Assessment of an evidence practice gap at the population level: Screening for osteoporosis in Ontario

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Glossary

ADGs: Aggregated Diagnosis Groups categories
AGREE: Appraisal of guidelines for research and evaluation.
BMD: Bone mineral density
BMI: Basal Metabolic Index
CADTH: Canadian Agency for Drugs and Technologies in Health
CaMOS: Canadian Multicentre Osteoporosis Study
CAROC: Canadian Association of Radiologist and Osteoporosis Canada
CPGs: Clinical Practice guidelines
DALY: Disability-Adjusted Life year
DXA: Dual-energy x-ray absorptiometry
FRAX ®: WHO Fracture risk assessment tool
ICC: Intra-class correlation coefficient
ICD: International Classification of Diseases
ICES: Institute for Clinical Evaluative Sciences
IOM: Institute of Medicine
ISCD: International Society for Clinical Densitometry
KTA: Knowledge to action
LHIN: Local Health Integrated Network
NGN: National Guidelines Network
NICE: The National Institute for Health and Care Excellence
NOF: National Osteoporosis Foundation
NOFSA: National Osteoporosis Foundation of South Africa
NOGG: National Osteoporosis Guideline Group
OHIP: Ontario Health Insurance Plan
OP: Osteoporosis
QUS: Quantitative Ultrasound
SD: Standard deviation.
SIGN: Scottish Intercollegiate Guideline Network
T-score: The number of standard deviations that a BMD measurement lies above or below the average value for young healthy women
WHO: World Health Organization

Authors' Contributions

I am first author of the two papers. Dr. Graham and I came up with the idea for the research project, developed the research protocol. I completed the research ethics board application and the ICES approval forms to obtain the data set, conducted the data analysis and the majority of the write up for each chapter.

Introduction (Chapter 1)

- I was main the author of this paper
- Dr. Ian Graham; planned the structure of the chapter, revised it and provided feedback.

Paper 1- Authors (Chapter 2) – Screening for Osteoporosis: Systematic assessment of the quality and content of the clinical practice guidelines using the AGREE II instrument and the IOM standards:

- I am the main author of this paper: searched database, screened, and appraised the studies, analyzed the data and interpreted the results.
- Dr. Ian Graham: developed the design for this paper, suggested the use of AGREE II and comparison to the IOM, revised the draft several times and provided feedback.
- Dr. Peter Tugwell: Revised the draft and provided feedback.
- Said Yousif: Screened a sample of full text articles and acted as one of the AGREE II appraisers.

Paper 2- Authors (Chapter 3) -

- I'm the primary author of this paper.
- Dr. Ian Graham suggested the use of ICES data to meet our objective.
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- Dr. Carl van Walraven helped with the analysis, providing guidance and answering questions for the ICES data coding and suitable approaches to reach the results.

Discussion of the thesis- (Chapter 4)

- I am the author of this chapter
- Dr. Ian Graham provided guidance to the structure and planning for this chapter, revised it and provided feedback

ABSTRACT

Osteoporosis is a common health problem and it is increasing in prevalence due to the increase in the aging population. The interest to treat osteoporosis has increased in recent years, due to availability of screening modalities, advances in medications that may prevent osteoporotic fractures. Many studies have showed the high medical and economic burden of the disease on the patients, their caregivers and on the health system.

Clinical practice guidelines for management of osteoporosis varied nationally and internationally, and the adherence of physicians to guidelines were always reported as suboptimal, though most studies were for after fragility fracture care gap and vert few looked at the primary screening to identify patients at risk before the occurrence of fractures.

This thesis is composed of two manuscripts research project assessing the development and impact of screening for osteoporosis guidelines. The first chapter is an overview of osteoporosis, definition, risk factors, diagnosis and treatment. A follow up discussion of the literature on adherence of physicians to the osteoporosis guidelines, which ends up with the rational for this thesis.

The first paper is a systematic review to identify guidelines for screening for osteoporosis from 2002-2016 (Chapter 2). We assessed the quality of these guidelines using the AGREE II and IOM standards, compared between the two tools, and assessed if the quality has changed over time. We extracted recommendations in key areas with summary of the systems that were used to assign the level of evidence and strength of recommendations. We found that the quality of guidelines has varied greatly between different countries with no significant change over time. The recommendations and systems for level of evidence were variable and all this may create confusion to clinicians.

In the second paper, we used an interrupted time series design to assess the effect of three clinical practice guidelines for screening for osteoporosis in Ontario on the baseline bone mineral density (BMD) testing for older adults 65 years of age and above using administrative data by ICES from 1998-2006. All three guidelines recommend baseline BMD testing for this age population. In addition, we analyzed the pattern of repeated testing in accordance with the latest guideline. We have found low rates of baseline BMD testing with a decreasing pattern of testing. The last guideline in 2010 had gradually increased the trend of BMD testing, though it was a very small change. Stratified analyses by sex showed that the decrease in the total BMD testing is due to decrease in the testing for female population while there is an increasing trend of BMD testing in male population. CPG by Osteoporosis Canada in 2010 caused an immediate reduction in the BMD testing for female, yet, over a period of time, the guideline increased the BMD testing. For male population; the 2002 CPG had immediately increased the BMD testing, while over time this trend has decreased.

Despite the low baseline BMD testing by physicians, there is an over use of repeated BMD testing in the low risk population, especially the annual and the 2 yearly BMD repeats.

In conclusion:

This research project found a varied quality of guideline development and reporting of guidelines for osteoporosis screening, and no improvement in the quality over time (2002-2016). Several systems were used to assign the level of evidence and strength of recommendations with conflicting recommendations between different health organizations in the same country such as in Canada. Many tools are available to appraise the quality of guidelines, however, comparing between two tools (AGREE II & IOM standards) showed that they may give conflicting results for guidelines quality. There is no effect of guidelines for screening for osteoporosis on the ordering of BMD testing to screen adults 65 years and above living in Ontario between 1998- 2016. A small increase the rate of baseline BMD testing followed the release of the 2010 guideline. For male population the 2002 guideline showed an evident immediate and gradual effect over time on the rate of baseline BMD testing ordering for male population. Despite the low baseline BMD testing rates for adults 65 years and above, there is an unnecessary repeated BMD testing for low risk population in Ontario between 2011-2016 which is not in compliance to the latest guideline for screening for osteoporosis.

Chapter 1 – Introduction

The number of effective health care interventions and innovations is growing exponentially, this includes evidence of new interventions that are demonstrated to be effective, and older ones found to now be ineffective. To give a sense of the volume of this new knowledge, more than 30, 000 randomized controlled trials are indexed in Cochrane Central Register of Controlled Trials in 2016 alone [1]. In the past 5 years, 1273 clinical practice guidelines were indexed in the National Guidelines Clearinghouse [2]. The challenge however, is that translating new healthcare interventions and innovations into daily practice is haphazard and slow[3] .It has been reported in US studies that patients are not getting the appropriate care, or they are receiving unnecessary or harmful care [2,3]. In Canada, the lack of standardized information about health care delivery and adherence to evidence based practices across the country hinders the ability to draw conclusion about the effectiveness of our health care [6]. A new report by the Common Wealth Fund reveals that we perform better than the United States, but lagging behind other countries [7], so there is much room for improving the uptake of evidence-based practice. Clinical practice guidelines are one way of translating new evidence into practice to improve patients' care.

Clinical Practice Guidelines (CPGs)-an overview

Clinical practice guidelines (CPGs) are defined by the Institute of Medicine as "Statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [8]. Guidelines are one approach of incorporating evidence into practice [9]. They provide an evaluation of the quality and level of the evidence from the relevant literature to find the benefits and harms of a particular intervention and use this evidence to formulate recommendations. Therefore, a good quality guideline benefits patients through better outcomes, fewer ineffective interventions, minimize variability of care and helps policy makers to support coverage of reimbursement decisions for most effective services [9]. Conversely, a faulty guideline could significantly harm both patients and clinicians, thereby it is important to have a vigorous methodology as a basis for

guideline development [10]. An important point to consider is that guidelines should not supersede professional judgment, Clinicians should always act and decide in the best way that can serve their patients, regardless of guideline recommendations [9].

Many types of documents are offered as practice guidelines, although some may not actually be based on systematic review and appraisal of the empirical evidnce[9]. A legitimate guideline must fulfill specific criteria; many instruments and tools have been developed listing certain criteria for guideline development. For example, The Appraisal of Guidelines Research & Evaluation (AGREE) instrument which was updated in 2010 is a widely used measure of guideline quality [11]; criteria of the AGREE II are found in *Appendix S2-B*. The institute of Medicine (IOM) developed a set of Standards for developing rigorous, trustworthy guidelines [8]; [*standards are shown in Appendix S2-C*]. The Conference on Guideline Standardisation Checklist (COGS) is another tool [12]. There is a number of papers that discuss the process of developing guidelines [12,13], and many guideline developer organizations reported their guideline methodology on their websites. Most approaches agree that key aspects in guideline development include a multidisciplinary panel, involvement of all stakeholders, identifying a priority topic or a problem, systematically reviewing and appraising the literature to grade the levels of evidence and draft the recommendations, external consultation and planned updating.

Factors affecting uptake of clinical practice guidelines

Despite the increasing number of guidelines that are being produced around the world which requires great effort and substantial cost, unfortunately it is constantly reported that there is a gap between guideline recommendations and real patient care [15]. This indicates that implementation of guidelines is not optimal. A myriad of literature discusses a variety of frameworks that describe the different factors that contribute to guideline uptake. Grol and Grimshaw identified three attributes that affect uptake of a guideline: 1) Attributes of the guideline which entails the quality of the guideline, the health problem type, complexity of the decision-making needed, skills and organizational change needed to follow the recommendations. 2) Barriers and facilitators to changing

practice which can arise at different levels, at the level of patients, the individual professional, the health care team, health care organization or wider environment. 3) effective dissemination and implementation strategies [3].

Graham et al 2006 developed a framework to transfer knowledge into practice referred to as the 'Knowledge To Action Cycle' [16] [*Figure S1- 1 in the Appendix of Chapter 1*]. Their model can be used as a template or a guide to systematically explain the multiple factors that may play a role in implementation of the guidelines[16]. In this cycle there are two main processes; the first is the creation of knowledge process which involves identifying an important topic, finding and synthesizing the evidence for that knowledge (such as a clinical guideline for osteoporosis). The second process of the cycle is applying this evidence (e.g. guideline) to practice. This involves seven actions or phases that are needed for the evidence to be implemented; (1) identify the knowledge to action gap, (2) adapt knowledge to local context, (3) assess barriers to knowledge use, (4) select, tailor and implement interventions, (5) monitor knowledge use, (6) evaluate outcomes, (7) sustained knowledge use [16].

According to their framework the uptake of knowledge (e.g. guidelines or evidence) can be affected by factors linked to the guideline, adopters of the guideline such as physicians, patients and organizations, and the setting in which the guideline be implemented [16]. Therefore, to assess the barriers for guideline implementation, we should assess the barriers at the different levels, and direct interventions at the appropriate target level.

Kastner et al 2015 in their review found six domains of guideline implementability within 2 broad categories: the creation of guideline content, and the communication of this content [17] . The creation of guidelines includes four domains: 1) stakeholder involvement which, 2) evidence synthesis, 3) considered judgement: supplementing evidence-based formulation of recommendations with considered judgement and 4) implementation feasibility. The communication of guidelines entails 2 domains: 1) the message of the guideline should be simple, clear, concise and persuasive. 2) The format of the guideline which should involve multiple formats, specific components within the guideline (purpose, methods and recommendations) and the appearance of the guideline which involves layout, structure and visualisation [17].

Osteoporosis definition and epidemiology

Bone strength is based on the integration of bone density and bone quality. Bone density is determined by peak bone mass and the amount of bone loss, while bone quality is reflected through the architecture, damage accumulation and mineralisation of bone [18].

Osteoporosis is a skeletal disease characterized by low bone mass and deterioration in the architectural arrangement of the bone tissue that leads to impaired skeletal strength, with an increased risk of fragility (osteoporotic) fractures [19]. This disease is usually silent without any symptoms until fractures have occurred. The most common sites for these fractures are in the vertebra (spine), proximal femur (hip), and distal forearm (wrist) and they are usually caused by a minimal force, that usually don't cause a fracture in a healthy bone (e.g. fall from standing height or less) [19].

Epidemiologic studies have found numerous factors that may lead to mismatch between bone formation and resorption leading to bone loss and resulting in osteoporosis; a thorough review of these factors and their mechanism is beyond the scope of this document. Some risk factors act independently from bone mineral density (BMD), while others increase fracture risk through lowering BMD (e.g. secondary causes of osteoporosis), Table S1-A in the Appendix of this chapter lists these factors [20].

Osteoporosis is very common; worldwide, one in three women and one in five men after the age of 50 will experience osteoporotic fractures in their lifetime, and majority of fractures occur in those at the age of 65 years or older [21–23]. In Canada; it was estimated that two million Canadians are affected by osteoporosis with 20% are having osteoporotic fractures [24]. Worldwide osteoporosis causes around 9 million fractures annually, of which more than 4.5 million in North America and Europe [25].

The adverse effects of osteoporotic fractures fall into three broad categories: mortality, morbidity and cost. The effect varies by fracture type; hip fractures are associated with higher mortality and morbidity since they usually require hospitalization, result in disability, and are associated with 10-36% excess in mortality in the first year post fracture with higher incidence in men than in women [26]. In the Canadian Multicentre

Osteoporosis Study (CaMOS), both men and women had increased incidence of death of 23.5% after hip fracture [27]. In Europe, the number of deaths causally related to hip fractures accounted from more than 1% of all deaths [28]. Recovery from hip fracture is slow and rehabilitation is usually insufficient, with almost 15-25% require admission to nursing homes which extend the waiting times for these homes [24].

Other types of osteoporotic fractures also account for a considerable proportion of the global health and economic burden of osteoporosis [25]. Vertebral fractures may have less complications, yet it is more common and only 30% of these fractures are clinically detected [29]. They are associated with substantial disability from pain and spine deformity, and it was shown that one vertebral fractures leads to increase risk of recurrent vertebral fracture by 2-folds [30]. The economic cost of osteoporosis related fractures is high because of the earlier discussed medical impact; it was estimated to cost the Canadian health system more than $ 4 billion per year using 2010 data [31].

Diagnosis of osteoporosis and fracture risk assessment

In 1994, the WHO proposed a diagnostic criteria to define osteoporosis based on measuring BMD by dual energy X-ray absorptiometry (DXA), this measure is transformed into T-score which gives the number of SDs by which the individual's BMD differs from the expected mean value for a young white female adult [32]. The T-score threshold of each definition category is given in Table 1-1 below [32].

Table 1-1 WHO diagnostic criteria for diagnosis of osteoporosis [34]

Definition	Criteria
Normal	BMD value within 1 SD of the young adult reference mean (T-score ≥ -1.0)
Osteopenia	T* score between (-1.0 and -2.5)
Osteoporosis	T score ≤ -2.5
Severe osteoporosis	T score <-2.5 plus one or more fragility fracture

*When standard deviation (SD) are used in relation to the healthy young adult population, this is referred as T score.

As discussed earlier, there are many factors that increase the risk for fracture either through BMD or independently (Table S1-A), thus there has been a growing opinion that intervention thresholds for osteoporosis should be based on absolute risk of fracture, rather than solely on diagnostic thresholds based on BMD. Data have showed that more than half of women who have fragility fracture don't have osteoporosis or a T-score lower than -2.5SD, but they have osteopenia (T-scores between -1.0 and -2.5) [33]. This has led to the development of many instruments and tools that integrated risk factors to predict the absolute risk for fracture, and one of the most widely used is the FRAX tool, which is a country specific tool, that was developed by the WHO and the National Osteoporosis Foundation to predict individual fracture risks [34], it is available on the website http://www.sheffield.ac.uk/FRAX/tool.jsp?country=19

The tool includes Femoral neck or total hip BMD (optional to use or not), with other risk factors: age, sex, height, body mass index, previous fracture, family history of hip fracture, glucocorticoid use, current smoking status, daily alcohol use, rheumatoid arthritis, other secondary causes of osteoporosis including (type I insulin dependent diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years), chronic malnutrition, or malabsorption and chronic liver disease). It is useful in predicting the risk of hip fracture and major osteoporotic fractures, i.e., clinical spine, hip, proximal humerus and distal forearm fractures in previously untreated men and women aged 40-90 years [35]. The fracture risk can be estimated as low (<10% in 10 years), moderate (10-20% in 10 years), or high (>20% in 10 years).

Another tool is developed by the Canadian Association for Radiologist and Osteoporosis Canada (CAROC), it is a paper based risk table and BMD test result is required to use this tool [36]. It is available at (http://www.osteoporosis.ca/health-care-professionals/clinical-tools-and-resources/fracture-risk-tool/). This tool is based on the Canadian 2010 Osteoporosis Guidelines [37]. It was validated in 2 Canadian cohorts and was found almost 90% in agreement with the FRAX score [38].

It is worth noting that the combination of BMD and clinical risk factors for fracture, predicts fracture risk better than BMD or risk factors alone. Thus, FRAX predicts fracture risk better if BMD results were available [39].

FRAX has many limitations; patient with previous fracture in the spine may have risk for vertebral fracture, which may not be captured with the FRAX model, since many vertebral fractures are not detected clinically, and maybe under-reported in the population based studies upon which FRAX was based [40]. In addition, dose effect is not considered in the tool, so it doesn't take in account if the patient had more than one previous fragility fracture and doesn't weight the number of cigarette per day. Secondary causes of osteoporosis are assigned an identical risk in FRAX, despite that in the studies, the strength of association with fracture has been shown to vary s depending on the underlying condition [40]. Furthermore, it doesn't take other risk factors such as increased risk of falls, other medications than steroid, and family history of spinal fractures into account [41]. Additionally, the algorithm that was used to develop the FRAX calculator was not published (in the public domain), thus it is not possible to validate it by independent researchers or organizations [40]. An important point to consider as well that FRAX has not been validated in patients receiving treatment, so it cannot be used to assess fracture risk for those patients or to assess response to therapy [39]. Other tools were developed and used by different countries, discussing these is out of this introduction scope.

There are many other techniques that can be used to measure bone mass, such as quantitative ultrasound (QUS*)* at the heel; Quantitative computed tomography (QCT), High resolution peripheral quantitative computed tomography (HR-pQCT), and Magnetic resonance imaging (MRI); till recently none have been found to be a substitute for DXA [25].

Clinical Practice Guidelines for Screening for Osteoporosis and the uptake of the Canadian guidelines

Many health agencies and jurisdictional Governments have developed recommendations and guidelines for screening and management of osteoporosis. Pervious reviews showed that they varied considerably between different organizations and

between different countries [42–44]. The quality of osteoporosis guidelines for postmenopausal women between 1998-2001 was assessed in a systematic review by Cranney et al 2002 using 37 items (not AGREE II). They found most guidelines were of low quality (rigour of development median score scored only 23%) with lack of dissemination strategies (median score for applicability was 0%) , and very few were acceptable to be used in their existing format (the content scored very low) [42]. Lewiecki in 2005 reviewed eight osteoporosis guidelines; none of them was developed in Canada, and reported inconsistency in some recommendations and considerable variation in the population addressed [44].

Several Canadian guidelines were developed by different organizations, all recommend screening all women and men ≥ 65 years of age, and screening for those at age of 50 years if they have certain risk factors [26,46–48]. In Canada, many studies and reports have shown low adherence of physicians in following the guidelines for management of osteoporosis; report using administrative data (ICES data) in 2006 reported that only 19% of those aged 65 years or older were tested for BMD (DXA) [48]. Another report using 2007 ICES data, found that BMD testing by DXA for adults 65-70 years of age, who were not previously tested, was only 21% [49]. Osteoporosis Canada reported in 2011, that a huge care gap existed; almost 80% of Canadians with fragility fractures were neither screened nor treated for their osteoporosis [24]. On the other hand, despite of low BMD testing, there is evidence of overtesting of low risk individuals; Hawker et al 2012 found high number of baseline BMD testing for midlife healthy women, and very few had low BMD [50]. A qualitative study by Munce et al. 2016, had identified a lack of clarity in BMD testing by family physicians with a tendency to over-test low risk healthy post-menopausal women, while under-testing of high-risk groups and specifically men [51].

Most identified studies in the literature focused on the after fracture care gap for patient, with emphasis on after fracture BMD testing, or measuring overall BMD testing trends. Few studies focused on the pre-fracture practice gap related to screening of osteoporosis before the occurrence of the fracture [52–54].Thus, intuitively we can conclude that those patients with fragility fractures were not primarily screened nor assessed for

risk of fracture by their physicians, which suggests an evidence practice gap. In order to prevent the burden of fragility fractures it is important to focus on the primary prevention of the fractures by early detection of high risk individuals.

To our knowledge, no previous study has assessed the impact of the Canadian osteoporosis guidelines on the baseline (first) BMD testing by clinicians, and very few studies assessed the baseline BMD testing trends. Additionally, no recent study has assessed the quality of osteoporosis guidelines since 2002, since high quality guidelines with rigorous methodology are an important factor in the uptake of recommendations. Based on the 'Knowledge to Action' framework that was discussed earlier, we divided the thesis into two parts: one part focused on systematically identifying the available guidelines for screening for osteoporosis and assessing their quality and content from 2002-2016. The second part is to assess the effect of the Canadian guidelines on the baseline BMD testing by physicians. The thesis objectives are presented below:

Objectives of the thesis

Objective 1: To systematically review the quality of osteoporosis clinical practice guidelines from 2002-2016.

To achieve this objective, we systematically reviewed the clinical practice guidelines for screening for osteoporosis between 2002-2016, assessing their quality using the AGREE II instrument and the Institute of Medicine (IOM) standards for trustworthy guidelines. We extracted the main recommendations and systems for level of evidence and strength of recommendations. (Chapter 2).

Objective 2: To assess the impact of Ontario clinical practice guidelines for screening for osteoporosis on the baseline bone mineral density testing by physicians, and the pattern of repeated testing and its accordance to the latest guidelines.

To achieve this objective, we have conducted a time series analyses to assess the effect of release of 2002, 2004, 2010 CPGs on the monthly baseline bone mineral density (BMD) testing by DXA for adults 65 years and older from 1998-2016. We identified the pattern of bone mineral density testing from 2011-2016 and examined its accordance with the latest osteoporosis guideline (Chapter 3).

APPENDIX FOR CHAPTER 1

Figure S1-1: Knowledge to Action Cycle [15].

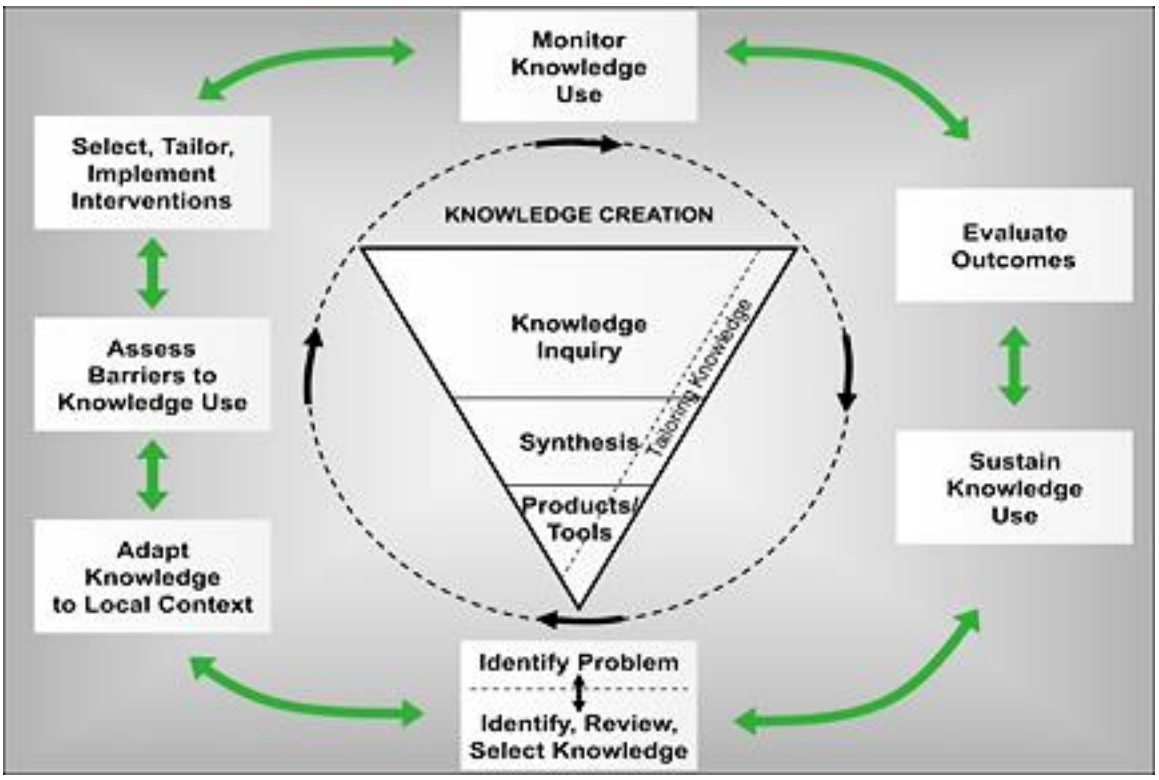

Table S1-A: Significant Risk factors for osteoporosis [19].

