be significant.

If we ignore the issue of significance and only look at the magnitude of the excess costs in comparisons to other disease, we see that incident and prevalent fractures have high excess costs (Figure 1). The cost ratio (cases/controls) for all incident fractures was 3.2, which was higher than episodes of Asthma/COPD (2.1) and Arthritis (2.9) but less than Diabetes (3.9). The cost ratio for incident hip fracture (4.8), multiple fracture (6.0) and traumatic fractures (5.8) are similar to the cost ratio for episodes of coronary heart disease (4.6) and stroke (5.9).

Prevalent fractures have an average cost ratio of 1.8, which is lower than the cost ratios for the other chronic diseases. However, prevalent hip fractures (2.3), multiple fracture (2.2), traumatic fracture (2.1) had higher cost ratios than Asthma/COPD (2.1). In addition, prevalent humerus (1.9), miscellaneous (1.7) and vertebral (1.9) were also high. The cost ratio for non-fracture osteoporosis was negligibly small (1.2).

The provincial burden for excess costs for incident fractures was $24.0 million for men and $48.8 million for women, for a total excess cost of incident fractures for both sexes

of $72.8 million. The provincial burden for excess costs for prevalent fractures was $70.3 million for men (2.9 times incident fractures), $181.8 million for women (3.7 times incident fractures), for a total excess costs of prevalent fractures for both sexes of $252.1 million (3.5 times incident fractures).

Using our provincial estimates, we projected the national cost of incident fractures as $2.1 billion, and the costs of major prevalent fractures (hip, multiple, traumatic and vertebral fractures) as $3.3 billion (including long term care of prevalent fractures $1.3 billion and excess costs of other services $2.0 billion), for a total burden of $5.4 billion (2.6 times incident costs), or $9.2 billion if we include all prevalent fractures. We compared our projected national estimate to concurrent national estimates obtained by Tarride, and found good agreement although the two sets of data had minimal overlap (Manitoba contains only 3.6% of the Canadian population). Tarride et al. reported the national burden of incident fractures to be $2.3 billion, which is very similar to our national projection of $2.1 billion. The sensitivity analysis from Tarride et al. reported $1.6 billion for long term care of major prevalent fractures, again similar to our national projection of $1.3 billion. Thus, the provincial population estimates appear to be representative of the national average.

Assessment of predictors of excess cost

Based on the random effects meta-regression, the base case male aged 50-59 years with non-fracture osteoporosis had a non-significant excess cost of $145 (P=0.872)

(Table 5). After adjusting for all other factors, the excess costs for women was not significantly different from men (P=0.706), and there were no significant differences by age group. Having an incident hip fracture resulted in significant mean excess costs of $40,302 (95% CI: $14,435 to $65,630: P=0.002). Having an incident fracture other than vertebral, traumatic or wrist also gave significant excess costs. Prevalent fractures of the hip ($11,945: 95%CI $4,065 to $19,825, P=0.003) also resulted in significant excess costs.

Sensitivity Analysis on assumption of normality

When we assessed the impact the assumption of non-normality had on the meta-regression estimates, two important differences occurred. First, using log-normal transformation the level of excess cost for the base case analysis, men aged 50-59 years with non-fracture osteoporosis, was now significant ($2,174: 95%CI: $409 to $11,563: P<0.001). Secondly, prevalent fractures were not a contributing factor in increasing excess costs relative to the base case, and the incident fractures of humerus and miscellaneous were not significant although the coefficients had similar values to the linear coefficients.

Discussion

This analysis demonstrates that there may exist significant excess costs for patients with incident fractures and for some types of prevalent fractures, but not for non-fracture

osteoporosis cases. For incident hip fractures, we report an excess cost of $44,963 for men and $45,715 for women. The mean costs for controls were 19% of those for men with incident hip fractures and 22% of those for women with incident hip fractures. In other work from the same province[6], the costs occurring in the year prior to hip fracture within the same patient represented 38% of the twelve month costs after the fracture for men and 33% for women. The higher correlation between pre and post fracture costs within patients compared with the correlation in post fracture costs between cases and matched controls is not unexpected, since the former approach partially adjusts for the costs of comorbidities. This has also been reported elsewhere, where closer matching increased the correlation between the controls and cases, thereby reducing the magnitude of the excess costs. For example, in an unadjusted matching analysis, the pre fracture costs were 16% to 17% of the incident costs [8]. When both the cases and controls are required to have osteoporosis, effectively matching for a greater level of comorbidity, the cost in the pre fracture period is 31% of the post fracture period, and 41% in a concurrent control group [11]. When the matching includes employment status, the cost in the controls is 40% of the incident fracture cases [10].

The different interpretation of the matching methods is important to address the underlying research question, and whether we looking at the incremental cost of a fracture to patients or the incremental cost to payers for patients with a disease. Matching pre-post with adjustment for comorbidities estimates the incremental cost of a fracture after adjusting for their previous level of care. The closer the match the more certain the cost attribution is to the clinical event alone. Matching to the general

population provides an estimate of the excess cost related to only one factor, the marker for the disease. This latter method is better suited for measuring the overall burden of disease, while pre-post matching is best used for analysis of clinical events [12]. Our results indicate that the excess cost of fracture alone is a significant cost driver because the excess cost for non-fracture osteoporosis is not significantly increased. This indicates that fracture is largely driving the costs and not the underlying osteoporosis and related comorbidities.

Beyond looking at costs in the one-year period before and after a fracture, our analysis included prevalent fractures. The magnitude of the excess costs is lower than that of an incident fracture, but our analysis indicates that excess costs may be significant for fractures, other than miscellaneous and wrist fractures. For example, the magnitude of the cost ratios (cases/controls) where higher than other chronic diseases such as Asthma/COPD which may have significant excess costs. This suggests that cost of illness studies that evaluate only incident fractures may underestimate the cost of fractures and osteoporosis.