Risk factors dependent on BMD	Risk factors independent on BMD
▪ Age ▪ Premature menopause (<45 years) ▪ Previous history of fragility fracture ▪ Maternal history of hip fracture ▪ Glucocorticoid therapy ▪ Smoking ▪ Alcohol intake >3units/day ▪ Rheumatoid Arthritis ▪ Low BMI (<20) ▪ Falls ▪ Caucasian ▪ Geography; latitude furthest than equator	▪ Untreated hypogonadism ▪ Malabsorption ▪ Endocrine diseases (e.g. hypothyroidism) ▪ Chronic renal disease ▪ Chronic liver disease ▪ Chronic obstructive pulmonary disease ▪ Immobility ▪ Drugs, e.g. Androgen deprivation therapy, aromatase inhibitors

BMD= bone mineral density

Chapter 2: Screening for Osteoporosis: A Systematic Assessment of the Quality and Content of Clinical Practice Guidelines, using the AGREE II Instrument and the IOM standards

ABSTRACT

Background: Numerous clinical practice guidelines (CPGs) are published to guide management of osteoporosis. Little is known about the quality and the recommendations of these guidelines and how they have changed over time.

Objective: To systematically assess the quality and content of the guidelines on screening for osteoporosis published since 2002, using the Appraisal of Guidelines for Research and Evaluation version II (AGREE II) tool and the Institute of Medicine (IOM) standards for trustworthy guidelines, investigating how the quality of the guidelines have changed over time, comparing the results of AGREE II tool with the IOM standards, and comparing the main recommendations between the recent guidelines.

Methods: We conducted a systematic search for osteoporosis CPGs released between 2002 and 2016 indexed in multiple databases and guideline websites. Two reviewers appraised the quality of eligible CPGs using the AGREE II, a standardised score and other descriptive statistics were calculated for each of the six domains. High quality CPGs were considered if they scored ≥ 60 in four or more domains including domain 3 for rigor of development. Non-parametric tests were used to test for the change of quality over time (≤2010 vs >2010). One reviewer assessed the guidelines with IOM standards with defined criteria to choose high quality guidelines. We summarized the different grading systems to assign the level of evidence and strength of recommendations and extracted and compared the recommendations in certain areas.

Results: A total of 33 CPGs were identified. Mean AGREE II, domain scores for clarity of presentation, scope and purpose, and rigor of development were (71%, 64%, and 63%) respectively. Lower mean domain scores for stakeholder involvement, editorial independence and applicability were 55%, 54%, and 42% respectively. Assessment by IOM standards showed that 67% and 64% of CPGs met standards for systematic review evidence and establishing evidence and rating strength of recommendation respectively. 64% and 61% of guidelines met standards for articulation of recommendation and establishing transparency correspondingly. Fewer guidelines met standards for management of conflict of interest, updating, external review and development group composition (55%, 42%, 39% and 27%) respectively. The difference in AGREE II and IOM defined guidelines' quality before and after the introduction of AGREE II in 2010, and IOM standards in 2011, was statistically insignificant for both tools (P values >0.05). The IOM

identified four more guidelines as high quality compared to the AGREE II. Examining these additional guidelines indicated that the two tools may give conflicting results especially for the rigor of development domain. Recommendations in areas of whom to screen, and when to treat showed substantial differences between guidelines; in different countries and sometimes between authorities in the same country.

Conclusion: This study found that the adherence of CPGs on screening for osteoporosis to the AGREE II and IOM guideline's quality criteria is variable. Furthermore, the actual recommendations are often not in agreement. However, many of the identified guidelines were of high quality based on the appraisal instruments used. Guidelines developers could improve the quality of their guidelines by paying greater attention to guideline applicability and editorial independence. Including all possible stakeholders in the guideline development process would also strengthen their guidelines. A lack of uniformity between recommendations was found in important areas of how and whom to initially screen, and when to treat patients with osteoporosis. In addition, there is variability in the use of grading systems for level of evidence and strength of recommendations. Differencing recommendations, and evidence grading systems can create confusion for clinicians and patients and may lead to poor guideline adherence. Differences between the appraisal tools (AGREEII vs IOM) may also affect clinicians' decisions about which guideline to implement with subsequent impact on patients' outcome. More studies are needed to validate the IOM standards and to compare the performance AGREE II with IOM standards.

BACKGROUND

Osteoporosis is a disease characterised by low bone mass and deterioration of the bone tissue structure leading to increased bone fragility and liability to fractures [1]. These fractures usually result from low mechanical forces such as a fall from standing height or less, that usually don't cause a fracture[2]. The most common sites of these fractures are in the spine, hip, and wrist [2]. Osteoporosis lead to nearly 9 million fractures annually worldwide [1].

Low bone mass is a major risk factor for fractures, however, there are many other factors that contribute to osteoporosis including age, sex, previous fractures, family history of osteoporosis, use of systemic glucocorticoids, excessive alcohol and smoking [3]. The prevalence of osteoporosis rises rapidly with age; thus the incidence of fractures is predicted to increase with the increased longevity of the population [4]. These fractures are associated with higher mortality and morbidity; in the Canadian Multicentre Osteoporosis Study (CaMOS), both men and women had increased incidence of death of 23.5% (20/85) after hip fracture.[5] In addition to decreased quality of life and burden on caregivers[6]. The economic cost of these fractures is high; Hopkins et al in 2016, estimated that it costs the Canadian health system more than $4 billion per year [7].

Osteoporosis is usually diagnosed based on bone mineral density 'BMD' measurement by dual energy x-ray absorptiometry 'DXA'. T-scores of 2.5 standard deviation below the expected mean value for a young white female adult, is considered diagnostic [8]. Since low bone density is not the only risk factor for osteoporosis, a variety of tools were developed to aid in diagnosis and decision to decide the initiation of pharmacological treatment. These tools incorporate the main risk factors for osteoporosis with or without the DXA testing T-score; such tools are CAROC, FRAX, QFracture, and others [9].

Clinical practice guidelines (CPGs); which are defined by the Institute of Medicine as "*Statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options*" [10]. Guidelines should consist of recommendations for assessment

and management of specific diseases based on the latest evidence. They are one of the options to improve patient's quality of care since they are intended to transfer evidence into practice, decrease variability in clinical practice and decrease costly and avoidable harms or mistakes [10,12]. The number of guidelines have increased substantially from just 437 indexed in MEDLINE in 1993 to 1320 in 2016. [13] . However, the effect of CPGs on improving the process and outcome of care have varied widely [14]. Furthermore, even for well- developed guidelines, their adoption and use is not an automatic process and depends greatly on the dissemination process and how they are implemented [16,17]. Therefore, a rigorous process of identifying, evaluating, and adapting evidence in a transparent manner with efficient management of conflict of interests during the development process is found crucial for guideline dissemination. [17].

In past years, there were many calls and efforts to improve the development of guidelines, and to standardize the method of development. The AGREE II instrument was developed by an international team of researchers to define the essential components of a good guideline [18]. A review by Vlayen et al 2005, for tools used to evaluate CPGs, found that the AGREE tool is the most validated compared to 24 other tools, with easy scored numerical scales [19]. Different frameworks to grade the level of evidence have been released; the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has been adopted by many organizations and guideline developers such as NICE, and WHO [20,21]. Recently, the GRADE Working Group has developed a framework "the Evidence to Decision (EtD)", to assist the process of progressing from evidence to making clinical recommendations, coverage decisions, and health system or public health recommendations and decisions [20]. This framework has three main sectors: Formulating the question, assessing the evidence, and additional considerations for each criterion and drawing conclusions [20]. Additionally, they published an article describing how to use this framework to inform the development of clinical practice guidelines [22].

Many guidelines for screening of osteoporosis have been developed by many agencies and organizations. Previous research reported that they conveyed mixed messages to primary care physicians [16,17]. A systematic review by Cranney et al (2002) of CPGs for postmenopausal osteoporosis released between 1998 and 2001 found that the guidelines

were of low quality [25]. Those which were of acceptable quality were most commonly developed by researchers in the United States, one was from Ontario, Canada, and two were from the United Kingdom.

Most studies from North American and European countries indicated that a high proportion of individuals whom are at risk of fragility fractures are not being screened, which reflects the low adherence of physicians to the CPG [4,6,23,26–30]. Thus, determining the quality of current guidelines is important and to our knowledge there is no recent review of the quality of CPGs relevant to osteoporosis screening. Therefore, we conducted a systematic review to:

1) Assess the quality of guidelines using the AGREE II and the IOM standards.
2) Determine whether osteoporosis guidelines quality has improved over time.
3) Summarize the grading systems for level of evidence and strength of recommendations.
4) To compare the recent guideline recommendations for management of osteoporosis for consistency /concordance.

METHODS

This systematic review followed the Cochrane Methodology [31], to identify, and select the CPGs and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide the reporting of the systematic review [32]. Ethics approval was not required as this work involved analyses of published literature.

Search Strategy

The search was developed with the help of a medical librarian at the University of Ottawa. One reviewer (LA) searched databases for relevant guidelines published between January 2002 and September 2016 using the following: Embase, Medline, Pubmed, Canadian Medical Association Infobase, National Guidelines Clearinghouse, and Guidelines International Network (http://www.g-i-n.net/). Some well-known guidelines developers such as: International Osteoporosis Foundation (IOF), National Institution for Clinical

Excellence (NICE), and the Scottish Intercollegiate Network (SIGN), were also searched. Additionally, individual guideline documents were reviewed for references to other relevant guidelines. There was no restriction for language, however non-English guidelines were excluded.

Key words used for the MEDLINE search can be found in the Appendix S2-A which are modified according to the indexing systems. The Canadian Agency for Drugs and Technologies in Health (CADTH) filters were used for searching related databases for guidelines keywords [33]. These are search filters which are develop and maintained by CADTH's Information Services Filters Working group. They have been extensively tested by the Information services team and used routinely in CADTH projects.

Guidelines meeting the following inclusion and exclusion criteria were found eligible:

Inclusion Criteria -those meeting the above definition of CPGs.

Population: Adult population, no restriction to age or sex or health status.

Intervention:

- Recommendations for screening for osteoporosis with or without treatment recommendations between 2002 -2016.
- Complete text of the guidelines available in English language.
- Recommendations intended for health professionals.

Comparator and outcome: Not applicable.

Exclusion Criteria

- Non-English language guidelines or incomplete text.
- Guidelines for treatment of osteoporosis only with no recommendation on screening.
- If they only addressed glucocorticoid induced osteoporosis or specific diseases/ conditions such as hyperthyroidism, inflammatory bowel disease, celiac disease, and post-gastrectomy states.
- We excluded position papers and consensus papers since they are not equivalent to guidelines.

Selection of the Studies and Data Extraction

All citations were exported to Mendeley; a citation software and to Covidence; a systematic review software, (www.covidence.org), where duplicates were removed automatically. Screening of titles and abstracts were carried out by one reviewer (LA) through Covidence, a second reviewer (SY) screened 100 articles to check the accuracy of screening. Guidelines that did not meet the inclusion criteria were excluded. One reviewer (LA) extracted the following information: Guidelines titles, Authors, publication year, country, the organization that produced the guideline, and main key recommendations.

Quality Assessment and Data Analysis

AGREE II instrument:

The AGREE instrument is a tool; developed in 2003 by a group of international researchers, and then was refined and updated in 2010 and became knows as the AGREEII instrument [18]. The purpose of the tool is to provide a systematic framework to assess the methodological rigour of guideline quality and a methodological strategy for developing the guidelines [18]. The tool consists of 23 items within 6 domains (scope and purpose, stakeholder involvement, rigour and development, clarity of presentation, applicability, and editorial independence). [*Please refer to Table S2-B in the Appendix for listing of the domains and attributes*]. Each item scores are calculated on 7-point scale ranging from 1 (absence of them) to 7 (exceptional quality of item). The AGREE Collaboration has published studies on the validity and reliability of the instrument and both were found to meet accepted standards; the quality ratings of the domains were significant predictors of the outcome measures associated with guidelines adoption, and the internal consistency of the tool ranged between 0.64-0.89 [34]. Construct validity assessment results showed that items detected the differences in guideline quality which the instrument was supposed to measure and the results of usability measurements of the user's manual were high [35].

Two appraisers (LA and SY) appraised each guideline independently using the (AGREE II). Each of the reviewers read the user's manual and completed the online AGREE II training tutorial available on the AGREE Enterprise website:

(http://www.agreetrust.org/agree-ii/). Only information included in the released guideline or documents referenced in the source guideline describing the guidelines development process were used in the appraisal process, i.e., the reviewers did not refer to additional supporting documents that were published separately, unless explicitly indicated by the CPGs, the rational for this is based on the assumption that busy clinicians would not search for more information about the guideline.

Domains scores were calculated by summing up item scores within each domain for each reviewer, then standardising it as a percentage of maximum possible score

$$\text{Scaled domain score} = \frac{obtained\ score - minimum\ possible\ score}{maximum\ possible\ score - minimum\ possible\ score} \times 100$$

We performed a descriptive statistical analysis for each domain including mean, median standard deviation, minimum and maximum.

Agreement between reviewers was assessed by using two-way random effects consistency model of intra-class correlation coefficients (ICC) taking the scores for all 23 items of each guideline [36]. The degree of reviewer agreement was categorized based on Cicchetti (1994) ICC<0.40 poor; 0.40 to 0.59 moderate; 0.60- 0.74 good; 0.75-1.00 excellent [37]. Analyses were preformed using Microsoft Excel, and SAS 9.4 statistical package, except Inter-rater reliability (ICC & weighted kappa)was performed using R for statistical computing (IRR package) [38]. We also measured and presented the weighted kappa to compare to ICC, however, ICC is a preferred method for inter-rater reliability for ordinal scales [39].

IOM standards for guideline trustworthiness:

The Institute of Medicine (IOM) in the United States in 2011 developed standards "Clinical Practice Guidelines We can Trust" to aid developers in producing quality evidence based guidelines[10]. The resulting instrument has eight standards (Establishing transparency, management of conflict of interest, guideline development group composition, systematic review intersection, establishing evidence foundation, articulation

of recommendation, external review, and updating) with 20 sub-criteria or attributes, with no proposed numerical scoring [*Table S2-C lists standards and attributes*] [40].

Unlike the AGREE II tool, IOM guideline standards focus more on (have more items) on domains such as on conflict of interests, systematic review and establishing the evidence foundation. It has separate standards for external review and for updating, while, there are no standards that assess applicability or resource implications, Table 2-1 lists the similar and different items in both tools. Few studies have tested these standards to assess the quality of guidelines [41–43]. Each of these studies used a different methodology to operationalize the tool, but none was found to be a good method to apply. For example; Kung et al 2012 used IOM standards to assess 114 CPGs, but they excluded seven items from the standards because they were "vague and subjective"[41]. They didn't list what items they used. Reams et al 2013 assessed oncology CPGs using IOM standards; they scored each item on dichotomous basis (yes/No), each standard was considered to be fulfilled only if all items were met [42]. We tested this approach, and it yielded many guidelines with zero scores in all standards, which may underestimate the quality of these guidelines. Bennett et al 2016 [43], used 0-3 scale to score for each standard based on confidence (not met, low confidence, moderate and high confidence), and they used the same methodology to score the AGREE II in order to compare it to the IOM scores, altering the scoring of the AGREE II. We opted not to do this, since the AGREE II scoring system has been used extensively in many studies, and we did not want to alter the established scoring system.

We developed our own methodology for scoring quality using the IOM standards tool which involved scoring each of the 20 sub-criteria by 1, or 0. A standard was considered to be met, if more than half of the sub-criteria were fulfilled, so for standards with 3 sub-criteria, 2 or more need to be fulfilled to consider that standard met, while those with 4 items, 3 had be met and so on. One reviewer (LA) used this tool to appraise the guidelines.

Table 2-1 Mapping IOM standards to the AGREE II domains

AGREE II Instrument	IOM (Standards matching the AGREE II)
Domain 1: Scope and purpose 1. The overall objective of the guideline is specifically described 2. The health question(s) covered by the guideline is (are) specifically described 3. The population to whom the guideline is meant to apply is specifically described	**No matching standard**
Domain 2: Stakeholder Involvement 4. The guideline development group includes individuals from all the relevant professional group 5. The views and preferences of the target population (patients, public, etc.) have been sought. 6. The target users of the guideline are clearly defined.	**Standards 3: Guideline development group composition** 3.1 The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG. 3.2 Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient and a patient advocate or patient/ consumer organization representative in the GDG. 3.3 Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.
Domain 3: Rigour of Development 7. Systematic methods were used to search for evidence. 8. The criteria for selecting the evidence are clearly described. 9. The strengths and limitations of the body of evidence are clearly described. 10. The methods for formulating the recommendations are clearly described. 11. The health benefits, side effects, and risks have been considered in formulating the recommendations. 12. There is an explicit link between the recommendations and the supporting evidence. 13. The guideline has been externally reviewed by experts prior to its publication. 14. A procedure for updating the guideline is provided.	**Standard 4: Systematic review section** 1. CPG developers should use systematic review that meet standers set by the IOM. 2. when SR are conducted specifically to inform the guideline, the team should interact regarding the scope, approach, and output of both processes. **Standard 5: Establishing Evidence Foundation and rating strength of recommendation** A clear description of potential benefits and harms. A summary of available evidence, description of the quality, quantity and consistency of the available evidence. Rating of the level of confidence, and rating of the strength of recommendation, a description and explanation of any differences of opinion regarding the recommendation **Standard 7: External review** **1**. External review should comprise a full spectrum of relevant stakeholder, including scientific and clinical experts, organizations, agencies, patents and representative of the public. 2. The authorship of the external reviews submitted by individuals or organizations should be kept confidential unless that protection has been waived by the reviewers. 3. The CDG should consider all external reviewer comments and keep a written record of the rationale of modifying or not modifying a CPGS in response to reviewers' comments 4. A draft of the CPG at the external review stage or immediately following it should be made available to the public for comment **Standard 8: Updating** 1. The CPG publication date, date of SR and proposed date for future CPG review should be documented 2. Literature should be monitored regularly following CPG publication 3. CPGs should be updated when new evidence suggests the need for modification of clinically important recommendations.

Table 2-1: Continued

AGREE II Instrument	IOM (Standards matching to the AGREE II)
Domain 4: Clarity of Presentation 15. The recommendations are specific and unambiguous. 16. **The different options for management of the condition or health issue are clearly presented**. 17. Key recommendations are easily identifiable	**Standard 6: Articulation of Recommendation** 1. Recommendation should be articulated in a standardized from detailing precisely what the recommended action is and under what circumstances it should be performed 2. Strong recommendations should be worded so that compliance with the recommendations can be evaluated
Domain 5: Applicability 18. **The guideline describes facilitators and barriers to its application.** 19. **The guideline provides advice and/or tools on how the recommendations can be put into practice.** 20. **The potential resource implications of applying the recommendations have been considered.** 21. **The guideline presents monitoring and/or auditing criteria**	No matching standard
Domain 6: Editorial Independence 22. The views of the funding body have not influenced the content of the guideline. 23. Competing interests of guideline development group members have been recorded and addressed	**Standard 2: Management of Conflict of interest** 1. Prior to selection of the Guideline Development Group individuals being considered for membership should declare all interests and activities potentially resulting in COI 2. Each panel member should explain how their COI could influence the CPG development process or specific recommendations. -Members of the GDG should divest themselves of financial investments they or their family members have 2.4 Exclusions: In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG. • **Members with COIs should represent not more than a minority of the GDG.** • **The chair or co-chairs should not be a person(s) with COI.** • Funders should have no role in CPG development. **Standard 1: Establishing Transparency** The process by which a CPGs is developed and funded should be detailed explicitly and publicly accessible

* Items in bold font don't have a match in the other tool.

Guidelines quality over time

We hypothesized that the quality of guidelines has improved over time especially after updating the AGEEII tool in 2010 and the introduction of IOM standards in 2011. We used a non-parametric test, the Wilcoxon Rank-Sum test (Mann-Whitney test) to test for statistically significant differences in domain scores between CPGs published before and

in/after 2010 (the date of the release of AGREE II) [44]. We used the same procedure to test for statistically significant differences in the total score of the IOM standards (out of 8) for each guideline before and after the introduction of IOM standards (≥ 2011 vs >2011). In addition, we used the Chi square test to determine whether the proportion of guidelines meeting each standard has improved following release of the IOM standards. If expected cell counts were less than five, then Fisher's exact test is used instead[44] . P values less than 0.05 were considered statistically significant.

Comparison of the AGREEII and IOM standards tools

Table 2-1; shows that these tools don't have the same items or domains (standards). We were only able to identify one study that compared guidelines quality using both instruments. Bennett et al 2016 [43], compared IOM instrument with the AGREE II, by scoring their domains in a similar way; assigning scores of 0-3 for each domain. Comparing the two tools by comparing the number of times each rating option (0,1,2, 3) was applied for each domain or standard. However, this method altered the accepted scoring for the AGREE II used in all CPGs evaluation studies and undermined the validity of the quality appraisal.

Given the prominence of both tools and the differences in items/domains, we decided to conduct our own comparison to determine whether both tools identify the same guidelines as being of high quality. For that purpose; guidelines were considered of high quality using the AGREEII instrument, if they scored ≥ 60% in 4 or more domains including domain 3 for rigor of development, since we consider this domain an important part of guideline quality. This approach in identifying high quality guidelines has been reported in other studies assessing for the quality of CPGs for Glaucoma, fertility preservation in cancer patients, and physical activity and safe movement in osteoporosis management and hypertension [37,45–47].The first study that reported this methodology was by Ou Y. et al 2011 for assessing CPGs for glaucoma [45]. Similarly, with the IOM standards, we defined high

quality guidelines if 5 or more standards were met including standards 4 and 5 (*CPG systematic review intersection and Establishing evidence foundations for and rating strength of recommendations*).

RESULTS

Search Results A total of 5,818 records were identified from our systematic search of databases, of which 3,143 were excluded as duplicates, and 2,448 were found to be irrelevant after screening the titles and abstracts. We found an additional 17 records from national guideline websites and hand searching references of identified guidelines. Thus, a total of 224 records were screened as full text, and 211 were excluded for the following reasons: not a guideline (n=114), non-English (n=53), treatment only (n=17), duplicates not previously removed (n=15), short summary (n=6), not eligible population (n=6), Finally 33 final guidelines were eligible for assessment (21 guidelines from databases, and 12 from other sources). [*Refer to Figure S2-1 for the Prisma Flow Diagram].*

Table 2-2 lists all the included guidelines, 33 CPGs from 13 different countries: 6 from Canada, 10 from USA, 3 from England, 1 from Scotland, 1 from Australia, 1 from Greece, 1 from Italy, 2 from Lebanon, 1 from Saudi Arabia, 2 from Malaysia, 1 from South Afric,1 from India, 1 from different Asian countries (South Korea, India, China, Malaysia, Singapore, Sri Lanka and Philippines), 1 from Singapore, and 1 from Taiwan. 13 CPGs were released between January 2002-January 2011, and 20 were released between January 2011- September 2016. Seven of these CPGs were updates of previous versions, however, we could not retrieve all the original versions of guidelines, since some were withdrawn and not accessible, such as the previous SIGN and NICE guidelines, and the Malaysian CPG 2006 was received from the publisher after the analyses was completed.