However, the Manitoba analysis used methods that were different in a few ways. First, the analysis included age 19 and over, which is different than our aged 50 and over analysis. Whether this difference leads to different ratios is uncertain because the cost of the cases and controls would both rise with age. Second, the Manitoba report provided 3 ratios for diseases including asthma/COPD, a gross population analysis of cases versus non-diseases controls (ratio=1.73), an age and sex matched analysis

(ratio =2.08) and a matched analysis based on age, sex, number of aggregated diagnostic groups (ratio=2.56). This trend in the rise in the ratio with further matching was consistent across all diseases. This trend suggests that the excess cost ratio for an analysis of fractures that included comorbidities would provide an even larger cost ratio.

A limitation to our analysis of the prevalent fractures is that the time-dependence for the costs was not established and the results were averaged for fractures occurring from 1995 to 2007. Since the excess costs of prevalent fractures were significant, having a prevalent fracture in past years is predictive of higher future excess costs for up to 15 years (average 7.5 years), but we cannot claim for which years the post fracture costs were highest. In addition, our analysis did not include cases with osteopenia (BMD between -1 and -2.5 standard deviations below peak reference levels). Also, our analysis looks at the cost of fractures and not necessarily osteoporosis related fractures, such as trauma ICD-10 V codes and E codes (ICD-9) for Accidents. The attribution to osteoporosis may vary by age and might be lower in the lower age groups, such as aged 50 to 59 years.

We also excluded all residents in Manitoba with zero health care expenditure. Although more than 90% of residents aged 50 and over require a physician visit in any given year, we may have excluded from our controls some residents with zero health care expenditure. This may have resulted in an underestimation of excess costs by up to 10%, though we could not calculate this overestimation with any accuracy.

Other limitations to our analysis are that we did not include the cost of emergency room visits because these data were not available in the linkable database Repository. In addition, in Manitoba Canada the codes used for hospitalizations and most institutional services are ICD-10-CA while the ICD codes for physician services are ICD-9-CM. This may have led to discrepancies in diagnostic coding.

Another limitation is the lack of patient level data to estimate variances. However, our analysis indicates that the excess cost of prevalent fractures is likely to be significant over a large range of variances. In addition, when we assumed different shapes of distributions, the results were consistent with the cost estimates based on normality. This finding is supported by simulation analyses of cost differences between two groups each having highly skewed data resulted in a distribution of incremental costs that was still approximately normally distributed, with p-values only changing from 0.05 to 0.06 after adjustment for non-normality [26,27]. However, we encountered a problem with interpretation of the results of our meta-regression of lognormal data where the re-transformed coefficients provided estimates of cost for geometric means instead of arithmetic means. An arithmetic mean is a more important estimate for budget prediction even if other measures such as medians or geometric means fit the data more efficiently [28].

Another limitation is the low level of matching for some of the subgroups where we sought three controls for every case but in some subgroups, we had more controls than cases. This implied that the average cost for all of the controls might be underweighted

by some subgroups if we wished to estimate a provincial average for the controls to estimate excess cost of cases versus the general population.

In conclusion, we observed that the highest excess costs were seen for patients with incident fractures. Patients who have prevalent fractures also incur excess costs, and these excess costs, while lower than the excess costs of incident fractures, may be significant. Patients with non-fracture osteoporosis are not different from non-fracture controls. This suggests that cost of illness studies that evaluate only incident fractures and exclude prevalent fractures may underestimate the cost of fractures and osteoporosis.

Conflict of interest: no disclosures

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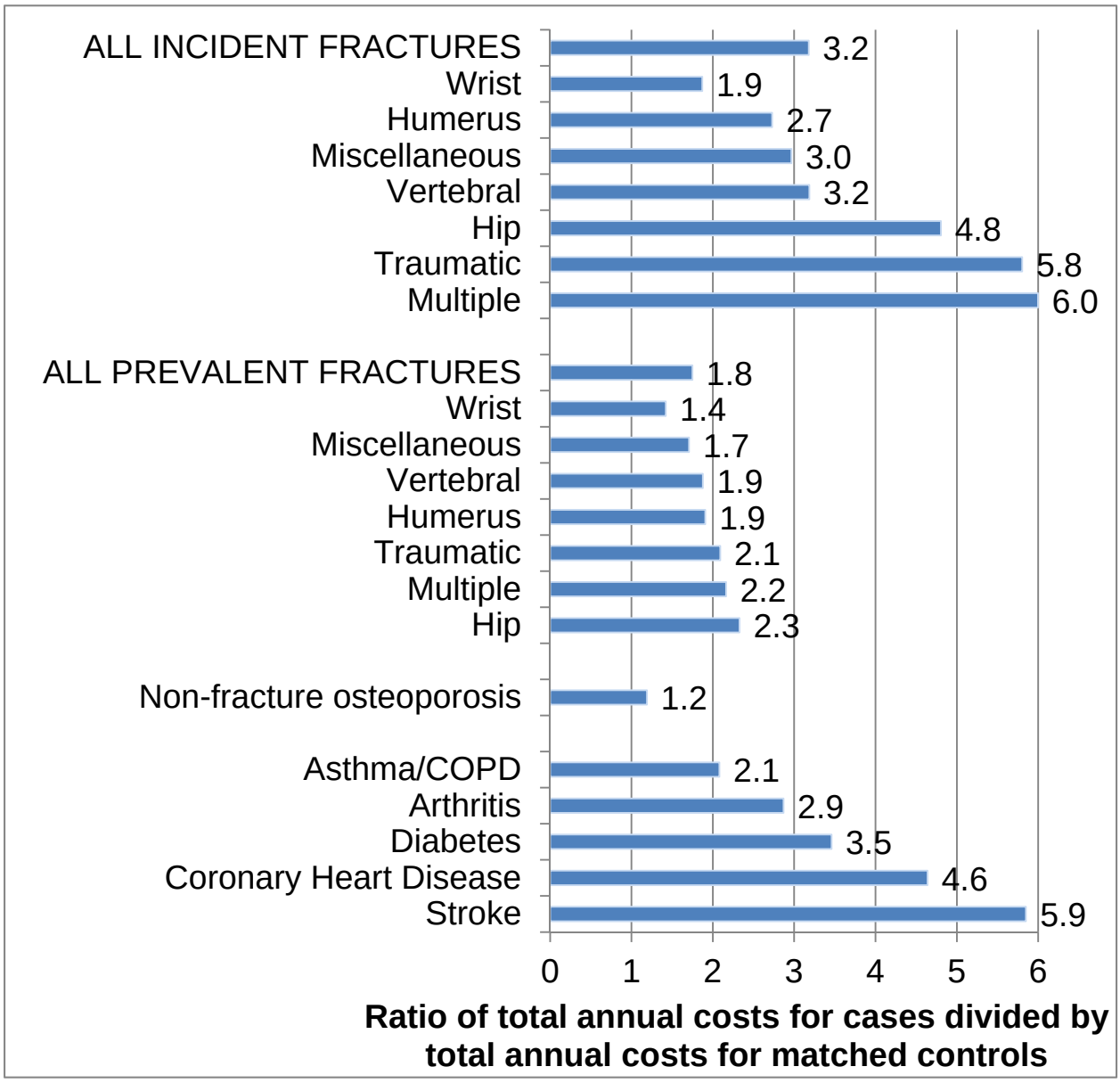
Figure 1. Comparison of the ratio of total annual costs for cases to controls for incident fractures, prevalent fractures, and non-fracture-osteoporosis in comparison to ratios of total annual costs for cases to controls for other chronic diseases for the province of Manitoba.



COPD: Chronic Obstructive Pulmonary Disease.

Table 1: Number of incident fractures, prevalent fractures, non-fracture osteoporosis cases and controls by age and sex in Manitoba.

Men	Total	Hip	Humerus	Multiple	Miscellaneous	Traumatic	Vertebral	Wrist
Incident fracture	1,273	244	96	6	584	14	120	209
Prevalent Fracture	15,784	1172	991	85	8167	1277	1201	2891
Non-fracture osteoporosis	7,705							
Total Cases	24,762							
Number of Matched Controls (N)	71,093							
Ratio controls: cases	2.87							
Provincial population (% captured)	183,137 (52%)							
Women	Total	Hip	Humerus	Multiple	Miscellaneous	Traumatic	Vertebral	Wrist
Incident fracture	2,503	507	310	20	795	70	148	653
Prevalent Fracture	27,622	3154	2867	191	9035	1302	2075	8998
Non-fracture osteoporosis	67,050							
Total Cases	97,175							
Number of Matched Controls (N)	91,078							
Ratio controls: cases	0.94							
Provincial population (% captured)	206,310 (91%)							
Both sexes								
Total Cases	121,937							
Number of Matched Controls (N)	162,171							
Ratio controls: cases	1.33							
Provincial population (% captured)	389,447 (73%)							

Table 2: Average excess health care resource utilization by sex for incident fracture, prevalent fracture and non-fracture osteoporosis cases

	Men				Women			
	Hospital Admissions # (LOS)	Physician (visits)	Home care use %(days)	Personal Care Homes use % (days)	Hospital Admissions # (LOS)	Physician (visits)	Home care use % (days)	Personal Care Homes use % (days)
Patients with Incident Fractures								
Hip	1.8 (34.2)	25.0	35.2% (36.7)	30.3% (47.4)	1.6 (36.2)	21.9	33.3% (38.0)	34.9% (50.3)
Humerus	0.8 (13.2)	15.4	21.8% (37.7)	6.6% NS (16.1)	0.6 (8.3)	10.3	21.8% (31.8)	6.9% (5.1)
Multiple	0.7 (19.8)	11.2	9.9% NS (7.9) NS	7.8% NS (14.1)	1.5 (38.7)	29.4	36.1% NS (22.0)	29.2% NS (40.9)
Miscellaneous	0.6 (7.8)	11.2	9.4% (15.0)	2.7% (2.7)	0.6 (12.5)	13.3	21.1% (32.9)	6.1% (7.4)
Traumatic	1.3 (26.2)	14.6	40.0% NS (60.8)	-1.0% NS (-6.2)	1.7 (53.6)	24.1	37.9% (43.9)	34.7% (22.2)
Vertebral	0.8 (10.3)	13.3	16.1% (22.9)	1.6% NS (-2.6)	0.7 (13.3)	15.3	27.0% (48.2)	10.9% (9.5)
Wrist	0.2 (2.7)	6.0	5.4% (11.5)	1.5% (3.8)	0.3 (2.0)	32.2	8.7% (15.8)	-0.1% (-0.7)
Patients with Prevalent Fractures								
Hip	0.2 (7.2)	5.2	12.7% (37.6)	18.4% (42.6)	0.1 95.8)	5.5	11.8% (36.1)	25.7% (71.3)
Humerus	0.1 (4.2)	4.5	7.0% (16.0)	5.6% (12.8)	0.2 (2.9)	4.4	10.0% (24.2)	7.5% (17.6)
Multiple	0.2 (2.4)	3.2	5.9% NS (15.7)	2.5% NS (6.8)	0.2 (3.8)	15.0	14.1% (46.2)	6.9% NS (19.7)
Miscellaneous	0.2 (1.5)	3.3	3.6% (8.1)	2.3% (4.9)	0.3 (2.5)	5.4	7.6% (21.0)	6.1% (15.3)
Traumatic	0.2 (4.5)	3.9	5.7% (12.6)	4.6% (6.2)	0.2 (5.3)	5.9	11.8% (33.7)	12.2% (26.1)
Vertebral	0.1 (2.0)	3.5	4.0% (9.3)	4.4% (9.0)	0.2 (4.4)	7.1	12.2% (33.5)	8.6% (20.7)
Wrist	0.1 (1.5)	2.6	1.7% (4.8)	1.9% (5.1)	0.2 (1.0)	3.1	3.9% (9.7)	2.4% (6.0)
Patients with Non-fracture osteoporosis								
Non fracture	0.2 (1.6)	5.4	3.5% (9.6)	2.2% (5.0)	0.1 (0.0)	3.4	0.9% (2.7)	-0.2% (-0.9)