Table 2-2: Details of the retrieved guidelines, 2002-2016

	Guideline Title	Country	Organization	Year	Accessed through
1	2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada [49]	Canada/ Ontario	Osteoporosis Canada	2002	Database
2	Screening for Osteoporosis in Postmenopausal Women: Recommendations and Rationale [50]	USA	US Preventive Service Task Force (USPSTF)	2002	Database
3	Prevention of osteoporosis and osteoporotic fractures in postmenopausal women: recommendation statement from the Canadian Task Force on Preventive Health Care [51]	Canada/ Ontario	Canadian Task Force on Preventive Health Care	2004	Database
4	Lebanese Guidelines for Osteoporosis Assessment and Treatment [52]	Lebanon	The American University of Beirut	2005	Database
5	Guidelines for diagnosing and prevention and treatment of osteoporosis in Asia [53].	South Korea, India, China, Malaysia, Singapore, Sri Lanka, Phillippines	Not reported	2006	Database
6	Screening for Osteoporosis in Men: A Clinical Practice Guideline from the American College of Physicians [54].	USA/ national	American College of Physicians	2008	Database & National Guideline Clearinghouse
7	Clinician's Guide to Prevention and Treatment of Osteoporosis. [55]	National	National Osteoporosis Foundation	2008	Reference
8	First Update of the Lebanese Guidelines for Osteoporosis Assessment and Treatment [56].	Lebanon	The American University of Beirut	2008	Database
9	Osteoporosis MOH Clinical Practice guidelines [57].	Singapore	Ministry of Health	2009	IOF
10	2010 Clinical Practice guidelines for the diagnosis and management of osteoporosis in Canada: a Summary [58].	Canada/ Ontario	Osteoporosis Canada	2010	Database
11	Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Postmenopausal Osteoporosis [59].	USA	American Association of Clinical Endocrinologist AACE	2010	National Guideline Clearinghouse
12	Clinical guideline for prevention and treatment of osteoporosis in postmenopausal women and older men [60].	Australia	The Royal Australian College of General Practitioners.	2010	IOF
13	NOFSA guideline for diagnosis and management of osteoporosis [61].	South Africa	The National Osteoporosis Foundation of South Africa (NOSFA)	2010	IOF
14	2011 Guidelines for the diagnosis and treatment of osteoporosis in Greece [62].	Greece	Greece National Medicine Agency	2011	Database Search
15	Screening for osteoporosis: the US Preventive Services Task Force Recommendations Statement [63].	USA/ National	USPSTF	2011	database and Nat. guideline clearinghouse
16	Guidelines for Clinical Care Ambulatory Osteoporosis Guideline Team Team Lead Ambulatory Clinical Guidelines Oversight Osteoporosis: Prevention and Treatment [64].	USA/ Michigan	University of Michigan Health System	2011	National Guideline Clearinghouse
17	Taiwan osteoporosis practice guidelines [65].	Taiwan/ National	Bureau of Health Promotion, Department of Health, ROC (Taiwan)	2011	National Guideline Clearinghouse
18	Osteoporosis: Diagnosis, Treatment and Fracture Prevention [66].	Canada/BC	British Columbia Medical Association	2012	IOF, CPG infobase
19	Clinical guidance on the management of osteoporosis, 2012 [67].	Malaysia	The Malaysian Osteoporosis Society	2012	Reference
20	Osteoporosis: Assessing the risk for fragility fracture [9].	UK/England	NICE	2012	IOF and NICE website
21	Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline [68].	USA	The Endocrine Society	2012	Database
22	Diagnosis and treatment of Osteoporosis [69]	USA/ Minnesota	Institute for Clinical System Improvement	2013	National Guideline Clearinghouse

Table: 2-2: Continued

	Guideline Title	Country	Organization	Year	Accessed through
23	Clinical Practice Guidelines on Postmenopausal osteoporosis: Executive Summary and Recommendations [70].	India	Indian Menopause Society	2013	Database
24	Clinician's Guide to Prevention and Treatment of Osteoporosis [71].	National	National Foundation of Osteoporosis	2014	Database
25	Osteoporosis in Menopause[72]	Canada/	Society of Obstetricians and Gynaecologists of Canada	2014	Database
26	Guidelines for the diagnosis, prevention and management of osteoporosis [73]	UK/National	National Osteoporosis Guideline Group (NOGG)/UK	2014	Database
27	Management of osteoporosis and the prevention of fragility fractures A national clinical guideline [74]	Scotland/UK	Scottish Intercollegiate Guidelines Network (SIGN)	2015	IOF
28	A summary of the Malaysian Clinical Guidance on the management of postmenopausal and male osteoporosis, 2015 [75].	Malaysia	The Malaysian Osteoporosis Society	2015	IOF
29	2015 Guidelines for Osteoporosis in Saudi Arabia: Recommendations from the Saudi Osteoporosis Society [76].	Saudi Arabia	Saudi Osteoporosis Society	2015	Database
30	Osteoporosis clinical guideline for prevention and treatment: Executive Summary [77].	UK/National	National Osteoporosis Guideline Group(NOGG)/UK	2016	Google Scholar
31	Guidelines for the diagnosis, prevention and management of osteoporosis [78].	Italy	Italian Society for Osteoporosis, Mineral metabolism and Bone Diseases (SIOMMMS)	2016	Database
32	Diagnosis and management of Osteoporosis [79]	Canada/ Alberta	Toward Optimized Practice/Alberta	2016	Database, CPG infobase
33	Clinical Practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2016 [80].	USA/National	American Association of Clinical Endocrinologists and American College of Endocrinology	2016	Database

Quality of CPGs based on the AGREE II Score

The standardized domain scores, and the Intra-class correlation coefficient (ICC) values for each guideline are depicted in Table 2-3. The agreement between the two reviewers is ranging between (ICC=0.75-0.97), which indicates good to very good agreement, except in one guideline (Australia 2010); where inter-rater agreement was fair; ICC: 0.25). The weighted kappa agreement scores were lower compared to ICC.

The descriptive statistics for each domain is presented in Table 2-4 with the mean standardized scores for each domain is shown in Figure 2-1 and Table 2-5, present the results of the testing for change in quality for each domain after the release of AGREE II (before and in 2010 vs after 2010).

Domain 1: Scope and purpose. This domain assesses the overall aim and objectives of the guidelines, the health questions and the target population. The mean score with (SD) for

this domain was 64.33% (20.95%), most guidelines did well in this domain; however, their scores varied widely, ranging from (17% to 100%). Osteoporosis Canada 2010 [58], and the Malaysian guidelines 2012 [81]; both scored 100%. The worst scores were for the Asian guidelines 2006 [53] (17%), and for the Canadian Task force, 2004 [51](31%). Table 2-5 shows, that this domain scored lower after release of AGREE II, however, this was statistically not significant (mean difference= -0.03; 95% CI= -0.11 to 0.22; P =0.58).

Domain2: Stakeholder involvement. This domain focuses on the participation of the professional experts, preferences of target population in the guideline development and whether target users are clearly defined. The mean score with (SD) was 54.57 % (25.96%) with a very wide range (8% for BC [66] to 100% for NICE, ICSI and SIGN [9,60,65]). Two thirds of guidelines (21/33) scored below 60% in this domain as most of the guidelines didn't seek the views of the other stakeholders such as patients, public, payers, and policy makers during guideline development. This domain showed a decrease in the domain scores after the introduction of AGREE II, but it was statistically insignificant (mean difference= -0.08; 95% CI= -0.11 to 0.28; P = 0.33).

Domain 3: Rigour of development. This domain includes eight items that assess the systematic methods used for gathering and synthesizing of the evidence, and formulating the recommendations, the external peer review process and the procedure for updating the guideline. The mean score for this domain with (SD) was 63% (25.53%). Some important guidelines that are constantly cited in the field of osteoporosis such as the National Osteoporosis Foundation guidelines of 2008, and 2014 [28,45]; scored low; 33%, and 22% respectively, as they did not report any systematic approach for developing their guideline. The score for this domain ranged from 10-99. The NOGG/UK scored 10% in 2014 [73] as this document was an update and only included a summary of the recommendations. We contacted the developers to get more details but received none. Most guidelines didn't describe the process of updating clearly. Like the previous domains, this domain score

decreased after 2010, however not statistically significantly (mean difference= -0.02; 95% CI=-0.18 to 0.21; P=0.97).

Domain 4: Clarity of presentation. This domain covers the language, structure and format of the guideline. It emphasizes on the clarity, unambiguity of the recommendations. The mean score with (SD) was 71.30 (16.52), indicating that most guidelines had clear recommendations. The guidelines' scores on this domain did not improve after 2010 (mean difference= 0; 95% CI= - 0.14 to 0.11; P=0.81).

Domain 5: Applicability. This domain considers the barriers and facilitators to implementation of the guideline, approaches to increase uptake, resource implications of applying the guideline, and monitoring of the uptake or adherence to the guideline.

Consistently across all the CPGs, this was the lowest scored domain with means score and (SD) of 41.75% (22.83), and a range between (8%-88%). Only 3 guidelines (SIGN [74], NICE[9] and ICSI[69]) reported monitoring and auditing criteria. Table 2-5 shows that scores on this domain improved after 2010 but not statistically significantly (mean difference= -0.07; 95% CI= -0.25 to 0.10; P =0.46,).

Domain 6: Editorial independence. This domain relates to the formation of recommendations under unbiased influence of the funding body, and with no competing interests of the developers. The mean score with (SD) was 53.57% (32.57), almost half of the guidelines either didn't provide statement about the funding or the competing interests. Some guidelines [24,28,53] scored 0% on this domain. The mean score on this domain improved after 2010 but the change was not statistically significant (mean difference= 0.20; CI=-0.50 to 0.00; P=0.06).

Table 2-3: AGREE II standardised domain scores and Intraclass correlation for CPGs from 2002-2016

Guideline	1.Scope and purpose	2.Stakeholder Involvement	3.Rigour of development	4.Clarity of presentation	5. Applicability	6.Editorial Independence	(ICC) %	Weighted Kappa %
Osteoporosis Canada 2002 [49].	83	69	81	92	52	75	50	50
US Preventive Services Task force 2002 [50].	61	36	75	50	13	33	93	92
Canadian Task Force on Preventive Health Care 2004 [51]	31	31	41	58	17	46	62	61
American University of Beirut Medical Center 2005 [52].	72	44	64	61	23	0	88	87
Guidelines in Asia 2006 [53].	17	22	18	42	33	0	72	70
the American College of Physicians guidelines 2008 [54].	83	58	55	69	33	79	67	66
National Osteoporosis Foundation 2008 [55].	58	61	33	69	27	42	89	88
First Update of the Lebanese Guidelines 2008 [56].	78	47	70	64	27	8	85	84
Singapore Clinical Guidelines 2009 [57]	47	92	64	78	56	13	89	65
Osteoporosis Canada 2010 [58].	100	75	83	75	48	50	76	76
American Association of Clinical Endocrinologist AACE 2010 [59]	78	56	65	72	33	46	71	70
The Australian Guidelines 2010 [60]	78	92	98	97	88	96	44	45
South Africa guidelines 2010 [61]	75	89	90	97	46	46	74	73
Greece National Medicine Agency 2011 [62]	36	22	20	44	17	50	75	74
USPSTF 2011 [63]	78	42	83	67	50	83	60	60
University of Michigan Health System guideline 2011 [64].	67	44	70	69	40	58	86	84
Taiwan Osteoporosis guideline 2011 [65]	67	75	92	94	54	96	61	60

Table 2-3 Continued

Guideline	1.Scope and purpose	2.Stakeholder Involvement	3.Rigour of development	4.Clarity of presentation	5. Applicability	6.Editorial Independence	(ICC) %	Weighted Kappa%
British Columbia Medical Association 2012 [66]	36	8	33	58	52	13	78	78
The Malaysian Osteoporosis Society Guideline 2012 [67]**.**	100	81	88	92	88	88	67	67
NICE guidelines 2012 [9]	81	100	94	92	88	96	70	70
The Endocrine Society 2012 [68]	42	33	71	67	40	92	73	72
Institute for Clinical System Improvement guideline, 2013 [69]**.**	92	100	91	97	81	100	74	74
Indian Menopause Society, 2013 [70]	72	50	84	78	58	33	68	67
National Foundation of Osteoporosis 2014 [71]	86	42	25	69	27	54	82	82
the Society of Obstetricians and Gynaecologists of Canada [72]	50	42	60	78	8	25	91	90
National Osteoporosis Guideline Group (NOGG)/UK 2014 [73]	36	17	10	33	23	71	75	74
The Malaysian Osteoporosis Society guideline, 2015 [75]	58	28	57	61	23	79	78	78
Scottish Intercollegiate Guidelines Network (SIGN) guideline, 2015 [74]	81	100	99	86	83	83	86	86
2015 Guidelines for Osteoporosis in Saudi Arabia [76]**.**	61	50	58	78	21	42	83	82
National Osteoporosis Guideline Group(NOGG)/UK, 2016 [77]**.**	50	67	61	75	58	100	79	78
Italian Society for Osteoporosis, Mineral metabolism and Bone Diseases 2016 [78]	36	28	50	50	15	0	75	74
Alberta Guidelines 2016 [79]	58	42	22	69	27	13	91	91
American Association of Clinical Endocrinologist AACE 2016 [80]	75	58	74	75	44	58	75	74

*ICC interpretation: ICC<0.40 poor; 0.40-0.59 fair; 0.60-0.74 good; 0.75- 1 excellent [82].

-CPGs which are shaded in green are considered high quality guidelines (achieved 60% or more in domain rigour of development with 3 other domains)

Table 2-4: Descriptive Statistics summarizing the AGREE II domain scores of all guidelines

AGREE II Domains	Mean and (Median) pre-AGREE	Mean and (Median) post-AGREE	Mean Difference	P value	Confidence Intervals
Scope and purpose	0.66 (75)	0.63 (64)	-0.03	0.58	-0.11 – 0.22
Stakeholder involvement	0.59 (58)	0.51(43)	-0.08	0.33	-0.11 – 0.28
Rigor of development	0.64 (65)	0.62 (65)	-0.02	0.97	-0.18 – 0.21
Clarity of presentation	0.71 (69)	0.71(72)	0	0.81	-0.14 – 0.11
Applicability	0.37 (33)	0.44 (42)	0.07	0.46	-0.25 – 0.10
Editorial dependence	0.41 (46)	0.61 (64)	0.20	0.06	-0.50 – 0.00

Figure 2-1: AGREE II mean standardized domain scores for each domain for all the guidelines

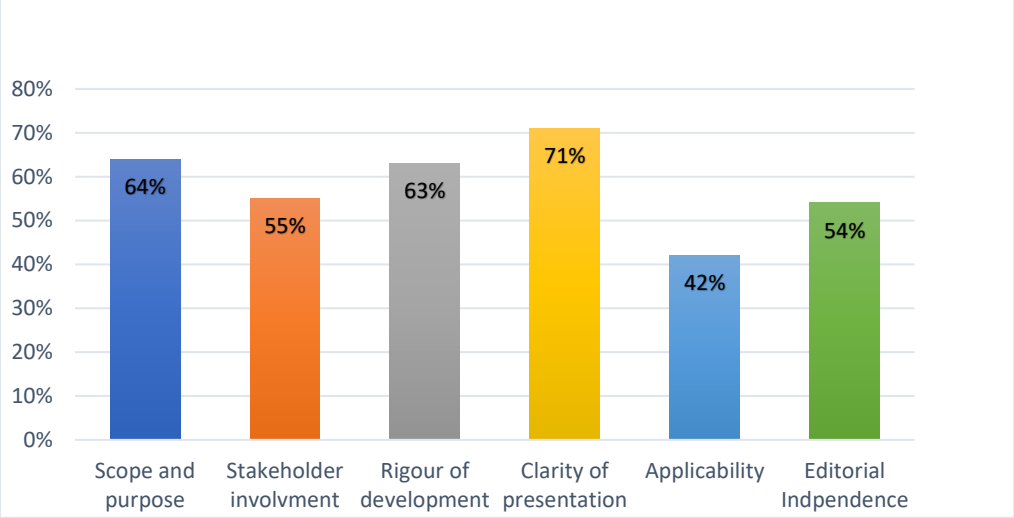

Table 2-5: Change in AGREE II domain scores (2002-2016), Pre-AGREEII release (n=13), post- AGREEII release (n=20).

AGREE II Domains	Mean and (Median) pre-AGREE	Mean and (Median) post-AGREE	Mean Difference	P value	Confidence Intervals
Scope and purpose	0.66 (75)	0.63 (64)	-0.03	0.58	-0.11 – 0.22
Stakeholder involvement	0.59 (58)	0.51(43)	-0.08	0.33	-0.11 – 0.28
Rigor of development	0.64 (65)	0.62 (65)	-0.02	0.97	-0.18 – 0.21
Clarity of presentation	0.71 (69)	0.71(72)	0	0.81	-0.14 – 0.11
Applicability	0.37 (33)	0.44 (42)	0.07	0.46	-0.25 – 0.10
Editorial dependence	0.41 (46)	0.61 (64)	0.20	0.06	-0.50 – 0.00

Quality of CPGs Determined by the IOM StandardsThe eight IOM standards with their scores are presented in the Appendix of this chapter, Table S2-C. The mean overall score is 4.18 out of 8 major standards. Four guidelines fulfilled all the eight standards (Australia CPGs 2010 [60], NICE 2012[9], Institute of Clinical Improvement CPG 2013 [69], and SIGN CPG 2015 [74]). Figure 2-2 shows that more than 60% (67%, 64%, 64%, 61%) of guidelines met standards for systematic review intersection, establishing evidence and rating strength of recommendation, articulation of recommendation, and establishing transparency respectively. 55% of CPGs met Standard 2 for Management of conflict of interest; which assesses the disclosure of conflict of interest of the guideline development group. Less than half of the guidelines fulfilled standards for external review and updating the guidelines (42%, 39%) respectively. The least fulfilled standard was for the development group composition; with only 9 (27%) of guidelines meeting this standard, as most CPGs did not involve patients or public representatives or involve strategies to increase participation of patients or consumers.

Table 2-6 presents the tests of significance for the difference in the proportion of guidelines that met the IOM standards pre and post their release in 2011(year of IOM standards publication). Guideline developer adherence to Four standards improved after 2011: Management of conflict of interest, development group composition, external review, and updating, though these improvements were not statistically significant (P>0.05). guideline developer adherence to the remaining four standards (Establishing transparency, systematic review intersection, establishing evidence and rating strength of recommendation, and articulation of recommendations), declined after 2011, but the declines were not statistically significant, except for the systematic review intersection standard in which the test of significance test was borderline (P=0.05). We also assessed the difference in the total IOM score (out of 8) for the guidelines before and after the IOM publication and found no statistically significant change in scores (mean difference= -1.08, P= 0.74, 95% CI=-2 to 2). In essence, the quality of osteoporosis guidelines as assessed by the IOM standards instrument has not change since the release of the tool in 2011.

Figure 2-2: The percentage of CPGs meeting the IOM Standards for guidelines Trustworthiness

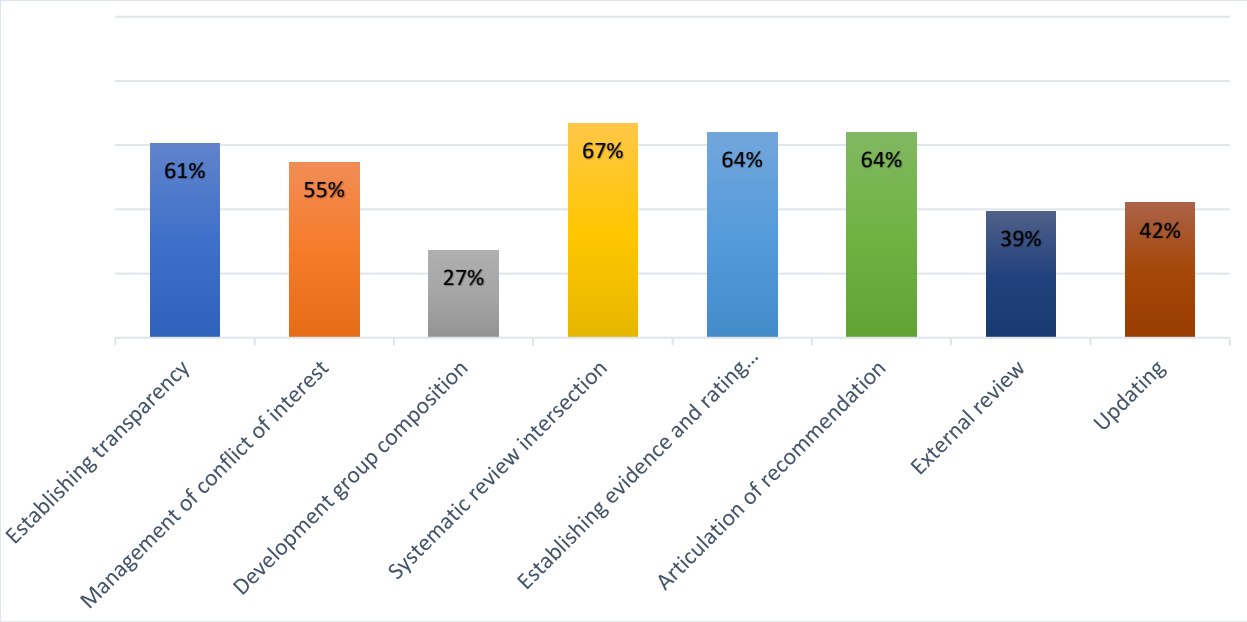

Table: 2-6: Proportion of CPGs meeting the IOM standards (2002-2016), Pre (n=17) and post (n=16) release of the IOM standards in 2011.

IOM Standards	Count and (%) of CPGs pre-IOM	Count and (%) of CPGs post- IOM	Difference in %	P value
1: Establishing transparency	11 (65%)	9 (56%)	-9%	0.63
2: Management of conflict of interests	7 (41%)	11 (69%)	28%	0.12
3: Guideline development group composition	4 (24%)	5 (31%)	7%	0.71
4: systematic review section	14 (82%)	8 (50%)	-32%	0.05
5: Establishing evidence for and rating strength of recommendations	13 (76%)	8 (50%)	- 26 %	0.11
6: Articulation of recommendations	12 (71%)	9 (56%)	-15%	0.39
7: External review	5 (29%)	8 (50%)	3 %	0.23
8: Updating	7(41%)	7 (44%)	3%	0.88

High Quality CPGs Identified by both the AGREE II and IOM Standards instruments

When applying our criteria to determine high quality guidelines, AGREE II identified 12 such guidelines (36%), and the IOM identified 15 (45%). 11 CPG were identified by both tools [22,31,33,34,36–38,40,41,43,48]. The National osteoporosis guideline group guideline (NOGG) 2016 [77] was additionally found to be high quality using AGREE II, but not according to IOM standards. The IOM standards identified 4 other additional guidelines as high quality: USPSTF 2002, American College of Physicians 2008, Singapore 2009, and Malaysia 2015 [23,27,30,49] which were not identified as high quality by the AGREE II instrument.

We examined the four additional high quality guidelines identified by IOM standards and found that both tools may produce different conclusions in regards to the domains of systematic review, and strength of evidence, which most clinicians may consider most important in deciding the implementation of a certain recommendation. For instance, in two guidelines (American College of Physicians 2008 [54], and the Malaysian guidelines 2015[75]), the domain for rigour of development using the AGREE II scored <60% , while the related IOM standards '4' and '5' were met. This is because questionnaires' content that assess these domains differ between the two tools (Table 2-1); the external review and updating are included as part of the rigor of development in AGREE II, while they have a separate standard in IOM. Additionally, the items in the systematic review section and the quality of evidence for formulating the recommendations are more detailed in the AGREE II compared to the IOM. So, we found that the AGREE II would give lower scores if the systematic review process or methodology were not reported in detail in the guideline.