(LOS): Excess number of hospital admissions per case (excess average length of stay)
NS: Not statistically different than zero based on testing of count data with an assumption of a Poisson distribution, adjusted for multiple testing.

Table 3: Average excess costs by source of costs by sex for incident fracture, prevalent fracture and non-fracture osteoporosis

	Men						Women					
	Excess Costs ($)						Excess Costs ($)					
	Hospital Admissions	Physician	Drugs	Home care	Personal Care Homes	Total costs	Hospital Admissions	Physician	Drugs	Home care	Personal Care Homes	Total costs
Patients with Incident Fractures												
Hip	$33,796	$2,683	$517	$1,362	$6,606	$44,963	$34,906	$2,441	$440	$913	$7,015	$45,715
Humerus	$9,080	$1,100	$499	$904	$2,249	$13,832	$7,954	$712	$773	$763	$714	$10,914
Multiple	$38,607	$4,654	$1,217	$641	$9,271	$54,390	$31,472	$3,252	$486	$528	$5,702	$41,439
Misc.	$8,420	$820	$550	$359	$379	$9,862	$10,815	$971	$729	$789	$1,037	$14,341
Traumatic	$35,675	$2,068	$2,591	$1,444	-$737	$41,042	$50,279	$2,550	$774	$1,055	$3,098	$57,755
Vertebral	$12,485	$1,471	$637	$903	-$256	$15,240	$13,405	$1,223	$1,255	$1,158	$1,325	$18,365
Wrist	$6,339	$662	$280	$313	$237	$7,831	$1,908	$1,648	$291	$378	-$93	$4,132
Patients with Prevalent Fractures												
Hip	$5,745	$301	$485	$990	$6,582	$14,103	$5,313	$306	$474	$866	$9,934	$16,894
Humerus	$4,855	$314	$434	$390	$1,988	$7,982	$2,422	$273	$611	$580	$2,449	$6,336
Multiple	$5,478	$217	$15	$114	$1,663	$7,486	$3,760	$925	$1,096	$1,108	$2,748	$9,636
Misc.	$1,631	$184	$312	$236	$727	$3,090	$2,293	$299	$615	$503	$2,135	$5,845
Traumatic	$3,041	$191	$382	$260	$543	$4,416	$5,657	$338	$652	$809	$3,635	$11,091
Vertebral	$2,660	$270	$491	$319	$1,567	$5,307	$3,547	$398	$897	$804	$2,885	$8,531
Wrist	$1,378	$114	$142	$73	$788	$2,767	$1,086	$159	$309	$232	$833	$2,618
Patients with Non-fracture osteoporosis												
Non fracture	$1,606	$280	$679	$211	$451	$3,227	$129	$143	$478	$64	-$124	$689

Table 4: Average cost per cases and controls, average excess cost with an assessment of uncertainty of cost distribution

	Men					Women				
	n	Case Average cost	Control Average costs	Excess costs (95% CI)	C.V.	n	Case average cost	Control average costs	Excess costs (95% CI)	C.V.
Patients with Incident fractures										
Hip	244	$55,521	$10,558	$44,963 ($38,498; $51,428)	7.0	507	$58,463	$12,748	$45,715 ($36,998; $54,433)	5.2
Humerus	101	$19,983	$6,152	$13,832 ($5,676; $21,987)	9.0	310	$17,905	$6,991	$10,914 ($8,724; $13,105)	5.0
Multiple	12	$60,515	$6,125	$54,390 ($52,098; $55,873)	36.7	27	$54,100	$12,661	$41,439 ($39,600; $43,279)	22.5
Miscellaneous	584	$16,126	$5,503	$10,624 ($7,612; $13,616)	3.5	795	$21,545	$7,204	$14,341 ($10,202; $18,481)	3.5
Traumatic	29	$50,903	$9,862	$41,042 ($39,025; $43,058)	20.4	75	$69,189	$11,434	$57,755 ($53,839; $61,672)	14.7
Vertebral	125	$22,442	$7,203	$15,240 ($13,312; $17,167)	7.9	148	$26,537	$8,172	$18,365 ($16,180; $20,550)	8.4
Wrist	209	$13,068	$5,237	$7,831 ($6,341; $9,321)	5.3	653	$10,301	$6,168	$4,132 ($2,148; $6,116)	2.1
Patients with Prevalent fractures										
Hip	1,172	$23,864	$9,762	$14,103 ($7,670; $20,536)	2.2	3,154	$30,040	$13,146	$16,894 ($5,138; $28,650)	1.4
Humerus	991	$13,951	$5,970	$7,982 ($4,496; $11,467)	2.3	2,867	$14,687	$8,351	$6,336 ($552; $12,120)	1.1
Multiple	87	$12,996	$5,510	$7,486 ($6,524; $8,448)	7.8	191	$18,614	$8,978	$9,636 ($7,788; $11,484)	5.2
Miscellaneous	8,167	$8,222	$5,132	$3,090 (-$3,008; $9,188)	0.5	9,035	$13,118	$7,273	$5,845 (-$2,986; $14,676)	0.7
Traumatic	1,277	$9,259	$4,842	$4,416 ($1,697; $7,136)	1.6	1,302	$19,844	$8,753	$11,091 ($6,046; $16,136)	2.2
Vertebral	1,201	$12,013	$6,706	$5,307 ($1,883; $8,781)	1.5	2,075	$17,727	$9,196	$8,531 ($2,691; $14,371)	1.5
Wrist	2,891	$7,701	$4,934	$2,767 (-$776; $6,310)	0.8	8,998	$9,541	$6,923	$2,618 (-$4,309; $9,546)	0.4
Patients with Non-fracture osteoporosis										
Non fracture	7,705	$8,754	$5,527	$3,227 (-$3,118 , $9,572)	0.5	67,050	$5,419	$4,730	$689 (-$8,492 , $9,870)	0.1