We tested whether the percentage of high quality guidelines differed before and after the introduction of AGREE II and the IOM standards (30.77% vs 40% after the AGREE and IOM introduction respectively). The percent change was 9.23% and statistically not significant. (% change= 9.23%, P=0.72).

Evidence and Recommendations Grading Systems in use by Guideline Developers

Another challenge for guideline users is that they use different grading systems to determine the level of evidence supporting recommendations and different systems for assigning the strength of recommendations. Table 2-7 summarises these systems. Nine out of the 33 guidelines didn't assign grades for level of evidence or strength of recommendation. These were the Canadian Task Force 2004 [51], Lebanese CPG 2005 [52] ,Guidelines in Asia 2006 [53], NOF 2008 [55] , Update of the Lebanese CPG 2008 [56], Greece 2011 [62], British Columbia CPG 2012 [66], NOF 2014 [71], Alberta CPG 2016 [79]. Some organizations used their own level of evidence framework such as the USPSTF [63], the Scottish Intercollegiate Guideline Network (SIGN) [74], and American Association of Clinical Endocrinologist (AACE)[80]. Seven guidelines used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [21], These are: American College of Physicians 2008 [54], South Africa CPGs 2010 [61], NICE 2012 [9], The Endocrine Society 2012[68], Indian Menopause Society 2013 [70], Institute for Clinical System Improvement 2013 [69], and the Scottish Intercollegiate Guideline Network 2015 [74]. There is a growing worldwide agreement to use this system and many respectful organizations moved their systems to GRADE like SIGN recommendations [74], ICSI [69], and NICE [9].

Summary of Comparison between the Recommendations

Regardless of the quality of the guidelines, do they make the same recommendations? Table 2-8 summarizes the recommendations of the 21 most recent and updated guidelines (2010 onward) in major areas of management of osteoporosis ["fracture risk estimation tool before BMD testing", "BMD testing before risk estimation", "Age of baseline BMD testing in men and women", "when to treat?", "considering 2 sites for BMD testing", and "BMD testing after treatment"]. Because of the variability between guidelines, we had to detail the recommendations for each area in each guideline.

Use of fracture risk estimation tool before BMD testing

Because of the limitation of BMD testing in identifying solely one factor that contributes to osteoporosis, many tools have been developed by researchers incorporating

other factors to estimate fractures risk over 5 or 10 years [83]. One of the most widely used and validated is the FRAX risk assessment tool; which was developed by the WHO in 2008 [83] . It is a free web portal that provides calculation of the 10-year absolute risk of fracture based on many risk factors such as age, gender, BMI, presence of previous fracture, parental hip fracture, smoking, use of alcohol, use of glucocorticoids, rheumatoid arthritis and other secondary diseases. Bone mineral density at the femoral neck is one of the factors and it is optional to use. In the past years, there was a shift towards using these tools to decide the need for DXA and to set the intervention threshold with or without BMD results. However, the FRAX probability varies by country, therefore, it was calibrated using country specific data where fracture rates and deaths are known [84].

The content analysis of recommendations for 21 CPGs recommending using a tool such as FRAX or other before DXA measurement did not show any pattern of difference or similarity based on high and low quality guidelines. Four guidelines were not clear in their recommendations whether to use FRAX first or BMD testing (Society of Obstetrician and Gynecologist of Canada 'SOGC' 2014[72], the Saudi Arabia CPG[76], the Italian CPG 2016 [78], and the American Association of Endocrinologist 2016 [80]).

Overall there is a substantial variation between the recommendations in this area and this variation is mostly by region or country. Twelve CPGs recommend the use of FRAX or another tool before BMD testing, yet, the age to do FRAX and the cut off point to perform DXA have varied. Furthermore, there were variations between guidelines in the same country; in Canada, variations between provinces are evident; British Columbia recommends using FRAX to determine the need for DXA [66], while in Ontario, BMD testing is performed before FRAX, which is used afterwards to calculate the fracture risk estimation [58]. In Alberta, they use osteoporosis self assessment tool (OST), and if score is <10 then BMD is indicated [79]. To calculate the 10-year fracture risk two tools are used in Canada; the Canadian Association of Radiologist and Osteoporosis Canada (CAROC), and the Fracture Risk Assessment tool Canadian population (FRAX).

Most American guidelines (USPSTF 2011[63], University of Michigan 2011[64], the Endocrine Society 2012 [68], Institute of Clinical Improvement 2013 [69], and the NOF 2014 [71]) recommend to use FRAX tool for women <65 of age to determine the need for DXA (BMD). If the 10-year fracture risk by FRAX is ≥9.3%, then DXA is indicated. Similarly, indicated in the Taiwan CPG 2011[65], and British Columbia CPG 2012[66]; however BMD is indicated if the 10-year risk for all osteoporotic fractures is between 10-20% or 1.5-3% for hip fracture.

The British Guidelines (NICE 2012 [9], SIGN 2015 [74], and NOGG 2016 [77]), also recommend using FRAX or QFracture before DXA for patients with risk factors and above 50 years of age. The cut off level to decide DXA was in most of the guidelines >10% risk for fracture. On the other hand, five guidelines (OP Canada 2010 [58] , Australia 2010 [60], National osteoporosis society of South Africa 2010[61], Greece 2011[62], and India 2013[70]) did not recommend to use of FRAX before BMD testing. For South Africa, and India the reason for not recommending FRAX was the lack of country specific data.

BMD testing before FRAX

Only four CPGs (Osteoporosis Canada 2010 [58], Australia 2010[60], National osteoporosis society of South Africa 2010[61], and Greece 2011[62]) recommend BMD testing before FRAX risk estimation especially for those <65 years of age. However, the recommendation for using FRAX is governed by the availability of country specific data and in countries like India where such data is not available, FRAX can't recommended to be use neither before or after BMD testing.

Age for baseline BMD testing

Advancing age is one of the risk factors for osteoporosis; all included guidelines discussed this key area. Most guidelines set a certain age for routine BMD testing, especially for countries with population-based screening, such as in North America. In contrast to the UK, where the screening is based on case finding strategy, the CPG does not recommend a specific age for baseline screening, but rather identifying high risk

individuals above 50 years of age. Most guidelines recommend screening for women ≥ 65 years, yet for men, this age limit varies. In USPSTF, they didn't find an evidence to recommend screening for men [63].

When to start treatment

In this section, we looked at the intervention threshold for individuals without previous fractures (primary intervention). We only focused on eighteen guidelines which discuss clear criteria for intervention threshold. There was no pattern of consistency or similarity between high or low quality guidelines, or in relation to the date of publication. In general, we found four approaches for setting intervention thresholds. The first approach in countries with no country specific FRAX data, the treatment is based on the T-score value of BMD testing, such as India and South Africa CPGs [60,69]. T-score≤ -2.5 is the cut off point to start treatment, an exception is the Indian CPG, that recommends a T-score of -3 as the cut off level [70]. As a second approach; some guidelines (all the Canadian CPGs) apply a fixed threshold of FRAX probability score that can be used for men and women irrespective of age. A 10-year risk of major osteoporotic fracture of ≥ 20% is the intervention threshold in most guidelines (Osteoporosis Canada 2010 [58], Taiwan 2011 [65], British Columbia 2012 [66], SOGC 2014 [72], and Alberta 2016 [79]). The third approach is using the T-score threshold, and if it is at the osteopenia level (T-score between -1 to -2.5), then FRAX score threshold is applied to decide treatment (treatment is indicated, if ≥20% risk of major osteoporotic fracture or ≥3% risk of hip fracture). CPGs that used this approach are: Greece CPG2011[62], Endocrine Society 2012 [68], Institute for clinical system improvement guideline 2013 [69], NOF 2014[71], The Malaysian osteoporosis society 2015 [75], and the Italian Society 2016 [78].

The last fourth approach is applying of an intervention threshold which is dependent on age; the National Osteoporosis Guideline Group (NOGG) has set a threshold of intervention at each age level after 40 years, provided through a chart with or without BMD testing [72,76].

Sites for BMD testing

Some guidelines were not very clear in this area. For most guidelines, the preferred sites to measure BMD are the femoral neck, total hip, and lumbar spine, and if not available then the lower 1/3 of the radius is preferred. Most CPGs recommend using the lowest BMD score from lumbar and hip measurements. Yet, because most CPGs decide their intervention threshold based on fracture risk assessment as discussed above, they recommend the use of femoral neck, or total hip sites for BMD testing, since they are the only sites that are validated to calculate the fracture risk by FRAX tool.

BMD testing after treatment

The period to assess BMD has varied between CPGs ranging between 1-2 years or 2-3 years or sometimes up to 8 years. However, most guidelines were in agreement in reporting that there is lack of evidence for the optimum period or the benefit of repeating BMD and that area is controversial.

Table 2-7: Grading systems used for determining the level of evidence and strength of recommendations

Guidelines	Grading System used for level of evidence	Description	System for strength of recommendations	Scale Description
Osteoporosis Canada 2002 [49]**.**	Same levels for diabetes guidelines by Meltzer et al 1998 [85] (it depends on the type of study i.e. interventional, prognostic…etc.)	1,2, 3, 4. For diagnosis and prognosis studies 1+, 1, 2+, 2, 3, 4, 5, 6 for intervention and treatment studies	same as diabetes guideline	A, B, C, D
US Preventive Services Task force 2002 [50]**.**	The USPSTF criteria	High, Moderate, Low	The USPSTF grades	A, B, C, D, I =(Insufficient)
Canadian Task Force on Preventive Health Care 2004 [51]	Levels of evidence were not assigned		Which system they followed was not reported	
American University of Beirut Medical Center 2005 [52]**.**	Levels of evidence were not assigned but only reported The Royal College of Physicians, London Criteria,2000.		Royal College of Physicians, London 2000.	A, B, C
Guidelines in Asia 2006 [53]**.**	Levels of evidence were not assigned		Grades of strength were not assigned	
the American College of Physicians guidelines 2008 [54]**.**	American college of physicians grading system which is adapted from the GRADE system [54]	High, Moderate, Low	American college of physicians grading system which is adapted from the GRADE system [54]	Strong, or Weak
National Osteoporosis Foundation 2008 [55]**.**	Not assigned		Not assigned	
First Update of the Lebanese Guidelines 2008 [56]**.**	Were not assigned		Not assigned.	
Singapore Clinical Guidelines 2009 [57]	Adapted from SIGN [74]	1++,1+,1-,2++,2+,2-, 3, 4	The previous SIGN grades before moving to GRADE	A, B, C, D
Osteoporosis Canada 2010 [58]**.**	Same criteria as 2002 guidelines[49], and diabetes guidelines in 1998	1,2, 3, 4. For diagnosis and prognosis studies 1+, 1, 2+, 2, 3, 4, 5, 6 for intervention and treatment studies	Same as evidence	A, B, C, D
American Association of Clinical Endocrinologist AACE 2010 [59]	Adapted from AACE protocol by Mechanick et al [86]	1 1 2 2 2 2 3 3 3 3 4	Adapted from AACE protocol by Mechanick et al [86]	1=strong 2=intermediate 3=weak 4=no evidence
Australian Guidelines 2010 [60]**.** [74]	NHRMC evidence matrix and grades of recommendation [60]	A, B, C, D	NHRMC	A, B, C, D
National Osteoporosis Foundation of South Africa CPG (NOFSA), 2010 [61]**.**	GRADE system [87]	High, Moderate, Low, very Low	GRADE [87]	1= strong "we recommend" 2=Weak "we suggest"
Greece National Medical Agency Guideline, 2011 [62]**.**	Not assigned		Not assigned	
USPSTF 2011 [63]**.**	USPTSF levels of certainty	High, Moderate, Low	USPSTF	A, B, C, D, I =Insufficient
University of Michigan Health System Guideline 2011 [64]**.**	Rating was assigned, but the source of the system was not reported	I, II, III	Grades assigned but the source was not reported	A, B, C, D

Table 2-7: Continued

Guidelines	Grading System used for level of evidence	Description	System for strength of recommendations	Scale Description
Taiwan osteoporosis practice guidelines 2011 [65].	SIGN system of evidence	1++,1+,1-,2++,2+,2-, 3, 4	Grades were created by the developers [65]	A, B, C, D
British Columbia Medical Association 2012 [66].	Levels were not assigned		Not assigned	
The Malaysian Osteoporosis Society Guideline 2012 [67].	Adapted from the National Guideline Clearinghouse [88]	I, Ia, II, IIb, III. IV	Modified SIGN by Harbour et al 2001 [89]	A, B, C
NICE guidelines 2012 [9]	They modified the GRADE system [90]	GRADE+ review of the quality of cost-effectiveness studies and don't provide a summary labels for the quality of evidence across all outcomes.	Used a special NICE way of wording [90]	Most recommendations should start with an action verb 'offer', 'consider', 'measure', 'advise', 'discuss', 'ask', 'about', 'commission'.
The Endocrine Society 2012 [68]	GRADE [87]	High, Moderate, Low Very Low.	GRADE [87]	1=Strong "we recommend". 2=Weak "we suggest"
Institute for Clinical System Improvement guideline (ICSI), 2013 [69].	Transition between the ICSI system and GRADE	High, Moderate, Low	Same as evidence	Strong, or weak.
Indian Menopause Society, 2013 [70]	GRADE [87]	High, Moderate, Low, Very Low	GRADE [87]	Strong = "recommend" Weak=" suggest"
National Foundation of Osteoporosis (NOF), 2014 [71]	Levels were not assigned		Grades were not assigned	
the Society of Obstetricians and Gynaecologists of Canada (SOGC), 2014 [72]	Canadian Task Force on preventive health Care 2003 [91]	I, II-1, II-2, II-3, III	Same as evidence	A, B, C, D, E (against), I (insufficient)
National Osteoporosis Guideline Group (NOGG)/UK 2014 [73]	Not assigned		Not assigned	
The Malaysian Osteoporosis Society guideline, 2015 [75]	National guidelines clearinghouse criteria, (shekelle et al 1999 [88])	I, Ia, II, IIb, III, IV	Modified SIGN by Harbour et al 2001 [89]	A, B, C
2015 Guidelines for Osteoporosis in Saudi Arabia [76].	London College of Physicians, 2002[92]	Ia, Ib, IIa, IIb, III, IV	London College of Physicians, 2002[92]	A, B, C
Scottish Intercollegiate Guidelines Network (SIGN) guideline, 2015 [74]	SIGN level of evidence [74]	1++,1+,1-,2++,2+,2-, 3, 4	GRADE System	-Strong -Conditional -Good Practice Points
National Osteoporosis Guideline Group(NOGG)/UK, 2016 [77].	Levels assigned but the system was not reported	Ia, Ib, IIa, IIb, III, IV	ABC grades were assigned	A, B, C
Italian Society for Osteoporosis, 2016 [78]	Levels of evidence were assigned but system was not reported	1, 2, 3,	Assigned	A, B, C, D
Alberta Guidelines 2016 [79]	Not assigned		Not assigned	
American Association of Clinical Endocrinologist (AACE), 2016 [80]	According to AACE protocol [86]	1 1 2 2 2 2 3 3 3 3 4	Grades were according to AACE protocol [86]	1=strong 2=intermediate, 3= weak 4=no evidence

Table 2- 8: Comparison of selective recommendations from the most recent guidelines from 2010-2016

GUIDELINE	FRACTURE RISK ESTIMATION TOOL BEFORE BMD TESTING	BMD TESTING BEFORE FRACTUR RISK ESTIMATION	AGE OF BASELINE BMD TESTING IN MEN AND WOMEN	WHEN TO TREAT (for patients with no previous fracture)	2 SITES FOR BMD TESTING	BMD ASSESSMENT AFTER TRETMENT
Osteoporosis Canada 2010 [58]**.**	No, after BMD to decide treatment	Yes, indications differ by age category and associated certain risk factors	BMD for all men and women≥ 65 years. For younger depends on the presence of certain risk factors	-Treatment for those at high risk (>20% of major osteoporotic fracture in 10 years) -For moderate risk (10-20% probability of osteoporotic fracture) treatment is based on patient preference and additional risk factors not captured by FRAX *	Lumbar spine or total hip. But only femoral neck is used to calculate risk of fracture score.	Reassess in 1-3 years
Australian Guidelines 2010 [60]**.**	No, history and PE to assess risk factors. The tool was for patients with osteopenia to decide treatment and not for initial assessment	BMD testing for women >50 and men >60 plus any of the risk factors **	If age >70 years of age for men & women	-Treat if BMD ≤ -2.5 -Not FRAX (other risk assessment monogram) for those with osteopenia to discuss treatment, categories and when to start treatment is not reported	Preferred on 2 sites: anteroposterior spine and hip.	Not before 2 years.
National Osteoporosis Foundation of South Africa CPG (NOFSA), 2010 [61]**.**	Not recommended since no country specific data, however assessment of same CRFs in FRAX + Vit D/Ca adequate intake and propensity to falls	Yes	Not clearly specified, clinical assessment of men and women over 50	-Treatment is recommended if BMD≤-2.5 -For those with osteopenia, simple algorithm with the same FRAX CRFs is suggested to identify if they are at greater risk. FRAX is not used till country specific data is available	No recommendation on most suitable site but suggested to use BMD values at the spine, total femur and femur neck and to use the lowest BMD value	After 18-24 months of therapy
Greece National Medical Agency Guideline, 2011 [62]**.**	No, but used to decide treatment with BMD Using the Italian population data and algorithm.	Yes	All men and women ≥65 and <65 based on same CRFs for FRAX	-Treat if BMD ≤-2.5 -If osteopenia and 10-yr risk for major osteoporotic fracture ≥20% and/or hip fracture ≥ 3% - if osteopenia and 10-yr risk for major osteoporotic fracture 10-20% with ≥1 parameter of risk factors.***	Both hip and lumbar spine (L1-L4) measurement is recommended. Forearm BMD if other sites can't be measured.	Not reported

CRFs: Clinical risk factors

Table2- 8: Continued

GUIDELINE	FRACTURE RISK ESTIMATION TOOL BEFORE BMD TESTING	BMD TESTING BEFORE FRACTUR RISK ESTIMATION	AGE OF BASELINE BMD TESTING IN MEN AND WOMEN	WHEN TO TREAT (FOR PATIENTS WITH NO PREVIOUS FRACTURE)	2 SITES FOR BMD TESTING	BMD ASSESSMENT AFTER TRETMENT
USPSTF 2011 [63]**.**	Yes; for women younger than 65 to decide the need for DXA	-For women≥ 65 - For women <65 years, if the 10-year fracture risk is = (9.3%)	- ≥65 years for women, - For men without previous fracture or secondary causes for OP is **NOT** recommended (insufficient evidence)	The guideline discussed only screening.	Hip and lumbar spine	Repeating up to 8 years after treatment /lack of evidence of optimal time
University of Michigan Health System Guideline 2011 [64]**.**	Yes, for women <65 to decide the need for DXA (if they have 10- year total fracture risk ≥ 9.3% then DXA is recommended).	Order DXA based on clinical risk factors other than those in FRAX	-women >65 and men ≥70 years.	-For naïve women, treatment is based on FRAX score, if >3% at hip or >20% total fracture risk then treat. -For other groups, it is based on risk factors with BMD scores: Treat, if T-score <-2.5. If T-score ≤-1 and a) steroid use, b) pending or post-transplant, c) postmenopausal women with high risk	For diagnosing OP at spine use the L1-L4 value and for hip use the femoral neck or total hip	Repeat based on rate of bone loss. -If prior T>-1 wait at least 3-5 years. -If prior T≤ -1 wait at least 2 years
Taiwan osteoporosis practice guidelines 2011 [65]**.**	Can be used to decide DXA. If the10-yr risk for all OP fractures is between 10-20%, or for hip fracture between 1.5-3% then DXA is indicated.	For women ≥ 65 years, and for men ≥70.	BMD should be done for women ≥65 and for men ≥70 years. For younger ages if there are risk factors	Treatment if 10-yr risk for major osteoporotic fracture > 20% and/or hip fracture >3%. (assessed after BMD testing)	Lowest T-score from lumbar spine or hip bone, if not available then non-dominant forearm	Every 2 years for treated women and every 3 years for untreated
British Columbia Medical Association 2012 [66]**.**	Yes, use FRAX without BMD and assess risk for falls	Only for women and men >65 years and 10-year moderate risk of fracture (10%-20%).	BMD is done for men and women >65 and for those with a moderate risk for fracture (10-20% 10-year risk) by FRAX	Treatment is only based on risk degree using FRAX is≥ 20% 10-year risk - If moderate risk (10-20%) with additional risk factors **§**	Not reported, but since it is using FRAX femoral neck or total hip should be done.	Insufficient evidence when to pretest. based on patient's risk profile test in 3-10 years

Table 2-8: Continued

GUIDELINE	FRACTURE RISK ESTIMATION TOOL BEFORE BMD TESTING	BMD TESTING BEFORE FRACTUR RISK ESTIMATION	AGE OF BASELINE BMD TESTING IN MEN AND WOMEN	WHEN TO TREAT (for patients with no previous fracture)	2 SITES FOR BMD TESTING	BMD ASSESSMENT AFTER TRETMENT
NICE guidelines 2012 [9]	Always assess the absolute risk first without BMD (if not done before) using FRAX or Q Fracture. For women aged 65-80, and for men between 75 and 80, immediately do the fracture risk assessment. For those below the above age range consider assessment if they had certain risk criteria ‡	NO, BMD is recommended only if the fracture risk based on FRAX or QFracture is in the region of intervention [cut off point was not specified by the guideline but it states following other local or national guidelines]	It doesn't depend on age, only on assessment of risk of fracture.	It is out of the scope of the guidelines to recommend intervention threshold	Proximal femur is the preferred sites for fragility risk prediction. [this is not included as a recommendation]	Not reported
The Endocrine Society 2012 [68]	For those below 70 years of age, FRAX, and Graven monogram can be used to assess the need for DXA.	For men ≥ 70 years of age.	Men ≥70 years of age and if younger, then based on risk factors [The guideline didn't specify which to use first, BMD or FRAX. It was unclear, it stated that FRAX, Garvan, or other fracture risk calculators can improve the assessment of fracture risk and the selection of patients for treatment.	-Treatment if BMD≤ -2.5 SD of the spine, femoral neck or total hip. -Treat If BMD between (-1.0 to -2.5) and FRAX≥20% for major osteoporotic fracture or ≥3% for hip fracture	DXA for hip, lumbar spine, and 1/3 radius if spine or hip cannot be interpreted.	DXA at the spine or hip every 1-2 years, if stabilize then reduce

Table2- 8: Continued

GUIDELINE	FRACTURE RISK ESTIMATION TOOL BEFORE BMD TESTING	BMD TESTING BEFORE FRACTUR RISK ESTIMATION	AGE OF BASELINE BMD TESTING IN MEN AND WOMEN	WHEN TO TREAT (FOR PATIENTS WITH NO PREVIOUS FRACTURE)	2 SITES FOR BMD TESTING	BMD ASSESSMENT AFTER TRETMENT
Institute for Clinical System Improvement guideline (ICSI), 2013 [69]**.**	Risk stratify patients based on personal risk factors, if high probability for fracture, then use FRAX without BMD. -Also, FRAX is indicated after BMD if the patient has osteopenia to assess the need for treatment	All women ≥65 and men ≥70 should do BMD testing. BMD testing indicated after FRAX if 10-year fracture risk is ≥9.3%.	Clinicians should screen for osteoporosis in women ≥ 65 and in younger women whose fracture risk is ≥ 9.3% from FRAX analysis or are at fracture risk.	Treatment if BMD≤ -2.5 SD of the spine, femoral neck or total hip. -Treat If BMD between -1.0 to -2.5 and 10-year fracture risk is ≥20% for major osteoporotic fracture or ≥3% for hip fracture.	Didn't specify in the recommendations. However, it was reported that T-scores from femoral neck or total hip is used to predict fracture and scores from non-hip sites are not recommended.	Every 12-24 months. However, it stated lack of evidence for best interval. It could be shorter if patients at risk of accelerated bone loss
Indian Menopause Society, 2013 [70] **{*men not included in the guideline*}**	FRAX tool not included, since no country specific data is available, however case finding using risk factors should begin in women>40	Yes	DXA indicated for women 5 years after menopause age and less than 5years with risk factors.	BMD T-score= -3 is the cut off point and not -2.5 to prevent overtreatment	DXA of spine, total hip and neck of femur, and the lowest BMD obtained from all sites is used.	They 'suggest' DXA every 2 years on the same machine
National Foundation of Osteoporosis (NOF), 2014 [71]	Use FRAX for assessment of fracture risk to identify further need for DXA especially for women <65 years and men <70 years of age.	For women ≥ 65 years of age and for men ≥70 years of age/	For all women ≥65 years and for those younger with FRAX score ≥9.3%. -For men >70 years of age.	-Treat if T-scores ≤−2.5 at the femoral neck, total hip, or lumbar spine by DXA -Treat if men and women with (T-score between −1.0 and −2.5, osteopenia) and a 10-year hip fracture probability ≥3 % or a 10-year major osteoporosis-related fracture probability ≥20 %	Either lumbar spine or femoral both are preferred sites. For FRAX analysis only femoral neck and total hip (femoral neck is better).	Every 1 to 2 years after initiating treatment and every 2 years thereafter
the Society of Obstetricians and Gynaecologists of Canada (SOGC), 2014 [72]**{Men not included}**	Not clear in the recommendations but it is reported to be use with BMD results and not before that.	Yes, BMD is recommended, however FRAX should be used to decide treatment.	Women ≥ 65 years, and younger with risk factors	-Treat if fracture risk assessment with FRAX is ≥20 % 10-year risk. -If moderate risk (10-20%), treatment is individualized	Lumbar spine, hip (femoral neck or total), or radius	Not reported in the guideline