95% confidence intervals estimated assuming the standard deviation equal to the mean.
C.V. coefficient of variation (standard deviation/mean) where 95% confidence interval includes zero.

Table 5 Meta-regression of subgroup level predictors of average excess cost

	Linear Meta-regression model			Log transform Meta-regression model		
Independent Variables	Estimate (95% CI)		P-value	Estimate (95% CI)		P-value
Women	$368	(-$1,544; $2,280)	0.706	$2,251	($583; $8,687)	0.960
Incident-Hip	$40,032	($14,435; $65,630)	0.002	$27,417	($2,434; $308,883)	0.040
Incident-Humerus	$7,341	($1,712; $12,971)	0.011	$6,980	($687; $70,943)	0.324
Incident-Multiple	$21,626	($3,504; $39,748)	0.019	$29,173	($2,351; $361,959)	0.043
Incident-Miscellaneous	$9,432	($2,444; $16,420)	0.008	$9,053	($903; $90,799)	0.225
Incident-Traumatic	$9,172	(-$231; $18,576)	0.056	$22,747	($2,118; $244,259)	0.053
Incident-Vertebral	$338	(-$1,571; $2,247)	0.728	$10,742	($858; $134,441)	0.215
Incident-Wrist	$1,339	(-$535; $3,213)	0.161	$1,435	($168; $12,274)	0.704
Prevalent-Hip	$11,945	($4,065; $19,825)	0.003	$9,127	($916; $90,963)	0.221
Prevalent-Humerus	$3,503	($573; $6,433)	0.019	$4,018	($428; $37,696)	0.591
Prevalent-Multiple	-$163	(-$1,920; $1,595)	0.856	$5,860	($555; $61,860)	0.410
Prevalent-Miscellaneous	$2,375	(-$33; $4,783)	0.053	$3,117	($340; $28,568)	0.750
Prevalent-Traumatic	$2,527	(-$164; $5,219)	0.066	$4,595	($489; $43,219)	0.513
Prevalent-Vertebral	$4,262	($979; $7,544)	0.011	$4,281	($421; $43,487)	0.567
Prevalent-Wrist	$820	(-$853; $2,494)	0.337	N.A.	N.A.	N.A.
Age 60 to 69 years	$1,016	(-$505; $2,537)	0.190	$2,672	($581; $12,281)	0.791
Age 70 to 79 years	$910	(-$1,632; $3,452)	0.483	$3,943	($716; $21,717)	0.494
Age 80 to 89 years	$3,269	(-$444; $6,982)	0.084	$5,094	($899; $28,862)	0.336
Age 90+ years	-$15	(-$2,366; $2,336)	0.990	$4,140	($818; $20,946)	0.436
Osteoporosis drug costs	-$17	(-$55; $21)	0.378	$2,170	($2,128; $2,213)	0.852
Constant	$145	(-$1,612; $1,902)	0.872	$2,174	($409; $11,563)	<0.001

Dependent variable is excess cost. The constant represents the base care result for men aged 50 to 59 years with non-fracture osteoporosis N.A. Prevalent-wrist was dropped in regression due to collinearity with other predictors. All predictors are binary except osteoporosis drugs, which is in the linear meta-regression is interpreted as 1 dollar extra in osteoporosis drugs, on average, is associated with a drop of $17 in excess cost. All other coefficients are interpreted as the change in the additional excess cost with the addition of the independent variable.

Additional File 1: Average cost of matched controls by sex for incident fracture, prevalent fracture and non-fracture osteoporosis