Table 2-8: continued

GUIDELINE	FRACTURE RISK ESTIMATION TOOL BEFORE BMD TESTING	BMD TESTING BEFORE FRACTUR RISK ESTIMATION	AGE OF BASELINE BMD TESTING IN MEN AND WOMEN	WHEN TO TREAT (for patients with no previous fracture)	2 SITES FOR BMD TESTING	BMD ASSESSMENT AFTER TRETMENT
The Malaysian Osteoporosis Society guideline, 2015 [75] **{*In this guideline, there is a difference in the management algorithm between men and women*}**	OSTA can be used to identify those at risk for OP who require BMD. -for those with risk factors, FRAX tool is indicated with or without BMD	BMD assessment based on OSTA^ category (moderate and high), should do BMD. *{The guideline was not very clear whether using FRAX before BMD first*}.	All women over 65 and men over 70 years of age.	-Treatment if BMD ≤-2.5. -Treat if osteopenia and FRAX ≥3% for hip and ≥20% for major OP fracture for 10 years -If osteopenia and FRAX is not available treat based on risk factors.	Only femoral neck BMD to be used.	Reassess every 2-3 years.
2015 Guidelines for Osteoporosis in Saudi Arabia [76]**.**	Didn't specify that, but it was clearly reported that BMD should be done for risk assessment with CRFs	Yes, it is used if women have risk factors and considering treatment	-All women >60 years of age -For men, it was not reported or recommended	It was stated that therapy decision should be formulated using FRAX tool but didn't give any thresholds for intervention or any recommendations	Not reported or recommended	BMD 1-2 years after treatment preferably 2 years.
Scottish Intercollegiate Guidelines Network (SIGN) guideline, 2015 [74]	Yes, fracture assessment should be done before BMD, using QFracture tool. And if BMD is already was done, fracture assessment should be done to decide treatment.	No, not recommended before fracture risk assessment, only after assessment if anti-osteoporotic treatment is considered and (10-year risk is >10%)	No baseline age was reported, it is all based on assessment of risk factors in those aged 50 years and above.	It was clearly stated that treatment decisions should not be solely based on fracture risk assessment tools results, and BMD score should be included. Treatment is indicated if 10-year fracture risk of 10% and DXA is ≤ -2.5.	BMD measurement at the spine and hip should be done	Repeat after 3 years
National Osteoporosis Guideline Group(NOGG)/UK, 2016 [77]**.**	Women and men ≥ 50 with certain CRFs, should be assessed using FRAX except if women have previous fragility fracture then no need (just do BMD)	Not recommended. Only for women with previous fragility fracture where fracture risk assessment is not needed.	No baseline age, those above 50 with moderate risk (≥10% 10-year risk of OP fracture) should do BMD.	-Treat if FRAX above intervention threshold even if without BMD. -If moderate risk, then do BMD and reassess and they provided different thresholds for intervention based on age.	Multiple sites are not recommended, femoral neck is preferred, however if not possible, spine BMD can be used.	BMD +FRAX after 3-5 year period.
Italian Society for Osteoporosis, Mineral metabolism and Bone Diseases (SIOMMMS) 2016 [78] **{*this guideline***	They stated to use the Italian DeFran algorithm derived from FRAX. But didn't specify when	Yes, it stated to use BMD with clinical risk factors tools, to assess the fracture risk. In all men ≥70, and at	In women, didn't specify any age for men it clearly stated in men 70 and over, BMD is	-Treat if T-scores ≤−2.5 at the spine or hip. -Treat, if over 50 years of age and 10-year major osteoporosis-related fracture	Lumbar spine (L1-L4) and proximal femur DXA is recommended.	Every 1.5-2 years

has low quality scores, recommendation were not clear and ambiguous}	to do it and what is the threshold for treatment using it. !!	any age if having major risk factors (same like women), or with ≥2 minor risk factors	indicated.	probability ≥20 % or ≥3% for hip fractures		
Alberta Guidelines 2016 [79]	For general population (50-64) use osteoporosis self assessment tool (OST): if low risk, reassess in 5 years. For those with risk factors and OSTA<10, order BMD based on certain risk factors. and assess absolute fracture risk by CORAC or FRAX	Order BMD only of OST score <10, indicating that patient in moderate and high risk. And for those with certain factors like ≥ 65 year, previous fracture and etc. Then use BMD to assess absolute risk of fracture.	-All women ≥ 65 years -Men ≥ 65 with 1+ risk factors	-Treat if FRAX score is >10% to >20%.	Not clearly reported, but they use FRAX so only BMD from femoral neck or total hip is used for calculation	There is a lack of evidence for the benefit of follow up BMD, thus, no recommendations is made.
American Association of Clinical Endocrinologist (AACE), 2016 [80] **{*Men are not included in this guideline*}**	FRAX should be included in the initial evaluation of all postmenopausal women ≥ 50 years	Not clear when to do BMD exactly. All women ≥ 50 year should be assessed by history and PE and fracture risk assessment	All women ≥ 65 years and younger women with certain CRFs.	-Treatment if BMD ≤-2.5 - Treatment if osteopenia and FRAX>3% for hip and >20% for major OP fracture for 10 years	Lumbar spine, total hip, femoral neck or lower radius	Get a baseline BMD then every 1-2 years till stable.

*Additional vertebral fracture(s) (by vertebral fracture assessment or lateral spine radiograph) • Previous wrist fracture in individuals aged > 65 and those with T-score ≤ –2.5 • Lumbar spine T-score << femoral neck T-score • Rapid bone loss • Men undergoing androgen-deprivation therapy for prostate cancer • Women undergoing aromatase inhibitor therapy for breast cancer • Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use • Recurrent falls (≥ 2 in the past 12 months) • Other disorders strongly associated with osteoporosis, rapid bone loss or fractures.

****** Presence of major risk factors: • Age over 60 years • Family history of osteoporotic fractures • Hypogonadism • Prolonged (>3 months) glucocorticoid use • Inflammatory conditions • Malabsorption • Hyperparathyroidism • Hyperthyroidism • Low body weight • Smoking • Recurrent falls • High alcohol intake (>2–4 standard drinks per day for men, less for women).

*******lateral thoracic and lumbar x-ray showed fracture, lumbar BMD lower than hip BMD, significant decrease (>5%) of BMD between two consecutive measurements within a period of >1year, women with breast cancer under aromatase inhibitors, men with prostatic ca under antiandrogen medication, long-term systemic treatment with steroid, repeated (>2 falls) during the last year due to gait balance disorders, vision problem.

§ Vertebral fractures (> 25% height loss with end-plate disruption) • Men receiving androgen deprivation therapy for prostate cancer • Women receiving aromatase inhibitor therapy for breast cancer • Long-term or repeated systemic corticosteroid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic corticosteroid use (i.e., ≥ 3 months (consecutive) therapy at a dose of prednisone ≥ 7.5 mg per day or equivalent) • Recurrent falls

‡ Previous fragility fracture, current or frequent recent use of oral or systemic steroid, history of falls, family history of hip fracture, other causes of secondary osteoporosis, low body mass index (BMD<18.5), smoking, high alcohol intake (>21 u/week for men; >14 U/week for women).

^ Self Assessment Tool for Asians

DISCUSSION

Clinical practice guidelines are developed with the goal of assisting health care professionals to analyze and integrate the best evidence available in management of health conditions and diseases; aiming to improve the quality of care and diminishing inappropriate variability in practice.

Osteoporosis is a common health problem in Canada which results in fragility fractures especially in elderly. These fractures have impact on mortality, quality of life and financially. Osteoporosis is one of the health conditions that showed variability in recommendations. Thus, we systematically identified and assessed 33 guidelines for screening for osteoporosis published between 2002-2016 from 13 countries, using the AGREE II instrument and the IOM standards for guideline trustworthiness, which are developed to appraise the quality of CPGs. Our findings reveal that osteoporosis guidelines released between 2002 and 2016 are of variable quality as measured by the AGREE II and IOM standards instruments, and make differing recommendations.

An examination of the mean of AGREE II domain scores showed that the highest mean domain scores were for Clarity of Presentation and Scope and Purpose, while the lowest mean scores were for Applicability and Editorial Independence domains. This finding was consistent with other reviews in other topics [20,21,65–67]. The applicability domain reflects the implementation of the guideline; however, most guidelines didn't give advice on how the guideline should be implemented. One of the reasons for this might be that most guidelines don't have experts in knowledge translation and economics within their development group which could advise on strategies for implementation and assessing economic barriers.

Regarding the domain of stakeholder involvement; most guideline developers didn't seek the views and preferences of their target population especially patients in guidelines development and even when they did they were vague about the process. This is worth considering by all guideline developers, since a patient centred approach to health care with shared decision making is associated with better application of guidelines and

improved health care [22,95]. The domain of rigor of development which is considered of importance to guideline quality scored only 60% of the guideline, thus, one third of CPGs had poor development methodology. This differs from the results of the previous review of postmenopausal osteoporosis CPGs by Cranney et al 2002 [25], in which the average score was almost 23% which is much lower than our score. Nonetheless, this review covered 2001-2002 published guidelines, so including more guidelines in our review may have resulted in higher and more accurate mean scores. Furthermore, they used a different appraisal items (not the AGREE II), thus we can not directly compare the results.

By assessing the adherence of guidelines to the criteria of the IOM standards, we found that 64%- 67% of guidelines fulfilled the standards for establishing evidence, strength of recommendations, and systematic review standards. However, most guidelines fell short in involving patients and public representatives in their guideline development and didn't adequately describe the method for external review. Though, the IOM standards were developed in 2011 and we found few studies that have assessed the quality of CPGs using these standards[16,17]. The studies that do use these standards each used different methodology, making it impossible to compare results. Reams et al 2013 [42] assessed the quality of guidelines for oncology using the IOM tool; their findings were similar to ours in particular to the lower score in guideline development group composition, yet, our study found a better performance on standards 3, 4 and 5 (Guideline development group composition, systematic review section, and establishing evidence foundation and rating strength of recommendations respectively) compared to their study. We found that the application of IOM standards to assess the guidelines quality is challenging, since no scoring system is assigned to the criteria and some of the subcriteria are vague. This was also found in the study by Kung et al using the IOM standards, they excluded many items reporting that they were "vague and subjective" [96]In our study, we found that the adherence of guidelines to the criteria of both tools (AGREE II and IOM) showed no improvement between 2002-2010 and 2011-2016, the time of the release of both tools. This finding aligns with previous studies evaluating CPGs over time which have found guideline quality is not improving over time[88,89,92,93], while it conflicts with others which demonstrated improvements in guideline quality[45,90,95,100].

Most guideline developers are should be aware of both tools, this lack of improvement in the quality of the development of osteoporosis guidelines needs further study of the reasons guideline developers are not following and reporting on widely accepted quality indicators of the guideline development process.

In comparing the results from AGREE II tool with those of the IOM standards tool; the AGREE II was more comprehensive, as it covered implementation and dissemination issues of the guidelines, while IOM did not cover this area. Both instruments identified domains relate to multidisciplinary development group composition with involvement of patients and public representatives, the influence of funding body, and conflict of interests, are falling short in most guidelines as very few CPGs met these criteria.

We used certain criteria to identify high quality guidelines; AGREE II identified 12 high quality guidelines, while the IOM identified 15; eleven CPGs were in common by both tools. By examining the items or criteria for domains of rigor of development and systematic review methodology in the four extra high quality guidelines; identified by IOM; we found that the AGREE II gave lower scores for these guidelines. This is because the AGREE II has more detailed quality items for this section, while, the IOM has fewer criteria in this section, which have resulted in higher scores for the guidelines. This may have important implications for clinicians and stakeholders, in deciding which guideline to implement based on using one of the two tools to assess the quality and rigour of the guidelines.

Our systematic review emphasizes the variability in the use of the different grading systems to aggregate the level of evidence and to rate the strength of recommendations. Establishing the level of evidence that underlies the recommendations is essential in guideline development. Without clarity of the system of evidence that is used, guidelines users cannot decide whether recommendations are built on strong evidence or weak evidence. Additionally, determining the strength of recommendations influences the applicability and implementation of the guideline. Different frameworks or grading

systems were developed, yet, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system is considered one of the best now, and has been adopted by many organizations [21]. Surprisingly nine guidelines did not use any system for level of evidence or strength of recommendation, and only seven guidelines used the GRADE system (Table 2-7).

The content analysis of selected areas of recommendations for screening of individuals without previous fractures revealed considerable variability. This variability did not differ between high or low quality guidelines but mainly differed by region or country. In terms of their approach for BMD screening, British CPG recommendations use risk assessment tools or algorithms to decide the need for BMD testing by DXA for all population. Whilst, in North America recommendations, are for universal screening of everyone over 65 years of age. The other conflicting area relates to choosing the intervention threshold for those at risk of fracture; some guidelines use bone mineral density T-score diagnostic criteria, others use BMD testing with FRAX scores and not solely the T-score results, and this approach is the most adopted in more recent guidelines.

Concordant recommendations were found for BMD testing sites. Additionally, there were variability in recommendations for follow up period of BMD testing after therapy, however most guidelines agreed that there was lack of evidence in this area, and that this topic is controversial.

We expected some variation between guideline recommendations since it is based on country specific data and cost-effectiveness. However, we found even in the same country guideline recommendations differ. For instance; in Canada; British Columbia CPGs recommend using FRAX before DXA [66], while in Ontario DXA is recommended before FRAX [58], and in Alberta, the use osteoporosis self assessment tool to decide the need for DXA [79]. This lack of uniformity between guidelines, likely creates confusion for the clinicians, and may subsequently affects adherence to the guidelines and may diminish quality of care to patients.

Study Limitations and Strengths

There are limitations to this review. First; we included only CPG in English, so guidelines in other languages were not assessed. Second, the AGREE website suggests 2-4 reviewers, and four is preferable to increase the reliability of the study. Third; in scoring the AGREE II, only the published information about the guidelines were used in assessment, i.e. we didn't look at the methodology documents of the organizations, which could have been on their websites (unless these citations were included in the released guideline). Thus, we may have underscored some domains. Fourth, assessing quality using the IOM standards was challenging because we could not find any suitable published methodology that was used in previous studies, and very few studies have used these standards to assess quality of guidelines (discussed in methods section). Thus, we are not certain about the validity of our methodology. This also may affect the results of comparison between the AGREE II and the IOM standards, which as a result of our IOM methodology, could be liable for bias. A final limitation is that we only assessed reporting of the guideline development process not the actual process- they may have done stuff they didn't report.

The main strength of this review is that we assessed the quality of osteoporosis screening guidelines over 14-year period to determine changes in guideline quality over time. Our search was systematic and comprehensive including all the general databases, guideline websites and major guideline developer groups, and by hand searching the references of all identified guidelines. Another strength, is that we used two recognised tools to assess guideline quality and compared the results from both tools which to our knowledge was done only by one study [43]. We had high interrater agreement between the two reviewers which increase the reliability of the study. The AGREE II tool does not assess the content of the recommendations of the guidelines, therefore, another strength is that we examined the content of the recommendations and provided a summary of comparison between the guidelines. In addition, we summarised the different grading systems for level of evidence and strength of recommendations.

CONCLUSION

Our assessment revealed that the quality of osteoporosis guidelines is variable as determined by The AGREII and IOM tools and that there is considerable room to improve the guideline development process as well as the reporting of the guideline development process. Guideline developers should develop their guidelines paying attention to the criteria and standards included in the AGREE II instrument and the IOM standards for trustworthy guideline. In particular the reporting of applicability considerations of the guideline and editorial independence areas appear week. The inclusion of patients, economists, and, knowledge translation experts as well as other stakeholders should be considered as a mean of improving the quality of guidelines and their likelihood of implementation. The lack of consensus on specific guideline recommendations for osteoporosis screening is problematic and creates confusion for clinicians and patients about what exactly is best practice. While one might expect to see variation in recommendations between countries given differences in context (social, economic, and health differences), the provision of differing recommendations by guideline developers in the same country is particularly problematic.

IMPLICATIONS

The findings of this systematic review show variability in the adherence of guidelines for osteoporosis screening to the criteria of guideline appraising tools. This adherence has not improved since the release of AGREE II and the IOM standards for guideline trustworthiness in 2010 and 2011 respectively. Osteoporosis guideline developers should consider strengthen their guideline development process to improve the domains they scored poorly on. Specifically, quality scores on the AGREE II and IOM standards tools could be improved by integrating patients and public stakeholders, and probably knowledge translation experts and others. Assessing the quality of existing guidelines is very important to primary care physicians and other policy makers, since it can aid in the decision of which recommendations to follow. However, if quality

instruments or tools offer conflicting results, this may affect clinicians' and stakeholders' judgements and subsequently the quality of patient's care. More studies using the IOM standards for trustworthiness are needed to validate this tool, and to test this tool's appropriateness for quality assessment of guidelines. Lastly, clarity of evidence level and strength of recommendations is important for increasing the implementation of the guidelines, as different grading systems may confuse clinicians. Thus, a consensus by guideline developers on using the same grading system for all guidelines could facilitate the adherence to the guidelines and assist in locating inconsistencies in the levels of evidence for recommendations between different CPGs.

The GRADE system is widely used by many respectful guidelines developing bodies and organizations, and recently the working group has published a framework 'Evidence to Decision (Etd)' to guide progression from evidence to recommendations. We encourage guideline developers to consider following the GRADE system for rating evidence and implementing the 'Etd' framework in clinical practice guideline development.

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SUPPLEMENTARY APPENDIX FOR CHAPTER 2

Table S2-A: Key words used for systematic search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 exp clinical pathway/ (5775)
2 exp clinical protocol/ (154284)
3 exp consensus/ (8029)
4 exp consensus development conference/ (11486)
5 exp consensus development conferences as topic/ (2739)
6 critical pathways/ (5775)
7 exp guideline/ (30701)
8 guidelines as topic/ (37891)
9 exp practice guideline/ (23568)
10 practice guidelines as topic/ (102001)
11 health planning guidelines/ (4378)
12 (guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt. (39834)
13 (position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw. (22878)
14 (standards or guideline or guidelines).ti,kf,kw. (89239)
15 ((practice or treatment* or clinical) adj guideline*).ab. (30162)
16 (CPG or CPGs).ti. (5681)
17 consensus*.ti,kf,kw. (20021)
18 consensus*.ab. /freq=2 (20234)
19 ((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw. (16533)
20 recommendat*.ti,kf,kw. (33459)
21 (care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw. (42022)
22 (algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw. (5860)
23 (algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw. (7141)
24 treatment guidelines.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (8345)
25 or/1-24 (519830)
26 exp Osteoporosis/ (52289)
27 osteoporosis.mp. (76133)
28 exp Bone Density/ (49627)
29 BMD.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (25453)
30 (bone? adj3 (loss* or lose* or losing)).ti,ab. (29496)
31 bone mineral density.ti,ab,kw. (35166)
32 (bone adj2 density).ti,ab,kw. (45159)
33 or/26-32 (127404)
34 25 and 33 (3512)
35 limit 34 to yr="2002 -Current" (2940)

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Table S2- B: AGREE II tool [10].

Domains and Items

Domain 1: Scope and Purpose

1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Domain 2: Stakeholder Involvement

4. The guideline development group includes individuals from all relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.

Domain 3: Rigour of Development

7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.

Domain 4: Clarity of Presentation

15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

Domain 5: Applicability

18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/or auditing criteria.

Domain 6: Editorial Independence

22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed

Table S2-C: IOM standards for Trustworthy Clinical Practice Guidelines

STANDARD 1

Establishing Transparency

1.1 The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible.

STANDARD 2

Management of conflict of interest (COI)

2.1 Prior to selection of the Guideline Development Group (GDG), individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity, by written disclosure to those convening the GDG.

• Disclosure should reflect all current and planned commercial (including services from which a clinician derives a substantial proportion of income), non-commercial, intellectual, institutional, and patient/public activities pertinent to the potential scope of the CPG.

2.2 Disclosure of COIs within GDG

• All COI of each GDG member should be reported and discussed by the prospective development group prior to the onset of their work.

• Each panel member should explain how their COI could influence the CPG development process or specific recommendations.

2.3 Divestment

• Members of the GDG should divest themselves of financial investments they or their family members have in, and not participate in marketing activities or advisory boards of, entities whose interests could be affected by CPG recommendations.

2.4 Exclusions

• Whenever possible GDG members should not have COI.

• In some circumstances, a GDG may not be able to perform its work without members who have COIs, such as relevant clinical specialists who receive a substantial portion of their incomes from services pertinent to the CPG.

• Members with COIs should represent not more than a minority of the GDG.

• The chair or co-chairs should not be a person(s) with COI.

• Funders should have no role in CPG development.

STANDARD 3

Guideline development group composition

3.1 The GDG should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG.

3.2 Patient and public involvement should be facilitated by including (at least at the time of clinical question formulation and draft CPG review) a current or former patient and a patient advocate or patient/ consumer organization representative in the GDG.

3.3 Strategies to increase effective participation of patient and consumer representatives, including training in appraisal of evidence, should be adopted by GDGs.

STANDARD 4

Clinical practice guideline–systematic review intersection

4.1 CPG developers should use systematic reviews that meet standards set by the Institute of Medicine's Committee on Standards for Systematic Reviews of Comparative Effectiveness Research.

4.2 When systematic reviews are conducted specifically to inform particular guidelines, the GDG and systematic review team should interact regarding the scope, approach, and output of both processes.

Table S2- C (Continued)

STANDARD 5

Establishing evidence foundations for and rating strength of recommendations

5.1 For each recommendation, the following should be provided:

• An explanation of the reasoning underlying the recommendation, including:

• A clear description of potential benefits and harms.

• A summary of relevant available evidence (and evidentiary gaps), description of the quality (including applicability), quantity (including completeness), and consistency of the aggregate available evidence.

• An explanation of the part played by values, opinion, theory, and clinical experience in deriving the recommendation

• A rating of the level of confidence in (certainty regarding) the evidence underpinning the recommendation.

• A rating of the strength of the recommendation in light of the preceding bullets.

• A description and explanation of any differences of opinion regarding the recommendation.

STANDARD 6

Articulation of recommendations

6.1 Recommendations should be articulated in a standardized form detailing precisely what the recommended action is and under what circumstances it should be performed

6.2 Strong recommendations should be worded so that compliance with the recommendation(s) can be evaluated.

STANDARD 7

External review

7.1 External reviewers should comprise a full spectrum of relevant stakeholders, including scientific and clinical experts, organizations (e.g., health care, specialty societies), agencies (e.g., federal government), patients, and representatives of the public.

7.2 The authorship of external reviews submitted by individuals and/or organizations should be kept confidential unless that protection has been waived by the reviewer(s).