	Men						Women					
	Control Costs ($)						Control Costs ($)					
	Hospital Admissions	Physician	Drugs	Home care	Personal Care Homes	Total Costs	Hospital Admissions	Physician	Drugs	Home care	Personal Care Homes	Total Costs
Incident fractures												
Hip	$4,670	$726	$1,403	$838	$2,921	$10,558	$4,080	$613	$1,338	$1,382	$5,335	$12,748
Humerus	$2,792	$555	$1,142	$400	$1,263	$6,152	$2,561	$520	$1,126	$665	$2,119	$6,991
Multiple	$2,683	$491	$1,020	$421	$1,510	$6,125	$4,139	$628	$1,373	$1,389	$5,131	$12,661
Other	$2,527	$533	$1,110	$338	$994	$5,503	$2,578	$514	$1,105	$701	$2,307	$7,204
Traumatic	$4,278	$664	$1,287	$762	$2,871	$9,862	$3,811	$606	$1,324	$1,242	$4,450	$11,434
Vertebral	$3,284	$617	$1,247	$502	$1,553	$7,203	$2,930	$549	$1,193	$831	$2,669	$8,172
Wrist	$2,404	$518	$1,082	$314	$920	$5,237	$2,330	$503	$1,082	$571	$1,682	$6,168
Prevalent Fractures												
Hip	$4,325	$697	$1,359	$753	$2,627	$9,762	$4,156	$614	$1,340	$1,425	$5,611	$13,146
Humerus	$2,746	$563	$1,160	$382	$1,119	$5,970	$2,960	$550	$1,193	$847	$2,801	$8,351
Multiple	$2,541	$540	$1,120	$338	$970	$5,510	$3,141	$563	$1,223	$927	$3,124	$8,978
Other	$2,369	$518	$1,086	$303	$856	$5,132	$2,606	$516	$1,114	$711	$2,326	$7,273
Traumatic	$2,250	$509	$1,073	$274	$736	$4,842	$2,988	$539	$1,164	$894	$3,170	$8,753
Vertebral	$3,045	$585	$1,189	$455	$1,433	$6,706	$3,169	$559	$1,214	$957	$3,296	$9,196
Wrist	$2,285	$510	$1,073	$284	$783	$4,934	$2,556	$521	$1,126	$666	$2,055	$6,923
Non-fracture osteoporosis												
Non-fracture	$2,552	$542	$1,127	$339	$967	$5,527	$1,875	$462	$988	$389	$1,016	$4,730

Average cost of controls varies by fracture type due to matching fractures by age groups.

Additional File 2: Average cost of cases by sex for incident fracture, prevalent fracture and non-fracture osteoporosis

	Men						Women					
	Average Costs for Cases ($)						Average Costs for Cases ($)					
	Hospital Admissions	Physician	Drugs	Home care	Personal Care Homes	Total Costs	Hospital Admissions	Physician	Drugs	Home care	Personal Care Homes	Total Costs
Incident fractures												
Hip	$38,466	$3,409	$1,920	$2,200	$9,527	$55,521	$38,986	$3,054	$1,778	$2,295	$12,349	$58,463
Humerus	$11,871	$1,655	$1,642	$1,304	$3,511	$19,983	$10,515	$1,232	$1,899	$1,428	$2,832	$17,905
Multiple	$41,290	$5,146	$2,237	$1,062	$10,781	$60,515	$35,611	$3,880	$1,859	$1,917	$10,832	$54,100
Other	$10,946	$1,353	$1,661	$636	$1,530	$16,126	$13,393	$1,485	$1,834	$1,490	$3,343	$21,545
Traumatic	$39,953	$2,732	$3,878	$2,206	$2,134	$50,903	$54,090	$3,155	$2,098	$2,297	$7,548	$69,189
Vertebral	$15,768	$2,088	$1,885	$1,405	$1,297	$22,442	$16,335	$1,773	$2,447	$1,989	$3,994	$26,537
Wrist	$8,743	$1,179	$1,362	$627	$1,157	$13,068	$4,238	$2,151	$1,373	$950	$1,589	$10,301
Prevalent fractures												
Hip	$10,070	$999	$1,844	$1,742	$9,209	$23,864	$9,469	$920	$1,814	$2,291	$15,545	$30,040
Humerus	$7,601	$877	$1,594	$772	$3,107	$13,951	$5,382	$823	$1,804	$1,427	$5,251	$14,687
Multiple	$8,019	$757	$1,135	$452	$2,633	$12,996	$6,900	$1,488	$2,320	$2,035	$5,872	$18,614
Other	$4,001	$702	$1,398	$539	$1,583	$8,222	$4,899	$815	$1,729	$1,214	$4,461	$13,118
Traumatic	$5,291	$700	$1,455	$534	$1,278	$9,259	$8,645	$876	$1,816	$1,703	$6,805	$19,844
Vertebral	$5,705	$855	$1,679	$775	$3,000	$12,013	$6,717	$957	$2,111	$1,761	$6,181	$17,727
Wrist	$3,877	$647	$1,218	$389	$1,571	$7,701	$3,641	$679	$1,435	$897	$2,888	$9,541
Non-fracture osteoporosis												
None	$4,158	$822	$1,806	$550	$1,418	$8,754	$2,004	$605	$1,466	$453	$891	$5,419

CHAPTER 5

Conclusions of the thesis

There are many clinical and methodological issues in the research of osteoporosis. A subset of such issues include; 1) estimating the national lifetime risk of hip fracture that incorporates national trends in the rate of hip fracture and mortality, 2) estimating relative efficacy between osteoporosis medications to reduce the rate of fracture in the absence of active comparator trials, and 3) testing the significance and magnitude of excess costs of incident and prevalence fractures in the absence of variance estimates.

We have conducted research on these important topics in a 'sandwich theses', with each chapter dedicated to investigating each of the issues. In this chapter, the findings of the research in this thesis are summarized and we discuss their implications.
In Chapter 2, we used national administrative data from fiscal year April 1, 2007 to March 31, 2008 to identify all hip fractures in Canada. We estimated the crude lifetime risk of hip fracture for age 50 years to end of life using life tables. We projected lifetime risk incorporating national trends in hip fracture and increased longevity from Poisson regressions. Finally, we removed the percentage of second hip fractures to estimate the lifetime risk of first hip fracture.

In 2008, we estimated the unadjusted lifetime risk of hip fracture was lower at 12.1% (95%CI: 12.1, 12.2%) for Canadian women and 4.6% (95%CI: 4.5, 4.7%) for Canadian

men. This compares to a previous national estimate of 14.0% for women and 5.2% for men in 1996 [1]. In addition, when we projected rates of mortality and hip fracture were both included in the estimation, the lifetime risk of hip fracture was not significantly different for women or men. When trends in mortality and hip fractures were both incorporated, the lifetime risk of hip fracture was lower 8.9% (95%CI: 2.3, 15.4%) and 6.7% (95%CI: 1.2, 12.2%). The lifetime risks for first hip fracture were 7.3% (95%CI: 0.8, 13.9%) and 6.2% (95%CI: 0.7, 11.7%).

Factors that may have contributed to decreased population risk of hip fracture in Canada and the United States include the increased use of calcium, vitamin D, recent introduction and uptake of bisphosphonates among other osteoporosis medications, decreased smoking and increased body mass index [2,3].

One negative consequence of increased longevity is that hip fractures may occur at a later age. This is concerning because with longevity there is an increased risk of developing comorbidities such as dementia, diabetes, peripheral neuropathy which are known predictors of falls and fractures [4]. In addition, the rate of mortality and costs of hip fractures increases with the number of comorbidities and age.

The strengths of this analysis are that we relied on national data for hip fractures and mortality over a common period, and we identified fractures from mandatory reporting in our public health care system. A limitation was that we used the rates of second hip fracture from a different country and time period, although similar estimates of the rate

of second hip fractures are found elsewhere [5,6]. Future research on whether the percent of fractures that are first or second by age is changing over time would be helpful. Similarly, future work on the lifetime risk of all fractures may be clinically useful. Another limitation was in the projection of the rates of hip fractures and mortality into the future, which is admittedly uncertain and could continue, stabilize or even reverse. If the risk of hip fracture can continue to decline or further accelerate, some mitigation of the burden due to the increased numbers of hip fracture arising from an ageing population may occur.

In Chapter 3, a systematic literature review of multiple databases identified randomized placebo-controlled trials with nine drugs for post-menopausal women. Odds ratio and 95% credibility intervals for the rates of hip, non-vertebral, vertebral, and wrist fractures for each drug and between drugs were derived using a Bayesian approach. A drug was ranked as the most efficacious if it had the highest posterior odds ratio, or had the highest effect size.

We identified 30 studies including 59,209 patients reported fracture rates for nine drugs: alendronate (6 studies), denosumab (1 study), etidronate (8 studies), ibandronate (4 studies), raloxifene (1 study), risedronate (7 studies), strontium (2 study), teriparatide (1 study), and zoledronic acid (1 study). Based on the combination of effect size and probability of being most efficacious, teriparatide, zoledronic acid and denosumab are consistently ranked highest for reducing non-vertebral and vertebral fractures. Estimates were consistent between Bayesian and classical approaches.

A few limitations were observed in using the highest posterior odds ratio and probability of being most efficacious based on ranking of posterior odds ratios. The primary concern is apparent with the drug etidronate, which was ranked high on probability of being most efficacious but there are reservations with this result. Specifically, etidronate does not have a statistically significant odds ratio versus placebo for non-vertebral fracture while other drugs do. The higher ranking may be due to a wide confidence interval that covers a lower region of odds ratio creating a favourable relative result over that region of low odds ratio. This suggests a limitation with this analysis where a requirement for ITC analysis may be that the odds ratio for different drugs should have similar widths. A second caution with the results for etidronate is that the trials were small resulting in small effect sizes and the trials were conducted prior to the year 2000. This suggests that there is a lack of current strong evidence for the efficacy of etidronate versus placebo. As a result of these two limitations, this analysis suggests that etidronate should not be considered among the most efficacious drugs based on current evidence, and a robust estimate would come from similar sized trials that occurred over a more recent and common time period.

This work updates the most recent study for ITC analysis in osteoporosis medications which looked at vertebral, hip and nonvertebral nonhip fractures [7] for five drugs, zoledronic acid, alendronate, ibandronate, risedronate and etidronate. In our analysis, we included more studies for etidronate, alendronate, and risedronate in addition to adding denosumab, raloxifene, strontium and teriparatide. The earlier work reported that zoledronic acid had the highest probability of preventing vertebral fractures (0.79),

but in our analysis this probability of being most efficacious becomes 0.40. In addition, denosumab (0.20) and teriparatide (0.30) have important rankings and were no previously analyzed. For non-vertebral fractures, the earlier work reported that risedronate had the highest probability of being most efficacious (0.87) while we report that teriparatide (0.41) and etidronate (0.42) have the highest rankings, and the probability that risedronate was most efficacious falls to 0.04.

The other objective of this analysis was to compare the results across two statistical methods. The first method was based on Bayesian ITC analysis in WinBUGS, and the second method was the results from classical Bucher analysis with ITC specific software. The estimates differed only by the second decimal place, which we suggest is not clinically important.

The analysis is limited in that the results are based on ITC comparisons. However, a recent review of the results of DTC and ITC analysis demonstrated that the DTC effect is smaller than the ITC effect size [8]. In our ITC analysis, there were non-significant differences for the rates of non-vertebral fracture and significant differences for vertebral fractures between drugs but the true effect between drugs may be even smaller.

The other assessment of strength of evidence in the indirect comparisons beyond looking at classical versus Bayesian analysis was to look at heterogeneity within drugs and across drugs. There was a high level of heterogeneity in the estimates of odds ratios for wrist fractures, and the evidence for wrist fractures should be considered

weak. Increased heterogeneity can be caused by differences in inclusion criteria or study design such as length of follow-up, and these are also important factors for consideration for analysis of DTC studies [9]. In our analysis, we did not have enough power to detect the impact of baseline characteristics because of a low number of studies for each drug [10].