7.3 The GDG should consider all external reviewer comments and keep a written record of the rationale for modifying or not modifying a CPG in response to reviewers' comments.

7.4 A draft of the CPG at the external review stage or immediately following it (i.e., prior to the final draft) should be made available to the general public for comment. Reasonable notice of impending publication should be provided to interested public stakeholders.

STANDARD 8

Updating

8.1 The CPG publication date, date of pertinent systematic evidence review, and proposed date for future CPG review should be documented in the CPG.

8.2 Literature should be monitored regularly following CPG publication to identify the emergence of new, potentially relevant evidence and to evaluate the continued validity of the CPG.

8.3 CPGs should be updated when new evidence suggests the need for modification of clinically important recommendations. For example, a CPG should be updated if new evidence shows that a recommended intervention causes previously unknown substantial harm, that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective, or that a recommendation can be applied to new populations.

Figure S2- 1: Prisma Flow chart for the selection of the guidelines

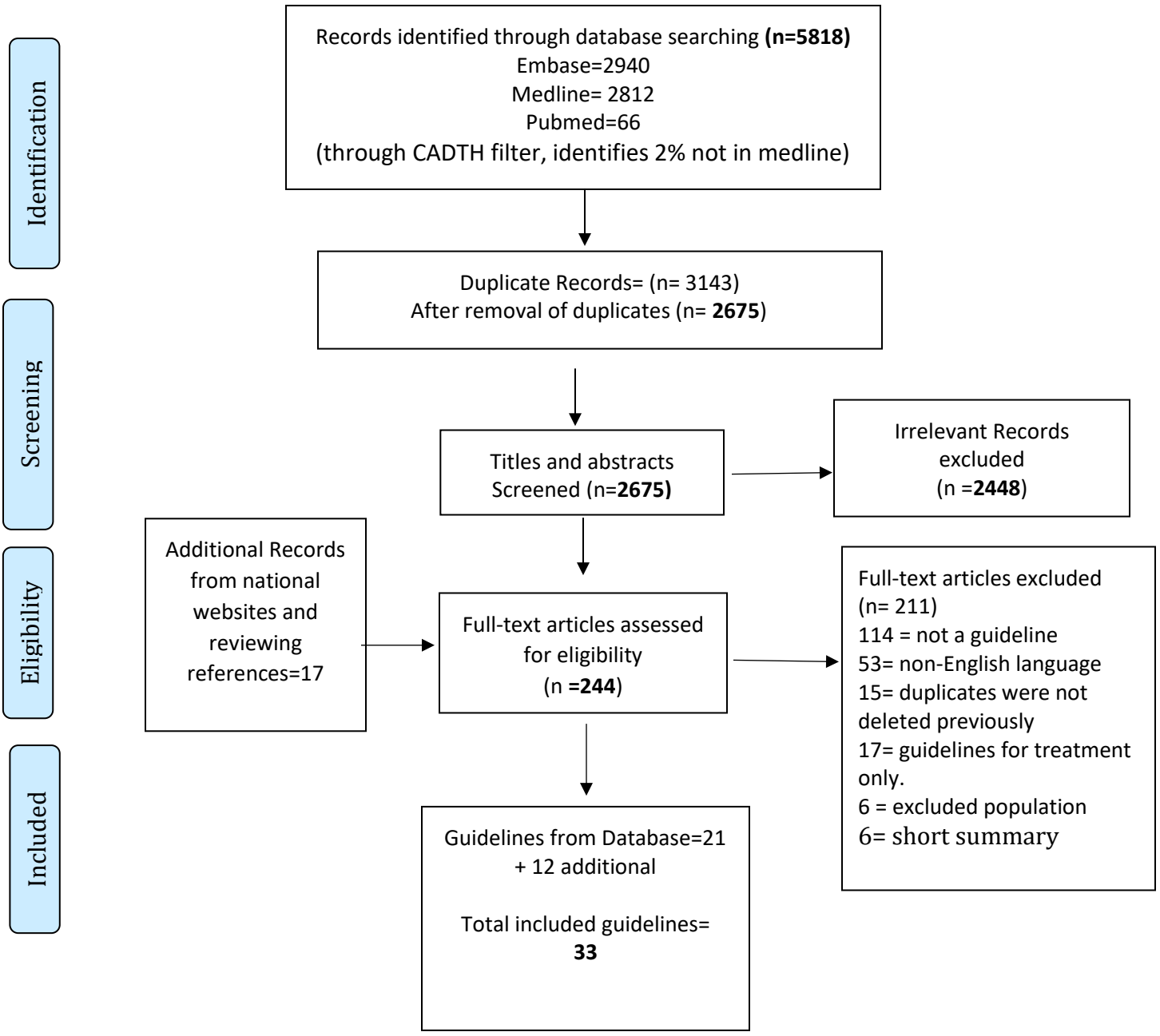

Table S2-D: Guidelines with Institute of Medicine Standards (yes or no)

	IOM Standards									
Guideline	**1.Establishing transparency**	**2.Management of conflict of interest (COI)**	**3.Guideline development group composition**	**4.Clinical practice guideline systematic review intersection**	**5.Establishing evidence foundation for and rating strength of recommendations**	**6.Articulatoin of recommendation**	**7.External review**	**8. Updating**	**Overall Score/ 8**	**High Quality**
Osteoporosis Canada 2002 [47]**.**	Y	N	N	Y	Y	Y	N	Y	5	✓
US Preventive Services Task force 2002 [87]**.**	Y	Y	N	Y	Y	N	Y	N	5	✓
Canadian Task Force on Preventive Health Care 2004 [48]	N	N	N	Y	Y	Y	N	N	3	
American University of Beirut Medical Center 2005 [88]**.**	N	N	N	Y	Y	Y	N	Y	4	
Guidelines in Asia 2006 [89]**.**	N	N	N	N	N	N	N	N	0	
the American College of Physicians guidelines 2008 [90]**.**	Y	Y	N	Y	Y	Y	N	N	5	✓
National Osteoporosis Foundation 2008 [91]**.**	N	Y	N	N	N	N	N	Y	2	
First Update of the Lebanese Guidelines 2008 [92]**.**	Y	N	N	Y	Y	N	N	Y	4	
Singapore Clinical Guidelines 2009 [93]	Y	N	Y	Y	Y	Y	N	Y	6	✓
Osteoporosis Canada 2010 [49]**.**	Y	N	Y	Y	Y	Y	N	N	5	✓
American Association of Clinical Endocrinologist AACE 2010 [94]	N	N	N	Y	Y	Y	N	N	3	
The Australian Guidelines 2010 [95]	Y	Y	Y	Y	Y	Y	Y	Y	8	✓

	IOM STANDARDS									
Guideline	**1.Establishing transparency**	**2.Management of conflict of interest (COI)**	**3.Guideline development group composition**	**4.Clinical practice guideline systematic review intersection**	**5.Establishing evidence foundation for and rating strength of recommendations**	**6.Articulatoin of recommendation**	**7.External review**	**8. Updating**	**Total Score /8**	**High Quality**
South Africa guidelines 2010 [96]	Y	N	Y	Y	Y	Y	N	N	5	✓
Greece National Medicine Agency 2011 [97]	N	N	N	N	N	N	N	N	0	
USPSTF 2011 [98]	Y	Y	N	Y	Y	Y	Y	N	6	✓
University of Michigan Health System Guideline 2011 [99]	Y	Y	N	Y	N	Y	Y	N	5	✓
Taiwan osteoporosis practice guidelines 2011 [100]**.**	Y	Y	N	Y	Y	Y	Y	Y	7	✓
British Columbia Medical Association 2012 [101]**.**	Y	Y	Y	N	N	N	N	N	3	
The Malaysian Osteoporosis Society 2012 [102]**.**	Y	Y	N	Y	Y	Y	Y	Y	7	✓
NICE guidelines 2012 [58]	Y	Y	Y	Y	Y	Y	Y	Y	8	✓
The Endocrine Society 2012 [103]	Y	Y	N	N	Y	Y	Y	N	5	
Institute for Clinical System Improvement guideline, 2013 [43]**.**	Y	Y	Y	Y	Y	Y	Y	Y	8	✓
Indian Menopause Society, 2013 [104]	N	N	N	Y	N	N	Y	Y	3	
National Foundation of Osteoporosis2014	N	Y	N	N	N	N	N	N	1	

Chapter 3- The influence of osteoporosis guideline recommendations on Ontario physicians' ordering of baseline BMD testing between 1998 and 2016: An interrupted time series analysis

ABSTRACT

Background: The risk for osteoporotic fractures increases with age. Canadian clinical practice guidelines (CPGs) regarding screening for osteoporosis were released in 2002, 2004 and 2010. Each CPG recommended baseline bone mineral density (BMD) testing with DXA for adults 65 years and above if not previously tested. The latest guideline recommends that BMD testing get repeated every 5 years for people with low osteoporosis risk. Previous studies primarily reported the low adherence of physicians to screen individuals after fragility fractures. However, no previous study has: i) assessed the rate of baseline screening for osteoporosis over time; ii) the impact of Ontario CPGs on the baseline BMD testing for older adults; or iii) repeat testing patterns.

Objectives: To evaluate the effect of three successive CPGs for screening for osteoporosis in Ontario on the baseline BMD (DXA) testing for adults 65 years and above between 1998-2016, and to determine the pattern of repeated BMD testing between 2011-2016, and its accordance with the current guideline.

Method: Population-based for Ontario data were analyzed within the Institute of Clinical Evaluative Science (ICES). We used an interrupted time series design with segmented regression analysis to measure the change of monthly rates of first (baseline) BMD tests per 1000 total population for all adults 65 years and older from April 1998 to January 2016, following the publication of new guidelines for screening for osteoporosis in 2002, 2004, and 2010. We stratified analyses by sex to find the impact of two guidelines only (2002 & 2010) and three guidelines for female population.We analysed the pattern of repeated BMD testing from 2011-2016 and calculated the proportion of individuals with high risk and low risk for osteoporosis who undergone repeated BMD to find if it is in accordance with the current osteoporosis management guideline.

Results: Overall there was a very low rate of baseline BMD testing for adults 65 years and older living in Ontario; for total population and for both male and female population. No change in the monthly rate of baseline BMD testing for total population after the release of the 2002 and 2004 osteoporosis CPGs. After the 2010 guideline there was no immediate effect, but there was a significant gradual increase in the monthly BMD rate over time by 0.018 per month greater than would otherwise be expected (95% CI: 0.01 to 0.02; p <0.0001). For the female population, after the release of 2010 CPG, there was an unexpected (i.e. counter to the CPG recommendation) significant decrease in the monthly baseline BMD testing for the female population (exponentiate [exp](estimate)=0.912, 95%

CI: 0.85 to 0.97, p = 0.01), which is equal to 9% decrease in monthly baseline BMD testing. However, over time, there was a slight increase the rate by 0.06% more than otherwise expected; 95% CI: 1.004 to1.009; p<0.0001). For the male population, the 2002 guideline release resulted in an immediate increase in baseline BMD testing by 13.9% per month (exp (estimate) = 1.139; 95% CI: 1.03 to 1.25; p=0.008). Yet, over time the baseline BMD testing rate decreased by 1% (exp (estimate)=0.99; 95% CI: 0.989 to 0.997; p=0.002). Between 2011-2016, we observed 6 patterns of repeat BMD testing:< 1 year (13%), annual (30%) of tests, 2 years (32%) of tests in, 3 years. 43% of patients who are considered low risk (not taking high dose of steroid medication, without previous fracture and not on anti-osteoporotic medication) are having repeat BMD testing in less than 5 years (not in agreement with the latest guideline); 40.32% of tests are conducted annually, and 41.52% are done after 2 years in the low risk population.

Conclusion: Overall there are very low rates of baseline BMD testing for adults 65 years and older living in Ontario. CPG recommendations for osteoporosis screening released in 2002, 2004, and 2010 had no immediate effect on the monthly baseline BMD testing for the total population. Minor increases in utilization after longer period of 2010 CPG were seen. Trend direction and analyses varied by sex. Despite that low rate of baseline BMD testing, there is unwarranted use of repeated BMD testing for patients with low risk which (40.3% of annual test and 41.5% of 2yearly tests were conducted for this low risk category, indicating waste of our resources.

BACKGROUND

Osteoporosis affects almost two million Canadians over 50 years of age according to Osteoporosis Canada, causing 70% of 30,000 hip fractures annually [130]. In a recent report in 2016, this disease costs the Canadian health system almost more than $4 billion per year [131].

Osteoporosis is asymptomatic until it results in a fracture which most commonly affects hip, spine, and wrist.[34] Without diagnosis and treatment for those at high risk, they will remain at risk for fractures. Many drugs have proven effectiveness, however, there is variability in the evidence of benefit to prevent non-vertebral fractures [132–135].

In Ontario three clinical practice guidelines have been developed for the management of osteoporosis in 2002, 2004, and 2010 [47–49]. Each of these three guidelines recommended that all individuals over age of 50 should be assessed for risk of fractures, to identify those at high risk. Individuals at and above 65 years of age should undergo bone mineral density testing (BMD) regardless of their risk factors. The 2002 guideline recommendations by Osteoporosis Canada were directed for all adult population. The guideline recommended a targeted case finding strategy for those at increased risk with one major or 2 minor listed factors (see Table 3-1), and BMD measurement with central DXA at age 65 [47]. The Canadian Task Force guideline released recommendations pertaining to postmenopausal women only, and recommended BMD screening using DXA in women who are 65 years and older [48]. In 2010, Osteoporosis Canada updated its 2002 guideline with a key change which is the assessment of 10-year absolute risk of fracture by the prediction tools: FRAX, developed by WHO in 2008; and CAROC by the Canadian Association of Radiologist and Osteoporosis Canada. Similarly, being at age 65 or above is an indication for BMD testing [49]. The main recommendations for baseline screening in the three guidelines were presented in Table 3-1.

Table 3-1: Main recommendations from the three Clinical practice guidelines for screening for osteoporosis in Ontario released in 2002, 2004 and 2010.

2002 clinical practice guidelines for the management and diagnosis of osteoporosis in Canada [47].
• Targeted case finding strategies for those at increased risk (at least one major or 2 minor risk factors) *. [Grade A]. • BMD measurement with central DXA at age 65 is recommended [Grade A]. • A height loss of >2cm in a year or historical height loss of>4 cm should be followed by thoracolumbar spine radiography to determine the presence of vertebral fracture [Grade C].
Prevention of osteoporosis and osteoporotic fractures in postmenopausal women: recommendation statement from the Canadian Task Force on Preventive Health Care, 2004 [48].
• Fair evidence to recommend BMD measurement using DXA to prevent fracture in postmenopausal women who (a) are 65 years or older, (b) weight less than 60 Kg, (c) have a history of previous fracture, (d) have an Osteoporosis risk assessment instrument (ORAI) score of 9 or greater [which is the score achieved if age is 65-74 years], or (e) have a score of 6 or greater on the SCORE questionnaire (Grade B)
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary [49] .
• BMD testing for all men and women ≥ 65 years. • For those aged 50-64 years BMD testing with: -fragility fracture after age 40, prolonged use of glucocorticoid or other high risk medication, parental hip fracture, vertebral fracture or osteopenia identified on radiography, high alcohol intake or current smoking, low body weight (<60k) or major weight loss (>10% of body weight at age 25), other disorders strongly associated with osteoporosis. • Assess 10 years absolute risk of fracture using CAROC or Canadian FRAX [Grade D]. **This is a key change from the previous guidelines.** • Initiation of pharmalogic treatment for osteoporosis should be predicted on an assessment of absolute fracture risk [Grade D].

*__Major risk factors__: age >65 years, vertebral compression fracture, fragility fracture after age 40, family history of osteoporotic fractures (especially maternal hip fracture), systemic glucocorticoid therapy of >3 months, malabsorption syndrome, primary hyperparathyroidism, propensity to fall, osteopenia apparent on x-ray film, hypogonadism, early menopause (before age 45). **Minor risk factors**: Rheumatoid arthritis, previous history of clinical hyperthyroidism, chronic anticonvulsant therapy, low dietary calcium intake, smoker, excessive alcohol intake, excessive caffeine intake, weight <57, weight loss>10% of weight at age 25, chronic heparin therapy.

The current 2010 guideline recommends that individuals with normal baseline BMD and without a major risk factor, a repeat BMD testing interval of 5-10 years is sufficient [49].

Many studies have measured the quality of care for osteoporosis and documented that there are low rates of baseline screening for adults at age of 65 years and older leading to underuse of treatment and "underscreening" (and care) for those with fragility fractures [50515368–70136] . A report by Institute of Clinical Evaluative Science (ICES) in 2010 measuring baseline BMD testing for adults 65-70 years of age in Ontario in 2007, estimated that only 21% were screened for osteoporosis [51]. Munce et al. 2016, have identified a lack of clarity in BMD testing with a tendency to over test low risk healthy postmenopausal women, while under-testing high risk groups and specifically men [53]. It was reported in a study that used ICES data that in 2005/2006, 34% of individuals <65 years of age who were of low risk were having a repeated BMD tests [50].

Most identified studies in the literature focused on the after fracture care gap for patients, with assessment of after fracture BMD testing [11,12,18,19]. Few studies focused on the pre-fracture practice gap related to screening of osteoporosis before the occurrence of the fracture [15,20]. Thus, intuitively we can conclude that those patients with fragility fractures were not primarily screened nor assessed for risk of fracture by their physicians, which suggests an evidence practice gap, thus to prevent the burden of fragility fractures baseline testing is an important area to focus on.

To our knowledge, no previous study has assessed the impact of the Canadian osteoporosis guidelines on the baseline (i.e. first) BMD testing by clinicians, and very few studies assessed the baseline BMD testing trends, which mostly were cross sectional. Therefore, the aim of this study was to: **1)** evaluate the impact of Ontario CPGs for screening of osteoporosis on baseline bone mineral density testing for adults 65 years and above between 1998 and 2016 using interrupted time series analysis. Our hypothesis was that there is low adherence to these guidelines (or low rates of baseline BMD testing) yet we did not know if the guidelines are associated with these rates since no previous study

had assessed this previously. We also aimed to: **2)** analyze the pattern of repeat BMD testing between 2011 and 2016 and determine if it adheres to the current 2010 osteoporosis guidelines recommending repeat BMD testing within a minimum of 5-year period for low risk for osteoporosis individuals. Based on previous literature, we assumed that despite low adherence to baseline BMD testing, unwarranted repeat testing is being done for individuals with low risk.

METHODS

Study Setting and Database used

The province of Ontario has a population of almost 14 million residents and represents about 39% of the population of Canada [139]. Citizens of the province of Ontario have universal access to publicly funded Medicare. The Ontario Health Insurance Program (OHIP) reimburses DXA BMD tests, the cost for 2 sites of DXA tests, irrespective of risk category is $59.44(Can.)[140] .

We analysed data from several databases housed at the Institute of Clinical Evaluative Science (ICES). Each of these datasets were linked deterministically using an encrypted anonymous patient identifier. The following primary databases were used to create our analytic dataset:

- Ontario Health Insurance plan (OHIP) database: OHIP records all claims submitted to the ministry for remuneration for physician and laboratory services. The claims submitted to the database each include a unique identifying number for the patient, date of the claim, physician code, and a code for the service [141]. Physicians' claims for DXA tests with the following codes (X145, X146, X149, X152, X153, and X155) were retrieved from this database for the period between April 1998 to January 2016. Thus, each row in this database included an encrypted patient identifier, code for the DXA test, and the date of the test. Monthly rates for DXA tests were adjusted using monthly population estimates from Statistics Canada.
  It was reported in a study by Jaglal et al 2014, that OHIP database captured at least 92% of the DXA tests that were billed to the province by physicians. Therefore, OHIP is a good presentation of the province's BMD testing.

- The above OHIP claims were linked to the Registered Person Database (RPD) by the patient identifier to obtain the sex and age of the individuals with BMD testing. RPD captures the sex, birthdate, death date, and location of all Ontarians.

- Ontario Drug Benefit (ODB) was used to determine each person's exposure to anti-osteoporosis medication or steroid drugs. ODB captures all publicly funded prescriptions for people over the age of 65.

- The Canadian Institute of Health Information Discharge Abstract database (CIHI-DAD): It contains data on inpatient hospital discharges across Canada, supplied to Canadian Institute for Health Information (CIHI) from participating hospitals. The DAD contains demographic, administrative and clinical data for hospital discharges (inpatient acute, chronic, rehabilitation) and day surgeries [139].

- The National Ambulatory Care Reporting System (NACRS) includes data for visits to the emergency departments by residents of Ontario who have a valid health card. Codes for the most responsible diagnoses of fractures of hip, spine and wrist were retrieved from DAD and NACRS database using the International Classification of Diseases,9th Revision (ICD-9) prior to 2004 and the 10th revision, Canadian version (ICD-10-CA) thereafter. Codes for data abstraction are shown Appendix (Tables S3-A-C).

We identified the presence of fractures by the presence or absence of the codes listed in the Appendix. The codes do not perfectly represent the conditions they are representing, and some misclassification can present. Table 3-2 lists the studies that previously examined the validity of these codes to diagnose the true fracture cases.

Table 3-2: Results of studies validating codes for fractures

Study	Country	Code	Fractures N	Sensitivity	PPV*
Hip Fractures					
Juurlink et al, 2006 [139]	Canada, Ontario	S72	356	0.95 (0.93 to 0.97)	0.95 (0.92- 0.97)
Jean et al, 2012 [142]	Canada, Quebec	S820-821	1,914	0.95 (0.91 -0.98)	0.93 (0.90 -0.96)
Vertebral fractures					
Curtis, 2009 [143]	USA	ICD-9 805-808	259	0.56 (0.43-0.68)	0.61(0.49-0.74)
Jean et al, 2012 [142]	Canada, Quebec	805, 806	1,914	0.40 (0.10 - 0.70)	0.82 (0.64 -1)
Wrist Fracturs					
Jean et al 2012 [142]	Canada,Quebec	ICD-9 813.4, 813.5 or 814		0.90 (0.88 -0. 92)	0.96 (0.93-0.98)

*PPV=Positive predictive value.

Creation of Analytic datasets

The first dataset was created to be used in the time series analyses. This dataset included adults 65 years and older undergoing a first BMD (DXA) test. Sex of patients, OHIP codes for DXA tests, and date of the tests which later were expressed as month/year, were also included. The second dataset was created for the repeat BMD tests. Each row of this dataset included the dates of all the initial DXA tests that were preformed by each patient, the date of the repeat DXA testing (if performed), the associated OHIP feecodes for these tests, dates of any previous fractures of hip, spine, or wrist, in additions to the dates of any previous steroid medication with its dose, dates of any osteoporosis medication.

Statistical Analysis

Interrupted time series analyses

We used an interrupted time series (ITS) design, which is a special kind of time series analysis that is used to measure the association or the impact of interventions upon the outcome variable expressed in the time series. In an ITS, a time series of observations on the same outcome, which normally is equally spaced, form segments that are separated by different interventions [144–146]. The segmented regression analysis of time series data allows us to estimate the effect of the intervention (i.e. the release of guideline recommendation) influenced the outcome of interest (physician ordering of baseline BMD testing) immediately and over time by measuring the change in the intercept and the change in the slope before and after the intervention respectively [22,23]. A major strength of this design is its ability to distinguish the effect of the intervention on the outcome from the underlying trend or seasonal variations [15,16].

Generally, it is recommended to have 12 data points before and after the intervention, in addition to a sufficient number of observations (a minimum of 100 at each data points) to achieve an acceptable level of variability of the estimate each time [146]. We followed these guidelines in our study.

We assessed the impact of recommendations of three CPGs released on 12 November 2002; 25 May 2004, and 12 October 2010, on the monthly rate of baseline BMD testing per 1000 population (outcome) of adults 65 years and older living in Ontario, between 01 April 1998 and 30 January 2016. For the male population we assessed the impact of only two guidelines since the 2004 the Canadian Task force guideline was only for postmenopausal women.

The monthly BMD rates per 1000 population (outcome) was calculated by obtaining the monthly first BMD (DXA) tests (numerator) for individuals 65 years and older. The denominator was the monthly Ontario population estimates from Statistics Canada after excluding those who were tested previously in the preceding time points (i.e. at each time

point we subtracted the cumulative sum of all previous numerators in the preceding time points from the denominator), then the rate was multiplied by 1000.