ITC is becoming a useful tool in the absence of DTC comparisons and increasing transparency of ITC analysis builds confidence for the evidence. In the future, stronger evidence may come from head-to-head studies but this is unlikely, because based on this analysis differences between comparators are not significant and studies would require very large sample sizes. In light of the lack of DTC evidence, the ITC analysis of RPCTs may be the strongest evidence that will be available that answers the important clinical question of determining the most efficacious treatment for preventing fractures.

In Chapter 4, men and women over age 50 years were selected from administrative records in the province of Manitoba, Canada in the fiscal year 2007-2008. Three types of cases were identified: 1) patients with incident fractures in the current year (2007-2008), 2) patients with prevalent fractures in previous years (1995-2007), and 3) non-fracture osteoporosis patients identified by specific pharmacotherapy or low bone mineral density. Cases were matched up to 1:3 with controls based on age, sex and area of residence. One hundred forty-eight subgroups based on sex, age group, fracture type (hip, humerus, wrist, vertebral, miscellaneous fracture, multiple site and trauma) grouped by history (incident, prevalent), and non-fracture osteoporosis were

created. Cost distributions were assumed normal with mean equal to standard deviation. The assumptions of normality and the mean-standard deviation relationship were tested in sensitivity analyses. Random effects regression was conducted to identify factors associated with excess costs.

We estimated that all incident fracture types had significant excess costs. Patients with incident hip fractures had the highest excess cost: men $44,963 (95% CI: $38,498 to $51,428) and women $45,715 (95% CI: $36,998 to $54,433), and prevalent fractures (other than miscellaneous or wrist fractures) also had significant excess costs. No significant excess costs were seen with non-fracture osteoporosis. This suggests that cost of illness studies that evaluate only incident fractures may underestimate the cost of fractures and osteoporosis. These results were robust to the lognormal specification and higher standard deviation values, and no differences existed by sex and older age. Matching to the general population provides an estimate of the excess cost related to only one factor, the marker for the disease. Our results suggest that residents that suffered a fracture up to 15 years ago have on average more health care costs than age and gender matched non-disease controls. The magnitude of the excess costs for prevalent fractures is lower than that of an incident fracture, but our analysis indicates that these excess costs may be significant for fractures other than miscellaneous and wrist.

A limitation in our analysis of the prevalent fractures is that the time-dependence for the costs was not established and the results are averaged for fractures occurring between

1995 and 2007. However, since the excess costs of prevalent fractures were significant, having a prevalent fracture in past years is predictive of higher future excess costs, but we cannot claim for which year the post fracture costs were highest.

The second limitation is the lack of use of patient level data to estimate variances. In the absence of variances for aggregated data, four methods were possible in this analysis; 1) substitute the arithmetic mean for the standard deviation, 2) assume a value for the coefficient of variation (standard deviation/mean), 3) use external data sources that provide estimates of the standard deviation, and 4) acknowledge the missing data and provide a narrative review of the magnitude of the estimates of the excess costs.

We found significant results when the standard deviation was set to the mean, and when the standard deviation was raised to be consistent with other studies. Our analysis indicates that the excess cost of prevalent fractures is likely to be significant over a large range of variances. In addition, the magnitude of the excess costs was similar to other chronic diseases for incident and prevalent fractures.

In addition, when we assumed different shapes of distributions, the results were consistent with the cost estimates based on normality, although the presence of approximate normality may be a reasonable assumption. However, we encountered a problem with interpretation of the results of our meta-regression of lognormal data where the re-transformed coefficients provide estimates of cost for geometric means instead of arithmetic means. An arithmetic mean is a more important estimate for

budget prediction even if other measures such as medians or geometric means fit the data more efficiently [11]. We suggest that more research on the interpretation and findings of meta-regression with log-normal data would be helpful.

In summary, we have provided some important clinical and economic findings. First, we have found that the lifetime risk hip fracture for men and women is falling for Canada. Second, we identified the most efficacious drugs for preventing fracture due to osteoporosis, although the differences between drugs are often not significant. Third, we detected that patients who have experienced a fracture have high costs in the year of the fracture but also have high costs for many years after their fracture.

In addition, we have identified and investigated some methodological problems in the research for osteoporosis. First, we showed that the creation of a life table to estimate the lifetime risk of hip fracture that is unadjusted for trends in rates of fracture and mortality is misleading. In Canada, both the age-specific rates for hip fracture and mortality are falling, and when balanced against each other, the declining rate of hip fracture has greater influence. However, the falling rate of hip fracture is not observed in other countries, and the precision of the lifetime risk is not certain due to high confidence intervals. Although hip fractures are one of the most common types of fracture, future research that investigates lifetime risks of all types of fracture would be clinically useful.

A second set of methodological issues relates to using ITC methods to infer relative efficacy between drugs. Based on this work, ITC methods must have some underlying characteristics before it is robust. First, there must be consistency and little heterogeneity within each drug for the estimate of effect. When we investigated wrist fractures, removing studies that contributed to high heterogeneity altered the results significantly, this produced further uncertainty of effect. In addition, the comparisons could be considered fair if the confidence intervals for each drug versus placebo were similar in sizes. We discovered that one drug, etidronate, had wide confidence intervals and was ranked higher for being most effective although it had an unfavourable odds ratio versus placebo in classical analysis for preventing fractures. We also discovered that different methodologies, Bayesian analysis with MCMC simulations, ITC specific software and STATA analysis using metaregression all produce similar results.

From the third paper we investigated two biostatistical problems; 1) dealing with the absence of measures of variance for aggregate data and 2) investigating a non-normality assumption in aggregate cost data. In the absence of variances from the estimates, we demonstrated that an assumed mean-standard deviation relationship that is consistent with other studies and magnitude of effect were useful for inference. When we investigated the non-normality assumption using meta-regression, the transformed estimates were difficult to interpret and to compare with the linear estimates. Further work on meta-regression using log transformation is required.

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