In time series analysis, it is important to decide the implementation time of the intervention; we expected it would take time for physicians to adopt the recommendation and change their test ordering for BMD. We have chosen a 5-month implementation period based on an exploratory analysis that was conducted by applying 12 simple linear regression models of the outcome and the guideline from month 1 to month 12 after publication of the guideline, to find the least AIC (Akaike Information Criterion), and the higher R squared for the fitted models. In most studies the implementation time is censored, however, we opted not to do that, in order not to lose observations and power. Thus, we have coded each intervention to have a gradual effect during these 5 months, so the intervention is coded as 0 before the guideline and 0.2, 0.4, 0.6, 0.8 and 1 afterwards starting from the first month after the guideline release.

In ITS, observations closer in time points may be similar to each other than further time points, resulting in serial autocorrelation of the error terms [148]. Failing to adjust for these correlations may underestimate the standard error and over-estimate the effect of the intervention. We used maximum likelihood estimation to estimate the model and we tested for autocorrelation using the Durbin-Watson test. Where required, autocorrelation parameters up to lag 12 were included and reduced using backward elimination. In addition, we tested each model for stationarity or non-seasonality using the Engle-Granger cointegration test and residual plots inspection.

To check linearity, we visually inspected the residual plots, and residual histograms. We found mild deviation from normality in the residual plot but not in the histogram. We conducted the analyses after transforming the outcome to log scale, and where we found this gave different results than the normal scale we depended on the parameters estimates for the log scale, and this was seen for female and male population. We log transformed the dependent variable (the monthly BMD rate) by taking the proportion of the rate (rate/1000) and then took the natural log of the proportion.

The regression equation for the effect of three guidelines was specified as follows:

Baseline BMD testing per 1000 population =β0+ β1* time + β2 * guideline 1 + β3*time after guideline 1+ β4 * Guideline 2+ β5*time after guideline 2+ β6 * guideline 3+ β7 *time after guideline 3+error

We expressed the effect of guidelines on the BMD rate as level and slope changes, where the former is the immediate effect of the guideline implementation and the latter as the gradual effect of guideline over time.

Separate analyses were conducted one for male (ITS for two guidelines only), and one for the female population. Level of significance was set at 0.05. All statistical analyses were performed using PROC AUTOREG in SAS Enterprise v7.1.

Patterns of repeat BMD testing analyses

Bone mineral density claims for adults 65 years and older for the period 2011- 2016 were analyzed to find the pattern of repeated testing and its accordance with the 2010 CPG by Osteoporosis Canada [49]. All individuals who have more than one test between 2011 and 2016 were included. The interval between the dates of each subsequent test was calculated. Total count and percentage of the pattern of repeated testing were obtained.

Through linking the datasets of BMD repeated tests, fracture data (extracted from DAD and NACR, steroids and antiosteoporosis medication by patient identifier, we analysed if those with repeated tests had previous fractures, were taking high dose of steroids for more than 90 days (mean of the cumulative use of steroids a year before the BMD date) , or were taking anti-osteoporosis medication before the index date of BMD testing. If they had one of these mentioned risk factors they were categorized as high risk, if not, they were considered low risk for osteoporosis. Frequency and percentage was calculated for each pattern of repeated testing by the risk category.

Other studies have used the BMD claims fee codes to categorize patients into high risk and low risk of osteoporosis. Though, BMD claims are defined in the fee schedule as high risk if individuals are at high risk of accelerated bone loss, have osteoporosis or osteopenia from previous DXA test results, otherwise they are coded as low risk. We didn't use these fee codes since, they were not previously validated, and we could not make ensure that they were miscoded.

RESULTS

Overall there were 918,904 first (baseline) BMD testing claims for Ontarians aged 65 years and older between 01 April 1998, and 30 January 2016 (214 months). Of these tests, 67.64% were for females, and 32.36 % for males (DXA for females is double that for males). The mean age of our population was 73.24 years (± SD 6.36; range: 65- 106 years).

There was a downward trend in rates of testing from 1998-2016. The rates fell from 5.34 to 2.16 per 1000 population between 1998 and 2016, i.e. 0.53% in 1998 to 0.22% in 2016, indicating very low baseline BMD testing throughout the study period.

In the male population the trend was opposite to the total and female population with a gradual increase of BMD rate over the years, In April 1998 the rate was very low (0.80 per 1000 population) which subsequently increased to 2.9 per 1000 population in January 2016.

The impact of guidelines recommendations on baseline BMD testing

Table 3-3presented the results of the segmented regression analysis for the rate of baseline BMD testing for total population of older adults ≥ 65 years of age in Ontario before and after introduction of the three CPGs, and this is graphically presented in Figure 3-1.

The results indicate that before the release of the guidelines the rate of baseline BMD testing was decreasing significantly by (0.028) from month to month (p -value for baseline

trend <0.0001). After the introduction of CPGs in 2002, there was no immediate effect on testing rates. The graph shows a clear increase in the trend (estimate=0.02), however this increase was not statistically significant (p=0.07). After the 2004 CPG release, there were no significant changes in the monthly BMD rates in either the level or the trend (p>0.05). Following the introduction of 2010 CPG by Osteoporosis Canada, there was no significant immediate effect (estimate= -0.13; 95% CI: -0.35 to 0.07; p = 0.21), however there was a significant gradual increase in the monthly basal BMD rate over time (monthly trend) by 0.018 per month than would otherwise be expected (95% CI: 0.01 to 0.02; p <0.0001).

Figure 3-1: Rate of baseline BMD claims per 1000 population for adults ≥ 65 years, in Ontario, before and after the CPGs (2002, 2004, 2010) between 01 April 1998 to Jan.30 2016.

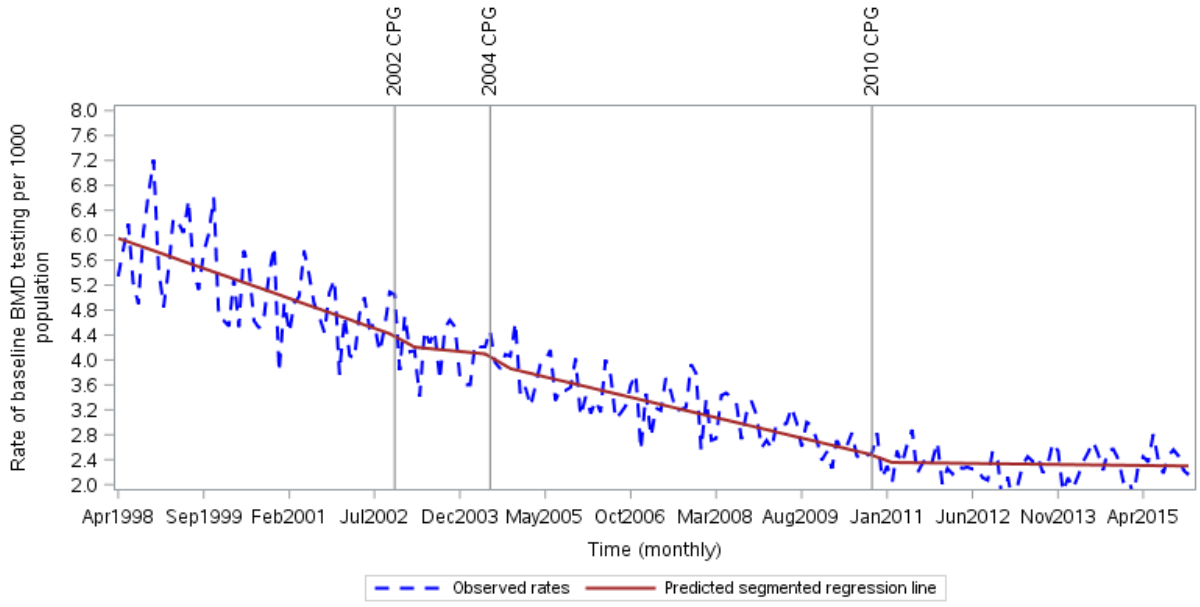

Table 3-3: Results of segmented regression analysis for the effect of CPGs of screening for osteoporosis on the rate of baseline BMD testing per 1000 population of adults ≥65 years, 1998-2016.

Parameter	Estimate	95% confidence interval	p-value
Intercept	5.97	5.79 to 6.16	<0.0001
Pre-intervention slope (Baseline trend per month)	-0.028	-0.03 to -0.02	<0.0001
2002 CPG for the diagnosis and management of osteoporosis in Canada			
Change in intercept (immediate effect) after 2002 CPG	-1.17	-0.49 to 0.14	0.28
Change in slope (gradual effect) after 2002 CPG	0.02	-0.002 to 0.04	0.07
Recommendation statement from the Canadian Task Force on Preventive Health Care, 2004			
Change in intercept (immediate effect) after 2004 CPG	-0.14	-0.38 to 0.11	0.26
Change in slope (gradual effect) after 2004 CPG	-0.011	-0.03 to 0.01	0.32
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada			
Change in intercept (immediate effect) after 2010 CPG	-0.13	-0.35 to 0.07	0.21
Change in slope (gradual effect) after 2010 CPG	0.018	0.01 to 0.02*	<0.0001*

*significant results

Figure 3-2 shows the observed and model based female basal BMD testing rates per 1000 for female population. A downward trend is shown; the monthly baseline BMD tests were 10.05 in 1998, increased to 12.35 in the same year, then fluctuated with a gradual decrease till it reached only 1.40 BMD testing per 1000 female population in January 2016.

Table 3-4 presents the results of the segmented regression analysis of the effect of the CPGs on the log of baseline BMD rate for female population, [*Table S3-D presents the non-transformed model with the estimates*]. There was no immediate nor gradual change in monthly rates following the 2002 and 2004 guidelines release. After 2010 guideline publication there was a significant change in the level of monthly baseline BMD testing 5 months after release of the recs (Log estimate= -0.092; exponentiate 'exp.' estimate =0.912; 95% CI: 0.85 to 0.97; p= 0.01), which is equal to 9% decrease ((0.912-1) *100) in monthly baseline BMD testing in contrast to the guidelines. However, over time, there was a small but significant change in the trend after the 2010 guideline with a 0.06% increase in the monthly baseline BMD testing from otherwise expected (Log estimate= 0.006; exp. estimate= 1.006; 95% CI: 1.004 to1.009; p<0.0001).

Figure 3-2: Rate of baseline DXA BMD claims per 1000 female population (≥65 years) in Ontario before and after the introduction of osteoporosis CPGs (2002, 2004 & 2010) between 1998-2016. [outcome is log transformed]

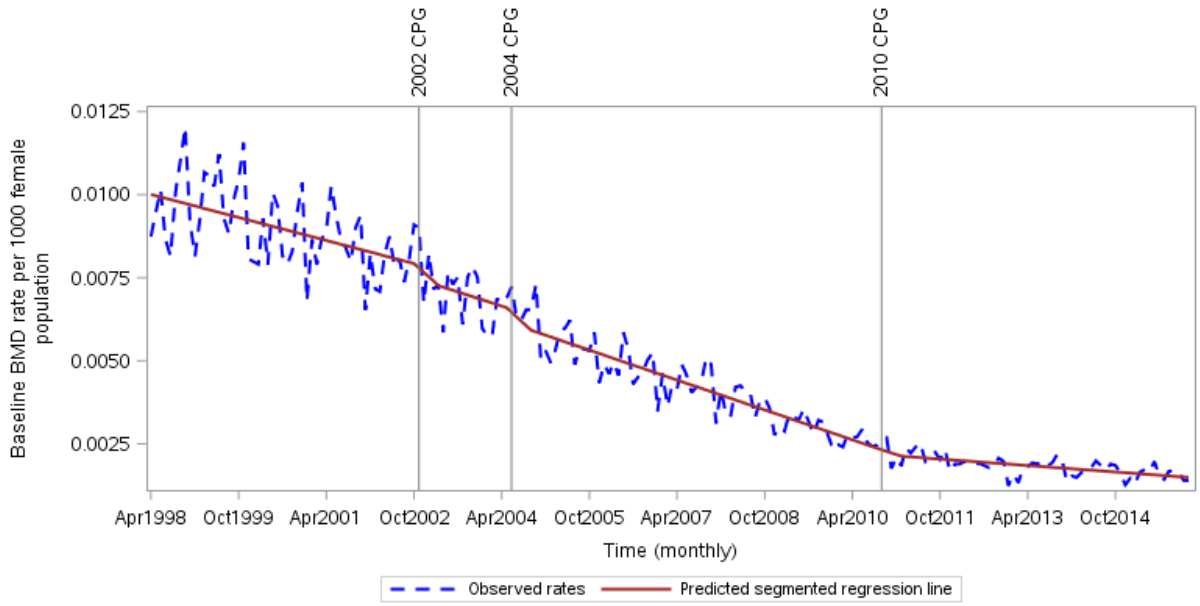

Table 3-4: Results of segmented regression analysis for the effect of CPGs on screening for osteoporosis on the log rate of baseline BMD testing per 1000 female population of adults ≥65 years, 1998-2016.

Parameter	Regression Coefficient	Exp.(β)	Confidence interval of Exp.(β)	P- value
Intercept (baseline rate)	-4.62	0.01	0.009 to 0.01	< 0.0001
Pre-intervention slope (Baseline trend)	-0.003	0.99	0.99 to 0.99	0.0005
2002 CPG for the diagnosis and management of osteoporosis in Canada				
Change in intercept (immediate effect) after 2002 CPG	-0.05	0.95	0.86 to 1.05	0.33
Change in slope (gradual effect) after 2002 CPG	-0.003	0.99	0.98 to 1.003	0.32
Recommendation statement from the Canadian Task Force on Preventive Health Care, 2004				
Chang in intercept (immediate effect) after 2004 CPG	-0.006	0.97	0.92 to 1.07	0.87
Change in slope (gradual effect) after 2004 CPG	-0.005	0.99	0.98 to 1.001	0.12
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada				
Change in intercept (immediate effect) after 2010 CPG	-0.092	0.912	0.85 to 0.97*	0.012*
Change in slope (gradual effect) after 2010 CPG	0.006	1.006	1.004 to 1.009*	<0.0001*

Exp.= exponentiate
*significant results

Figure 3-3 shows the time series of baseline BMD testing rate per 1000 the male population with the fitted predicted pre and post release of the 2004 and 2010 recommendations. Contrasting with the trend in baseline BMD testing in total and female population; the trend of BMD testing in male has increased over the years in keeping with the recommendation. In April 1998 the rate was very low; 0.81 per 1000 population, it increased gradually over the period of study with upward and downward fluctuations. In 2015, it reached 3.5 then decreased to reach 2.7 testing per 1000 population in January

2016. Table 3-5 presents the autoregressive analysis for the log model of the change in monthly baseline BMD rates for the male population, which shows that before the introduction of 2002 CPG, the baseline BMD testing was increasing by log (0.01) tests per month, which equals to 2% increase in the monthly baseline BMD. After the introduction of 2002 CPG, the baseline BMD testing increased significantly by 13.9% per moth (estimate= 0.131, exp.(estimate)= 1.139; 95% CI: 1.03 to 1.25; p=0.008). Over time the baseline BMD testing has decreased by 1% per month (estimate= -0.006; exp. estimate= 0.99; 95% CI: 0.989 to 0.997; p=0.002), therefore the overall trend of the BMD testing after the release of 2002 guideline is increasing monthly by only 0.4% than otherwise would be expected [exponentiate (baseline trend (0.01) +trend after 2002 (-0.006))-1*(100)]. After the release of 2010 CPG there was no significant change in the level nor trend (p=0.6, p=0.16) respectively. [*Table S3-E in the appendix presents the non-log transformed model*].

Figure 3-3: Rate of baseline DXA BMD claims per 1000 male population (≥65 years) in Ontario before and after the introduction of osteoporosis CPGs (2002, 2010) between 1998-2016. [BMD is log transformed]

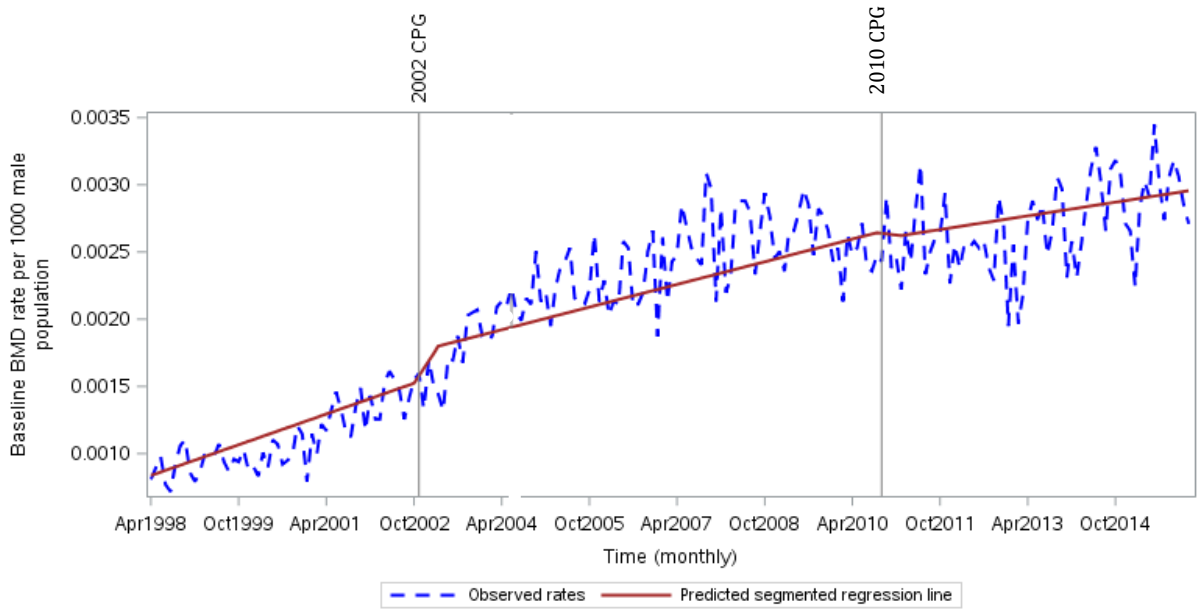

Table 3-5: Results of segmented regression analysis for the effect of CPGs on screening for osteoporosis on the log of baseline BMD testing for the male population of adults (≥65 years), 1998-2016.

Parameter	Estimate	Exp.(β)	95% confidence interval of exp.(β)	p-value
Intercept	-7.09	0.0008	0.0007 to 0.0009	<0.0001
Pre-intervention slope (Baseline trend per month)	0.01	1.01	1.008 to 1.014	<0.0001
2002 CPG for the diagnosis and management of osteoporosis in Canada				
Change in intercept (immediate effect) after 2002 CPG	0.131	1.139	1.03 to 1.25	0.008*
Change in slope (gradual effect) after 2002 CPG	-0.006	0.99	0.98 to 0.99	0.002*
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada				
Change in intercept (immediate effect) after 2010 CPG	-0.025	0.97	0.88 to 1.07	0.61
Change in slope (gradual effect) after 2010 CPG	-0.0026	0.99	0.99 to 1.001	0.16

Repeated BMD tests patterns and analyses

There were 300,868 BMD repeat tests for the period 2011-2016. Six patterns of intervals between the repeated tests were found; Table 3-6 shows that 32% of the BMD repeated tests were conducted after 2 years, 30% of tests were annual, and 18% were conducted after 3 years. Less commonly were after 4 years interval (8.4%), and only 1% of BMD tests were after 5 years. There were 13% of BMD tests that were conducted in the same year (i.e. <1 year), we think that this is maybe due to technical problems of the DXA test which warranted a repeat testing, yet, this is not a very low percentage.

Table 3-6: Patterns of baseline BMD repeated testing according to the interval between the tests for the period 2011- 2016. (N= 300868)

Pattern of repeated BMD	n (%)
< 1 year	39198 (13)
Annual	89973 (30)
2 years	96970 (32)
3 years	53863 (18)
4 years	18245 (06)
5 years	2619 (01)

The profile of patients in each of these interval patterns were analysed according to the presence or absence of fracture (spine, hip, or wrist) before the BMD test date, and the use of high dose of steroid treatment (>7.5 mg of prednisolone or its equivalent doses of other steroid medication [31] for more than 90 days), and the use of anti-osteoporosis medication before the indexed date of testing. Those with any of these stated factors above, were categorized as high risk, otherwise they were considered as low risk.

Table 3-7 shows that 43% who are considered of low risk had a repeated BMD testing. According to the pattern of BMD testing, 40.32% of annual tests are for low risk patients, and 41.52% of those who are tested after 2 years are of low risk. After 4 years and 5 years the low risk testing increases to above 50%. 40% of repeated BMD testing for patients with no strong risk factors is being conducted in less than one year.

Table 3-7: Patterns of baseline BMD repeated testing according to the interval between the tests for the period 2011- 2016. (N= 300868)

Pattern of repeated BMD (interval between the tests)	High risk * n (%)	Low risk n (%)	Total
< 1 year	23756 (60.61)	15442 (39.39)	39198
Annual	53693 (59.68)	36280 (40.32)	89973
2 years	56708 (58.48)	40262 (41.52)	96970
3 years	27500 (51.06)	26363 (48.94)	53863
4 years	8336 (45.69)	9909 (54.31)	18245
5 years	1098 (41.92)	1521 (58.08)	2619
Total; n (%)	171091 (56.87)	129777 (43.13)	300868

*High risk are individuals who are having previous fracture (spine, or hip, or wrist), or taking high dose of steroids medication, or prescribed anti-osteoporosis medication.

DISCUSSION

To our knowledge this is the first population level study measuring the relationship between the release of clinical practice guidelines for osteoporosis on the baseline bone mineral density testing rates for older adults (≥ 65 years) in Ontario. During the period 998 to 2016, we observed a gradual decrease in the trend of baseline BMD testing by DXA for the total population, with no immediate or gradual effects of 2002, and 2004 CPGs on physician ordering .The last osteoporosis guideline published in October 2010, was associated with a gradual significant increase in the baseline BMD testing but far from the guideline expectation of near universal screening (post 2010 guideline overall trend was only 0.01 tests per 1000 population).

The stratified analyses by sex, showed that baseline BMD testing for female population actually decreased over the study period, and this downward trend in BMD testing is probably the cause for the apparent decreasing trend in total population. There was no effect of 2002 and 2004 CPGs, however the 2010 guideline has decreased the baseline BMD testing after 5 months of implementation by 9%, which is in contrast to the

recommendations. We searched the literature to find if there was a possible release of a certain policy or a study that coincides with the release of the guideline that could explain this decrease, yet we didn't find any explanation for this significant reduction. Over time, the 2010 guideline increased the baseline BMD testing by only 0.06%. Despite the 2010 guideline developers developed a toolkit and a dissemination plan after nationally consulting with many stakeholders to promote the use of the guideline and its recommendations [10], our study has failed to find evidence that the guideline recommendations have been widely adopted by Ontario physicians.

In the male population there was an increasing trend in the monthly baseline BMD testing in contrast to the total population and female population. After 2002 guideline release, there was a significant immediate effect after the 5 months by 14% increase in testing. A possible explanation is that the 2002 guideline recommended to screen men 65 and over, which was not previously recommended in the 1996 osteoporosis guideline. Over time the rates of screening men started to decrease significantly by 1% in contrast to the guidelines. Therefore, the overall trend continued its increment, but it was attenuated by the latter decrease (from 1% increase in testing per moth pre-2002 guideline to 0.4% increase in monthly testing post-2002 guideline). The downward trend in baseline BMD testing was not found in other studies; Jaglal et al 2014 examined the rate of BMD testing for individuals aged 67-80 who were not previously tested by DXA, and found that the rate was increasing till 2008 when a change in fee schedule was introduced in Ontario leading to a decrease in rate [20]. However, we failed to replicate the same finding.

Analyses of Repeated BMD testing during the period 2011-2016 showed that higher proportion of repeated tests is being conducted after 2 years or annually. In our study, we estimated that 43% of those considered low risk had a repeated BMD testing. We categorized patients as low risk if they didn't have previous fracture in the most common sites for fragility fractures, and not taking anti-osteoporotic medication, or high dose of steroids for more than three months, within a year before the index date of a BMD test. We

found that 40% of the annual repeated tests were for low risk patients., and 42% of the 2-yearly repeated tests were for low risk. Surprisingly, we also found that almost 40% of the tests that were conducted before one year (less than 12 months) were for low risk patients. This is an indication of over use of BMD testing by patients at low risk for osteoporosis and who are not expected to have rapid change in BMD. Though, we don't have the results of previous DXA tests, some patients may have had a low bone density in a previous DXA scan which led them to be categorized by their physicians as high risk and encouraged their physicians to repeat the test. However, studies have found that BMD doesn't change very rapidly especially if patients doesn't take steroids or on anti-osteoporotic drugs; Gourlay et al found that the interval during which at least 10% of women developed osteoporosis if they have normal BMD or mildly osteopenic was 15 years, while it is 5 years if they were moderately osteopenic [32]. Another study using the Framingham osteoporosis study data examined whether changes in BMD after four years can quantify the change in the fracture risk after a second BMD measure, they found that for individuals not using osteoporosis medication a second BMD measure after 4 years did not meaningfully improve the prediction of hip or major osteoporotic fracture [33].

According to our results patients maybe categorized by their physician as high risk due to other factors that we didn't measure, which is most likely the results of a previous DXA scan. Nevertheless, regardless of the cause, studies are suggesting that bone density change after one year will be equal to the measurement error and at least 2-3 years till a second BMD testing is warranted [34–36]. The current recommendation by osteoporosis Canada clearly states that a repeat BMD testing is warranted 5-10 years if the patient at low risk of osteoporosis [10].

Our study indicates that despite very low adherence rate of physicians to baseline BMD testing that is recommended by all the guidelines for the period 2002 to 2016, there is overtesting of low risk individuals and many unwarranted tests are being conducted without evidence of benefit.

Our study is unique in its interrupted time series (ITS) design which is considered one of the most powerful quasiexperimental designs [21,33,34]. The ITS design can be used to

describe the rate of change of the outcome following the intervention as well as the effect size and the persistence of the effect (i.e., looking at whether the change remains over time), and it has many strengths. First, the interrupted times series design has the advantage of being able to account for underlying trends in the data, such as seasonal trends and autocorrelation. Our analysis spanned a long period of time (214-time points) with many preintervention time points that will adequately control for any pre-existing underlying trends. Another strength is we used a high quality data from the Institute of Clinical Evaluative Science and we had a large number of cases at each monthly time point, thus meeting Shadish, Cook, and Cmapbell's recommendation of a good quality ITS to include at least 100 observations in a time point in order to correctly model autocorrelation [38]. Using population data, avoids individual-level confounding factors and selection bias, therefore the results are more generalizable to the population [39]. Furthermore, we conducted stratified analyses by sex in order to evaluate the differential impact of guidelines on subpopulation of male and female.

The literature on ITS analyses recommends including a control group that had not experienced the intervention of interest [28], however, due to limited time and difficulty in getting access to data in other jurisdictions, this was not possible. A Population from another province such as British Columbia could potentially be a good control group, since they have different guidelines and recommendations for osteoporosis [40]. If results of the impact of guidelines were only detected for Ontario population and were not observed in the control group that will give more confidence to our findings.

One of the major potential biases for ITS is an apparent intervention effect that may be due to the onset of some other confounding factors or other interventions that may have occurred either prior to or at the time of the intervention of interest (release of a guideline). From the literature we only found that on April 1, 1998 there was a policy that changed the fee schedule for DXA tests for individuals at low risk of osteoporosis making it only once every 36 months, and a new code for baseline DXA test was also added and individuals were limited to one baseline test in their lifetime. A study examined the effect of this policy and found it had led to decrease in BMD testing after 1998 [20]. We didn't

consider this policy as a confounding factor as it is not close in time to any of the guideline release dates and the downward trend in rates before 1998. It could be that it affected the total BMD testing and not the baseline BMD which we are mainly measuring.

In categorizing the risk for osteoporosis in our analyses for repeated BMD testing we only used previous fracture, prescription of anti-osteoporosis medication, high dose of steroid medication as indicators of high risk for osteoporosis and we did not have data for other risk factors such as alcohol consumption and smoking, rheumatoid arthritis and other causes that may cause rapid bone loss such as organ transplant and some malignancy, Thus, the low risk patients are overestimated, however, even if we think only 50% of our low risk individuals with repeated test is a true estimate, still 64,888 BMD (129777 tests/2) tests are being un-necessarily ordered for the period 2011-2016.

CONCLUSION

Development of guidelines requires many resources, so it is important to know how effective they are at influencing physician behavior. Our study showed that guideline recommendations for the management of osteoporosis had little effect on the rates of baseline BMD testing for individuals 65 years and older for whom the recommendations deemed the appropriate for baseline screening. The release of latest guideline in 2010 was associated with a significant increase in the testing over time, though the actual rates of testing remained suboptimal with only 1.4 per 1000 adult population 65 years and older are being screened. For the male population the trend in screening increase following the release of the 2002 recommendation significantly increased the BMD testing, yet still the rate of baseline BMD testing is very low.

Despite this low baseline BMD testing for eligible populations (underuse of screening as prescribed by the guidelines); our study also reveals considerable overuse of repeated bone mineral density testing for individuals at low risk for osteoporosis which may be contributing to the lack of sustainability of the healthcare system. More clear guidance that is based on the latest available evidence is needed to guide physicians about the proper

time interval between repeated BMD tests. The latest evidence suggests that change in bone mineral density is not rapid and frequent BMD testing will not improve fracture prediction especially in patients not taking osteoporosis treatment or steroid medications. This will save the health system fiscal resources that can be wisely spent on needed health areas.

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SUPPLEMENTARY APPENDIX FOR CHAPTER 3

Table S3-A: Extracted medication for osteoporosis and steroids from Ontario drug benefit data (ODB data).

Anti-osteoporosis prescriptions extracted	Steroids prescriptions extracted
Etidronate	Prednisone
Calcium carbonate and Etidronic Acid disodium	Hydrocortisone
Etidronic Acid Disodium	Prednisolone
Risedroante Sodium	Fludrocortisone Acetate
Alendronate	Cortisone Acetate
Alendronate Sodium	Methylprednisolone
Alendronate Sodium and Cholecalciferol	Methylprednisolone Acetate
Zoledronic Acid	Dexamethasone
Estradiol hemihydrate	Dexamethasone sodium phosphate
Raloxifene HCL	-
Calcitonin (Salmon Synthetic)	-
Teriparatide	-

Table S3-B: ICD-9 and ICD-10 Codes used to extract fracture data from

Fracture	ICD-9	ICD-10
Hip Fracture	820* -821*	S72.0, S72.1, S72.2*
Wrist Fracture	813*	S52*, S62.9*
Vertebral fracture	805.5-805.9	S32*, M80*,

*All subcategories

Table S3-C: Results of segmented regression analysis for the effect of CPGs of screening for osteoporosis on the (log) rate of baseline BMD testing per 1000 population of adults ≥65 years, 1998-2016

Parameter	Regression Coefficient (log scale)	Standard error	Exp (β)	Confidence interval of Exp.(β)	P- value
Intercept (baseline rate)	-5.127	0.030	0.005	–5.185 to –0.068	< 0.0001
Baseline trend	-0.005	0.001	0.995	–0.006 to –0.003	<0.0001
2002 CPG for the diagnosis and management of osteoporosis in Canada					
Change in level after 2002 CPG	-0.050	0.036	0.951	–0.121 to 0.019	0.159
Change in slope (trend) after 2002 CPG	0.004	0.003	1.004	–0.001 to 0.011	0.143
Recommendation statement from the Canadian Task Force on Preventive Health Care, 2004					
Change in level after 2004 CPG	-0.048	0.041	0.953	–0.128 to 0.032	0.241
Change in slope(trend) after 2004 CPG	-0.005	0.003	0.995	–0.0121to 0.000	0.066
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada					
Change in level after 2010 CPG	–0.023	0.029	0.977	–0.082 to 0.034	0.424
Change in slope (trend) after 2010 CPG	0.005	0.001	1.005	0.003 to 0.007	<0.0001*

*significant results. This model is similar to the non-transformed model.

Table S3-D: Results of segmented regression analysis for the effect of CPGs on screening for osteoporosis on the rate of baseline BMD testing per 1000 female population of adults ≥65 years, 1998-2016 (non-log transformed model)

Parameter	Estimate	95% confidence interval	p-value
Intercept	10.05	9.82 to 10.28	<0.0001
Pre-intervention slope (Baseline trend per month)	-0.038	-0.045 to -0.03	<0.0001
2002 CPG for the diagnosis and management of osteoporosis in Canada			
Change in intercept (immediate effect) after 2002 CPG	-0.93	-0.93 to 0.15	0.15
Change in slope (gradual effect) after 2002 CPG	-0.01	-0.05 to 0.03	0.57
Recommendation statement from the Canadian Task Force on Preventive Health Care, 2004			
Change in intercept (immediate effect) after 2004 CPG	-0.42	-0.81 to - 0.03	0.03*
Change in slope (gradual effect) after 2004 CPG	-0.0003	-0.04 to 0.04	0.98
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada			
Change in intercept (immediate effect) after 2010 CPG	-0.18	-0.48 to 0.11	0.22
Change in slope (gradual effect) after 2010 CPG	0.04	0.03 to 0.05	<0.0001*

*significant results; different from log transformed model.

Table S3-E: Results of segmented regression analysis for the effect of CPGs on screening for osteoporosis on the of baseline BMD testing per 1000 male population of adults ≥65 years, 1998-2016 (non-log transformed model).

Parameter	Estimate	95% confidence interval	p-value
Intercept	0.84	0.57 to 1.09	<0.0001
Pre-intervention slope (Baseline trend per month)	0.01	0.006 to 0.02	<0.0001
2002 CPG for the diagnosis and management of osteoporosis in Canada			
Change in intercept (immediate effect) after 2002 CPG	0.22	0.03 to 0.39	0.02*
Change in slope (gradual effect) after 2002 CPG	-0.003	-0.01 to 0.004	0.43
2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada			
Change in intercept (immediate effect) after 2010 CPG	-0.035	-0.22 to 0.14	0.71
Change in slope (gradual effect) after 2010 CPG	-0.003	-0.016 to 0.004	0.36

*significant results, different from log transformed model (in log model both level and slope for 2002 CPG is significant)

Chapter 4– Synthesis and integrated discussion

Osteoporosis is a common disease that is increasing in prevalence with the increase in the aging population. A myriad of literature indicates that there is low adherence of physicians to screen eligible individuals by bone mineral density using DXA [23,50,53,57–60]. Most literature indicates the presence of evidence practice gap especially in the after fracture BMD testing [23,57–61]. Only few studies have assessed the trend of baseline BMD testing of adults 65 years and older and most of them are not recent [51,57,64]. Thus, we developed this thesis to address this knowledge gap aiming to find the rate of baseline BMD testing between 1998-2016, and to assess the impact of Canadian guidelines on the baseline (first) BMD tests ordering in Ontario, which was not previously assessed in any previous study using large population data that spanned a long period of time.

Based on the framework of 'Knowledge to Action' cycle that we discussed in Chapter one [Please refer to Appendix S1-Figure1] and the need to determine the evidence practice gap, the first study involved identifying best practice for osteoporosis screening as determined by the practice guidelines. This involved systematically identifying guidelines for osteoporosis screening released between 2002-2016, assessing their quality and extracting main recommendations on when to screen. We used two tools (AGREE II, and Institute of Medicine Standards for trustworthy guidelines 'IOM') to assess the quality of 33 CPGs for screening for osteoporosis between 2002 till September 2016. We found that the quality of guidelines was considerably variable. Overall, they performed better in areas for *Clarity of presentation, Scope and purpose and Rigor of development,* and lower in S*takeholder involvement, Editorial independence, and Applicability*. Almost a similar conclusion was found when using the IOM tool, though many items are different between the two tools and not falling under the same domains.

The quality of guidelines has not improved over time (before and after 2011), and the comparison between the two appraising tools, revealed that they may give conflicting results with special attention to the *Rigour of Development* area which is considered the most important as it determines the validity of the evidence used to formulate the recommendations.

When extracting certain recommendation in important areas such as when to screen, how to screen and when to treat; there was little agreement between guidelines of different countries of when to be tested for bone mineral density and what is the threshold to start treatment. Differences were found not only between different countries, but between different organizations or authorities in the same country. Additionally, systems for level of evidence and strength of recommendation were variable between guidelines and some guidelines didn't report any grade for their recommendations or level of evidence. Given the heterogeneity of these guidelines, it would not be surprising that health care providers become confused to the point of inaction or misguided action.

We identified three Canadian guidelines for management of osteoporosis, released in 2002 by Osteoporosis Canada [45], 2004 by the Canadian Task Force on Preventive Health Care [46], and the latest one is in 2010 an update by Osteoporosis Canada [47]. They all recommended that all adults 65 years and older should be tested for bone mineral density. To identify the effect of these guidelines on the baseline BMD testing for this eligible population, in our second study, we used an interrupted time series design to measure the influence the release of these three Canadian guidelines on the monthly baseline (first ever) bone mineral density rate for adults 65 years and older living in Ontario for the period between 1998-2016.

We found that for the total population and the female population of adults 65 years and older there was a decreasing trend in screening between 1998 to 2016. During this time period, the rates fell from 5.34 to 2.16 per 1000 for the total population i.e. 0.53% in 1998 to 0.22% in 2016. Given the magnitude of the rates it appears that for the eligible population, there are very low levels of osteoporosis screening (i.e. a considerable evidence-practice gap as determine by the practice guideline recommendations of interest). There was only a gradual effect of the 2010 guideline on screening rates which increased the testing of the total population. This effect was not seen following release of the other two guidelines.

Analyses by sex showed that for the female population 65 years and older, there was an immediate reduction in BMD testing following release of the 2010 guideline which we could not be explained by any secular changes reported around the same time in the literature. Yet, after a period of time this guideline increased the baseline BMD testing, though the effect was very small, and the rate remained very low at only 1.40 BMD testing per 1000 female population. For the male population, the 2002 guideline had an immediate effect on increasing the monthly baseline testing by 13.9% while there was no effect of the 2010 guideline. The overall trend of BMD testing in men showed an increasing pattern after the 2002 and 2010 guidelines, yet, it is still very low at the end of the analysis period for our study (at the end of January 2016) with only 2.7 baseline monthly testing per 1000 male population.

Repeated bone mineral testing for adults 65 years and above from 2011-2016 were analyzed according to the interval between repeated tests and we observed six patterns of repeated testing, most tests are being conducted after 2 years, and annually, while less repeated tests were conducted after 3 years and very few after 5 years. Therefore, most of the tests are being repeated every 2 years (32%) or annually (30%). Almost 40% of the repeated annual tests are for individuals with no previous fracture, not taking osteoporosis medication, or high does of steroids, and similarly, 40.3% which are being conducted after 2 years are for those without the above risk factors not in keeping with the 2010 guideline recommendations. We understand that we did not include all the possible risk factors for osteoporosis in classifying patients with low risk or high risk for osteoporosis, and we could not use the ICD-9 codes for high risk or low risk since it was not validated. Therefore, there could be a misclassification of the patients to the risk category. Yet, we included the most important risk factors in that age population and patients with rheumatoid arthritis and excessive alcohol consumption tend to be at younger age [62].

The findings from the second study indicated very low rates of baseline BMD testing for adults 65 years and older who are eligible for testing according to three Canadian guidelines recommendations. There was a very negligible impact of the 2010 osteoporosis

guidelines after a period of time (after 5 months of guideline release) on the baseline BMD testing for total population and female population. For men, the release of the 2002 guideline increased the baseline BMD testing by 13.9%. The analysis of the pattern of repeat BMD testing confirmed the findings in previous papers [50,52,57], that there is overtesting of patients with low risk for osteoporosis which is not in agreement of recommendations of BMD testing for low risk individuals.

Implications and Future Research

The results of our study have information that can help in improving the baseline screening for osteoporosis. The knowledge to Action cycle described how knowledge (osteoporosis guidelines) should be developed and then what are the pathways to be successfully implemented. The implications of the thesis and future research can be categorized based on this cycle process.

Guideline synthesis

The quality of guidelines is an important factor that ensure that high quality evidence was used in the synthesis of the recommendations, with an increase in the trust of the end user of these guidelines. In our first study we found that the quality is very variable and some of the most adopted guidelines in the field were of low quality. The guideline developers should pay a special attention to the involvement of different stakeholders especially patients, as very few guidelines have involved them in the development process. Additionally, many guidelines scored low in proper management of conflict of interest. In a letter by Sehmer J.; a physician in response to an article about adherence of physician to osteoporosis guidelines, he reported that most guidelines are sponsored by pharmaceutical industries, which make physicians skeptical about the recommendations especially when there is a controversy in the evidence about the effectiveness of the BMD [63]. Regardless of the veracity of the claim, the point remains valid, with any topic (but especially for controversial ones), managing conflict of interest maybe a crucial step in improving physicians' perceptions of a guideline and their potential adherence to it. For instance the

diversity of Canadian recommendations between different authorities; physicians may be aware of the recommendations in other Canadian guidelines such as in British Columbia which is doesn't recommend screening for all individuals 65 years and above, only if the FRAX threshold was high [64]. This may affect their decision especially if the guideline is produced or endorsed by a Governmental agency and not sponsored by pharmaceutical or private companies as the 2010 CPG for Ontario. Another area that guideline developers should notice is involving knowledge translation experts, very few guidelines reported details about the applicability of the guideline.

Our study found different grading systems that were used to report the level of evidence and strength of recommendations, which is an essential part of the guidelines quality and an important factor for clinicians to decide the level of recommendations. Clinicians need a simple grading system that they can trust and understand to guide them in their everyday clinical decisions. We encourage all guidelines to consider using the GRADE system which is now used by many respectful organizations and guideline authorities. Recently, the GRADE group released the Evidence to Decision 'EtD' framework to help panels of developers to use evidence in a structured way to inform decisions and they have a special framework for guidelines formation [6,7].

Epidemiologist/Researchers

In the first study we used two appraisal instruments (AGREE II and IOM) to assess the quality of guidelines and found that they can give conflicting results especially in the *Rigour of Development* domain which includes systematic assessment of evidence, assigning the evidence level and strength of recommendations. This may affect the physician's decision if they choose to assess the guideline using one tool over the other. Very few studies have compared results generated by both instruments, thus we need more studies to be done to compare these tools and to validate the IOM standards which we found challenging to use.

Clinicians/patients

There are many studies had assessed the barriers for management and screening of osteoporosis [67–69], and found factors that relate to patients; thus we shouldn't conclude that physicians are not adhering to guidelines without also considering patient preferences. Most patients think that osteoporosis is a natural process of aging, and they are not fully aware of the risks and consequences of fragility fractures [44,45]. Surprisingly a study reported that even some physicians think that " it is not a disease, it is a natural process of aging" [70]. In addition, the negative messages from media concerning safety of anti-osteoporosis medications which is affecting patients' decisions. Some studies have reported that the media has negatively decreased patients adherence and acceptance to drug treatment for osteoporosis, which also may affected their decision of the being screened for osteoporosis, since the are not willing to consider treatment if found to be at risk after screening [71]. Though, the medication side effects are very rare. For that reason, more education about the consequence of osteoporosis and how fragility fractures may lead to decrease in life expectancy or quality of life.

Despite physicians not screening most adults 65 years and older, our study found for the same age category, the repeated bone density testing is more frequent after one year and after 2 years of the first BMD test. Studies [76,77] and even most guidelines [49,66,78] report that at least 2 years are needed to detect a change in patients treated with anti-osteoporosis drugs. For low risk patients the Canadian guidelines recommend at least five years before repeating a BMD test [47]. Studies show that there is no need to repeat the BMD tests annually especially in patients not taking steroids medication, or with a previous fracture, or on anti-osteoporosis medication (which is the same cohort of our study) [73]. More research is needed to find why there is this tendency to over test low risk individuals, while undertest high risk patients. Through a personal communication with physicians to get some insight on why there is this tendency, we understood that most BMD test repeats are based on the results of the first BMD testing and the recommendation of the radiology reports. Many of these reports recommend repeating BMD testing after one year from the first test, this doesn't align with the evidence about the expected change in BMD, therefore,

research that investigates radiologists' knowledge of the evidence in relation to the evidence about the BMD change is warranted in the future.

In the first study, we reviewed the British osteoporosis guidelines, which are based on case finding strategy and not universal screening of all population aged 65 and older and this was based on evidence and cost effectiveness studies. We suggest revising the cost-effectiveness of screening all adults 65 years and older in Ontario, since most physicians think that this is a waste of resources and that can be the reason of low screening rates. Having said that, we need to be cautious of underscreening, to avoid missing cases at high risk of this disease.

Personal implications

A final implication of this thesis is the personal achievement of the learning outcomes that are required to fulfill the degree of Master of Epidemiology program. In this program I learned the contribution of epidemiology and biostatistics to health research, the design, conduct of epidemiologic studies, critical appraisal of epidemiologic studies, synthesis and integration of epidemiologic research, and communication of scientific research. Table S4-A in the Appendix of this chapter lists the learning outcomes that were achieved.

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APPENDIX FOR CHAPTER 4

Table S4-A: Learning outcomes for Graduate programme in Epidemiology.

Attribute	Required learning outcomes	Outcomes achieved in conducting this thesis
Depth and breadth of knowledge	1.Define concepts, terms, methods used in Epidemiology and public health to describe the health of a population	Understood methods of systematic review and interrupted time series methodology
	2. Summarize basic facts concerning the health of populations and health determinants	Summarized in tables and graphs the BMD testing parameters of the population
	3.Identify and classify common primary and secondary sources of data for epidemiologic research	I used secondary data in both of my papers. Say what ICES data used
	4. Define core terms and concepts used in descriptive and inferential biostatistics	We used means, medians and proportions and significance non-parametric testing (Mann Whitney test) to provide descriptive testing. For inferential biostatistics, provided regression coefficients for the time series analyses
	5. Developed specialized knowledge about a health research topic or method	I developed a specialized knowledge in systematic review conduction, synthesis and reporting. I developed a specialized knowledge in the interrupted time series analyses method and interpretation of the results.
Application of knowledge	6. Evaluate and critically appraise the strengths and limitations of an epidemiologic study from its design to the conclusions drawn	This is summarized in the section of strengths and limitations in the thesis
	7. Critically and systematically synthesize existing knowledge about a health topic	The first paper was a systematic review which achieved this outcome
	8. Design feasible studies with appropriate study designs to address health research questions	I have chosen an interrupted time series analysis to answer my second question and a systematic review to answer my first paper question.
	9. Choose, apply and interpret appropriate biostatistical methods	Application of different significance results such as Mann Whitney test, chi square test, for the first paper. For the second paper the application of autoregressive analysis.
	10. Proficiently use statistical software to analyse epidemiologic data	Used excel, SAS and R software.
Engaged scholarship,	12. Describe the best practices for	The thesis has discussed a gap in

knowledge translation, and communication	facilitating uptake of evidence into policy programs, patient care and/or the design or analysis of future research.	knowledge translation and estimated the magnitude of this gap.
	13. prepare a clearly written and logically argued report from epidemiologic analyses.	We prepared two manuscripts with results and clear interpretation.
	14. Effectively disseminate and communicate epidemiologic evidence to academic and non-academic audiences in written and oral formats.	We submitted the first manuscript for publication. We presented orally the results of the first manuscript in the School of Epidemiology Research Day.
	15. Describe the implication of epidemiologic evidence for policy, programs, patient care and/or future research	This was describe in Chapter 4 of the thesis.
Autonomy professional capacity, leadership and mentorship	16. Identify and adhere to ethical principles relevant to epidemiologic research that apply locally, nationally and internationally, including Tri-Council policy statement: Ethical conduct for Research involving Humans (TCPS).	This was learned by applying to the Ottawa Health Sciences Network Research Ethics Board (OHSN-REB).
	17. Adhere to principles of academic integrity according to the policies of the University of Ottawa	

*There are other learning objectives of the program, which was learned through the course work of the MSc program and not through the thesis, these objectives were not reported here.